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Copper-mediated trimethylsilyl azide in amination of bromoflavonoids to synthesize unique aminoflavonoids

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ABSTRACT

Aminoflavonoids are unique antioxidants comparing to other abundant flavonoids in nature. Their syntheses and biological activities were scarcely reported. An effectively copper-mediated amination of the corresponding bromoflavonoids to synthesize a series of new aminoflavonoids is described.

1. Introduction

Flavonoids are an important class of natural products that exhibited a variety of biological activities.[1] They are mainly obtained from the plants[2] and widely used, for example, as health care agents,[3] antioxidants,[1b,4] antiinflamatory,[5] and anticancer drugs,[1,4,6] etc. The hydroxyl groups are the most common functional groups on flavonoids' scaffolds and play as chelating roles as well as radical inhibitors (Fig. 1).[1a,4c] Even though the amino groups were considered showing the same behaviors[7] as the hydroxyl groups in flavonoids, however, the aminoflavonoids were less reported in the syntheses and biological data to date.[8] Early, the synthetic aminoflavones were used to evaluate their inhibitory activities against protein tyrosine kinase.[8c] A recent report showed aminoflavones as potent agents against HIV-2 virus.[8g] Therefore, it prompted our interests in aminoflavones' properties and their syntheses.[9] In this regard, one of aminoflavones synthesized by us[9,10] exhibited the potent inhibition against cell proliferation in Her2 cancer cells based on the preliminary data.[11]

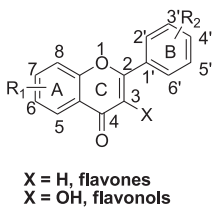

Fig. 1. The frameworks of flavonoids.

Conventionally, the amino groups in synthetic aminoflavonoids are generally derived from the reduction of the existing nitro groups,[8a,c] deprotection of amides[8c,g] or amino derivatives[8d] on flavones' skeletons. The reported methods in syntheses of aminoflavonoids sometimes required few steps for preparing the designated material.[8c] In our previous report, we have synthesized a reported aminoflavone in three steps rather than six steps by literature.[9] The only drawback suffered was the lower yields owing to the various substituent groups on the A or B rings of flavones. In order to overcome this obstacle, we highlight a modified strategy in this article. Unlike our reported method,[9] we utilized the corresponding bromoflavonoid's framework then replaced the bromo group(s) with the amino group(s) via efficiently copper-mediated amination to synthesize a series of unique aminoflavonoids. Our synthetic routes were shorter or equivalent steps to the established methods[8] but more versatile, especially, the starting materials are cheap.

2. Results and discussion

Preparations of bromoflavones **4a**–**h** (Tables 1 and 2) are required for syntheses of aminoflavones **5** (Table 3). The strategy for our target molecules employed the Baker–Venkataraman

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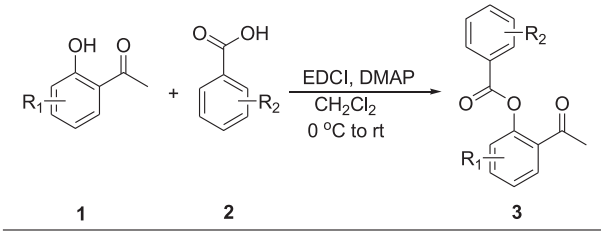
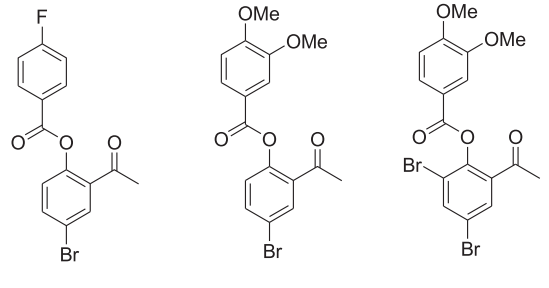
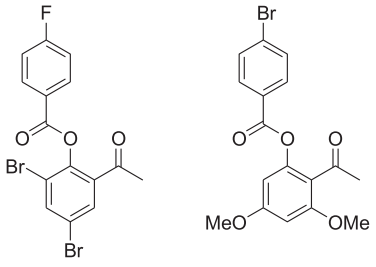
Table 1
Synthesis of esters **3**



1 2 3

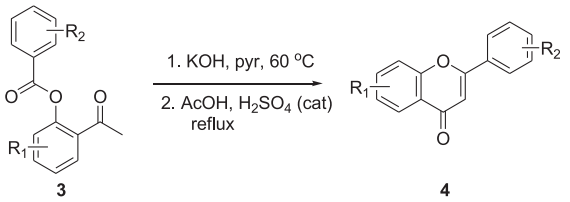


3a (91%) **3b** (86%) **3c** (90%)

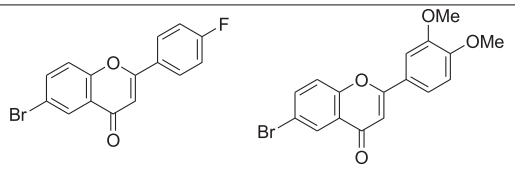


3d (93%) **3e** (90%)

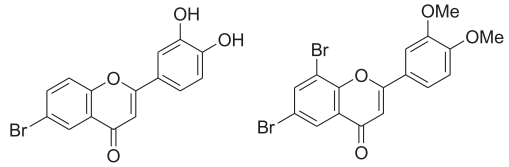
Table 2
Synthesis of bromoflavones **4**



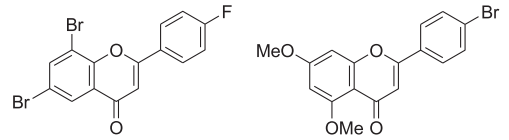
3 **4**



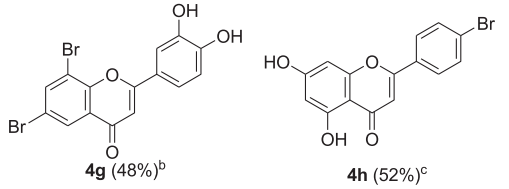
4a (75%) **4b** (82%)



4c (31%)[a] **4d** (73%)



4e (74%) **4f** (65%)



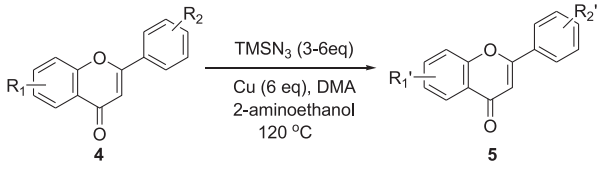
4g (48%)[b] **4h** (52%)[c]

[a] acid cyclization and demethylation of **3b** by 48% HBr.
[b] acid cyclization and demethylation of **3c** by 48% HBr.
[c] acid cyclization and demethylation of **3e** by 48% HBr.

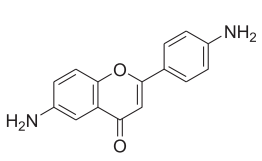
rearrangement,[12] acid-catalyzed cyclization, and copper-catalyzed amination on either the A or B rings of bromoflavones at the final stage. The cheap and commercially available starting materials **1** and **2** were used. Coupling between **1** and **2** mediated by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) afforded high yields of ester adducts **3** (Table 1). The base mediated rearrangement by KOH in pyridine at 60 °C followed by the acid-catalyzed cyclization (H_2SO_4) in AcOH affords **4a**–**f** in two steps, respectively (Table 2). In order to receive the higher yields of cyclic adducts **4a**–**f**, it is noteworthy that the complete removal of pyridine by washing with hexanes before acid treatment is necessary (see Experimental). The amination of **4a** was first applied Cu_2O/NH_4OH/H_2O/NMP at 80 °C.[13] However, the desired **5a** was obtained in only 15%. It is probably owing to the high volatility of NH_4OH at 80 °C. Another method, CuI/L-proline/NH_4Cl/K_2CO_3/80 °C,[14] was also tried but gave a complex mixture. The most efficient condition was using $TMSN_3$/Cu/2-aminoethanol/*N*,*N*-dimethylacetamide (DMA)/120 °C[15] (Table 3). This method was originally applied in amination of simple haloaromatic compounds.[15a] It is noticed that the fluoride group of **4a** was also aminated during the reaction course to give diamino compound **5a**[8c] (41%). Applying the same condition on **4b** and **4f** gives the corresponding aminoflavones **5b** (80%) and **5f** (51%), respectively. On the other hand, we intended the preparation of 6,8-diaminoflavone **5d** from the corresponding dibromide **4d**. The expected **5d** was received in 37% yield along with the unexpected mono aminoflavone **5b** (35%). Obviously, the bromide at C8 position of **4d** is more readily to be cleaved than its C6 bromide before amino groups are incorporated. Unlike the amination of **4a**, compound **4e** was completely decomposed during the reaction condition and no desired product was received.

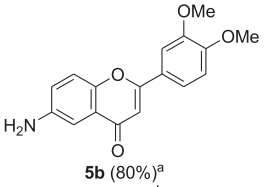
Flavonols are with an external hydroxy group at C3 position of flavones' scaffolds. We can apply the similar strategy of the above-mentioned method for aminoflavanol's synthesis. We tried to introduced two amino groups on the A ring of dibromoflavols **8** to synthesize diaminoflavonols. The condensations of **1** and **6** were conducted by Claisen–Schmidt reaction[16] to give high yields of **7** (Table 4). Different ether protections (OMe and OMOM) of **6** were used. It was found that the choice of protecting groups dramatically influenced the yields of final deprotecting step (vide infra). Oxidation of compounds **7** were carried out hydrogen peroxide and sodium hydroxide (Algar–Flynn–Oyamada reaction)[17] to provide dibromoflavonols **8** (Table 5). We are also intended on the synthesis of diaminoflavonols from compounds **8a**–**c** applying condition of $TMSN_3$/Cu/2-aminoethanol/DMA/120 °C. However, not only the mono amino substitution **9a**–**c** were isolated as the major components but also obtained in lower yields (Table 6). None of the expected 6,8-diaminoflavonols were detected or isolated from column chromatography. Therefore, compound **8b** was selected for study in improvement of copper-mediated amination conditions and an array of catalysts was screened in order to optimize the yields. We applied the same condition as in Table 6 except with

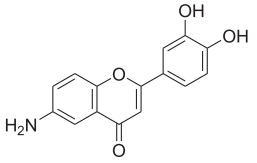
Table 3
Synthesis of aminoflavones **5** via copper-mediated amination of bromoflavones **4**

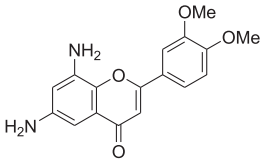


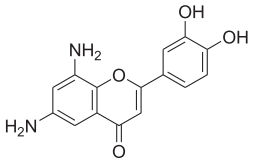
4 **5**

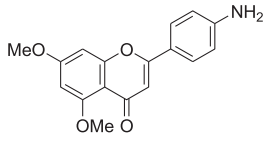

5a (41%)

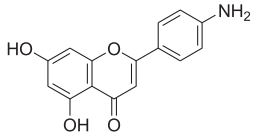

5b (80%)[a] (35%)[b]


5c (43%)[c]


5d (37%)

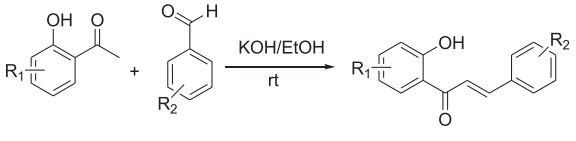

5e (41%)[d]


5f (51%)

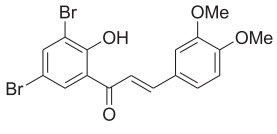

5g (30%)[e]

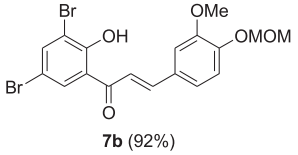
[a] from amination of **4b**.
[b] from amination of **4d**.
[c] demethylation of **5b** by 48% HBr
[d] demethylation of **5d** by 48% HBr.
[e] demethylation of **5f** by 48% HBr.

Table 4
Synthesis of **7** via Claisen–Schmidt reaction



1 **6** **7**


7a (96%)


7b (92%)

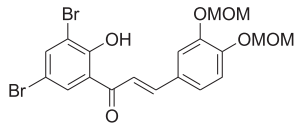
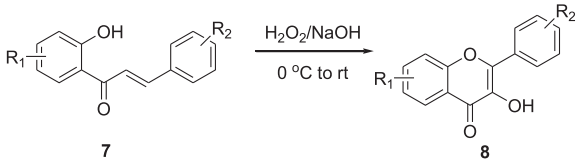
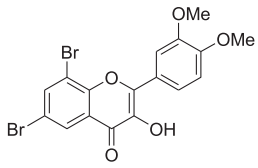
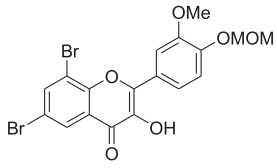

7c (87%)

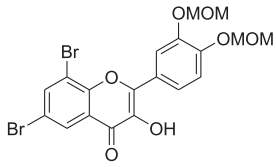
Table 5
Synthesis of bromoflavonols **8**

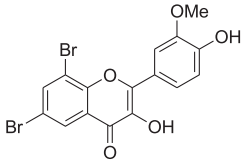


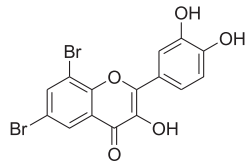
7 **8**


8a (56%)


8b (56%)


8c (51%)


8d (96%)[a]


8e (94%)[b]

[a] demethoxymethylether of **8b** by 3 N HCl.
[b] demethoxymethylether of **8c** by 3 N HCl.

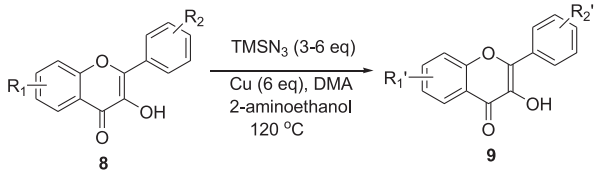
various copper catalysts. The yields were low by Cu_2O and CuI with 11% and 7%, respectively. Other catalysts, such as CuCl, CuBr, CuO, $CuCl_2$, $CuBr_2$, and $Cu(OAc)_2$, were used but all failed to obtain the desired product **9b** and a complicated mixture was observed by TLC. On the other hand, conditions with different ligands were tried, such as, Cu_2O/NaN_3/L-proline/DMSO/100 °C,[13,18] CuI/L-ascorbic acid/NH_4OH/100 °C,[19] CuI/L-proline/K_2CO_3/NH_4OH/DMSO/90 °C,[20] CuI/4-hydroxy-L-proline/NH_4OH/DMSO/50 °C,[21] again, to fail receiving the desired compound **9b**. Therefore, the best catalyst is copper for synthesis of aminoflavonols under this condition. We suspect that the C3–OH is labile under this harsh condition and require further protection before amination.[22]

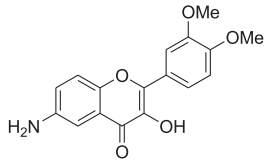
We found the final deprotecting step of **9a**–**c** by either 48% HBr or 3 N HCl was critical. Demethylation of **9a** by 48% HBr under reflux was not practical and low yield of **9e** (21%) was received. On the other hand, the MOM protection in **9b** and **9c** could be easily removed to afford higher yields of **9d** (85%) and **9e**[8a] (66%), respectively, under 3 N HCl condition.

3. Conclusion

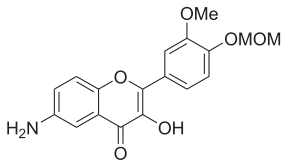
The condition of $TMSN_3$/Cu/2-aminoethanol/DMA/120 °C is effective in copper-mediated amination of the corresponding bromoflavonoids to synthesize unique aminoflavone **5a** and derivative**s 5b**,**d**,**f** in moderate to good yields. Deprotection of the compounds **5b**,**d**,**f** affords **5c**,**e**,**g**, respectively. It is worthwhile notice that aminoflavones **5c** and **5e** can not be synthesized from the corresponding nitro starting materials **1**, which are not commercially available. We provide an alternative and a more flexible method in construction of amino group(s) on flavonoids' motifs comparing with the conventional methods. The strategy in

Table 6
Copper-mediated amination of bromoflavonols **8** in synthesis of aminoflavonols **9**

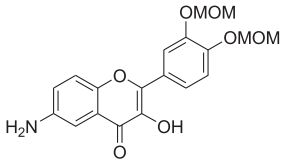




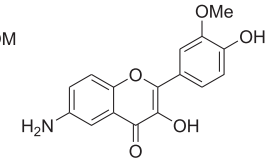
9a (30%)



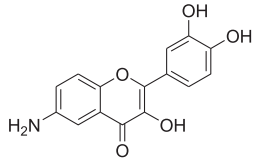
9b (28%)



9c (26%)



9d (85%)[a]



9e (21%)[b]
(66%)[c]

[a] ether cleavage of **9b** by 3 N HCl.
[b] ether cleavage of **9a** by 48% HBr.
[c] ether cleavage of **9c** by 3 N HCl.

synthesis of 6-aminoflavonol's derivatives **9a**–**c** from amination of bromoflavonols **8** needs improvement owing to the fragile structures under reaction conditions. The new aminoflavonoids **5c** and **5e** may show potentials biological activities than other natural flavonoids and require further studies.

4. Experimental section

4.1. General

All chemicals and solvents were purchased from the commercial providers and used without further purification except otherwise stated. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Bruker 600 MHz instrument.

Purification by flash column chromatography was performed on silica gel 230–400 mesh except otherwise mentioned. All samples were dissolved in designated *d*-solvents with the internal reference as the following: $CDCl_3$ (^{1}H: 7.26 ppm; ^{13}C: 77.0 ppm); DMSO-d_6 (^{1}H: 2.50 ppm; ^{13}C: 39.51 ppm). Melting points were measured on a MP–2D apparatus and uncorrected. LRMS and HRMS were determined by Finnigan Mat 95s mass spectrometer.

4.1.1. General procedure of esterification. Compound **1** (1.200 g, 4.08 mmol) and **2** (1.490 g, 8.16 mmol), for example, were dissolved in CH_2Cl_2 (20 mL). To this mixture was added EDCI (1.960 g, 10.21 mmol) and DMA (0.250 g, 2.04 mmol) at 0 °C and stirred to ambient temperature for 12 h. The reaction was quenched with saturated $NaHCO_3$ solution, diluted with CH_2Cl_2 and stirred for 10 min. The organic layer was separated, dried over $MgSO_4$, filtered, and purified with flash column chromatography (230–400 mesh SiO_2) to provide **3b**.

4.1.2. General procedure of Baker–Venkataraman rearrangement and cyclization. A mixture of **3** (2.050 g, 4.48 mmol), for example, and KOH (0.380 g, 6.72 mmol) in pyridine (15 mL) was heated at 60 °C for 2 h. The reaction was neutralized by 2 N HCl and diluted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a yellow-brown solid. The solid was used for the next step without further purification. The solid was dissolved in acetic acid (15 mL) and catalytic amount of H_2SO_4 (0.3 mL) to heat under reflux for 1 h. The mixture was cooled to ambient temperature and diluted with H_2O and EtOAc. The organic layer was separated and washed with saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (230–400 mesh SiO_2) to provide **4d**.

4.1.3. General procedure of Claisen–Schmidt reaction. Compound **7a** (1.060 g, 2.40 mmol) in 1,4-dioxane (10.6 mL) was sequentially added ethanol (30 mL), 5.4% NaOH (10.6 mL, 0.015 mmol), and 35% H_2O_2 (1.2 mL, 0.12 mmol) at 0 °C. The mixture was stirred at that temperature for 12 h before neutralized by 2 N HCl. The precipitate was filtered and washed with ice water. The solid was dissolved in CH_2Cl_2, dried with $MgSO_4$, and concentrated. Purification by flash column chromatography (230–400 mesh SiO_2) afforded a yellow solid.

4.1.4. General procedure of copper-catalyzed amination. All of reactions were conducted under a sure-sealed bottle. Compound **4d** (0.440 g, 1.00 mmol), for example, and copper powder (0.450 g, 6.00 mmol) was dissolved in DMA (5 mL). To this mixture was added 2-aminoethanol (0.42 mL, 7.00 mmol) and $TMSN_3$ (0.79 mL, 6.00 mmol) and heated at 120 °C for 4 h (note: the equivalents of $TMSN_3$ were three times of the number(s) of bromide atom(s) to the corresponding flavone). The solution was cooled to ambient temperature, diluted with EtOAc, and filtered. The solid was washed sequentially with EtOAc, H_2O, and NH_4OH. The organic layer was extracted with EtOAc, dried with $MgSO_4$, and purified by flash column chromatography (230–400 mesh SiO_2) to provide **5d**.

4.1.5. General procedure of ether bond cleavage

4.1.5.1. Cleavage of methyl ether. Compound **5b** (21 mg, 0.067 mmol), for example, was dissolved in 48% HBr (3 mL) and heated under reflux for 12 h. The solution was cooled to ambient temperature, diluted with H_2O, saturated Na_2SO_3, and extracted with 1-butanol. The solvent was removed and the resulting syrup was purified by flash column chromatography (230–400 mesh SiO_2) to afford **5c**.

4.1.5.2. Cleavage of methoxymethyl ether. Compound **9c** (30 mg, 0.08 mmol) in MeOH (2.5 mL) was added 3 N HCl (1.5 mL) and heated under reflux for 7 h. The solution was cooled to ambient temperature and diluted with H_2O. The solvent was removed under reduced pressure and diluted with EtOAc and H_2O. The organic layer was separated and the aqueous layer was neutralized with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layers were combined and dried over $MgSO_4$. The residue was purified by flash column chromatography (230–400 mesh SiO_2) to afford **9e**.

4.2. 2-Acetyl-4-bromophenyl-4-fluorobenzoate (3a)

1 (1.6040 g, 7.46 mmol), **2** (1.5290 g, 10.91 mmol). Purification by flash column chromatography (Hex:EtOAc=40:1–10:1; R_f 0.5,

Hex:EtOAc=20:1) afforded a white solid. Yield=2.2820 g (91%). Mp 112–114 °C. ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, J=9.0, 5.4 Hz, 2H), 7.96 (d, J=2.4 Hz, 1H), 7.69 (dd, J=8.4, 2.4 Hz, 1H), 7.20 (t, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 196.0, 166.5 (J_{C-F}=255.0 Hz), 163.9, 148.2, 136.2, 133.0, 132.9, 132.7, 125.7, 125.2, 119.4, 116.1, 116.0, 29.5. HRMS (EI) calcd for $C_{15}H_{10}BrFO_3$ ([M$^+$]) 335.9797. Found: 335.9796.

4.3. 5′-Bromo-2′-(3,4-dimethoxybenzoyloxy)acetophenone (3b)

1 (1.4470 g, 6.728 mmol), **2** (1.5930 g, 8.746 mmol). Purification by flash column chromatography (Hex:EtOAc=5:1–2:1; R_f 0.3, Hex:EtOAc=4:1) afforded a white solid. Yield=2.1880 g (86%). Mp 144–146 °C. ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J=2.5 Hz, 1H), 7.85 (dd, J=8.4, 2.0 Hz, 1H), 7.67 (dd, J=8.6, 2.5 Hz, 1H), 7.64 (d, J=2.0 Hz, 1H), 7.12 (d, J=8.6 Hz, 1H), 6.96 (d, J=8.5 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 196.2, 164.5, 154.0, 149.0, 148.5, 136.0, 133.0, 132.8, 125.7, 124.7, 121.1, 119.2, 112.5, 110.6, 56.1 (×2), 29.8. HRMS (EI) calcd for $C_{17}H_{15}BrNaO_5$ ([M+Na]$^+$) 401.0001. Found: 400.9995.

4.4. 2-Acetyl-4,6-dibromophenyl-3,4-dimethoxybenzoate (3c)

1 (1.200 g, 4.08 mmol), **2** (1.490 g, 8.16 mmol). Purification by flash column chromatography (Hex:EtOAc=10:1–4:1; R_f 0.5, Hex:EtOAc=5:1) afforded a white solid. Yield=1.6740 g (90%). Mp 141–142 °C. ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J=2.3 Hz, 1H), 7.91 (dd, J=8.5, 2.0 Hz, 1H), 7.87 (d, J=2.3 Hz, 1H), 7.67 (d, J=2.0 Hz, 1H), 6.98 (d, J=8.5 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 195.4, 163.4, 154.2, 149.0, 146.2, 138.9, 134.8, 131.9, 125.0, 120.6, 119.7, 119.6, 112.6, 110.6, 56.2, 56.1, 29.6. HRMS (EI) calcd for $C_{17}H_{14}Br_2NaO_5$ ([M+Na]$^+$) 478.9106. Found: 478.9100.

4.5. 2-Acetyl-4,6-dibromophenyl-4-fluorobenzoate (3d)

1 (1.000 g, 3.40 mmol), **2** (0.950 g, 6.80 mmol). Purification by flash column chromatography (Hex:EtOAc=20:1–10:1; R_f 0.7, Hex:EtOAc=10:1) afforded a pale white solid. Yield=1.3090 g (93%). Mp 113–114 °C. ^{1}H NMR ($CDCl_3$) δ 8.26–8.22 (m, 2H), 7.95 (d, J=2.3 Hz, 1H), 7.89 (d, J=2.3 Hz, 1H), 7.22 (t, J=11.4 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 195.1, 166.6 (J_{C-F}=254 Hz), 162.8, 145.9, 139.0, 134.3, 133.2 (×2), 132.8, 132.5, 132.1, 130.9, 124.6, 119.8, 116.2, 116.0, 29.4. LRMS (ESI) m/z ([M+Na]$^+$) 437 (100%), 413 (10%), 381 (60%).

4.6. 2-Acetyl-3,5-dimethoxyphenyl-4-bromobenzoate (3e)

1 (0.500 g, 2.55 mmol), **2** (1.020 g, 5.1 mmol). Purification by flash column chromatography (Hex:EtOAc=10:1–3:1; R_f 0.3, Hex:EtOAc=10:1) afforded a white solid. Yield=0.8680 g (90%). Mp 123–124 °C. ^{1}H NMR (DMSO-d_6) δ 7.99 (d, J=1.7 Hz, 1H), 7.98 (s, 1H), 7.63 (d, J=1.7 Hz, 1H), 7.62 (s, 1H), 6.41 (d, J=2.1 Hz, 1H), 6.35 (d, J=2.1 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 199.1, 164.4, 162.3, 159.4, 149.8, 131.9 (×2), 131.7 (×2), 128.9, 128.2, 117.0, 100.1, 96.8, 55.9, 55.7, 31.9. HRMS (EI) calcd for $C_{17}H_{15}BrO_5$ ([M]$^+$) 378.0103. Found: 378.0101.

4.7. 2-(4′-Fluorophenyl)-6-brmomo-4*H*-chromen-4-one (4a)

3a (2.1450 g, 6.363 mmol). Purification by flash column chromatography (Hex:EtOAc=40:1–0:1; R_f 0.53, Hex:EtOAc=4:1) afforded a pale white solid. Yield=1.5220 g (75%) (two steps). Mp 177–179 °C. ^{1}H NMR (DMSO-d_6) δ 8.13 (dd, J=8.8, 5.4 Hz, 2H), 8.04 (d, J=2.3 Hz, 1H), 7.94 (dd, J=8.8, 2.5 Hz, 2H), 7.73 (d, J=8.9 Hz, 1H), 7.39 (t, J=8.8 Hz, 2H), 7.03 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 175.8, 164.3 (J_{C-F}=249 Hz), 161.9, 154.5, 136.8, 129.2, 129.1, 127.3, 126.9, 124.7, 121.2, 117.9, 116.3, 116.1, 106.8. HRMS (EI) calcd for $C_{15}H_8BrFO_2$ ([M]$^+$) 317.9692. Found: 317.9698.

4.8. 2-(3′,4′-Dimethoxyphenyl)-6-bromo-4*H*-chromen-4-one (4b)

3b (1.000 g, 2.637 mmol). Purification by flash column chromatography (CH_2Cl_2; R_f 0.25, CH_2Cl_2) afforded a pale purple solid. Yield=0.7820 g (82%) (two steps). Mp 207–209 °C. ^{1}H NMR (DMSO-d_6) δ 8.09 (d, J=2.5 Hz, 1H), 7.97 (dd, J=8.9, 2.5 Hz, 1H), 7.80 (d, J=8.9 Hz, 1H), 7.72 (dd, J=8.5, 2.1 Hz, 1H), 7.60 (d, J=1.8 Hz, 1H), 7.13 (d, J=8.6 Hz, 1H), 7.10 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 175.7, 163.0, 154.6, 152.1, 149.0, 136.6, 126.8, 124.8, 123.0, 121.3, 120.1, 117.7, 111.7, 109.5, 105.7, 55.9, 55.7. HRMS (EI) calcd for $C_{17}H_{13}BrO_4$ ([M]$^+$) 359.9997. Found: 359.9995.

4.9. 6-Bromo-2-(3′,4′-dihyoxyphenyl)-4*H*-chromen-4-one (4c)

3b (0.300 g, 0.791 mmol). Purification by flash column chromatography (Hex:EtOAc=1:1–0:1; R_f 0.18, Hex:EtOAc=1:1) afforded a yellow solid. Yield=0.0820 g (31%) (two steps). Mp 236–238 °C. ^{1}H NMR (DMSO-d_6) δ 8.07 (d, J=2.5 Hz, 1H), 7.94 (dd, J=8.9, 2.5 Hz, 1H), 7.71 (d, J=8.8 Hz, 1H), 7.44 (dd, J=8.3, 2.3 Hz, 1H), 7.41 (d, J=1.9 Hz, 1H), 6.86 (d, J=8.2 Hz, 1H), 6.78 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 175.5, 163.7, 154.5, 150.6, 146.0, 136.6, 126.9, 124.9, 121.0 (×2), 119.2, 117.6, 115.9, 113.1, 104.5. HRMS (EI) calcd for $C_{15}H_8BrO_4$ ([M−H]$^+$) 330.9606. Found: 330.9600.

4.10. 6,8-Dibromo-2-(3′,4′-dimethoxyphenyl)-4*H*-chromen-4-one (4d)

3c (2.050 g, 4.48 mmol). Purification by flash column chromatography (CH_2Cl_2; R_f 0.3, CH_2Cl_2) afforded a pale white solid. Yield=1.5350 g (73%) (two steps). Mp 249–251 °C. ^{1}H NMR (DMSO-d_6) δ 8.28 (d, J=2.3 Hz, 1H), 8.01 (d, J=2.3 Hz, 1H), 7.62 (dd, J=8.5, 2.1 Hz, 1H), 7.50 (d, J=2.1 Hz, 1H), 7.00 (d, J=8.5 Hz, 1H), 6.78 (s, 1H), 3.98 (s, 3H), 3.97 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 176.2, 163.5, 152.6, 151.6, 149.4, 139.1, 127.8, 126.0, 123.2, 120.3, 118.4, 112.8, 111.3, 108.9, 105.8, 56.1, 56.0. HRMS (EI) calcd for $C_{17}H_{12}Br_2O_4$ ([M]$^+$) 437.9102. Found: 437.9103.

4.11. 6,8-Dibromo-2-(4′-fluorophenyl)-4*H*-chromen-4-one (4e)

3d (0.970 g, 2.35 mmol). Purification by flash column chromatography (Hex:CH_2Cl_2=2:1–0:1; R_f 0.7, CH_2Cl_2) afforded a pale yellow solid. Yield=0.6870 g (74%) (two steps). Mp 251–252 °C. ^{1}H NMR ($CDCl_3$) δ 8.29 (d, J=2.1 Hz, 1H), 8.04 (d, J=2.1 Hz, 1H), 8.00 (dd, J=8.5, 5.2 Hz, 2H), 7.25 (d, J=8.5 Hz, 2H), 6.81 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 176.5, 166.0, 164.3, 162.7, 151.8, 139.4, 128.8, 127.9, 126.9 (J^1_{C-F}=223.0 Hz), 118.7, 116.6 (J^2_{C-F}=23.0 Hz), 113.0, 107.0. HRMS (EI) calcd for $C_{15}H_7Br^{79}Br^{81}FO_2$ ([M]$^+$) 397.8776. Found: 397.8775.

4.12. 2-(4′-Bromophenyl)-5,7-dimethoxy-4*H*-chromen-4-one (4f)

3e (0.840 g, 2.21 mmol). Purification by flash column chromatography (Hex:EtOAc=2:1–1:2; R_f 0.45, Hex:EtOAc=1:2) afforded a pale yellow solid. Yield=0.5170 g (65%) (two steps). Mp 197–198 °C. ^{1}H NMR (DMSO-d_6) δ 7.97 (d, J=8.6 Hz, 2H), 7.74 (d, J=8.6 Hz, 2H), 6.84 (d, J=1.9 Hz, 1H), 6.80 (s, 1H), 6.50 (d, J=1.9 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 175.8, 164.1, 160.6, 159.4, 158.8, 132.3 (×2), 130.4, 128.2 (×2), 125.3, 108.8, 108.6, 96.6, 93.6, 56.4, 56.3. HRMS (EI) calcd for $C_{17}H_{13}BrO_4$ ([M]$^+$) 359.9997. Found: 359.9991.

4.13. 6,8-Dibromo-2-(3′,4′-dihydroxyphenyl)-4*H*-chromen-4-one (4g)

4d (0.290 g, 0.64 mmol). Purification by flash column chromatography (Hex:EtOAc=1:1–0:1; R_f 0.15, Hex:EtOAc=1:1) afforded a yellow solid. Yield=0.1260 g (48%). Mp 297–298 °C. ^{1}H NMR (DMSO-d_6) δ 8.34 (d, J=2.3 Hz, 1H), 8.05 (d, J=2.3 Hz, 1H), 7.50 (d, J=1.9 Hz, 1H), 7.49 (dd, J=8.3, 2.3 Hz, 1H), 6.91 (d, J=8.2 Hz, 1H), 6.87 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 175.1, 163.5, 151.3, 150.2, 145.9, 138.7, 126.7, 125.7, 121.2, 119.2, 117.7, 116.1, 113.6, 113.0, 104.7. HRMS (EI) calcd for $C_{15}H_8Br_2O_4$ ([M]$^+$) 409.8789. Found: 409.8795.

4.14. 2-(4′-Bromophenyl)-5,7-dihydroxy-4*H*-chromen-4-one (4h)

4f (0.100 g, 0.26 mmol). Purification by flash column chromatography (Hex:EtOAc=10:1–2:1; R_f 0.4, Hex:EtOAc=3:1) afforded a yellow solid. Yield=0.0460 g (52%). Mp 282–283 °C. ^{1}H NMR (DMSO-d_6) δ 7.99 (d, J=8.6 Hz, 2H), 7.76 (d, J=8.6 Hz, 2H), 6.97 (s, 1H), 6.50 (d, J=2.0 Hz, 1H), 6.21 (d, J=2.0 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 181.8, 164.6, 162.1, 161.5, 157.4, 132.2 (×2), 130.0, 128.4 (×2), 125.8, 105.6, 104.0, 99.2, 94.2. HRMS (EI) calcd for $C_{15}H_9BrO_4$ ([M]$^+$) 331.9684. Found: 331.9693.

4.15. 6-Amino-2-(4′-aminophenyl)-4*H*-chromen-4-one (5a)[8a]

4a (0.1570 g, 0.4918 mmol). Purification by flash column chromatography (Hex:EtOAc=1:2–0:1; R_f 0.58, EtOAc) afforded an orange-yellow solid. Yield=0.0520 g (41%). Mp 265–275 °C. ^{1}H NMR (DMSO-d_6) δ 7.70 (d, J=8.8 Hz, 2H), 7.39 (d, J=8.9 Hz, 1H), 7.06 (d, J=2.8 Hz, 1H), 6.99 (dd, J=8.8, 2.9 Hz, 1H), 6.65 (d, J=8.7 Hz, 2H), 6.55 (s, 1H), 5.90 (s, 2H), 5.38 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 176.8, 163.0, 152.3, 147.7, 146.3, 127.7 (×2), 124.2, 121.1, 118.6, 117.6, 113.5 (×2), 105.3, 102.1. HRMS (EI) calcd for $C_{15}H_{12}N_2O_2$ ([M]$^+$) 252.0899. Found: 252.0904.

4.16. 6-Amino-2-(3′,4′-dimethoxyphenyl)-4*H*-chromen-4-one (5b)

4b (0.500 g, 1.38 mmol). Purification by flash column chromatography (Hex:EtOAc=3:2–0:1; R_f 0.83, EtOAc) afforded a yellow-green solid. Yield=0.3280 g (80%). Mp 210–212 °C. ^{1}H NMR (DMSO-d_6) δ 7.63 (dd, J=8.5, 2.2 Hz, 1H), 7.53 (d, J=2.1 Hz, 1H), 7.48 (d, J=8.9 Hz, 1H), 7.11 (d, J=8.6 Hz, 1H), 7.08 (d, J=2.8 Hz, 1H), 7.04 (dd, J=8.8, 2.8 Hz, 1H), 6.84 (s, 1H), 5.46 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 177.1, 161.8, 151.6, 149.0, 147.9, 146.5, 124.2, 123.9, 121.5, 119.6, 118.9, 109.3, 105.0, 104.7, 55.8, 55.7. HRMS (EI) calcd for $C_{17}H_{15}NO_4$ ([M]$^+$) 297.1001. Found: 297.1003.

4.17. 6-Amino-2-(3′,4′-dihydroxyphenyl)-4*H*-chromen-4-one (5c)

5b (0.0210 g, 0.0672 mmol). Purification by flash column chromatography (Hex:EtOAc=1:0–2:1; R_f 0.55, EtOAc) afforded a yellow solid. Yield=0.0082 g (43%). Mp 250 °C (decomposed). ^{1}H NMR (DMSO-d_6) δ 7.40 (d, J=8.8 Hz, 1H), 7.36 (s, 1H), 7.35 (dd, J=8.0, 2.1 Hz, 1H), 7.07 (d, J=2.8 Hz, 1H), 7.02 (dd, J=8.9, 2.8 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 6.56 (s, 1H), 3.70–3.10 (br s, 2H). ^{13}C NMR (DMSO-d_6) δ 176.9, 162.4, 149.1, 147.7, 146.4, 145.7, 124.2, 122.4, 121.3, 118.6, 118.4, 115.9, 113.1, 105.1, 103.8. HRMS (EI) calcd for $C_{15}H_{11}NO_4$ ([M]$^+$) 269.0688. Found: 269.0680.

4.18. 6,8-Diamino-2-(3′,4′-dimethoxyphenyl)-4*H*-chromen-4-one (5d)

4d (0.440 g, 1.0 mmol). Purification by flash column chromatography (Hex:EtOAc=1:1–0:1; R_f 0.3, EtOAc) afforded a brown solid. Yield=0.1160 g (37%). Mp 240–242 °C. ^{1}H NMR (DMSO-d_6) δ 7.78 (dd, J=8.6, 2.1 Hz, 1H), 7.56 (d, J=2.1 Hz, 1H), 7.07 (d, J=8.6 Hz, 1H), 6.77 (s, 1H), 6.36 (d, J=2.6 Hz, 1H), 6.34 (d, J=2.6 Hz, 1H), 5.44 (s, 2H), 5.11 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 177.4, 161.0, 151.4, 148.9, 146.4, 138.8, 137.6, 124.7, 124.1, 119.9, 111.6, 109.5, 104.7, 104.5, 93.6, 55.7 (×2). HRMS (EI) calcd for $C_{17}H_{16}N_2O_4$ ([M]$^+$) 312.1110. Found: 312.1112.

4.19. 6,8-Diamino-2-(3′,4′-dihydroxyphenyl)-4*H*-chromen-4-one (5e)

5d (0.160 g, 0.44 mmol). Purification by flash column chromatography (CH_2Cl_2:MeOH=12:1–2:1; R_f 0.5, EtOAc) afforded a brown solid. Yield=0.0510 g (41%). Mp 201–202 °C. ^{1}H NMR (DMSO-d_6) δ 7.47 (dd, J=8.4, 2.3 Hz, 1H), 7.40 (d, J=2.2 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 6.49 (s, 1H), 6.34 (d, J=2.5 Hz, 1H), 6.32 (d, J=2.5 Hz, 1H), 5.32 (s, 2H), 5.06 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 171.5, 161.6, 149.0, 146.4, 145.7, 138.7, 137.6, 124.7, 122.7, 118.7, 115.9, 113.4, 104.9, 103.6, 93.9. HRMS (ESI) calcd for $C_{15}H_{13}N_2O_4$ ([M+H]$^+$) 285.0875. Found: 285.0870.

4.20. 2-(4′-Aminophenyl)-5,7-dimethoxy-4*H*-chromen-4-one (5f)

4f (0.100 g, 0.276 mmol). Purification by flash column chromatography (Hex:EtOAc=2:1–0:1; R_f 0.5, EtOAc) afforded a yellow solid. Yield=0.0420 g (51%). Mp 201–202 °C. ^{1}H NMR (DMSO-d_6) δ 7.69 (d, J=8.8 Hz, 2H), 6.78 (d, J=2.3 Hz, 1H), 6.63 (d, J=8.8 Hz, 2H), 6.45 (d, J=2.3 Hz, 1H), 6.42 (s, 1H), 5.87 (s, –NH_2, 2H), 3.87 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 175.8, 163.5, 161.0, 160.2, 159.1, 152.2, 127.5, 116.9, 113.6, 108.3, 104.3, 96.0, 93.3, 56.1, 56.0. HRMS (EI) calcd for $C_{17}H_{15}NO_4$ ([M]$^+$) 297.1001. Found: 297.1006.

4.21. 2-(4′-Aminophenyl)-5,7-dihydroxy-4*H*-chromen-4-one (5g)

5f (0.080 g, 0.2401 mmol). Purification by flash column chromatography (Hex:EtOAc=1:1–0:1; R_f 0.5, EtOAc) afforded a yellow solid. Yield=0.020 g (30%). Mp 316–318 °C. ^{1}H NMR (DMSO-d_6) δ 7.74 (d, J=8.7 Hz, 2H), 6.66 (d, J=8.7 Hz, 2H), 6.60 (s, 1H), 6.43 (d, J=2.0 Hz, 1H), 6.15 (d, J=2.0 Hz, 1H), 6.06 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 181.6, 164.7, 164.1, 161.5, 157.3, 153.0, 128.2 (×2), 116.6, 113.6 (×2), 103.6, 100.8, 98.8, 93.9. HRMS (ESI) calcd for $C_{15}H_{12}NO_4$ ([M+H]$^+$) 270.0766. Found: 270.0755.

4.22. (*E*)-1-(3,5-Dibromo-2-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (7a)

1 (3.120 g, 10.62 mmol), **6** (1.470 g, 8.85 mmol). Purification by flash column chromatography (Hex:EtOAc=15:1–1:1; R_f 0.65, Hex:EtOAc=2:1) afforded an orange solid. Yield=3.760 g (96%). Mp 152–153 °C. ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J=2.0 Hz, 1H), 7.96 (d, J=15.2 Hz, 1H), 7.87 (d, J=2.0 Hz, 1H), 7.39 (d, J=15.2 Hz, 1H), 7.30 (dd, J=8.3, 1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 6.93 (d, J=8.3 Hz, 1H), 3.99 (s, 3H), 3.96 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 192.2, 159.2, 152.5, 149.5, 148.0, 141.0, 131.0, 127.1, 124.3, 121.7, 116.4, 113.4, 111.2, 110.6, 110.2, 56.2, 56.2. HRMS (EI) calcd for $C_{17}H_{14}Br_2O_4$ ([M]$^+$) 439.9259. Found: 439.9252.

4.23. (*E*)-1-(3,5-Dibromo-2-hydroxyphenyl)-3-(3-methoxy-4-(methoxymethoxy)phenyl)prop-2-en-1-one (7b)

1 (2.090 g, 7.12 mmol), **6** (1.270 g, 6.47 mmol). Purification by flash column chromatography (Hex:EtOAc=8:1–1:1; R_f 0.4, Hex:EtOAc=1:1) afforded an orange solid. Yield=2.8130 g (92%). Mp 150–151 °C. ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J=2.2 Hz, 1H), 7.95 (d,

J=15.2 Hz, 1H), 7.87 (d, J=2.2 Hz, 1H), 7.40 (d, J=15.2 Hz, 1H), 7.28 (dd, J=8.4, 1.8 Hz, 1H), 7.21 (d, J=8.4 Hz, 1H), 7.18 (d, J=1.8 Hz, 1H), 5.31 (s, 2H), 3.99 (s, 3H), 3.53 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 192.2, 159.2, 150.0, 149.9, 147.8, 141.1, 131.0, 128.4, 123.7, 121.7, 116.9, 115.8, 113.4, 111.3, 110.2, 95.1, 56.5, 56.2. HRMS (ESI) calcd for $C_{18}H_{17}Br_2O_5$ ($[M+H]^+$) 470.9443. Found: 470.9454.

4.24. (*E*)-3-(3,4-Bis(methoxymethoxy)phenyl)-1-(3,5-dibromo-2-hydroxyphenyl)prop-2-en-1-one (7c)

1 (0.1090 g, 0.37 mmol), **6** (0.070 g, 0.31 mmol). Purification by flash column chromatography (Hex:EtOAc=6:1–3:1; R_f 0.65, Hex:EtOAc=2:1) afforded an orange solid. Yield=0.135 g (87%). Mp 129–131 °C. ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J=2.3 Hz, 1H), 7.93 (d, J=15.2 Hz, 1H), 7.87 (d, J=2.3 Hz, 1H), 7.48 (d, J=2.1 Hz, 1H), 7.40 (d, J=15.2 Hz, 1H), 7.33 (dd, J=8.5, 2.1 Hz, 1H), 7.22 (d, J=8.5 Hz, 1H), 5.32 (s, 2H), 5.31 (s, 2H), 3.57 (s, 3H), 3.53 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 192.3, 159.2, 150.5, 147.5, 147.4, 141.1, 131.1, 128.5, 124.8, 121.6, 117.2, 116.6, 116.2, 113.4, 110.2, 95.6, 95.1, 56.4 (×2). HRMS (ESI) calcd for $C_{19}H_{19}Br_2O_6$ ($[M+H]^+$) 500.9548. Found: 500.9565.

4.25. 6,8-Dibromo-3-hydroxy-2-(3,4-dimethoxyphenyl)-4*H*-chromen-4-one (8a)

7 (1.060 g, 2.398 mmol). Purification by flash column chromatography (CH_2Cl_2; R_f 0.4, CH_2Cl_2) afforded a yellow solid. Yield=0.6130 g (56%). Mp 258–259 °C. ^{1}H NMR (DMSO-d_6) δ 8.31 (d, J=2.0 Hz, 1H), 8.04–8.02 (m, 2H), 7.95 (s, 1H), 7.09 (br s, 1H), 7.03 (d, J=8.6 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 171.4, 151.2, 150.4, 148.9, 145.9, 138.8, 137.9, 127.3, 123.1, 122.7, 122.1, 117.4, 113.0, 111.1, 110.5, 56.0, 55.9. HRMS (EI) calcd for $C_{17}H_{12}Br_2O_5$ ($[M]^+$) 453.9051. Found: 453.9036.

4.26. 6,8-Dibromo-3-hydroxy-2-(3′-methoxy-4′-(methoxymethoxy)phenyl)-4*H*-chromen-4-one (8b)

7 (0.1150 g, 0.244 mmol). Purification by flash column chromatography (CH_2Cl_2; R_f 0.5, CH_2Cl_2) afforded a yellow solid. Yield=0.0660 g (56%). Mp 251 °C (decomposed).^{1}H NMR ($CDCl_3$) δ 8.32 (d, J=1.5 Hz, 1H), 8.03 (d, J=1.5 Hz, 1H), 7.98 (d, J=8.3 Hz, 1H), 7.97 (s, 1H), 7.31 (d, J=8.3 Hz, 1H), 7.02 (s, 1H), 5.33 (s, 2H), 3.99 (s, 3H), 3.54 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 171.5, 150.5, 149.6, 148.7, 145.8, 138.9, 138.1, 127.4, 124.5, 122.7, 121.9, 117.5, 115.7, 113.1, 111.2, 95.2, 56.4, 56.0. HRMS (EI) calcd for $C_{18}H_{14}Br_2O_6$ ($[M]^+$) 483.9157. Found: 483.9167.

4.27. 2-(3′,4′-Bis(methoxymethoxy)phenyl)-6,8-dibromo-3-hydroxy-4*H*-chromen-4-one (8c)

7 (0.160 g, 0.319 mmol). Purification by flash column chromatography (CH_2Cl_2; R_f 0.5, CH_2Cl_2) afforded a yellow solid. Yield=0.0850 g (51%). Mp 197–198 °C. ^{1}H NMR (DMSO-d_6) δ 8.30 (d, J=2.3 Hz, 1H), 8.21 (d, J=2.0 Hz, 1H), 8.02 (dd, J=8.1, 2.0 Hz, 2H), 7.32 (d, J=8.7 Hz, 1H), 6.98 (s, 1H), 5.33 (s, 4H), 3.57 (s, 3H), 3.55 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 171.5, 150.5, 149.5, 147.0, 145.5, 138.9, 138.1, 127.3, 124.5, 123.4, 122.6, 117.5, 116.5, 116.1, 113.2, 95.7, 95.1, 56.4, 56.3. HRMS (ESI) calcd for $C_{19}H_{17}Br_2O_7$ ($[M+H]^+$) 514.9341. Found: 514.9357.

4.28. 6,8-Dibromo-3-hydroxy-2-(4′-hydroxy-3′-methoxyphenyl)-4*H*-chromen-4-one (8d)

8b (0.050 g, 0.103 mmol). Purification by flash column chromatography (Hex:EtOAc=1:1–0:1, R_f 0.25, Hex:EtOAc=1:1) afforded a yellow solid. Yield=0.0440 g (96%). Mp 275–276 °C. ^{1}H NMR (DMSO-d_6) δ 9.90 (s, 1H), 9.81 (s, 1H), 8.28 (s, 1H), 8.11 (d, J=1.9 Hz, 1H), 7.86–7.82 (m, 2H), 6.96 (d, J=8.4 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 171.0, 149.8, 149.2, 147.6, 146.5, 138.4, 138.0, 126.6, 123.6, 122.2, 122.0, 116.7, 115.8, 113.0, 111.4, 55.7. HRMS (EI) calcd for $C_{16}H_{10}Br_2O_5$ ($[M]^+$) 439.8895. Found: 439.8884.

4.29. 6,8-Dibromo-3-hydroxy-2-(3′,4′-dihydroxyphenyl)-4*H*-chromen-4-one (8e)

8c (0.080 g, 0.154 mmol). Purification by flash column chromatography (Hex:EtOAc=1:1–0:1; R_f 0.4, Hex:EtOAc=1:1) afforded a yellow solid. Yield=0.0620 g (94%). Mp 287 °C (decomposed). ^{1}H NMR (DMSO-d_6) δ 9.73 (s, 1H), 9.40 (s, 1H), 8.29 (s, 1H), 8.13 (d, J=2.3 Hz, 1H), 7.82 (s, 1H), 7.67 (dd, J=8.5, 2.1 Hz, 1H), 6.92 (d, J=8.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 170.9, 149.8, 148.2, 146.9, 145.3, 138.2, 137.9, 126.6, 123.7, 121.9, 120.3, 116.6, 115.8, 115.4, 112.9. HRMS (EI) calcd for $C_{15}H_8Br_2O_5$ ($[M]^+$) 425.8738. Found: 425.8752.

4.30. 6-Amino-3-hydroxy-2-(3′,4′-dimethoxyphenyl)-4*H*-chromen-4-one (9a)

8a (0.100 g, 0.22 mmol). Purification by flash column chromatography (Hex:EtOAc=3:1–0:1; R_f 0.7, EtOAc) afforded a dark yellow solid. Yield=0.0210 g (30%). Mp 223–224 °C. ^{1}H NMR (DMSO-d_6) δ 9.09 (s, 1H), 7.82 (dd, J=8.8, 2.0 Hz, 1H), 7.76 (d, J=1.6 Hz, 1H), 7.48 (d, J=8.9 Hz, 1H), 7.14–7.12 (m, 2H), 7.06 (dd, J=8.9, 2.7 Hz, 1H), 5.43 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 172.3, 150.1, 148.4, 147.1, 145.8, 144.7, 137.5, 124.1, 122.0, 121.2, 118.8, 111.5, 110.9, 104.1, 55.6, 55.5. HRMS (ESI) calcd for $C_{17}H_{16}NO_5$ ($[M+H]^+$) 314.1028. Found: 314.1020.

4.31. 6-Amino-3-hydroxy-2-(3′-methoxy-4′-(methoxymethoxy)phenyl)-4*H*-chromen-4-one (9b)

8b (0.200 g, 0.411 mmol). Purification by flash column chromatography (Hex:EtOAc=3:1–1:1; R_f 0.2, Hex:EtOAc=1:1) afforded a dark yellow solid. Yield=0.0380 g (28%). Mp 216–217 °C. ^{1}H NMR (DMSO-d_6) δ 9.13 (s, 1H), 7.80 (s, 1H), 7.76 (dd, J=8.8, 1.4 Hz, 1H), 7.48 (d, J=8.9 Hz, 1H), 7.22 (d, J=8.6 Hz, 1H), 7.14–7.13 (m, 1H), 7.07 (dd, J=9.1, 2.6 Hz, 1H), 5.44 (s, 2H), 5.24 (s, 2H), 3.86 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 172.4, 149.3, 147.1, 145.8, 144.5, 137.6, 125.7, 122.8, 122.1, 120.9, 118.8, 115.9, 112.6, 111.6, 104.1, 94.6, 55.9, 55.7. HRMS (EI) calcd for $C_{18}H_{17}NO_6$ ($[M]^+$) 343.1056. Found: 343.1050.

4.32. 2-(3′,4′-Bis(methoxymethoxy)phenyl)-6-amino-3-hydroxy-4*H*-chromen-4-one (9c)

8c (0.100 g, 0.194 mmol). Purification by flash column chromatography (Hex:EtOAc=3:1–0:1; R_f 0.6, EtOAc) afforded a yellow solid. Yield=0.0190 g (26%). Mp 138–140 °C. ^{1}H NMR (DMSO-d_6) δ 9.13 (s, 1H), 7.92 (d, J=2.0 Hz, 1H), 7.83 (dd, J=8.8, 2.0 Hz, 1H), 7.45 (d, J=8.9 Hz, 1H), 7.26 (d, J=8.7 Hz, 1H), 7.13 (d, J=2.7 Hz, 1H), 7.07 (dd, J=9.0, 2.9 Hz, 1H), 5.44 (s, 2H), 5.28 (s, 2H), 5.24 (s, 2H), 3.45 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 172.4, 148.3, 147.1, 146.4, 145.8, 144.3, 137.7, 125.6, 122.5, 122.1, 122.0, 118.8, 116.7, 116.2, 104.1, 95.2, 94.5, 55.9 (×2). HRMS (EI) calcd for $C_{19}H_{19}NO_7$ ($[M]^+$) 373.1162. Found: 373.1172.

4.33. 6-Amino-3-hydroxy-2-(4′-hydroxy-3′-methoxyphenyl)-4*H*-chromen-4-one (9d)

9b (0.0220 g, 0.064 mmol). Purification by flash column chromatography (Hex:EtOAc=1:1–1:2; R_f 0.25, Hex:EtOAc=1:2) afforded a yellow solid. Yield=0.0160 g (85%). Mp 197–198 °C. ^{1}H NMR (DMSO-d_6) δ 9.64 (s, 1H), 8.99 (s, 1H), 7.77 (s, 1H), 7.70 (d, J=8.3 Hz, 1H), 7.46 (d, J=8.9 Hz, 1H), 7.13 (s, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.93 (d, J=8.5 Hz, 1H), 5.42 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 172.2,

148.4, 147.4, 147.1, 145.7, 145.2, 137.2, 122.8, 122.1, 121.9, 121.6, 118.8, 115.5, 111.7, 104.2, 55.8. HRMS (ESI) calcd for $C_{16}H_{14}NO_5$ ($[M+H]^+$) 300.0872. Found: 300.0852.

4.34. 6-Amino-3-hydroxy-2-(3′,4′-dihydroxyphenyl)-4*H*-chromen-4-one (9e)[8c]

9c (0.030 g, 0.08 mmol). Purification by flash column chromatography (Hex:EtOAc=1:1–1:4; R_f 0.7, EtOAc) afforded a dark yellow solid. Yield=0.0150 g (66%). Mp 231 °C (decomposed). ^{1}H NMR (DMSO-d_6) δ 7.65 (s, 1H), 7.53 (d, J=8.3 Hz, 1H), 7.40 (d, J=8.9 Hz, 1H), 7.11 (d, J=2.3 Hz, 1H), 7.04 (dd, J=9.1, 2.8 Hz, 1H), 6.82 (d, J=8.4 Hz, 1H), 5.39 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 172.1, 147.2, 147.0, 145.7, 145.3, 145.0, 137.1, 122.7, 122.0, 121.9, 119.7, 118.6, 115.5, 115.1, 104.2. HRMS (EI) calcd for $C_{15}H_{11}NO_5$ ($[M]^+$) 285.0637. Found: 285.0645.

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Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR data for all new products. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.04.022.

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