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# Synthesis of Coumestan Derivatives via $FeCl_3$-Mediated Oxidative Ring Closure of 4-Hydroxy Coumarins

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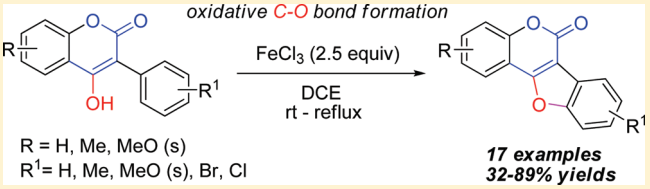
Supporting Information

**ABSTRACT:** A concise and efficient approach to the syntheses of coumestan analogues has been developed. The underpinning strategy involves a $FeCl_3$-mediated direct intramolecular oxidative annellation of 4-hydroxy-3-phenyl-2*H*-chromen-2-one derivatives. Utilizing this synthetic protocol, a variety of coumestan derivatives were conveniently obtained from readily available reagents.




## INTRODUCTION

Coumestan, known systematically as 6*H*-benzofuro[3,2-*c*]-[1]benzopyran-6-one, comprises a class of widely occurring natural analogues which have been reported to possess diverse pharmacological properties such as phytoestrogenic, antibacterial, antifungal, antimyotoxic, and phytoalexine effects.[1−6] Until now, many synthetic approaches have been developed to construct the basic fused-tetracyclic rings of coumestans.[7−26] All of these methods have their own merits in the preparation of the individual target compounds. However, a general method that can efficiently lead to diversified coumestan derivatives is still in high demand. Herein, we describe a more convenient and less complicated route to the syntheses of a variety of coumestan analogues from readily available reagents.

In our approach, the target coumestan molecule **1** was retrosynthetically disconnected by the cleavage of the aromatic (phenyl ring B) $sp^2$ carbon−oxygen bond to afford 4-hydroxy-3-phenyl-2*H*- chromen-2-one **2**. We envisaged that this coumarin compound **2** might undergo $FeCl_3$-mediated intramolecular cyclization via direct oxidative aromatic C−O bond formation,[27] a strategy that has been successfully applied by us to the syntheses of 3-functionalized benzo[*b*]furans from the readily available electron-rich α-aryl ketones.[28] Compound **2** can be prepared via intramolecular Claisen condensation of intermediate **3**,[29,30] which can be easily tracked back to the substituted methyl salicylate **4** and phenylacetic acid derivative **5**[28] (Figure 1). Alternatively, the mono- or dimethoxylated substrate **2′** (on ring A) can be obtained from intermediate **6** through methoxycarbonylation and in situ lactonization.[31] Compound **6** can be prepared through a simple regioselective methylation of 1,3-dihydroxyl phenol derivative **7**, which can be easily formed by the reaction of polyphenols **8** with benzyl cyanide derivative or phenylacetic acid derivative **9** catalyzed by a Lewis acid (Figure 2).[32,33]

## RESULTS AND DISCUSSION

With various substituted 4-hydroxy-3-phenyl-2*H*-chromen-2-ones having been prepared by the above strategies, we proceeded to investigate their intramolecular oxidative annellation mediated by anhydrous $FeCl_3$. In our previous investigation on the formation of benzo[*b*]furan-3-carboxylates, we found that the presence of the two electron-donating methoxy groups on the benzene ring of the α-aryl ketones was crucial for the oxidative intramolecular cyclization to occur.[28] Bearing this in mind, 3-(3,4-dimethoxyphenyl)-4-hydroxy-2*H*-chromen-2-one (**2a**) was chosen to test the feasibility of the ring closure. As expected, the desired coumestan **1a** was obtained in 86% yield after the reaction mixture was stirred in DCE at room temperature for 12 h. It was also found that the application of a combination of $FeCl_3$ and $SiO_2$ instead of $FeCl_3$ alone delivered a better yield and allowed an easier workup.[34−37] Our further study showed that the introduction of a methyl group or methoxy group(s) to the phenyl ring A does not affect the cyclization and the desired products **1b**−**d** can also be obtained in useful yields. Next, the monomethoxylated coumarins **2e**−**h** were also investigated under the same conditions. Compounds **2e**−**h** also furnish the desired cyclized products **1e**−**h** in acceptable to good yields. This result was somewhat contrary to our expectation since we had previously found that the similar monomethoxylated α-aryl ketones bearing a benzylic ester group hardly underwent cyclization to afford benzo[*b*]furans.[28] Inspired by this finding, we decided to examine whether the other coumarin substrates bearing substituents other than a methoxy group at the para-position of the phenyl ring B can undergo the expected oxidative cyclization. It was found that when the *p*-methoxy group was replaced with a methyl group, substrate **2i,j** gave only a trace amount of the desired cyclized products **1i,j** after the reaction mixture was stirred at room temperature for 24 h. However, when the reaction was carried out under reflux for 12 h, the expected products **1i** and **1j** were achieved in moderate to good yields. This result suggests that the presence of the electron-donating methoxy group on the phenyl ring B is not the determinant factor for the cyclization to occur. Encouraged by this

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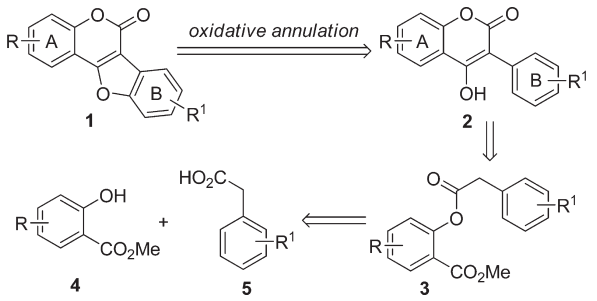



**Figure 1.** A general retrosynthetic analysis of coumestan **1**.

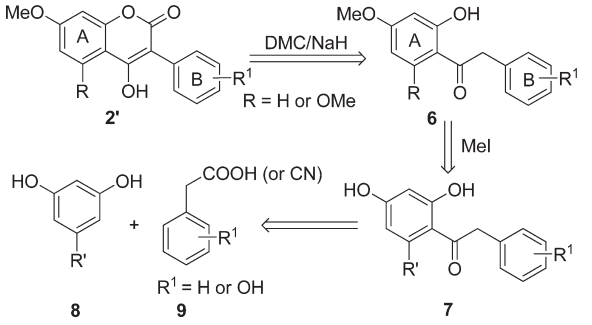



**Figure 2.** Retrosynthetic analysis of the methoxylated substrate **2′**.

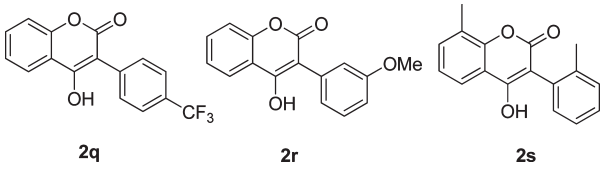


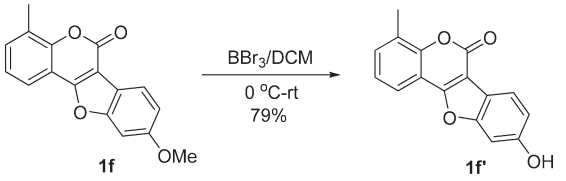

**Figure 3.** Substrates that failed to undergo oxidative annellation.

finding, we started to test the coumarin compounds without any aromatic substituent on the phenyl B and found that compounds **2k**−**m** also afforded the cyclized coumestan derivatives **1k**−**m** at reflux temperature. Surprisingly, for the substrates bearing a *p*-chloro or bromo (**2n**−**p**) group on phenyl ring B, the reaction also furnished the cyclized products in acceptable yields under reflux conditions. This result further demonstrates that the electron-donating substituent on phenyl ring B is not indispensable for the annellation process of this class of coumarin substrates.

In our investigation of the scope and generality of this method, we found that substrates with a *p*-trifluoromethyl group or a *m*-methoxy group (**2q,r**) on the phenyl ring B failed to provide any cyclized products at reflux conditions after 24 h (Figure 3). Furthermore, no desired annellated product was separated when substrate **2s**, bearing an *o*-methyl group on the phenyl ring B, was subjected to the identical conditions. The presence of the *o*-methyl group that hinders free rotation of the phenyl ring B is presumably the cause of the unsuccessful cyclization.

As many biologically active natural coumestan members possess hydroxyl group(s) on either phenyl ring A or B, one of the valuable applications of this method is to convert the mono- or multimethoxylated coumestans to the corresponding hydroxylated compounds. For example, the hydroxylated coumestan **1f′**, which is also a new compound, can be obtained from **1f** via the known $BBr_3$-mediated demethylation approach (Scheme 1, Table 1).[7,38] Considering that some natural coumestan compounds

**Scheme 1. Formation of Hydroxylated Coumestan via Demethylation Mediated by $BBr_3$**




bear concurrently both methoxy group and hydroxyl group(s) on the phenyl rings A and B, we also applied our method to synthesize the naturally occurring **13**,[38−41,39−42] which bears a hydroxyl group on the phenyl ring A and a methoxy group on the phenyl ring B by using a protection−deprotection protocol. To realize this goal, the readily available **7′** was treated with $^{i}$PrCl under basic conditions, and the regioselectively protected **10** was obtained in 55% yield. Further treatment of **10** with dimethyl carbonate (DMC)/NaH in reflux toluene gave 3-aryl-4-hydroxyl coumarin **11**, which can undergo $FeCl_3$-mediated oxidative cyclization by our approach to give the $^{i}$Pr-protected coumestan **12** in good yield.[43] Finally, the desired **13** was achieved via $^{i}$Pr-deprotection with $AlCl_3$ in DCM (Scheme 2).[44] We assume that such a protection−deprotection protocol can also be applied to the synthesis of other such coumestan members.

Because of the difference in reactivity caused by the subtle change in the electronic configuration of the enol type substrate **2** in comparison with the previously employed carbonyl type of substrate,[28] we propose a different mechanistic pathway, which is outlined in Scheme 3. A hydrogen atom is initially abstracted from the enol substrate **2**, possibly via a single electron transfer (SET) process, facilitated by $FeCl_3$. This process will furnish oxygen radical **A**, stabilized by resonance structures **B** and **C**. A second $FeCl_3$-mediated SET process occurs to convert the radical intermediate **C** to a benzene cation intermediate **D**, which can be stabilized by a para-positioned methoxy, methyl, bromo, or chloro group, but destabilized by a strong electron-withdrawing trifluoromethyl group. The unsuccessful annellation of **2r** might be attributed to the presence of a *m*-methoxy, which cannot provide stabilization to the carbocation in intermediate **D** via resonance effect. Next, the oxygen of the side chain carbonyl group nucleophilicly attacks the ring carbocation to give **E**. Finally, rearomatizaton of **E** by the loss of a proton gives the title compounds **1** (Scheme 3).

## CONCLUSION

In conclusion, we have reported herein a concise approach to diversified coumestan-based compounds through a $FeCl_3$-mediated direct intramolecular oxidation of 4-hydroxyl-3-aryl coumarin compounds. The present method uses readily available starting materials at low cost and a simple workup. In view of the broad range of interesting biological activities possessed by coumestan compounds, this method shows promising potential applications in exploring biologically potent compounds of the coumestan family.

## EXPERIMENTAL SECTION

**General Information.** $^{1}$H and $^{13}$C NMR spectra were recorded on a 400 MHz spectrometer at 25 °C. Chemical shift values are given in


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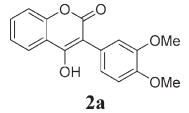
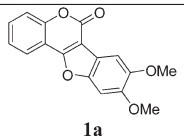
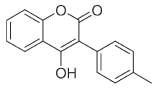
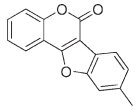
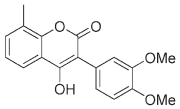
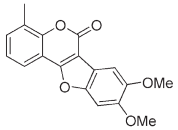
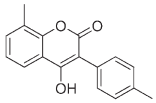
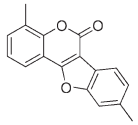
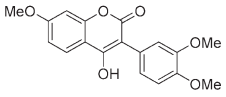
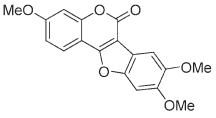
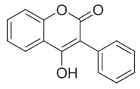
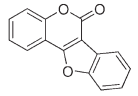
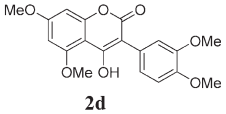
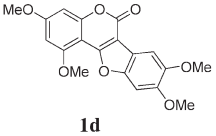
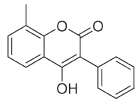
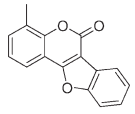
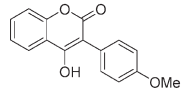
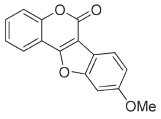
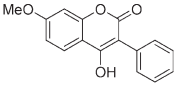
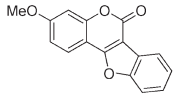
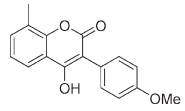
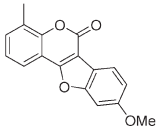
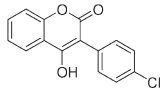
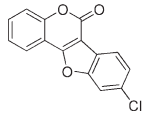
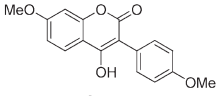
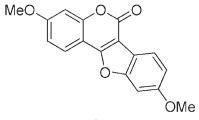
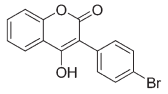
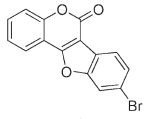
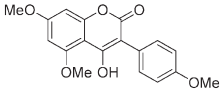
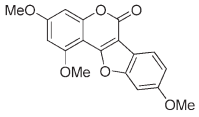
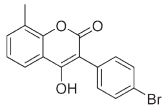
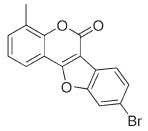
**Table 1. Synthesis of Coumestans 1 via Intramolecular Heterocyclization of 4-Hydroxy-3-phenyl-2*H*-chromen-2-one 2 Mediated by $FeCl_3/SiO_2$[a]**


| entry | substrate **2** | product **1** | time (h) | yield (%)[b] | entry | substrate **2** | product **1** | time (h) | yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  **2a** |  **1a** | 12 | 86 | 9[c] |  **2i** |  **1i** | 12 | 86 |
| 2 |  **2b** |  **1b** | 24 | 52 | 10[c] |  **2j** |  **1j** | 12 | 63 |
| 3 |  **2c** |  **1c** | 24 | 50 | 11[c] |  **2k** |  **1k** | 24 | 60 |
| 4 |  **2d** |  **1d** | 24 | 33 | 12[c] |  **2l** |  **1l** | 12 | 69 |
| 5[c] |  **2e** |  **1e** | 24 | 89 | 13[c] |  **2m** |  **1m** | 12 | 64 |
| 6[c] |  **2f** |  **1f** | 24 | 83 | 14[c] |  **2n** |  **1n** | 12 | 87 |
| 7[c] |  **2g** |  **1g** | 24 | 70 | 15[c] |  **2o** |  **1o** | 12 | 50 |
| 8 |  **2h** |  **1h** | 24 | 32 | 16[c] |  **2p** |  **1p** | 12 | 46 |

[a] Conditions: all reactions were carried out with 1 equiv of **1** and 2.5 equiv of anhydrous $FeCl_3/SiO_2$ in DCE at rt unless otherwise stated. [b] Yields after silica gel chromatography. [c] Reaction occurred at reflux temperature.

ppm and referred as the internal standard to TMS: 0.00 ppm. The peak patterns are indicated as follows: s, singlet; d, doublet; m, multiplet; and dd, doublet of doublets. The coupling constants, *J*, are reported in hertz (Hz). ESI-MS were obtained on an ion trap microspectrometer. High-resolution mass spectra (HRMS) were obtained on a Q-TOF microspectrometer. Melting points were determined with a national micromelting point apparatus without corrections. 1,2-Dichloroethane, pyridine, $Et_2O$, toluene, and DCM were dried over $CaH_2$ before use. Phosphorus oxychloride was redistilled before use, and other reagents and solvents were purchased as reagent grade and were used without further purification. Flash column chromatography was performed over silica gel 200−300 m and the eluent was a mixture of ethyl acetate and petroleum ether.

## Preparation of Substrates

**1. Preparation of Intermediates 3a,b, 3e,f, 3i−*l*, 3n−p, 3r, s, and 2a,b, 2e,f, 2i−*l*, 2n−p, 2r,s..** The title coupounds were prepared according to the procedures in refs 29 and 30.

**Methyl 2-(2-(3,4-dimethoxyphenyl)acetoxy)benzoate, 3a:** white solid; yield 70%, mp 53−54 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$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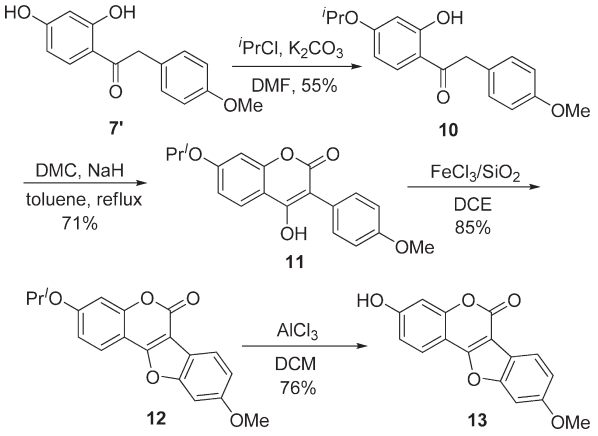
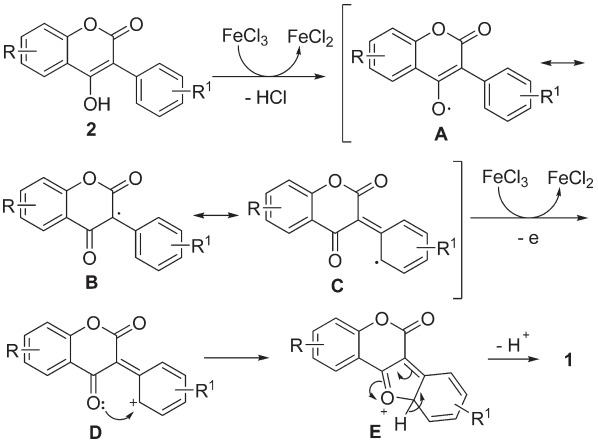
**Scheme 2. Synthesis of 13 via $FeCl_3$-Mediated Oxidative Annellation Using a Protection−Deprotection Protocol**




**Scheme 3. Possible Mechanistic Pathway for the Formation of the Coumestan Skeleton**




8.01 (d, 1H, $J$ = 8.0 Hz), 7.56−7.52 (m, 1H), 7.31 (t, 1H, $J$ = 7.6 Hz), 7.06 (d, 1H, $J$ = 8.0 Hz), 6.98−6.93 (m, 2H), 6.86 (d, 1H, $J$ = 8.0 Hz), 3.90 (s, 5H), 3.88 (s, 3H), 3.79 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.5, 164.9, 150.7, 149.0, 148.3, 133.8, 131.8, 126.1, 125.9, 123.7, 123.3, 121.8, 112.8, 111.3, 56.0, 55.9, 52.1, 40.7. ESI-MS $m/z$ $[M + Na]^+$ 353.4. HRMS (ESI) calcd for $C_{18}H_{19}O_6^+$ $[M + H]^+$ 331.1176, found 331.1179.

**Methyl 2-(2-(3,4-dimethoxyphenyl)acetoxy)-3-methylbenzoate, 3b:** white solid, yield 48%, mp 72 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (d, 1H, $J$ = 7.6 Hz), 7.39 (d, 1H, $J$ = 7.2 Hz), 7.19 (t, 1H, $J$ = 7.6 Hz), 6.97 (t, 2H), 6.86 (d, 1H, $J$ = 8.0 Hz), 3.89 (d, 8H), 3.81 (s, 3H), 2.06 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.0, 165.2, 149.2, 149.0, 148.3, 135.4, 132.2, 129.4, 126.0, 126.0, 123.1, 121.8, 112.7, 111.2, 55.9, 55.9, 52.1, 40.8, 16.1. ESI-MS $m/z$ $[M + Na]^+$ 367.6. HRMS (ESI) calcd for $C_{19}H_{21}O_6^+$ $[M + H]^+$ 345.1333; found 345.1337.

**Methyl 2-(2-(4-methoxyphenyl)acetoxy)benzoate, 3e:** white solid, yield 76%, mp 81 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (d, 1H, $J$ = 7.6 Hz), 7.53 (t, 1H, $J$ = 8.0 Hz), 7.34−7.28 (m, 3H), 7.06 (d, 1H, $J$ = 8.0 Hz), 6.90 (d, 2H, $J$ = 8.4 Hz), 3.89 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.5, 165.0, 158.9, 150.7, 133.8, 131.8, 130.7, 126.0, 125.5, 123.8, 123.3, 114.1, 55.3, 52.2, 40.3. ESI-MS $m/z$ $[M + Na]^+$ 323.4. HRMS (ESI) calcd for $C_{17}H_{17}O_5^+$ $[M + H]^+$ 301.1071, found 301.1072.

**Methyl 2-(2-(4-methoxyphenyl)acetoxy)-3-methylbenzoate, 3f:** white solid, yield 51%, mp 52 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82 (d, 1H, $J$ = 7.6 Hz), 7.38−7.33 (m, 3H), 7.18 (t, 1H, $J$ = 7.6 Hz), 6.90 (d, 2H, $J$ = 8.4 Hz), 3.90 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 2.05 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.00, 165.3, 158.9, 149.2, 135.4, 132.2, 130.7, 129.4, 125.7, 125.6, 123.2, 114.1, 55.3, 52.1, 40.3, 16.1. ESI-MS $m/z$ $[M + Na]^+$ 337.3. HRMS (ESI) calcd for $C_{18}H_{19}O_5^+$ $[M + H]^+$ 315.1227, found 315.1232.

**Methyl 2-(2-*p*-tolyacetoxy)benzoate, 3i:** white solid, yield 74%, mp 62 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (d, 1H, $J$ = 6.8 Hz), 7.61 (t, 1H, $J$ = 7.6 Hz), 7.42−7.36 (m, 3H), 7.28 (d, 2H, $J$ = 7.6 Hz), 7.16 (d, 1H, $J$ = 8.0 Hz), 4.02 (s, 2H), 3.87 (s, 3H), 2.45 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 165.1, 150.7, 136.9, 133.8, 131.8, 130.4, 129.5, 129.4, 126.1, 123.8, 123.4, 52.2, 40.8, 21.2. ESI-MS $m/z$ $[M + Na]^+$ 307.4.

**Methyl 3-methyl-2-(2-*p*-tolylacetoxy)benzoate, 3j:** white solid, yield 46%, mp 39 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (d, 1H, $J$ = 8.0 Hz), 7.38 (d, 1H, $J$ = 7.2 Hz), 7.32 (d, 2H, $J$ = 7.6 Hz), 7.19 (t, 3H), 3.93 (s, 2H), 3.80 (s, 3H), 2.36 (s, 3H), 2.07 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.9, 165.3, 149.2, 136.9, 135.3, 132.2, 130.5, 129.5, 129.4, 129.3, 125.6, 123.2, 52.1, 40.8, 21.2, 16.1. ESI-MS $m/z$ $[M + H]^+$ 321.4. HRMS (ESI) calcd for $C_{18}H_{19}O_4^+$ $[M + H]^+$ 299.1278, found 299.1278.

**Methyl 2-(2-phenylacetoxy)benzoate, 3k:**[30]**.** white solid, yield 68%, mp 55 °C (lit.[29] mp 56 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02−7.99 (dd, 1H, $J$ = 8.0, 1.2 Hz), 7.55−7.51 (m, 1H), 7.43−7.25 (m, 6H), 7.06 (d, 1H, $J$ = 8.0 Hz), 3.95 (s, 2H), 3.76 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 165.0, 150.6, 133.8, 133.4, 131.8, 129.7, 128.7, 127.3, 126.1, 123.7, 123.3, 52.1, 41.2. ESI-MS $m/z$ $[M + Na]^+$ 293.3.

**Methyl 3-methyl-2-(2-phenylacetoxy)benzoate, 3*l*:** white solid, yield 48%, mp 53 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82 (d, 1H, $J$ = 7.6 Hz), 7.44−7.28 (m, 6H), 7.17 (t, 1H), 3.96 (s, 2H), 3.78 (s, 3H), 2.04 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.7, 165.3, 149.1, 135.4, 133.6, 132.2, 129.7, 129.4, 128.7, 127.3, 125.7, 123.2, 52.1, 41.3, 16.0. ESI-MS $m/z$ $[M + Na]^+$ 307.4. HRMS (ESI) calcd for $C_{17}H_{17}O_4^+$ $[M + H]^+$ 285.1121, found 285.1126.

**Methyl 2-(2-(4-chlorophenyl)acetoxy)benzoate, 3n:** white solid, yield 68%, mp 74−75 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (d, 1H, $J$ = 7.6 Hz), 7.55−7.53 (m, 1H), 7.36−7.25 (m, 5H), 7.05 (d, 2H, $J$ = 8.0 Hz), 3.92 (s, 2H), 3.79 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.8, 164.8, 150.6, 133.9, 133.3, 131.9, 131.8, 131.1, 128.8, 126.2, 123.7, 123.1, 52.1, 40.4. ESI-MS $m/z$ $[M + Na]^+$ 327.7.

**Methyl 2-(2-(4-bromophenyl)acetoxy)benzoate, 3o:** white solid, yield 68%, mp 82−83 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (d, 1H, $J$ = 7.6 Hz), 7.63−7.56 (m, 3H), 7.39−7.36 (m, 3H), 7.13 (d, 1H, $J$ = 8.0 Hz), 3.98 (s, 2H), 3.87 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.8, 164.8, 150.6, 133.9, 132.4, 131.8, 131.7, 131.5, 126.2, 123.7, 123.1, 121.4, 52.2, 40.4. ESI-MS $m/z$ $[M + Na]^+$ 371.0, 373.0. HRMS (ESI) calcd for $C_{16}H_{14}BrO_4^+$ $[M + H]^+$ 349.0070, found 349.0073.

**Methyl 2-(2-(4-bromophenyl)acetoxy)-3-methylbenzoate, 3p:** white solid, yield 41%, mp 55 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (d, 1H, $J$ = 7.6 Hz), 7.49 (d, 2H, $J$ = 8.4 Hz), 7.39 (d, 1H, $J$ = 7.2 Hz), 7.31 (d, 2H, $J$ = 8.4 Hz), 7.21−7.18 (t, 1H), 3.93 (s, 2H), 3.81 (s, 3H), 2.08 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.2, 165.1, 149.1, 135.4, 132.5, 132.1, 131.7, 131.4, 131.4, 129.4, 125.8, 123.0, 121.4, 52.1, 40.5, 16.1. ESI-MS $m/z$ $[M + Na]^+$ 384.6, 386.7. HRMS (ESI) calcd for $C_{17}H_{16}BrO_4^+$ $[M + H]^+$ 363.0226, found 363.0227.

**Methyl 2-(2-(3-methoxyphenyl)acetoxy)benzoate, 3r:** colorless liquid, yield 49%. $^1$H NMR (400 MHz, $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01−7.99 (dd, 1H, $J$ = 7.6, 2.0 Hz), 7.54−7.50 (m, 1H), 7.31−7.25 (m, 2H), 7.06 (d, 1H, $J$ = 8.0 Hz), 6.99 (d, 2H, $J$ = 7.2 Hz), 6.86−6.84 (m, 1H), 3.92 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.1, 165.0, 159.8, 150.6, 134.8, 133.8, 131.8, 129.6, 126.1, 123.7, 123.3, 122.0, 115.2, 113.0, 55.2, 52.1, 41.1. ESI-MS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$m/z$ $[M + Na]^+$ 323.3. HRMS (ESI) calcd for $C_{17}H_{17}O_5^+$ $[M + H]^+$ 301.1071, found 301.1071.

**Methyl 3-methyl-2-(2-*o*-tolylacetoxy)benzoate, 3s:** white solid, yield 38%, mp 49 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82 (d, 1H, $J$ = 7.6 Hz), 7.37 (d, 2H, $J$ = 7.6 Hz), 7.21−7.17 (m, 4H), 3.99 (s, 2H), 3.81 (s, 3H), 2.44 (s, 3H), 2.06 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.5, 165.3, 149.2, 137.1, 135.3, 132.2, 132.1, 130.6, 130.4, 129.4, 127.6, 126.2, 125.6, 123.2, 52.1, 39.0, 19.7, 16.0. ESI-MS $m/z$ $[M + Na]^+$ 321.3. HRMS (ESI) calcd for $C_{18}H_{19}O_4^+$ $[M + H]^+$ 299.1278, found 299.1279.

**3-(3,4-Dimethoxyphenyl)-4-hydroxy-2*H*-chromen-2-one, 2a:** white solid, yield 68%, mp 243−245 °C. $^1$H NMR (400 MHz, $d^6$-DMSO): $\delta$ 11.15 (br s, 1H), 7.97 (d, 1H, $J$ = 7.6 Hz), 7.67−7.63 (t, 1H), 7.42−7.36 (m, 2H), 7.03−6.92 (m, 3H), 3.80 (s, 3H), 3.75 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.4, 160.4, 152.7, 148.9, 148.8, 132.6, 124.5, 124.4, 124.1, 124.0, 116.9, 116.6, 115.3, 112.1, 106.4, 56.0, 56.0. ESI-MS $m/z$ $[M - H]^-$ 297.1.

**3-(3,4-Dimethoxyphenyl)-4-hydroxy-8-methyl-2*H*-chromen-2-one, 2b:** white solid, yield 45%, mp >300 °C. $^1$HNMR (400 MHz, $d^6$-DMSO) $\delta$ 7.71 (d, 1H, $J$ = 7.6 Hz), 7.49 (s, 1H), 7.31 (d, 1H, $J$ = 8.0 Hz), 7.20 (d, 1H, $J$ = 6.8 Hz), 6.96 (t, 1H), 6.78 (d, 1H, $J$ = 8.4 Hz), 3.73 (s, 3H), 3.70 (s, 3H), 2.31 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 172.4, 164.2, 152.1, 147.5, 145.5, 132.4, 130.8, 124.2, 124.0, 123.6, 123.4, 121.2, 116.0, 111.3, 97.1, 56.2, 55.9, 16.0. ESI-MS $m/z$ $[M - H]^-$ 311.2. HRMS (ESI) calcd for $C_{18}H_{17}O_5^+$ $[M + H]^+$ 313.1071, found 313.1075.

**4-Hydroxy-3-(4-methoxyphenyl)-2*H*-chromen-2-one, 2e:**[45]. white solid, yield 66%, mp 242−244 °C (lit.[46] mp 242−243 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.23 (br, s, 1H), 8.00−7.98 (dd, 1H, $J$ = 8.0, 1.2 Hz), 7.65 (t, 1H, $J$ = 8.4 Hz), 7.42−7.36 (m, 2H), 7.33 (d, 2H, $J$ = 8.8 Hz), 7.00 (d, 2H, $J$ = 8.8 Hz), 3.80 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.5, 160.4, 159.1, 152.7, 132.7, 132.6, 124.4, 124.4, 124.1, 116.9, 116.6, 114.0, 106.3, 55.6. ESI-MS $m/z$ $[M - H]^-$ 267.1.

**4-Hydroxy-3-(4-methoxyphenyl)-8-methyl-2*H*-chromen-2-one, 2f:** white solid, yield 50%, mp 208−210 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.12 (br, s, 1H), 7.82 (d, 1H, $J$ = 7.6 Hz), 7.51 (d, 1H, $J$ = 7.2 Hz), 7.34−7.25 (m, 3H), 6.99 (d, 2H, $J$ = 8.4 Hz), 3.80 (s, 3H), 2.39 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.5, 160.9, 159.0, 151.0, 133.5, 132.6, 125.4, 124.6, 123.8, 121.8, 116.8, 114.0, 105.9, 55.6, 15.7. HRMS (ESI) calcd for $C_{17}H_{15}O_4^+$ $[M + H]^+$ 283.0965, found 283.0965.

**4-Hydroxy-3-*p*-tolyl-2*H*-chromen-2-one, 2i:** white solid, yield 37%, mp 221−222 °C (lit.[47] mp 225−226 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.26 (br, s, 1H), 8.00 (d, 1H, $J$ = 8.8 Hz), 7.67−7.63 (t, 1H), 7.42−7.36 (m, 2H), 7.30−7.23 (m, 4H), 2.36 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.43, 160.6, 152.7, 137.1, 132.6, 131.3, 129.5, 129.1, 124.4, 124.2, 117.0, 116.6, 106.5, 21.4. HRMS (ESI) calcd for $C_{16}H_{13}O_3^+$ $[M + H]^+$ 253.0859, found 253.0869.

**4-Hydroxy-8-methyl-3-*p*-tolyl-2*H*-chromen-2-one, 2j:** white solid, yield 46%, mp 167−169 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (d, 1H, $J$ = 8.0 Hz), 7.86 (d, 1H, $J$ = 7.6 Hz), 7.45 (t, 2H), 7.32−7.26 (m, 3H), 2.56 (s, 3H), 2.55 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.0, 158.2, 156.0, 151.9, 137.3, 132.9, 127.0, 126.4, 124.1, 121.3, 120.9, 119.3, 112.5, 111.9, 105.7, 21.9, 16.2. ESI-MS $m/z$ $[M + H]^+$ 267.5. HRMS (ESI) calcd for $C_{17}H_{15}O_3^+$ $[M + H]^+$ 267.1016, found 267.1022.

**4-Hydroxy-3-phenyl-2*H*-chromen-2-one, 2k:** white solid, yield 56%, mp 232−233 °C (lit.[48] mp 232−233 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.38 (br s, 1H), 8.01 (d, 1H, $J$ = 7.2 Hz), 7.67 (t, 1H, $J$ = 7.2 Hz), 7.45−7.34 (m, 7H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.4, 160.8, 152.8, 132.8, 132.6, 131.5, 128.5, 127.9, 124.4, 124.2, 117.0, 116.7, 106.6. ESI-MS $m/z$ $[M - H]^-$ 237.0. The $^1$H NMR data were consistent with that in the literature.[12]

**4-Hydroxy-8-methyl-3-phenyl-2*H*-chromen-2-one, 2l:** white solid, yield 43%, mp 225−226 °C (lit.[49] mp 251 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.32 (s, 1H), 7.85 (d, 1H, $J$ = 8.0 Hz), 7.53 (d, 1H, $J$ = 7.2 Hz), 7.46−7.34 (m, 5H), 7.28 (t, 1H, $J$ = 7.6 Hz), 2.40 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.3, 160.9, 151.1, 133.7, 132.6, 131.5, 128.5, 127.9, 125.5, 123.9, 121.9, 116.6, 106.4, 15.7. HRMS (ESI) calcd for $C_{16}H_{13}O_3^+$ $[M + H]^+$ 253.0859, found 253.0869.

**3-(4-Chlorophenyl)-4-hydroxy-2*H*-chromen-2-one, 2n:**[45]. white solid, yield 56%, mp 252 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 8.04 (d, 1H, $J$ = 8.0 Hz), 7.69−7.65 (m, 1H), 7.50−7.38 (m, 6H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.2, 161.1, 152.8, 133.4, 132.9, 132.6, 131.5, 128.5, 124.5, 124.3, 116.8, 116.7, 105.4. ESI-MS $m/z$ $[M - H]^-$ 271.3.

**3-(4-Bromophenyl)-4-hydroxy-2*H*-chromen-2-one, 2o:** white solid, yield 70%, mp 242−245 °C (lit.[50] mp 260 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.70 (s, 1H), 8.09 (t, 1H), 7.69−7.61 (m, 3H), 7.43−7.37 (m, 4H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.2, 161.2, 152.8, 133.7, 132.9, 132.0, 131.4, 124.4, 124.4, 121.2, 116.9, 116.7, 105.4. ESI-MS $m/z$ $[M - H]^-$ 315.0, 317.1.

**3-(4-Bromophenyl)-4-hydroxy-8-methyl-2*H*-chromen-2-one, 2p:** white solid, yield 45%, mp 235 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 7.85 (d, 1H, $J$ = 7.6 Hz), 7.62 (d, 2H, $J$ = 8.4 Hz), 7.54 (d, 1H, $J$ = 7.2 Hz), 7.37 (d, 2H, $J$ = 8.4 Hz), 7.28 (t, 1H, $J$ = 7.6 Hz), 2.39 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 174.9, 162.1, 161.3, 151.1, 133.9, 133.7, 132.0, 131.4, 125.6, 123.9, 121.9, 121.2, 116.5, 105.2, 29.5. ESI-MS $m/z$ $[M - H]^-$ 329.0, 331.0. HRMS (ESI) calcd for $C_{16}H_{12}BrO_3^+$ $[M + H]^+$ 330.9964, found 330.9973.

**4-Hydroxy-3-(4-nitrophenyl)-2*H*-chromen-2-one, 2q:** prepared according to the procedure in ref 45; white solid, yield 30%, mp 287−289 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 8.06−8.04 (dd, 1H, $J$ = 8.8, 1.2 Hz), 7.78 (d, 2H, $J$ = 8.0 Hz), 7.71−7.65 (m, 3H), 7.45−7.39 (m, 2H).

**4-Hydroxy-3-(3-methoxyphenyl)-2*H*-chromen-2-one, 2r:** white solid, yield 50%, mp 262−264 °C (lit.[51] mp 265−266 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.33 (s, 1H), 8.01−7.98 (dd, 1H, $J$ = 8.0, 0.8 Hz), 7.68−7.65 (m, 1H), 7.42−7.32 (m, 3H), 6.97−6.93 (m, 3H), 3.77 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.2, 160.7, 159.5, 152.8, 133.7, 132.8, 129.6, 124.5, 124.2, 123.8, 117.1, 116.9, 116.7, 113.7, 106.5, 55.5. ESI-MS $m/z$ $[M - H]^-$ 267.1.

**4-Hydroxy-8-methyl-3-*o*-tolyl-2*H*-chromen-2-one, 2s.** white solid, yield 41%, mp >300 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.17 (s, 1H), 7.81 (d, 1H, $J$ = 8.0 Hz), 7.54 (d, 1H, $J$ = 7.2 Hz),7.31−7.26 (m, 2H), 7.18−7.15 (m, 3H), 2.41 (s, 3H), 2.13 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 173.0, 161.9, 161.2, 151.3, 138.4, 133.7, 131.9, 130.3, 128.5, 127.3, 126.2, 123.9, 121.8, 116.5, 105.7, 19.8, 15.7. ESI-MS $m/z$ $[M - H]^-$ 265.2. HRMS (ESI) calcd for $C_{17}H_{15}O_3^+$ $[M + H]^+$ 267.1016, found 267.1019.

**2. Preparation of the Substituted 3-Aryl-4-hydroxy Coumarins 2c, 2g, and 2m.** (I) **7c**, **7g** and **7m** were prepared according to the procedure in ref 30.

**1-(2,4-Dihydroxyphenyl)-2-(3,4-dimethoxyphenyl)ethanone, 7c:** white solid, yield 72%, mp 177−179 °C (lit.[32] mp 177−178 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 12.55 (s, 1H), 10.64 (s, 1H), 7.93 (d, 1H, $J$ = 8.8 Hz), 6.87 (t, 1H), 6.77 (d, 1H, $J$ = 7.6 Hz), 6.38−6.36 (dd, 1H, $J$ = 8.8, 6.0 Hz), 6.24 (d, 1H, $J$ = 6.0 Hz), 4.18 (s, 2H), 3.70 (s, 6H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 202.8, 165.4, 165.1, 149.1, 148.1, 134.0, 127.9, 122.0, 113.9, 112.6, 112.4, 108.7, 103.0, 55.99, 55.96, 44.2. ESI-MS $m/z$ $[M + Na]^+$ 311.5.

**1-(2,4-Dihydroxyphenyl)-2-(4-methoxyphenyl)ethanone, 7g:** white solid, yield 74%, mp 159 °C (lit.[33] mp 159 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 12.55 (s, 1H), 10.66 (s, 1H), 7.94 (d, 1H, $J$ = 8.8 Hz), 7.20 (d, 2H, $J$ = 8.8 Hz), 6.87 (d, 2H, $J$ = 8.4 Hz), 6.40−6.37 (dd, 1H, $J$ = 8.8, 2.4 Hz), 6.25 (d, 1H, $J$ = 2.4 Hz), 4.20 (s, 2H), 3.72 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 202.9, 165.4, 165.1, 158.5, 134.0, 131.0, 127.5, 114.3, 112.6, 108.7, 103.0, 55.5, 43.7. ESI-MS $m/z$ $[M - H]^-$ 257.2.

**1-(2,4-Dihydroxyphenyl)-2-phenylethanone, 7m:** white solid, yield 65%, mp 106−107 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 12.50 (s, 1H), 10.67 (s, 1H), 7.94 (d, 1H, $J$ = 8.8 Hz), 7.32−7.20

(m, 5H), 6.38 (d, 1H, $J$ = 8.8 Hz), 6.24 (s, 1H), 4.27 (s, 2H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 202.6, 165.5, 165.1, 135.7, 134.0, 130.0, 128.9, 127.1, 112.7, 108.8, 103.0, 44.6. ESI-MS $m/z$ $[M - H]^-$ 227.2.

(II) **6c**, **6g**, and **6m** were prepared according to the procedure in ref 32.

**2-(3,4-Dimethoxyphenyl)-1-(2-hydroxy-4-methoxyphenyl)-ethanone, 6c:** white solid, yield 70%, mp 116−117 °C (lit.[52] mp 118 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 12.74 (s, 1H), 7.76 (d, 1H, $J$ = 8.8 Hz), 6.85−6.79 (m, 3H), 6.46−6.43 (m, 2H), 4.16 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.2, 166.2, 165.9, 149.1, 148.2, 132.0, 126.8, 121.5, 113.2, 112.5, 111.4, 107.9, 101.1, 55.9, 55.6, 44.5.

**1-(2-Hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-ethanone, 6g:** white solid, yield 72%, mp 101 °C (lit.[53] mp 100−102 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 12.74 (s, 1H), 7.75 (d, 1H, $J$ = 8.8 Hz), 7.19 (d, 2H, $J$ = 8.4 Hz), 6.88 (d, 2H, $J$ = 8.4 Hz), 6.46−6.43 (m, 2H), 4.16 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.3, 166.2, 165.9, 158.7, 132.0, 130.4, 126.4, 114.2, 113.2, 107.8, 101.1, 55.6, 55.3, 44.0.

**1-(2-Hydroxy-4-methoxyphenyl)-2-phenylethanone, 6m:** white solid, yield 86%, mp 83−85 °C (lit.[54] mp 87−88 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 12.85 (s, 1H), 7.84 (d, 1H, $J$ = 8.8 Hz), 7.43−7.36 (m, 5H), 6.53 (d, 2H, $J$ = 9.2 Hz), 4.29 (s, 2H), 3.90 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.0, 166.3, 165.9, 134.5, 132.1, 129.4, 128.8, 127.1, 113.2, 107.9, 101.1, 55.6, 44.9.

(III) **2c**, **2g**, and **2m** were prepared according to the procedure in ref 30.

**3-(3,4-Dimethoxyphenyl)-4-hydroxy-7-methoxy-2*H*-chromen-2-one, 2c:** white solid, yield 70%, mp 212 °C (lit.[52] mp 212 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.03 (s, 1H), 7.87 (d, 1H, $J$ = 8.8 Hz), 6.99−6.88 (m, 5H), 3.85 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 163.0, 162.8, 160.9, 154.5, 148.7, 148.7, 125.3, 124.8, 124.1, 115.4, 112.3, 112.1, 110.0, 103.9, 100.8, 56.4, 56.0, 55.9.

**4-Hydroxy-7-methoxy-3-(4-methoxyphenyl)-2*H*-chromen-2-one, 2g:** white solid, yield 74%, mp 214−216 °C (lit.[55] mp 213-214 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.11 (s, 1H), 7.93 (d, 1H, $J$ = 8.4 Hz), 7.30 (d, 2H, $J$ = 8.4 Hz), 6.97 (d, 4H, $J$ = 8.4 Hz), 3.87 (s, 3H), 3.79 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.96, 162.89, 161.0, 158.9, 154.5, 132.7, 125.4, 124.7, 113.9, 112.3, 110.0, 103.7, 100.8, 56.4, 55.6. ESI-MS $m/z$ $[M - H]^-$ 297.3.

**4-Hydroxy-7-methoxy-3-phenyl-2*H*-chromen-2-one, 2m:** white solid, yield 50%, mp 198−200 °C (lit.[56] mp 198−200 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.26 (s, 1H), 7.94 (d, 1H, $J$ = 8.4 Hz), 7.43−7.31 (m, 5H), 6.99 (d, 2H), 3.88 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 163.1, 162.7, 161.2, 154.6, 132.8, 131.6, 128.4, 127.7, 125.4, 112.4, 109.9, 104.1, 100.9, 56.4. ESI-MS $m/z$ $[M - H]^-$ 267.1.

**3. Preparation of the Substituted 3-Aryl-4-hydroxy Coumarins 2d and 2h.** (I) **7d** and **7h** were prepared according to the procedure in ref 32.

**2-(3,4-Dimethoxyphenyl)-1-(2,4,6-trihydroxyphenyl)-ethanone, 7d:** white solid, yield 65%, mp 179−180 °C (lit.[46] mp 181 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 12.23 (s, 2H), 10.39 (s, 1H), 6.87 - 6.84 (m, 2H), 6.72 (d, 1H, $J$ = 8.0 Hz), 5.81 (s, 2H), 4.26 (s, 2H), 3.71 (d, 6H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 203.1, 165.3, 164.7, 148.9, 147.9, 128.7, 122.1, 114.3, 112.2, 104.1, 95.2, 56.0, 55.9, 48.9. ESI-MS $m/z$ $[M - H]^-$ 303.3.

**2-(4-Methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)ethanone, 7h:** white solid, yield 67%, mp 198 °C (lit.[48] mp 195−197 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 12.22 (s, 2H), 10.38 (s, 1H), 7.12 (d, 2H, $J$ = 8.4 Hz, 6.83 (d, 2H, $J$ = 8.4 Hz), 5.80 (s, 2H), 4.25 (s, 2H), 3.34 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 203.2, 165.3, 164.7, 158.3, 131.1, 128.2, 114.0, 104.1, 95.2, 55.5, 48.5. ESI-MS $m/z$ $[M - H]^-$ 273.2.

(II) **6d** and **6h** were prepared according to the procedure in ref 32.

**2-(3,4-Dimethoxyphenyl)-1-(2-hydroxy-4,6-dimethoxy-phenyl)ethanone, 6d:** white solid, yield 90%, mp 117 °C (lit.[57] mp 118−119 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.90 (s, 1H), 6.84 (d, 1H, $J$ = 8.4 Hz), 6.76 (d, 2H, $J$ = 7.2 Hz), 6.08 (s, 1H), 5.94 (s, 1H), 4.28 (s, 2H), 3.87 (t, 12H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.0, 167.9, 166.2, 162.6, 148.8, 147.8, 127.9, 121.8, 112.9, 111.2, 105.7, 93.8, 91.0, 55.9, 55.8, 55.6, 55.6, 49.9. ESI-MS $m/z$ $[2M + Na]^+$ 687.5.

**1-(2-Hydroxy-4,6-dimethoxyphenyl)-2-(4-methoxyphenyl)-ethanone, 6h:** white solid, yield 63%, mp 86−87 °C (lit.[58] mp 88 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.91 (s, 1H), 7.13 (d, 2H, $J$ = 8.4 Hz), 6.87 (d, 2H, $J$ = 8.4 Hz), 6.07 (d, 1H, $J$ = 2.0 Hz), 5.93 (d, 1H, $J$ = 2.0 Hz), 4.27 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.2, 167.9, 166.2, 162.6, 158.4, 130.6, 127.5, 113.9, 105.7, 93.7, 90.9, 55.6, 55.6, 55.3, 49.4. ESI-MS $m/z$ $[2M + Na]^+$ 626.9.

(III) Compounds **2d** and **2h** were prepared according to the procedure for the preparation of **2c**.

**3-(3,4-Dimethoxyphenyl)-4-hydroxy-5,7-dimethoxy-2*H*-chromen-2-one, 2d:** white solid, yield 60%, mp 200 °C (lit.[31] mp 201 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 7.09 (s, 1H), 7.01 (d, 1H, $J$ = 8.4 Hz), 6.88 (d, 1H, $J$ = 8.4 Hz), 6.53 (s, 1H), 6.49 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 172.5, 164.5, 162.9, 162.4, 158.5, 155.7, 148.2, 147.7, 126.7, 124.0, 115.6, 111.5, 101.1, 95.6, 94.1, 57.3, 56.4, 56.0, 56.0. ESI-MS $m/z$ $[M + H]^+$ 359.3.

**4-Hydroxy-5,7-dimethoxy-3-(4-methoxyphenyl)-2*H*-chromen-2-one, 2h:** white solid, yield 61%, mp 242−243 °C (lit.[31] mp 243−245 °C). $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 9.99 (s, 1H), 7.32 (d, 2H, $J$ = 7.2 Hz), 6.92 (d, 2H, $J$ = 7.2 Hz), 6.65 (s, 1H), 6.59 (s, 1H), 3.98 (s, 3H), 3.86 (s, 3H), 3.76 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 163.5, 162.1, 161.5, 158.6, 158.0, 155.3, 132.4, 124.6, 113.5, 102.2, 98.7, 96.0, 94.5, 57.6, 56.6, 55.5. ESI-MS $m/z$ $[M + Na]^+$ 329.7.

**General Procedure for the Preparation of Coumestan Analogues.** To a solution of substituted 4-hydroxy coumarin **2** (2.5 mmol) in dried 1,2-dichloroethane (30 mL) was added ferric chloride/$SiO_2$ (50/50, w/w, 6.25 mmol) in one portion with stirring at ambient or reflux temperature, and the reaction process was monitored by TLC analysis. The reaction mixture was then evaporated under vacuum to remove the solvent. The residue was purified by silica gel chromatography to give the desired products.

**8,9-Dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1a:** white solid, mp 219−220 °C (lit.[59] mp 223 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, 1H, $J$ = 7.6 Hz), 7.58−7.48 (m, 3H), 7.41−7.37 (m, 1H), 7.20 (s, 1H), 4.01 (s, 3H), 4.00 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.9, 158.4, 153.0, 150.4, 149.6, 148.2, 131.1, 124.6, 121.3, 117.4, 115.4, 113.0, 106.3, 102.3, 95.5, 56.6, 56.4. ESI-MS $m/z$ $[2M + Na]^+$ 615.2.

**8,9-Dimethoxy-4-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1b:** white solid, mp 229−231 °C (lit.[60] mp 229−231 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (d, 1H, $J$ = 7.6 Hz), 7.57 (s, 1H), 7.45 (d, 1H, $J$ = 7.2 Hz), 7.32 (d, 1H, $J$ = 7.6 Hz), 7.23 (s, 1H), 4.08 (s, 3H), 4.05 (s, 3H), 2.61 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.3, 158.4, 151.4, 150.3, 149.5, 148.1, 132.4, 126.9, 124.1, 118.9, 115.5, 112.6, 106.0, 102.4, 95.5, 56.5, 56.4, 16.2. ESI-MS $m/z$ $[M + H]^+$ 311.7.

**3,8,9-Trimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1c:** white solid, mp 255 °C (lit.[61] mp 254 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.85 (d, 1H, $J$ = 8.4 Hz), 7.50 (s, 1H), 7.18 (s, 1H), 6.98−6.96 (m, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.91 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.4, 159.7, 158.7, 154.9, 150.0, 149.1, 148.0, 122.3, 115.6, 113.0, 106.3, 103.9, 102.3, 101.5, 95.6, 56.6, 56.4, 55.8. ESI-MS $m/z$ $[M + H]^+$ 327.4.

**1,3,8,9-Tetramethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1d:** white solid, mp 248−250 °C (lit.[62] mp 247−248 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.51 (s, 1H), 7.24 (s, 1H), 6.62 (s, 1H), 6.43 (s, 1H), 4.04 (s, 3H), 4.00 (s, 3H), 3.97 (s, 3H), 3.89 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.8, 159.4, 158.7, 156.5, 155.8, 150.0, 148.8, 147.9, 115.2,

103.4, 102.0, 98.2, 95.8, 95.7, 93.8, 56.5, 56.4, 55.9. ESI-MS $m/z$ $[2M + Na]^+$ 735.6.

**9-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1e:** white solid, mp 216 °C (lit.[63] mp 212−213 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00−7.97 (m, 2H), 7.59−7.56 (m, 1H), 7.49 (d, 1H, $J$ = 8.4 Hz), 7.40 (t, 1H), 7.18 (d, 1H, $J$ = 2.0 Hz), 7.07−7.05 (dd, 1H, $J$ = 8.4, 2.0 Hz), 3.91 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.7, 159.3, 158.2, 156.8, 153.2, 131.3, 124.6, 122.0, 121.5, 117.4, 116.5, 113.6, 112.9, 106.1, 96.8, 55.9. ESI-MS $m/z$ $[2M + Na]^+$ 555.0.

**9-Methoxy-4-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1f:** white solid, mp 196 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.97 (d, 1H, $J$ = 8.8 Hz), 7.79 (d, 1H, $J$ = 7.6 Hz), 7.40 (d, 1H, $J$ = 7.2 Hz), 7.27 (t, 1H), 7.16 (s, 1H), 7.04 (d, 1H, $J$ = 8.4 Hz), 3.90 (s, 3H), 2.54 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.7, 159.6, 158.2, 156.8, 151.6, 132.6, 127.0, 124.1, 122.0, 119.1, 116.5, 113.5, 112.5, 105.8, 96.7, 55.9, 16.1. ESI-MS $m/z$ $[2M + Na]^+$ 583.1. HRMS (ESI) calcd for $C_{17}H_{13}O_4^+$ $[M + H]^+$ 281.0808, found 281.0814.

**3,9-Dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1g:** white solid, mp 199−200 °C (lit.[63] mp 198−199 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.94 (d, 1H, $J$ = 8.8 Hz), 7.86 (d, 1H, $J$ = 9.2 Hz), 7.15 (s, 1H), 7.04 (d, 1H, $J$ = 8.4 Hz), 6.97 (d, 2H, $J$ = 6.8 Hz), 3.90 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.6, 160.1, 159.3, 158.5, 156.5, 155.1, 122.5, 121.6, 116.7, 113.2, 113.0, 106.1, 103.5, 101.4, 96.9, 55.9, 55.8. ESI-MS $m/z$ $[2M + Na]^+$ 615.2.

**1,3,9-Trimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1h:** white solid, mp 224−227 °C (lit.[6] mp 220−225 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.94 (d, 1H, $J$ = 8.4 Hz), 7.21 (d, 1H, $J$ = 1.6 Hz), 7.05−7.02 (dd, 1H, $J$ = 8.4, 1.6 Hz), 6.61 (d, 1H, $J$ = 1.6 Hz), 6.42 (d, 1H, $J$ = 1.6 Hz), 4.04 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.0, 159.8, 159.0, 158.5, 156.7, 156.5, 156.1, 121.3, 116.2, 113.3, 103.0, 98.1, 96.8, 95.7, 93.8, 56.4, 55.9, 55.9. ESI-MS $m/z$ $[2M + Na]^+$ 675.4.

**9-Methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1i:** white solid, mp 198−200 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (s, 2H), 7.59−7.42 (m, 4H), 7.26 (s, 1H), 2.54 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.4, 158.0, 155.8, 153.4, 137.5, 131.5, 126.5, 124.5, 121.7, 121.1, 120.7, 117.3, 112.7, 111.9, 105.8, 21.9. ESI-MS $m/z$ $[M + H]^+$ 251.6. HRMS (ESI) calcd for $C_{16}H_{11}O_3^+$ $[M + H]^+$ 251.0703, found 251.0709.

**4,9-Dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1j:** white solid, mp 179 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, 1H, $J$ = 7.6 Hz), 7.44 (d, 1H, $J$ = 7.6 Hz), 7.36 (s, 4H), 2.50 (s, 3H, 2.42 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.9, 158.1, 155.9, 151.9, 137.3, 132.9, 126.9, 126.4, 124.1, 121.2, 120.9, 119.3, 112.4, 111.9, 105.6, 21.9, 16.1. HRMS (ESI) calcd for $C_{17}H_{13}O_3^+$ $[M + H]^+$ 265.0859, found 265.0867.

**6*H*-Benzofuro[3,2-*c*]chromen-6-one, 1k:** white solid, mp 172−173 °C, (lit.[64] mp 172−173 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.16−8.15 (m, 1H), 8.05 (d, 1H, $J$ = 7.6 Hz), 7.69−7.60 (m, 2H), 7.53−7.41 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.0, 158.0, 155.5, 153.7, 131.9, 126.8, 125.2, 124.6, 124.7, 123.4, 121.9, 117.5, 112.6, 111.8, 105.9. ESI-MS $m/z$ $[2M + Na]^+$ 495.1.

**4-Methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1*l*:** white solid, mp 195−197 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20−8.18 (m, 1H), 7.89 (d, 1H, $J$ = 7.6 Hz), 7.71−7.69 (d, 1H, $J$ = 7.2 Hz), 7.55−7.48 (m, 3H), 7.34 (t, 1H), 2.60 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.4, 158.0, 155.5, 152.1, 133.2, 127.1, 126.6, 125.1, 124.2, 123.5, 121.9, 119.5, 112.3, 111.7, 105.6, 16.2. ESI-MS $m/z$ $[2M + Na]^+$ 523.1.

**3-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1m:** white solid, mp 189 °C (lit.[39] mp 190 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01−7.99 (m, 1H), 7.92 (t, 1H), 7.64 (d, 1H, $J$ = 8.4 Hz), 7.46−7.42 (m, 2H), 7.01−6.99 (m, 2H), 3.93 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.3, 163.1, 155.7, 155.3, 132.0, 126.2, 125.1, 122.9, 122.9, 121.6, 113.2, 111.6, 105.9, 103.4, 101.5, 55.9. ESI-MS $m/z$ $[2M + Na]^+$ 555.2.

**9-Chloro-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1n:** white solid, mp 229 °C (lit.[65] mp 239 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07−8.03 (m, 2H), 7.70 (d, 1H, $J$ = 1.2 Hz), 7.64 (t, 1H, $J$ = 8.0, 7.6 Hz), 7.53 (d, 1H, $J$ = 8.4 Hz), 7.48−7.42 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.5, 157.7, 155.5, 153.7, 132.7, 132.3, 126.1, 124.8, 122.3, 122.2, 121.9, 117.6, 112.5, 112.4, 105.6. ESI-MS $m/z$ $[2M + Na]^+$ 563.3/565.3.

**9-Bromo-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1o:** white solid, mp 200−202 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (t, 2H, $J$ = 8.4 Hz), 7.85 (s, 1H), 7.66−7.59 (m, 2H), 7.52 (d, 1H, $J$ = 8.4 Hz), 7.43 (t, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.4, 157.7, 155.7, 153.8, 132.3, 128.8, 124.8, 122.7, 122.6, 121.9, 120.1, 117.6, 115.4, 112.4, 105.7. HRMS (ESI) calcd for $C_{15}H_8BrO_3^+$ $[M + H]^+$ 314.9651, found 314.9659.

**9-Bromo-4-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one, 1p:** white solid, mp 227 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.99 (d, 1H, $J$ = 8.4 Hz), 7.84 (d, 2H, $J$ = 11.2 Hz), 7.58 (d, 1H, $J$ = 8.0 Hz), 7.47 (d, 1H, $J$ = 7.2 Hz), 7.31 (t, 1H, $J$ = 7.6 Hz), 2.55 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.8, 157.7, 155.7, 152.2, 133.7, 128.7, 127.2, 124.4, 122.7, 119.9, 119.5, 115.3, 112.0, 105.4, 16.2. HRMS (ESI) calcd for $C_{16}H_{10}BrO_3^+$ $[M + H]^+$ 328.9808, found 328.9815.

**Procedure for the Synthesis of 1f′. 1f′** was prepared by $BBr_3$ demethylation according to a similar procedure.[38] White solid, yield 79%, mp >300 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 10.13 (s, 1H), 7.78 (d, 1H, $J$ = 7.6 Hz), 7.72 (d, 1H, $J$ = 8.4 Hz), 7.50 (d, 1H, $J$ = 7.6 Hz), 7.33 (t, 1H, $J$ = 7.6 Hz), 7.16 (d, 1H, $J$ = 1.6 Hz), 6.98−6.95 (dd, 1H, $J$ = 8.4, 2.0 Hz), 2.42 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 159.0, 158.1, 157.5, 156.9, 151.3, 133.1, 126.5, 124.9, 121.6, 119.4, 114.8, 112.3, 105.6, 99.1, 16.0. ESI-MS $m/z$ $[2M + Na]^+$ 555.3. HRMS (ESI) calcd for $C_{16}H_{10}O_4^+$ $[M + H]^+$ 266.0579, found 266.0584.

**Procedure for the Synthesis of 13.** (I) Compound **10** was prepared according to the procedure in ref 66: white solid, yield 55%, mp 102 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 12.56 (s, 1H, OH), 7.99 (d, 1H, $J$ = 9.2 Hz), 7.21 (d, 2H, $J$ = 8.4 Hz), 6.88 (d, 2H, $J$ = 8.4 Hz), 6.52−6.49 (dd, 1H, $J$ = 8.8, 2.4 Hz), 6.45 (d, 1H, $J$ = 2.4 Hz), 4.76−4.70 (m, 1H), 4.24 (s, 2H), 3.72 (s, 3H), 1.28 (d, 6H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 203.2, 165.0, 164.6, 158.5, 133.7, 131.0, 127.3, 114.3, 113.2, 108.7, 102.5, 70.5, 55.5, 43.9, 22.1. ESI-MS $m/z$ $[M + H]^+$ 301.2. HRMS (ESI) calcd for $C_{18}H_{21}O_4^+$ $[M + H]^+$ 301.1434, found 301.1437.

(II) Following the above procedure for **2c**, compound **11** was obtained as a white solid: yield 71%, mp 201−203 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 11.06 (s, 1H), 7.88 (d, 1H, $J$ = 8.4 Hz), 7.30 (d, 2H, $J$ = 8.8 Hz), 6.99−6.92 (m, 4H), 4.81−4.75 (m, 1H, CH), 3.79 (s, 3H), 1.32 (d, 6H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 162.9, 161.2, 160.9, 158.9, 154.5, 132.7, 125.3, 124.6, 113.9, 113.3, 109.7, 103.7, 102.1, 70.6, 55.6, 22.1. ESI-MS $m/z$ $[M + H]^+$ 327.2. HRMS (ESI) calcd for $C_{19}H_{19}O_5^+$ $[M + H]^+$ 327.1227, found 327.1227.

(III) Following the general procedure for the synthesis of **1a**−**p**, compound **12** was obtained as a white solid: yield 85%, mp 145 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.93 (d, 1H, $J$ = 8.8 Hz), 7.84 (d, 1H, $J$ = 8.8 Hz), 7.15 (d, 1H, $J$ = 2.0 Hz), 7.04−7.02 (dd, 1H, $J$ = 8.8, 2.0 Hz), 6.96−6.92 (m, 2H), 4.68−4.62 (m, 1H, CH), 3.90 (s, 3H), 1.42 (d, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.0, 160.1, 159.2, 158.6, 156.4, 155.2, 122.5, 121.6, 116.7, 114.2, 113.1, 105.8, 103.4, 102.9, 96.9, 70.8, 55.6, 21.9. HRMS (ESI) calcd for $C_{19}H_{17}O_5^+$ $[M + H]^+$ 325.1071, found 325.1074.

(IV) Compound **13**[67] was prepared according to a similar procedure:[44] white solid, mp >300 °C. $^1$H NMR (400 MHz, $d^6$-DMSO) $\delta$ 10.81 (s, 1H), 7.88 (d, 1H, $J$ = 8.4 Hz), 7.79 (d, 1H, $J$ = 8.8 Hz), 7.50 (d, 1H, $J$ = 2.4 Hz), 7.12−7.10 (dd, 1H, $J$ = 8.8, 2.0 Hz), 6.98−6.93 (m, 2H), 3.87 (s, 3H). $^{13}$C NMR (100 MHz, $d^6$-DMSO) $\delta$ 161.9, 159.3, 158.1, 157.6, 156.4, 155.3, 123.3, 121.1, 116.4, 114.4, 114.0, 104.6, 103.6, 102.4, 97.8, 56.4.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Spectral data for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) For isopropyl groups in 3,3′-diisopropoxybiphenyl being concurrently removed in an aryl oxidative coupling reaction using excess $FeCl_3$ in $CH_2Cl_2$/MeOH, see: Bushby, R. J.; Lu, Z. *Synthesis* **2001**, 763. We thank one of the reviewers for bringing this to our attention. After repetition of our reaction and some extended investigation, the following results were obtained: (i) In addition to the expected **12**, no deprotected product **13** was observed when **11** was treated with 2.5 equiv of either $FeCl_3/SiO_2$ (50/50, w/w) or $FeCl_3$ alone in DCM at rt. (ii) Under similar conditions, when the amount of $FeCl_3/SiO_2$ was increased to 5 equiv, no formation of compound **13** was detected either. (iii) When 5.0 equiv of $FeCl_3$ was used and the reaction was operated at 50 °C, product **13** was observed and isolated in 42% yield, while 5.0 equiv of $FeCl_3/SiO_2$ gave only 15% yield of **13**.

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