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Three-component synthesis of pyran-fused biscoumarins: an entry to pyridinone- and pyranone-fused coumarins†

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A base-mediated, three-component synthesis of symmetric and unsymmetric pyran-fused biscoumarins *via* the coupling of 4-hydroxycoumarin with 4-chloro-3-formylcoumarin in ethanol is reported. This methodology is further extended to the construction of various indole/coumarin-substituted symmetric pyran-fused biscoumarins. The unsymmetric pyran-fused biscoumarin can react with amines and 4-hydroxycoumarins under basic and acidic conditions to afford pyridinone-fused coumarins and pyranone-fused coumarins, respectively. The mechanisms of their formation are proposed.

1 Introduction

Coumarin-fused heterocycles are a class of organic compounds that combine the fused-ring structure of coumarins with one or more heterocyclic rings. The fusion of coumarins with heterocycles can result in molecules with a diverse range of biological activities. For instance, the pyran-fused biscoumarin **1** belongs to the class of nonpeptidic HIV protease inhibitors.¹ Pyridinone coumarin conjugate **2a** is an adenosine receptor,^{2a} and pyridinone coumarin conjugate **2b** exhibits mild anti-microbial activity against both Gram positive and negative bacteria.^{2b} Frutinone A (**3**) is an active ingredient extracted from the lipophilic fraction of the *Polygala fruticosa*, demonstrating various anti-fungal properties.³ Pyranone coumarin conjugate **4** exhibits good anti-fungal activity against *B. cinerea* and *C. capsica* (Fig. 1).⁴

In addition to their biological activities, coumarin-fused heterocycles also have a wide range of potential applications in organic functional materials. For example, pyranocoumarin **5** possesses photochromic properties.⁵ Pyrrolocoumarin **6** serves as a light-sensitive organic redox switch.⁶ Pyrrolocoumarin **7** is electrochromic and changes color when an external potential is applied (Fig. 2).⁷

Owing to their potential as therapeutic agents and functional materials, the synthesis of coumarin-fused heterocycles has become an active area of research. While various methodologies

for the preparation of pyranocoumarin derivatives have been reported in the literature,⁸ the development of multi-component synthesis of these compounds from readily available precursors is still needed to facilitate the progress of unearthing their unprecedented properties. Here we report the three-component synthesis of two isomeric pyran-fused biscoumarins *via* base-promoted reaction of 4-hydroxycoumarin with 4-chloro-formylcoumarin in ethanol. Subsequent investigation of their chemical reactivity toward nucleophilic reagents such as amines and 4-hydroxycoumarins under acidic and basic conditions are also explored.

2 Results and discussion

We began our study by coupling of 4-hydroxycoumarin (**8**) with 4-chloro-formylcoumarin (**9**) in the presence of triethylamine as

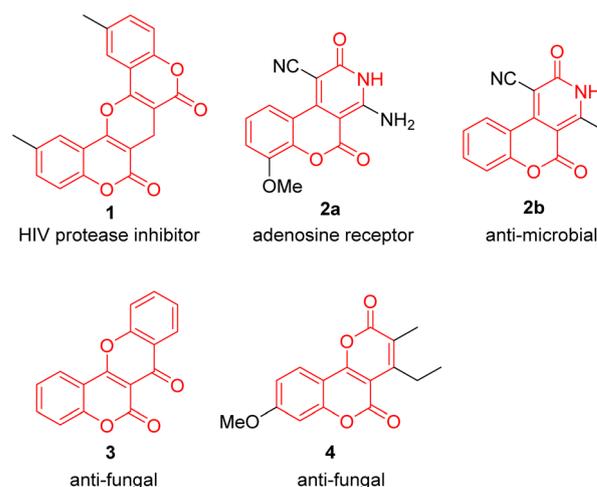


Fig. 1 Representative structures of biologically active coumarin-fused heterocycles 1–4.

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† Electronic supplementary information (ESI) available: General procedure for the synthesis of **10**, **11**, **12a–e**, **14a–d**, **16a–e**, and **17a** and **17b** and CIF files. CCDC 2264217–2264220, 2018939, 1985012, 1985024. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ra01681e>



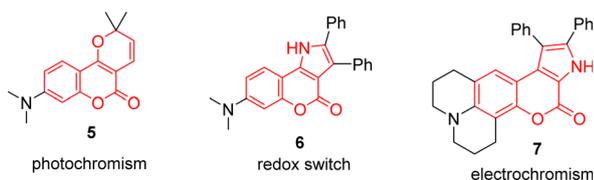
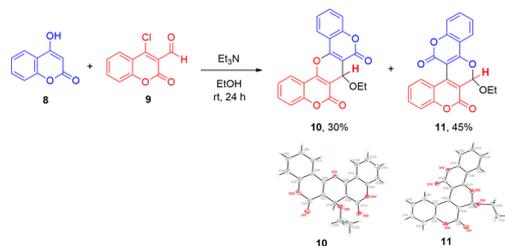


Fig. 2 Representative structures of coumarin-fused heterocycles 5–7 with functional properties.

a base in ethanol under room temperature for 24 hours to give compound **10** in 30% yield as a minor product and compound **11** in 45% as a major product, as shown in Scheme 1. The structures of isomeric pyran-fused biscoumarins **10** and **11** could be easily differentiated by their proton NMR spectra. The characteristic singlet absorption peak that appeared at a chemical shift of 5.59 ppm was assigned to the pyran hydrogen for the biscoumarin **10**, whereas the singlet absorption peak that appeared at a more downfield shift of 6.53 ppm was assigned to the acetal hydrogen for the biscoumarin **11**. The molecular structures of both **10** and **11** were further unambiguously characterized by the X-ray crystallography as shown in Scheme 1.⁹

Table 1 summarizes the optimization for the regioselective preparation of the biscoumarins **10** and **11** in ethanol at room temperature. When an organic base such as triethylamine was employed, as shown in Scheme 1, a mixture of both isomers **10** and **11** were received (Table 1, entry 1). Interestingly, when DABCO was used as a base, the biscoumarin **10** was obtained as an exclusive product in 35% and 50% yields for 12 and 24 h, respectively (Table 1, entries 2 and 3). On the other hand, biscoumarin **11** was obtained as the major product even though in low yields when K_2CO_3 or Na_2CO_3 was employed as the inorganic base (Table 1, entries 4 and 5). When Cs_2CO_3 was used as a base, to our delight, we observed the selective formation of **11** in 43% for 12 h at room temperature (Table 1, entry 6). Prolonged reaction time from 12 h to 24 h increased the yield of biscoumarin **11** from 43% to 72%, along with only about 5% of biscoumarin **10** (Table 1, entry 7).

Scheme 2 outlines the proposed mechanism for the formation of biscoumarins **10** and **11** *via* this three-component reaction.¹⁰ In Path A, it presumably starts with 1,2-addition of 4-hydroxycoumarin (**8**) with 4-chloro-formylcoumarin (**9**) to give



Scheme 1 Three-component synthesis of isomeric biscoumarins **10** and **11**, and ORTEP crystal structures of **10** and **11** with atomic displacement shown at 50% probability.

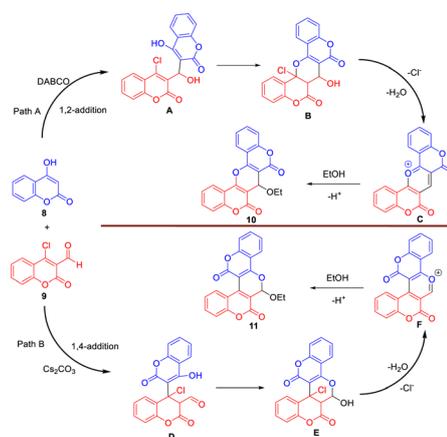
Table 1 Optimization for the synthesis of biscoumarins **10** and **11**^a

Entry	Base	Time (h)	Yield (%) (10)	Yield (%) (11)
1	Et_3N	24	30	45
2	DABCO	12	35	—
3	DABCO	24	50	—
4	K_2CO_3	24	Trace	15
5	Na_2CO_3	24	Trace	12
6	Cs_2CO_3	12	Trace	43
7	Cs_2CO_3	24	5	72

^a Reaction conditions: **8** (0.31 mmol, 1.0 equiv.), **9** (0.31 mmol, 1.0 equiv.), base (0.32 mmol, 1.0 equiv.), ethanol (2.5 mL) at rt.

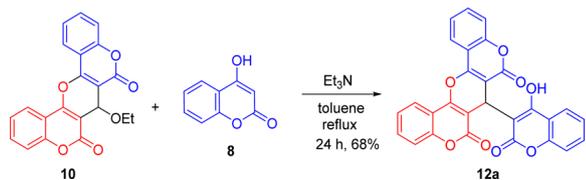
the alcohol **A**, and follows by cyclization to generate the intermediate **B**. The subsequent aromatization of **B** *via* elimination of chloride ion and H_2O yields the biscoumarin-fused pyrylium ion **C**. Final 1,4-addition of ethanol to **C** affords the biscoumarin **10**. In Path B, the reaction begins with preferential 1,4-addition of 4-hydroxycoumarin (**8**) with 4-chloro-formylcoumarin (**9**) in the presence of Cs_2CO_3 to give the aldehyde **D**, and follows by cyclization to furnish the hemiacetal **E**. The subsequent elimination of chloride ion and H_2O of **E** yields the biscoumarin-fused pyrylium ion **F**. Final 1,2-addition of ethanol to **F** furnishes the biscoumarin **11**.

With biscoumarins **10** and **11** in hand, we then investigated their chemical reactivity toward some common nucleophilic agents. When biscoumarin **10** was reacted with 4-hydroxycoumarin in the presence of triethylamine as a base in toluene under reflux conditions for 24 h, the coumarin-substituted pyran-fused biscoumarin **12a** was obtained in 68% yield (Scheme 3). Later, we found that this **12a** could also be prepared under the same reaction conditions *via* a pseudo three-component reaction of two equivalents of 4-hydroxycoumarin with 4-chloro-formylcoumarin (**9**) in 78% yield. Scheme 4 lists the structures and yields of the prepared pyran-fused biscoumarins **12a–e**.¹¹ In addition to 4-chloro-3-formylcoumarin (**9**), 3-chloro-3-phenylacrylaldehyde could also serve as a valid



Scheme 2 Proposed mechanism for the formation of compounds **10** and **11**.

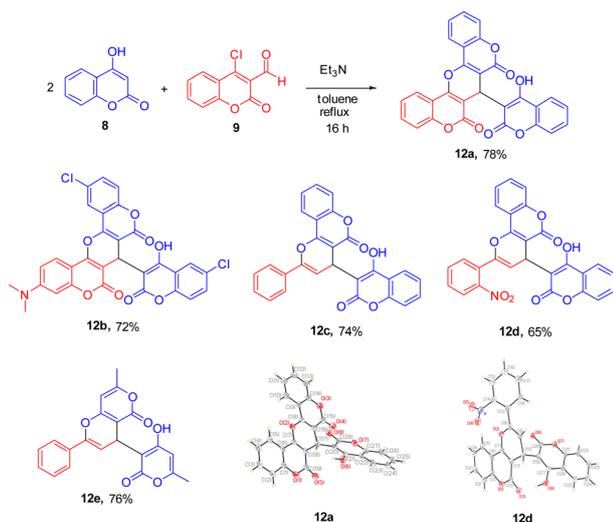
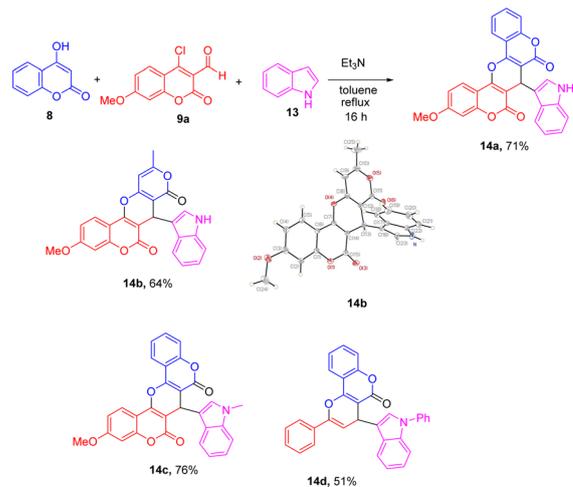


Scheme 3 Synthesis of pyran-fused biscoumarin **12a**.

substrate to give the corresponding products **12c** and **12e** in good yields. The molecular structures of compounds **12a** and **12d** were further confirmed by the X-ray crystal analysis as shown in Scheme 4.⁹ While it has been previously documented that compound **12a** can also be synthesized *via* the same two substrates under acidic conditions in aqueous media,^{11b} here we provide alternate basic conditions for its preparation and further extend the substrate scope from 4-chloro-3-formylcoumarin to 3-chloro-3-phenylacrylaldehyde derivatives.

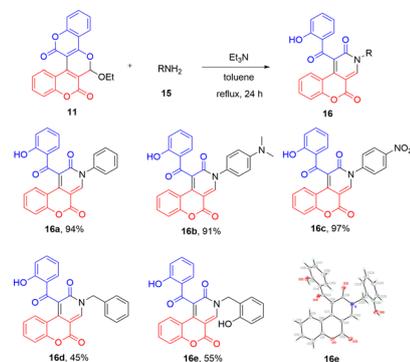
In an effort to expand the scope of this reaction from a pseudo three-component reaction to a three-component one, indole (**13**) was introduced as a third substrate for this potential multi-component reaction (MCR). To our delight, the biscoumarin **14a** was obtained *via* triethylamine-mediated MCR of 4-hydroxycoumarin (**8**), 4-chloro-3-formyl-7-methoxycoumarin (**9a**) and indole (**13**) in 71% yield. Scheme 5 lists the structures and yields of the prepared pyran-fused biscoumarins **14a–d** along with the X-ray crystal structure of compound **14b**.⁹ The formation mechanism of this MCR product presumably follows the reaction steps outlined in Scheme 2, except that the final pyrylium ion is captured by indole instead of ethanol, giving the product **14**.

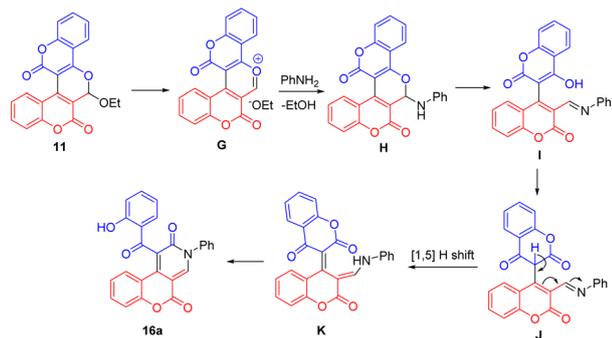
Interestingly, when biscoumarin **11** was reacted with amines (**15**) under the same conditions as the preparation of compounds **12**, the novel pyridinone-fused coumarins **16** were isolated in fair to excellent yields (Scheme 6). On the proton NMR spectra, intramolecular hydrogen bonding absorption peaks appearing at 11.87–11.75 ppm and singlet pyridinone

Scheme 4 Synthesis of pyranocoumarins **12a–e**.Scheme 5 Synthesis of pyranocoumarins **14a–d**, and X-ray crystal structure of **14b**.

hydrogen absorption peaks appearing at 9.02–8.77 ppm were observed for all prepared compounds **16**. Scheme 6 lists the structures and yields of the prepared pyridinone-fused coumarins **16a–e** along with the X-ray crystal structure of **16e**.⁹ While both aniline and benzylamine could serve as valid nucleophilic agents to react with compound **11**, the yield of the former was found to be much better than that of the latter.

Scheme 7 outlines the proposed mechanism for the formation of **16a** from **11** and aniline. It begins with the elimination of ethoxide ion from **11** to form the pyrylium ion **G**. The 1,2-addition of aniline nitrogen onto the pyrylium ion **G** yields the pyranoamine **H**, which then undergoes ring opening to give the imine **I**. The subsequent enol–keto tautomerization of the imine **I** generates the keto **J**. The [1,5] shift of C-3 hydrogen on coumarin to the imine nitrogen of **J** furnishes the enamine **K**. Final intramolecular lactamization of **K** affords the product **16a**. Note that formation of proposed intermediate **I** appeared to be favored when aniline was used as the nucleophile, presumably due to the favorable extended conjugation. This may explain why using aniline as the nucleophile in this reaction gives better yields than benzylamine.

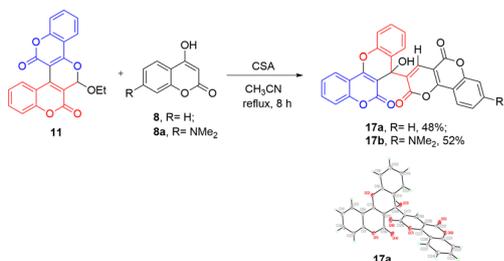
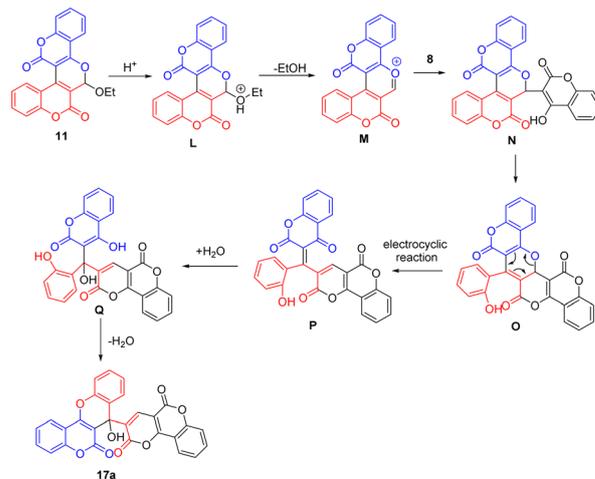
Scheme 6 Preparation of pyridinone-fused coumarins **16a–e**, and the X-ray crystal structure of **16e**.



Scheme 7 Proposed mechanism for the formation of compound 16a.

On the other hand, when compound **11** was reacted with 4-hydroxycoumarin (**8**) and 7-*N,N*-dimethylamino-4-hydroxycoumarin (**8a**) in the presence of one equivalent of camphorsulfonic acid in wet acetonitrile under reflux conditions for 8 h, the major products isolated were found to be the benzopyrano[3,2-*c*]coumarin-linked pyranone-fused coumarins **17a** and **17b**, respectively (Scheme 8). The characteristic singlet absorption peaks for pyranone hydrogens of **17a** and **17b** that appeared at chemical shifts of 8.76 and 8.68 ppm were clearly observed on the proton NMR spectra. The molecular structure of the pyranone-fused coumarin **17a** was further confirmed by the X-ray crystallography as shown in Scheme 8.⁹

Scheme 9 depicts the proposed mechanism for the formation of **17a** from **11** and **8**. It begins with protonation of acetal oxygen of **11** to give the oxonium ion **L**. The elimination of ethanol from **L** yields the pyrylium salt **M**. The subsequent nucleophilic attack of 4-hydroxycoumarin to the oxonium carbon of **M** generates the pyran **N**. The electrocyclic reaction to open up the pyran ring of **N** furnishes the α,β -unsaturated keto **P**, which is subjected to the conjugate addition by H_2O to give the alcohol **Q**. Final intramolecular cyclization of **Q** *via* elimination of one molecule of H_2O affords the compound **17a**. This reaction provides quick access to compounds with the linkage of two biologically active molecular scaffolds; that is, benzopyrano[3,2-*c*]coumarin and pyranone-fused coumarin. Since hybridization of two potent pharmacophores into a single molecule is one of the current strategies to synthesize compounds with improved pharmacological activity,¹² the discovery of biological activity from these readily available coumarin-fused heterocycles is highly anticipated.

Scheme 8 Synthesis of pyranone-fused coumarins **17a** and **17b**, and X-ray crystal structure of **17a** with atomic displacement shown at 50% probability.Scheme 9 Proposed mechanism for the formation of compound **17a**.

3 Conclusions

In summary, we have developed a base-mediated, three-component reaction for the construction of symmetric and unsymmetric pyran-fused biscoumarins *via* the coupling of 4-hydroxycoumarin with 4-chloro-3-formylcoumarin in ethanol. The symmetric and unsymmetric pyran-fused biscoumarins could serve as precursors to react with different nucleophilic agents including 4-hydroxycoumarins, indoles, and amines to afford products such as substituted biscoumarins, pyridinone-fused coumarins, and pyranone-fused coumarins. The biological activities of those prepared compounds are currently under investigation.

4 Experimental section

4.1. General information

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. Infrared (IR) spectra were recorded using 1725XFT-IR spectrophotometer. High resolution mass spectra (HRMS) were obtained on a Thermo Fisher Scientific Finnigan MAT95XL spectrometer using magnetic sector analyzer. ¹H NMR (400 MHz) and ¹³C NMR (100) spectra were recorded on a Bruker 400 spectrometer. Chemical shifts were reported in parts per million on the scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ¹H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Visualization was accomplished by using portable UV light, ninhydrin spray, or iodine chamber. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. Solvents, unless otherwise specified, were reagent grade and distilled once prior to use. All new compounds exhibited satisfactory spectroscopic and analytical data.



4.2. Procedure for preparation of compound 10

To a 10 mL round bottom flask equipped with a magnetic stirrer was charged with 4-hydroxycoumarin (**8**, 0.31 mmol, 1.0 equiv.), 4-chloro-3-formylcoumarin (**9**, 0.31 mmol, 1.0 equiv.) and DABCO (0.32 mmol, 1.0 equiv.) in ethanol (2.5 mL) at room temperature. The resulting mixture was then stirred at that temperature for 24 h. Upon completion of the reaction (monitored by TLC) and the solvent was concentrated under reduced pressure. The residue was purified by column chromatography with ethyl acetate and hexane as the eluent to afford a pale yellow solid of compound **10** (56 mg; yield 50%). $R_f = 0.4$ (2% MeOH/DCM); mp 231–233 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.07 (d, $J = 7.2$ Hz, 2H), 7.68 (t, $J = 7.2$ Hz, 2H), 7.47–7.43 (m, 4H), 5.57 (s, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3): δ 161.1, 155.0, 152.9, 133.5, 124.9, 122.7, 117.4, 113.5, 105.1, 70.4, 62.1, 15.9; IR ν_{max} (neat): 2924, 1727, 1713, 1670, 1610, 1398, 1192, 1059, 1044, 889, 759 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{14}\text{O}_6$ 362.0790; found 362.0801.

4.3. Procedure for preparation of compound 11

To a 10 mL round bottom flask equipped with a magnetic stirrer was charged with 4-hydroxycoumarin (**8**, 0.31 mmol, 1.0 equiv.), 4-chloro-3-formylcoumarin (**9**, 0.31 mmol, 1.0 equiv.) and Cs_2CO_3 (0.32 mmol, 1.0 equiv.) in ethanol (2.5 mL) at room temperature. The resulting mixture was then stirred at that temperature for 24 h. Upon completion of the reaction (monitored by TLC) and the solvent was concentrated under reduced pressure. The residue was purified by column chromatography with ethyl acetate and hexane as the eluent to afford a pale yellow solid of compound **11** (81 mg; yield 72%). $R_f = 0.6$ (2% MeOH/DCM); 51 mg; yield 46%; mp 194–196 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.05 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.02 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.71 (td, $J = 8.4, 1.2$ Hz, 1H), 7.57 (td, $J = 8.4, 1.2$ Hz, 1H), 7.46–7.38 (m, 3H), 7.30 (td, $J = 8.4, 1.2$ Hz, 1H), 6.55 (s, 1H), 4.04–3.91 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3): δ 164.1, 158.9, 158.8, 154.1, 153.8, 139.6, 134.6, 132.5, 128.8, 124.9, 123.9, 123.8, 117.3, 117.1, 115.2, 114.9, 114.4, 101.2, 96.5, 66.3, 15.2; IR ν_{max} (neat): 2990, 1709, 1608, 1533, 1453, 1403, 1061, 1036, 913, 862, 748, 737 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{14}\text{O}_6$ 362.0790; found 362.0796.

4.4. Procedure for preparation of compound 12a via two-component reaction

To a stirred solution of 4-hydroxycoumarins (**8**, 0.27 mmol, 1.0 equiv.) and 7-ethoxy-6*H*,7*H*,8*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8-dione (**10**, 0.27 mmol, 1.0 equiv.) in toluene was added triethylamine (0.13 mmol, 0.5 equiv.) dropwise at room temperature. The resulting mixture was then heated to reflux for 24 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. The resulting solid was filtered and washed with hexanes and diethyl ether (5 mL \times 3 times each), and the solid was dried under vacuum to get the desired product.

4.5. General procedure for preparation of compound 12a–e via pseudo-3-component reaction

To a stirred solution of 4-hydroxycoumarins (**8**, 0.48 mmol, 2.0 equiv.) and 4-chloro-3-formylcoumarins or 3-chloro-3-phenylacrylaldehyde (0.24 mmol, 1.0 equiv.) in toluene was added triethylamine (0.12 mmol, 0.5 equiv.) dropwise at room temperature. The resulting mixture was then heated to reflux for 16 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. The resulting solid was filtered and washed with hexanes and diethyl ether (5 mL \times 3 times each), and the solid was dried under vacuum to get the desired product.

4.5.1 7-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-6*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8(7*H*)-dione (12a). $R_f = 0.3$ (5% MeOH/ CH_2Cl_2); white solid; 90 mg; yield 78%; mp > 300 °C; $^1\text{H NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 12.35 (brs, 1H), 8.39 (dd, $J = 7.6, 1.2$ Hz, 2H), 8.04 (d, $J = 8.0$ Hz, 1H), 7.77 (td, $J = 8.8, 1.6$ Hz, 2H), 7.61 (td, $J = 8.8, 1.6$ Hz, 1H); 7.56–7.50 (m, 4H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 1H), 5.56 (s, 1H); ^{13}C { ^1H } NMR (100 MHz, $\text{DMSO-}d_6$): δ 161.6, 160.1 (3C), 155.2, 152.8, 152.4 (2C), 133.5 (3C), 132.8, 125.4 (3H), 124.4, 123.6 (3H), 117.0 (3H), 116.7, 113.5 (3H), 102.9, 25.8; IR ν_{max} (KBr): 3357, 3191, 2920, 2850, 1715, 1667, 1609, 1519, 1372, 1186, 1044, 759 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{28}\text{H}_{14}\text{O}_8$ 478.0689; found 478.0681.

4.5.2 2-Chloro-7-(6-chloro-4-hydroxy-2-oxo-2*H*-chromen-3-yl)-11-(dimethylamino)-6*H*-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8(7*H*)-dione (12b). $R_f = 0.3$ (5% MeOH/ CH_2Cl_2); brown solid; 103 mg; yield 72%; mp > 300 °C; $^1\text{H NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 9.77 (brs, 1H), 8.12 (d, $J = 2.0$ Hz, 1H), 8.00 (d, $J = 8.8$ Hz, 1H), 7.63–7.59 (m, 2H), 7.39 (d, $J = 8.8$ Hz, 1H), 7.33 (dd, $J = 8.8, 2.4$ Hz, 1H) 7.06 (d, $J = 8.8$ Hz, 1H), 6.62 (d, $J = 8.8$ Hz, 1H), 6.40 (d, $J = 2.0$ Hz, 1H), 5.16 (s, 1H), 2.96 (s, 6H); ^{13}C { ^1H } NMR (100 MHz, $\text{DMSO-}d_6$): δ 163.0, 160.8 (3C), 159.7, 154.8, 154.2, 153.0, 152.9, 152.6, 150.6 (2C), 132.0, 129.7, 129.1, 126.3, 125.1, 124.2, 124.1, 122.2, 118.6, 117.9, 115.5, 109.2, 105.4, 102.1, 98.6, 97.3, 40.1, 25.1; IR ν_{max} (KBr): 3350, 2946, 2912, 1659, 1657, 1615, 1519, 1399, 1374, 1182, 795 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{30}\text{H}_{17}\text{Cl}_2\text{NO}_8$ 589.0331; found 589.0326.

4.5.3 4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-2-phenylpyrano[3,2-*c*]chromen-5(4*H*)-one (12c). $R_f = 0.5$ (5% MeOH/ CH_2Cl_2); off-white solid; 96 mg; yield 74%; mp 231–233 °C; $^1\text{H NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.12 (dd, $J = 8.0, 1.2$ Hz, 1H), 8.00 (d, $J = 7.6$ Hz, 1H), 7.86 (d, $J = 7.6$ Hz, 1H), 7.70 (td, $J = 7.6, 1.2$ Hz, 1H), 7.61 (td, $J = 8.0, 1.2$ Hz, 1H), 7.52–7.38 (m, 5H), 7.35 (d, $J = 8.4$ Hz, 1H), 5.93 (d, $J = 4.4$ Hz, 1H), 5.16 (d, $J = 4.4$ Hz, 1H); ^{13}C { ^1H } NMR (100 MHz, $\text{DMSO-}d_6$): δ 161.8, 161.5, 161.0, 156.9, 152.7, 152.5, 147.4, 132.9, 132.7, 132.6, 129.5, 129.2, 129.0, 125.1, 124.7, 124.4, 124.0, 123.1, 117.0, 116.7, 114.4, 105.9, 101.4, 100.6, 27.1; IR ν_{max} (KBr): 3418, 3252, 3070, 2952, 2929, 1718, 1627, 1610, 1395, 1207, 760 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{27}\text{H}_{16}\text{O}_6$ 436.0947; found 436.0943.

4.5.4 4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-2-(2-nitrophenyl)pyrano[3,2-*c*]chromen-5(4*H*)-one (12d). $R_f = 0.5$ (5% MeOH/ CH_2Cl_2); off-white solid; 74 mg; yield 65%; mp 247–249 °C; $^1\text{H NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.04–8.01 (m, 2H), 7.76–7.60 (m, 5H), 7.55 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.45–7.34 (m, 4H), 5.79–



5.77 (m, 1H), 5.17–5.16 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 161.8, 160.8 (2C), 156.9, 152.7, 152.4, 148.2, 146.3, 133.7, 133.1, 132.7, 131.5, 131.3, 127.2, 125.1, 124.7 (2C), 124.4, 124.1, 122.2, 117.1, 116.7 (2C), 113.8, 105.3, 101.3, 27.3; IR ν_{max} (KBr): 3357, 2956, 2917, 2846, 1709, 1657, 1629, 1607, 1528, 1390, 1207, 754 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{27}\text{H}_{15}\text{NO}_8$ 481.0798; found 481.0792.

4.5.5 4-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-7-methyl-2-phenylpyrano[4,3-*b*]pyran-5(4H)-one (12e). $R_f = 0.5$ (5% MeOH/ CH_2Cl_2); off-white solid; 81 mg; yield 76%; mp 174–176 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 11.45 (s, 1H), 7.67–7.64 (m, 2H), 7.43–7.36 (m, 3H), 6.30 (s, 1H), 6.00 (s, 1H), 5.65 (d, $J = 4.8$ Hz, 1H), 4.66 (d, $J = 4.8$ Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 162.6 (2C), 161.8, 161.6, 161.5 (2C), 132.7, 129.2, 129.0 (2C), 124.5 (2C), 102.3, 100.8, 100.5, 99.3, 98.1, 88.5, 25.3, 19.8, 19.7; IR ν_{max} (KBr): 3192, 2950, 2917, 2846, 1700, 1659, 1640, 1577, 1448, 1404, 1278, 1190; 760 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{16}\text{O}_6$ 364.0947; found 364.0939.

4.6. General procedure for preparation of compounds 14a–d via three-component reaction

To a stirred solution of 4-hydroxycoumarin (**8**, 0.31 mmol, 1.0 equiv.), and 7-methoxy-4-chloro-3-formylcoumarin or 3-chloro-3-phenylacrylaldehyde (0.31 mmol, 1.0 equiv.) in toluene was added indole (**13a**, 0.31 mmol, 1.0 equiv.) followed by triethylamine (0.15 mmol, 0.5 equiv.) dropwise at room temperature. The resulting mixture was then heated to reflux for 16 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. The resulting solid was filtered and washed with hexanes and diethyl ether (5 mL \times 3 times each), and the solid was dried under vacuum to get the desired product.

4.6.1 7-(1H-Indol-3-yl)-3-methoxy-6H-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8(7H)-dione (14a). $R_f = 0.3$ (5% MeOH/ CH_2Cl_2); off-white solid; 102 mg; yield 71%; mp > 300 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 11.06 (s, 1H), 8.36 (d, $J = 7.6$ Hz, 1H), 8.26 (d, $J = 8.4$ Hz, 1H), 7.72 (t, $J = 7.6$ Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 1H), 7.44–7.41 (m, 2H), 7.32–7.30 (m, 2H), 7.07–6.99 (m, 3H), 6.90 (t, $J = 7.6$ Hz, 1H), 5.10 (s, 1H), 3.87 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 161.6, 160.1 (3C), 155.2, 152.8, 152.4 (2C), 133.5 (3C), 132.8, 125.4 (3H), 124.4, 123.6 (3H), 117.0 (3H), 116.7, 113.5 (3H), 102.9, 25.8; IR ν_{max} (KBr): 3412, 2950, 2912, 1731, 1665, 1615, 1371, 1267, 1171, 1150, 1050, 735 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{28}\text{H}_{17}\text{NO}_6$ 463.1056; found 463.1051.

4.6.2 7-(1H-Indol-3-yl)-3-methoxy-10-methyl-6H-pyrano[3',4':5,6]pyrano[3,2-*c*]chromene-6,8(7H)-dione (14b). $R_f = 0.6$ (5% MeOH/ CH_2Cl_2); off-white solid; 108 mg; yield 64%; mp 272–274 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 11.02 (s, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.33 (t, $J = 8.4$ Hz, 2H), 7.25 (d, $J = 2.0$ Hz, 1H), 7.08–6.99 (m, 3H), 6.90 (t, $J = 7.6$ Hz, 1H), 6.60 (s, 1H), 4.95 (s, 1H), 3.85 (s, 3H), 2.25 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 163.5, 162.8, 162.0, 160.5, 158.1, 154.2, 153.8, 136.7, 126.0, 125.6, 124.1, 121.2, 119.2, 118.4, 115.4, 113.3, 112.2, 106.5, 102.8, 102.5, 101.3, 98.6, 56.5, 25.7, 19.9; IR ν_{max} (KBr): 3357, 2956, 2920, 2850, 1723, 1630, 1615, 1377, 1268, 1154, 1027,

742 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{25}\text{H}_{17}\text{NO}_6$ 427.1056; found 427.1046.

4.6.3 3-Methoxy-7-(1-methyl-1H-indol-3-yl)-6H-pyrano[3,2-*c*:5,6-*c'*]dichromene-6,8(7H)-dione (14c). $R_f = 0.5$ (60% EtOAc/hexanes); off-white solid; 110 mg; yield 76%; mp 298–300 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 8.34 (d, $J = 7.6$ Hz, 1H), 8.24 (d, $J = 8.4$ Hz, 1H), 7.72 (t, $J = 8.0$ Hz, 1H), 7.53–7.44 (m, 4H), 7.34–7.28 (m, 1H), 7.10–7.03 (m, 3H), 6.96 (t, $J = 7.2$ Hz, 1H), 5.06 (s, 1H), 3.87 (s, 3H), 3.67 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 163.6, 160.5, 160.1, 154.3, 153.5, 153.0, 152.3, 136.9, 133.4, 130.0, 126.7, 125.3, 124.6, 123.5, 121.5, 119.4, 119.0, 117, 115.3, 113.6, 113.5, 110.3, 106.5, 106.0, 102.9, 101.2, 56.5, 32.8, 25.8; IR ν_{max} (KBr): 3361, 2956, 2922, 2852, 1731, 1666, 1615, 1369, 1272, 1153, 754 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{29}\text{H}_{19}\text{NO}_6$ 477.1212; found 477.1219.

4.6.4 2-Phenyl-4-(1-phenyl-1H-indol-3-yl)-4H,5H-pyrano[3,2-*c*]chromen-5-one (14d). $R_f = 0.5$ (50% EtOAc/hexanes); off-white solid; 74 mg; yield 51%; mp 154–156 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 8.18 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 7.6$ Hz, 2H), 7.73–7.68 (m, 2H), 7.63 (s, 1H), 7.55–7.51 (m, 6H), 7.49–7.42 (m, 4H), 7.37–7.34 (m, 1H), 7.17 (t, $J = 7.6$ Hz, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 6.27 (d, $J = 4.8$ Hz, 1H), 5.00 (d, $J = 4.8$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 161.0, 155.9, 152.6, 145.9, 139.3, 135.9, 132.9, 132.5, 130.2, 129.6, 129.3, 127.8, 127.5, 126.8, 125.1, 124.8, 124.1, 123.3, 122.9, 120.7, 119.8, 119.5, 117.0, 114.5, 111.1, 103.9, 102.8, 27.6; IR ν_{max} (KBr): 3565, 3015, 2957, 2871, 1718, 1629, 1596, 1499, 1456, 1012, 751 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{32}\text{H}_{23}\text{NO}_3$ 467.1521; found 467.1516.

4.7. General procedure for preparation of compounds 16a–e

To a 10 mL round bottom flask equipped with a magnetic stirrer and a reflux condenser was charged with **11** (0.14 mmol, 1.0 equiv.), amine (0.14 mmol, 1.0 equiv.) and triethylamine (0.14 mmol, 1.0 equiv.) in toluene (3.0 mL) at room temperature. The reaction mixture was heated at 100 °C in an oil bath for 24 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, and the solvent was concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate and hexane as the eluent to give the desired products.

4.7.1 1-(2-Hydroxybenzoyl)-3-phenyl-2H-chromeno[3,4-*c*]pyridine-2,5(3H)-dione (16a). $R_f = 0.6$ (40% EtOAc/hexanes); white solid; 53 mg; yield 94%; mp 212–214 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 11.82 (s, 1H), 8.86 (s, 1H), 7.59–7.47 (m, 9H), 7.31 (d, $J = 8.4$ Hz, 1H), 7.14–7.10 (m, 2H), 6.84 (t, $J = 7.6$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 200.7, 163.1, 160.0, 159.4, 152.8, 146.6, 139.3, 138.6, 138.0, 133.8, 131.6, 130.0, 129.7, 127.9, 126.2, 125.4, 122.2, 120.1, 119.9, 118.86, 118.85, 114.5, 103.6; IR ν_{max} (neat): 3084, 3051, 2337, 1734, 1645, 1621, 1605, 1532, 1193, 1100, 990, 757 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{25}\text{H}_{15}\text{NO}_5$ 409.0950; found 409.0955.

4.7.2 3-(4-(Dimethylamino)phenyl)-1-(2-hydroxybenzoyl)-2H-chromeno[3,4-*c*]pyridine-2,5(3H)-dione (16b). $R_f = 0.4$ (40% EtOAc/hexanes); yellow solid; 57 mg; yield 91%; mp 250–252 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 11.85 (s, 1H), 8.86 (s, 1H), 7.56 (t, $J =$



= 8.8 Hz, 2H), 7.49 (t, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 8.8$ Hz, 3H), 7.12–7.08 (m, 2H), 6.83 (t, $J = 7.6$ Hz, 1H), 6.74 (d, $J = 8.8$ Hz, 2H), 3.01 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 201.1, 163.1, 160.4, 159.6, 152.8, 151.0, 146.9, 138.9, 137.8, 133.6, 131.8, 127.9, 127.2, 126.7, 125.3, 121.7, 120.02, 120.01, 118.80, 118.77, 114.7, 112.1, 103.1, 40.5; IR ν_{max} (neat): 2919, 1739, 1645, 1615, 1521, 1443, 1338, 1233, 1195, 1098, 990, 741 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{27}\text{H}_{20}\text{N}_2\text{O}_5$ 452.1372; found 452.1365.

4.7.3 1-(2-Hydroxybenzoyl)-3-(4-nitrophenyl)-2H-chromeno[3,4-c]pyridine-2,5(3H)-dione (16c). $R_f = 0.7$ (40% EtOAc/hexanes); yellow solid; 61 mg; yield 97%; mp 239–241 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 11.75 (s, 1H), 8.83 (s, 1H), 8.41 (d, $J = 8.8$ Hz, 2H), 7.74 (d, $J = 8.8$ Hz, 2H), 7.58–7.53 (m, 4H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.15–7.11 (m, 2H), 6.85 (t, $J = 7.6$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 200.1, 163.2, 159.6, 159.0, 152.9, 148.2, 145.3, 143.4, 139.7, 138.2, 134.3, 131.4, 128.1, 127.6, 125.7, 125.1, 122.6, 120.2, 119.7, 119.1, 119.0, 114.2, 104.5; IR ν_{max} (neat): 2956, 2928, 2856, 1739, 1649, 1621, 1521, 1344, 1231, 1194, 1102, 744 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{25}\text{H}_{14}\text{N}_2\text{O}_7$ 454.0801; found 454.0808.

4.7.4 3-Benzyl-1-(2-hydroxybenzoyl)-2H-chromeno[3,4-c]pyridine-2,5(3H)-dione (16d). $R_f = 0.6$ (40% EtOAc/hexanes); pale yellow solid; 27 mg; yield 45%; mp 260–262 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 11.87 (s, 1H), 8.77 (s, 1H), 7.56–7.41 (m, 9H), 7.28–7.27 (m, 1H), 7.12 (d, $J = 8.8$ Hz, 1H), 7.08 (t, $J = 7.6$ Hz, 1H), 6.82 (t, $J = 7.6$ Hz, 1H), 5.34, 5.18 (ABq, $J = 14.0$ Hz, 1H each); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 201.0, 163.2, 160.4, 159.3, 152.8, 146.0, 139.1, 138.0, 134.2, 133.7, 131.5, 129.5, 129.3, 129.0, 127.8, 125.4, 121.5, 120.0, 119.9, 119.0, 118.8, 114.6, 103.4, 53.6; IR ν_{max} (neat): 3045, 2940, 1969, 1728, 1620, 1605, 1527, 1457, 1196, 1149, 1109, 750 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{26}\text{H}_{17}\text{NO}_5$ 423.1107; found 423.1115.

4.7.5 1-(2-Hydroxybenzoyl)-3-(2-hydroxybenzyl)-2H-chromeno[3,4-c]pyridine-2,5(3H)-dione (16e). $R_f = 0.4$ (40% EtOAc/hexanes); white solid; 34 mg; yield 55%; mp 252–254 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 11.79 (s, 1H), 9.02 (s, 1H), 8.34 (s, 1H), 7.56–7.48 (m, 3H), 7.39 (t, $J = 7.2$ Hz, 2H), 7.30–7.28 (m, 2H), 7.13 (d, $J = 8.4$ Hz, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 6.95–6.92 (m, 2H), 6.80 (t, $J = 7.6$ Hz, 1H), 5.29, 5.21 (ABq, $J = 14.0$ Hz, 1H each); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 199.0, 161.0, 159.9, 158.9, 155.8, 152.3, 147.1, 137.3, 137.2, 133.3, 131.7, 130.9, 129.8, 126.8, 124.8, 122.1, 121.0, 120.9, 119.8, 119.1, 118.4, 118.0, 115.3, 114.7, 102.0, 49.0; IR ν_{max} (neat): 3249, 1731, 1704, 1622, 1529, 1457, 1226, 1147, 749 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{26}\text{H}_{17}\text{NO}_6$ 439.1056; found 439.1053.

4.8. General procedure for preparation of compounds 17a and 17b

To a 10 mL round bottom flask equipped with a magnetic stirrer and a reflux condenser was charged with **11** (0.14 mmol, 1.0 equiv.), 4-hydroxycoumarins (0.14 mmol, 1.0 equiv.) and camphorsulfonic acid (0.14 mmol, 1.0 equiv.) in acetonitrile (3.0 mL) at room temperature. The resulting reaction mixture was heated at 80 °C in an oil bath for 8 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, and the solvent was concentrated under

reduced pressure. The residue was purified by column chromatography using ethyl acetate and hexane as the eluent to give the desired products.

4.8.1 3-(7-Hydroxy-6-oxo-6H,7H-chromeno[4,3-b]chromen-7-yl)-2H,5H-pyrano[3,2-c]chromene-2,5-dione (17a). $R_f = 0.5$ (40% EtOAc/hexanes); off-white solid; 32 mg; yield 48%; mp 217–219 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 8.76 (s, 1H), 8.21 (d, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.66 (t, $J = 7.2$ Hz, 2H), 7.51–7.32 (m, 7H), 7.24 (t, $J = 6.8$ Hz, 1H), 5.40 (s, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 162.7, 161.3, 159.2, 157.4, 157.3, 153.6, 153.0, 148.8, 135.4, 134.6, 133.3, 132.0, 130.2, 127.7, 125.9, 125.3, 125.0, 124.0, 123.5, 122.2, 117.6, 117.1, 116.8, 114.1, 113.0, 103.8, 100.8, 67.0; IR ν_{max} (neat): 2926, 2854, 1729, 1636, 1563, 1392, 1050, 754 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{28}\text{H}_{14}\text{O}_8$ 478.0689; found 478.0686.

4.8.2 8-(Dimethylamino)-3-(7-hydroxy-6-oxo-6H,7H-chromeno[4,3-b]chromen-7-yl)-2H,5H-pyrano[3,2-c]chromene-2,5-dione (17b). $R_f = 0.4$ (40% EtOAc/hexanes); yellow solid; 36 mg; yield 52%; mp 243–245 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 8.68 (s, 1H), 8.20 (d, $J = 7.6$ Hz, 1H), 7.63 (d, $J = 8.8$ Hz, 2H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.46–7.33 (m, 5H), 6.62 (d, $J = 8.0$ Hz, 1H), 6.49 (s, 1H), 5.41 (s, 1H), 3.10 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 162.6, 162.3, 160.1, 158.0, 157.0, 156.0, 154.5, 152.8, 148.6, 136.2, 132.9, 129.7, 127.8, 127.5, 125.6, 124.7, 124.4, 123.8, 122.7, 116.9, 116.4, 114.1, 109.9, 101.2, 101.1, 99.2, 97.7, 66.7, 40.2; IR ν_{max} (neat) 3426, 2927, 2854, 2326, 1723, 1716, 1705, 1611, 1566, 1519, 1406, 1183, 1047, 757 cm^{-1} ; HRMS (EI) m/z : $[\text{M}]^+$ calcd for $\text{C}_{30}\text{H}_{19}\text{NO}_8$ 521.1111; found 521.1116.

Conflicts of interest

There are no conflicts to declare.

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