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Multicomponent synthesis of pyrano[2,3-*c*]coumarins†

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A base-catalyzed, pseudo-four-component reaction of 4-hydroxycoumarin, two molecules of acetone, and amine towards the synthesis of pyrano[2,3-*c*]coumarins is reported. The mechanism of this multicomponent reaction is proposed. The reaction is further extended to the preparation of coumarin-substituted pyrano[2,3-*c*]coumarins by a base-catalyzed, pseudo four-component reaction of two molecules of 4-hydroxycoumarin and two molecules of acetone.

Introduction

Coumarins and pyrans are privileged chemical entities in most biologically important heterocycles.¹ When coumarins and pyrans are fused together in a molecule, the resulting pyranocoumarins typically exhibit more effective properties than when they are alone.² In particular, the angularly fused pyrano[3,2-*c*]coumarins represent an indispensable and integral part of a variety of biologically active compounds. They have been shown to possess a wide range of biological activities including antibacterial,^{3a} antifungal,^{3b} anticancer,^{3c} anti-inflammatory, and antioxidants activities.^{3d} For instance, cyclocoumarol⁴ is a semiacetalic form of warfarin was recently found to inhibit the cyclooxygenase-2 (Fig. 1).^{4a} Pterophyllin III (ref. 5a and b) possesses inhibitory activity against the proliferation of human lymphocytes.^{5a} Ethuliacoumarin A is one of the important examples of pyranocoumarins which shows the anticoagulant effects and interferes with the life cycle of parasitic trematodes.⁶ Ferprenine⁷ is an effective inhibitor of vitamin K epoxide reductase complex subunit 1 that helps in clotting. In light of their associated broad ranges of pharmacological activities, the synthesis of pyrano[3,2-*c*]coumarins has attracted considerable attention of organic and medicinal chemists. One of the earlier preparations of pyrano[3,2-*c*]coumarins was reported by Talapatra⁸ in 1984. It involved the condensation of 4-hydroxycoumarin (**1a**) with mesityl oxide to afford the hemiketal **2a**, as shown in Scheme 1. Subsequently, Liu⁹ has shown that pyrano[3,2-*c*]coumarins can be prepared by gold(-III)-catalyzed tandem conjugate addition of 4-hydroxycoumarins with α,β -unsaturated ketones. Recently, Lee¹⁰ has demonstrated that substituted pyranocoumarins can be effectively prepared by

coupling of 4-hydroxycoumarins with α,β -unsaturated aldehydes in water medium.

Among various synthetic approaches to these compounds, few utilized multicomponent reactions (MCRs) of readily accessible starting materials. Further, most preparations of pyrano[3,2-*c*]coumarins employed reagents or catalysts that are either expensive or less environmentally benign.¹¹ Thus, the search for a cost-effective and simple protocol for the synthesis of pyrano[3,2-*c*]coumarins remains desirable. In our continuing effort to develop new MCRs for the preparation of the coumarin-based heterocycles¹² to investigate their potential biological or functional properties, here we report the efficient synthesis of pyrano[3,2-*c*]coumarins *via* a base-catalyzed, pseudo four-component reaction of 4-hydroxycoumarin, acetone, and amine, as well as a base-catalyzed, pseudo four-component reaction of 4-hydroxycoumarin and acetone. A plausible mechanism is also proposed on the basis of the experimental results.

Results and discussion

To realize the preparation of pyrano[2,3-*c*]coumarins *via* a MCR manner, we speculated that the common substrate mesityl

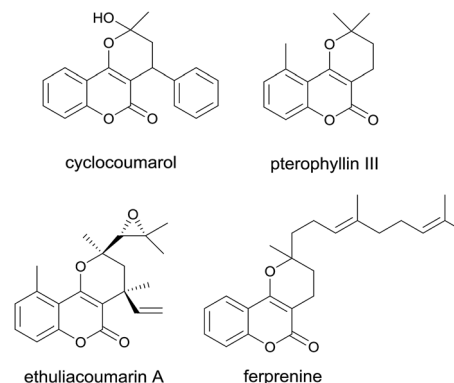
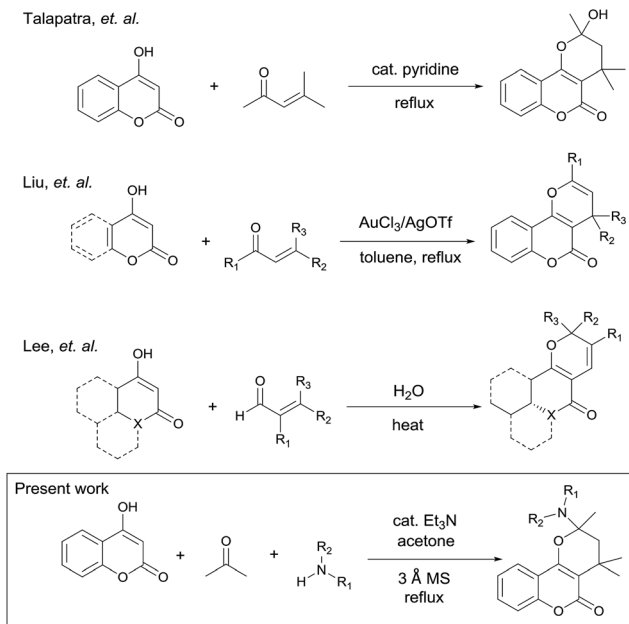


Fig. 1 Structures of some biologically active pyranocoumarins.

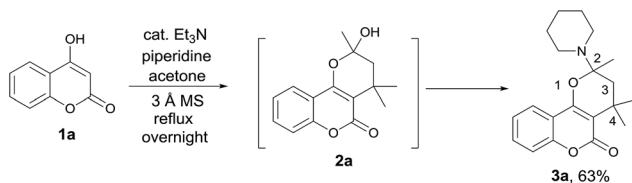
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Scheme 1 Previous and present attempts to the synthesis of pyranocoumarins.



Scheme 2 Pseudo four-component synthesis of pyranocoumarins 3a.

oxide (4-methylpent-3-en-2-one) employed by Talapatra and Lee can be generated *in situ* by a base-catalyzed aldol condensation of two molecules of acetone. Thus, by heating of 4-hydroxycoumarin (**1a**) in acetone in the presence of trimethylamine as a base, we expected that hemiketal (**2a**) may be obtained in a pseudo-three-component reaction. The resulting hemiketal (**2a**) can presumably undergo dehydration to generate the oxonium ion which may be trapped by an external nucleophile such as an amine to afford a nitrogen-containing heterocycle. To test the aforementioned hypothesis, we initiated our studies by refluxing of 4-hydroxycoumarin (**1a**) and piperidine in the presence of a catalytic amount of trimethylamine and some 3 Å molecular sieves in acetone overnight, as shown in Scheme 2. To our delight, a pseudo-four-component product, that is, pyrano[2,3-*c*]coumarin **3a** was obtained in 63% yield. Further studies indicate that compound **3** can be readily accessed by refluxing 4-hydroxycoumarin, a primary or secondary amine, and a catalytic amount of trimethylamine in acetone overnight.

Fig. 2 lists the structures and yields of the synthesized pyranocoumarins **3a–o**. The molecular structures of **3a–o** were elucidated by ^1H and ^{13}C NMR spectroscopy. In proton NMR spectra, a characteristic AB quartet absorption peaks appeared at a chemical shift of 2.39–2.03 and 2.12–1.55 ppm were

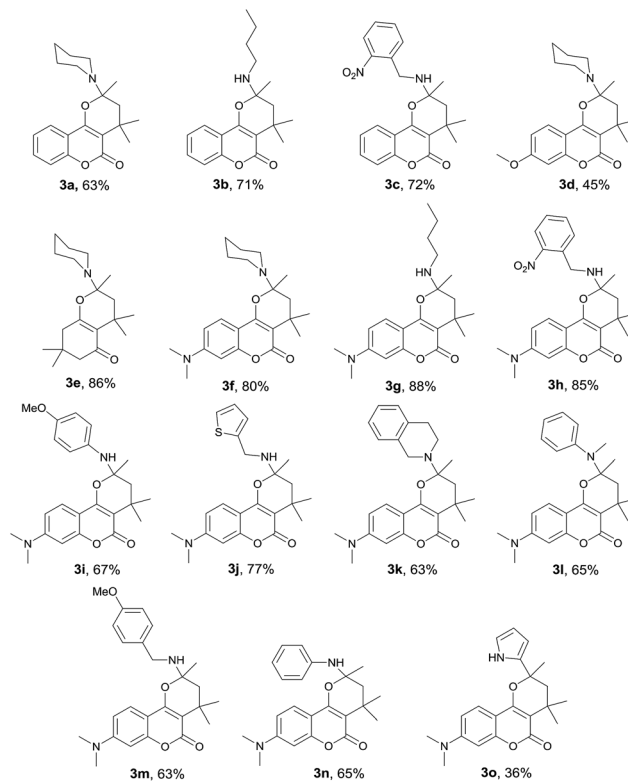


Fig. 2 Structures and yields of prepared pyranocoumarins **3a–o**.

assigned to the two methylene hydrogens on C-3 position (see compound **3a** in Scheme 2 for atom-numbering). The molecular structures of **3a**, **3e**, and **3h** were further verified by X-ray crystallography¹³ as depicted in Fig. 3. Our studies indicate that 4-hydroxycoumarin substrate with an electron-donating substituent generally gave a better yield than that of an electron-withdrawing one. As for amine substrates, the primary amine normally gave higher yields than the secondary amines and anilines. When the amine was replaced with pyrrole, the corresponding pyranocoumarin **3o** was obtained, although with a lower yield. No expected product was detected when the amine was replaced with either furan, thiophene or phenol. For most of the reactions, the formation of a trace by-product was constantly observed. This by-product was isolated and subsequently identified to be 8-(dimethylamino)-2,2,4-trimethyl-2H,5H-pyrano[3,2-*c*]chromen-5-one (**4**) whose X-ray crystal structure is also shown in Fig. 3.¹³ Isolation of the compound **4** provides crucial insights into the mechanism of this multi-component reaction.

Scheme 3 depicts a plausible mechanism of this pseudo-four-component synthesis of the pyrano[2,3-*c*]coumarin **3f**. It starts with the base-catalyzed aldol condensation of two molecules of acetone to yield the 4-methylpent-3-en-2-one. The subsequent conjugate addition of 7-*N,N*-dimethylamino-4-hydroxycoumarin (**1b**) to 4-methylpent-3-en-2-one yields the major hemiketal **2b**. Dehydration of **2b** gives the reactive oxonium ion **5** which is then trapped by piperidine to furnish the final product **3f**. Alternatively, the simple addition of 4-hydroxycoumarin to 4-methylpent-3-en-2-one yields the minor



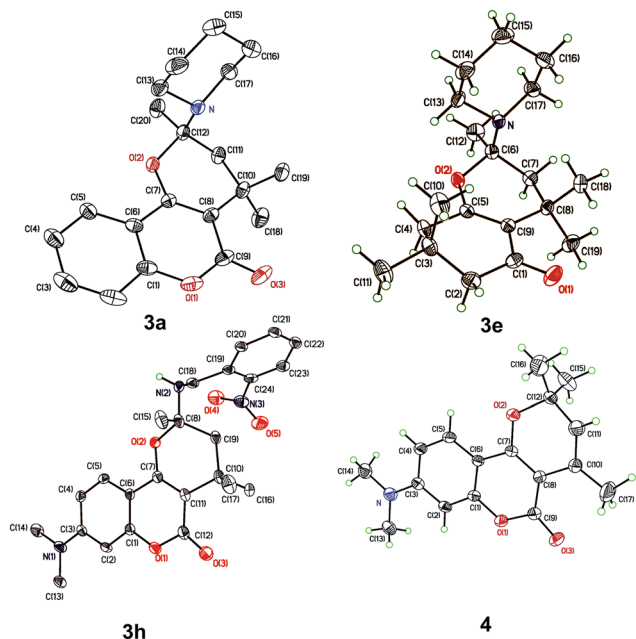
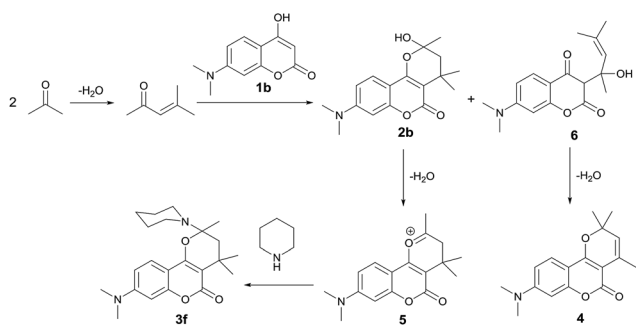


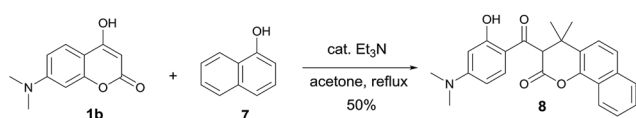
Fig. 3 ORTEP crystal structures of **3a**, **3e**, **3h**, and **4**.



Scheme 3 Proposed mechanism for the synthesis of pyranocoumarins **3f** and **4**.

tertiary alcohol **6**, which further undergoes dehydration and follows by electrocyclic reaction to give the by-product **4**. Since the ketone substrate of this MCR is limited to acetone only, few positions on pyran moiety of the pyrano[2,3-*c*]coumarins are available for variation. Nevertheless, the bond formation during the construction of the pyranocoumarin scaffold in this pseudo-four-component reaction is highly atom-economical, generating two C–C bonds, one C–O bond, and one C–N bond in the final product.

In an effort to further explore the scope of this pseudo-four-component reaction, the amine was replaced with 1-naphthalenol (**7**) in expectation to obtain a different product. Under these reaction conditions, the isolated compound was found to



Scheme 4 Three-component synthesis of β -keto ester **8**.

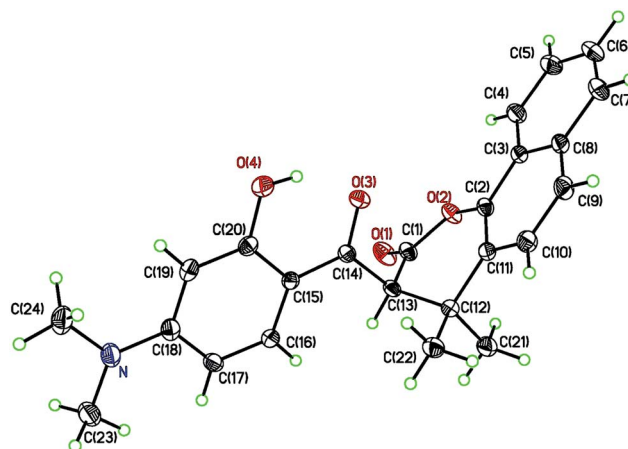
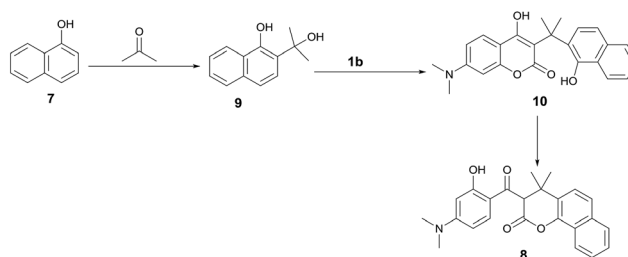


Fig. 4 ORTEP crystal structure of **8**.

be the β -keto ester **8** (Scheme 4). The molecular structure of **8** was confirmed by the X-ray crystal analysis as shown in Fig. 4.¹³ The crystal structure and ¹H NMR spectrum of β -keto ester **8** indicates that it exists exclusively in the keto form in both solid state and solution, and the two keto groups are almost orthogonal to each other. Scheme 5 depicts the proposed mechanism for the formation of **8**. It presumably involves the first coupling of 1-naphthalenol (**7**) with acetone to give the alcohol **9**. The subsequent condensation of **9** with 7-*N,N*-dimethylamino-4-hydroxycoumarin (**1b**) affords the intermediate **10**. Final intramolecular ring-opening of the coumarin lactone ring of **10** by the nearby 1-naphthalenol hydroxyl group furnishes the final product β -keto ester **8**.

Interestingly, when 4-hydroxycoumarin (**1a**) was refluxed in acetone for 24 hours in the absence of any external nucleophile such as a primary amine, the major product obtained was found to be the pyrano[2,3-*c*]coumarin **11a**. Fig. 5 lists the structures and yields of the prepared pyranocoumarins **11a–c**. Similar to pyranocoumarins **3**, the 4-hydroxycoumarin substrate with an electron-donating substituent generally gave a higher yield than that of an electron-withdrawing one. A representative X-ray crystal structure of **11b** is shown in Fig. 6.¹³ Apparently, the proposed intermediate **5** (Scheme 3) generated *in situ* in the reaction was trapped by a second molecule of 4-hydroxycoumarin to give the observed product. This pseudo-four-component reaction of two molecules of 4-hydroxycoumarin and two molecules of acetone provides quick access to coumarin-substituted pyranocoumarins with extreme simplicity



Scheme 5 Proposed mechanism for the formation of β -keto ester **8**.



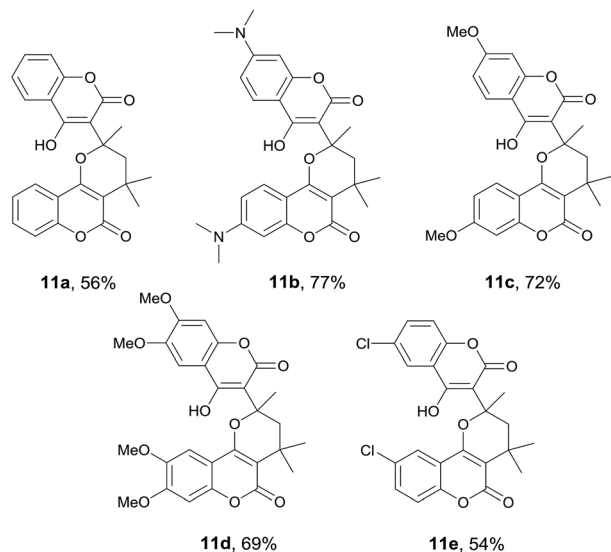


Fig. 5 Structures and yields of prepared pyranocoumarins 11a–e.

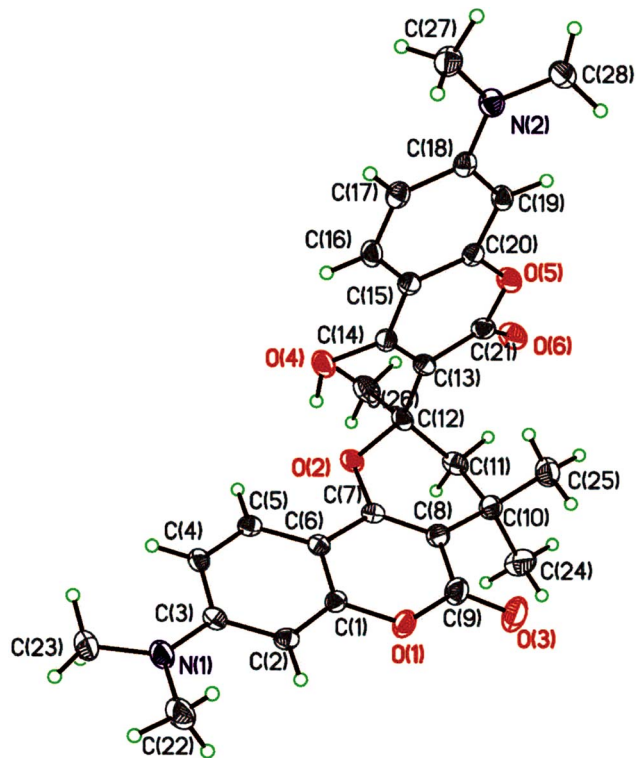


Fig. 6 ORTEP crystal structure of 11b.

and high atom economy, forming three C–C bonds and one C–O bond in the final product.

Conclusions

In summary, we have demonstrated that pyrano[2,3-*c*]coumarins 3a–o can be efficiently synthesized *via* pseudo-four-component reaction of 4-hydroxycoumarin, two molecules of acetone, and a primary or secondary amine in the presence of

a catalytic amount of trimethylamine as a base in acetone under refluxed conditions. Moreover, the coumarin-substituted pyrano[2,3-*c*]coumarins 11a–e can be readily constructed in good to excellent yields *via* pseudo-four-component reaction of two molecules of 4-hydroxycoumarin and two molecules of acetone in acetone under refluxed conditions.

Experimental

4.1. General

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 (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded on a Varian Unity 300 or Bruker 400 spectrometer. Chemical shifts were reported in parts per million on the δ 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. General procedure for the synthesis of 3

To a mixture of 4-hydroxycoumarin (1.00 mmol, 1 equiv.) in acetone (10 mL) was added amine (2 equiv.), Et_3N (0.5 equiv.), and 3 Å molecular sieves (3.0 g) at room temperature. The resulting mixture was then refluxed overnight. The progress of the reaction was monitored by TLC. After cooled down to room temperature, the mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was re-dissolved in water (30 mL) and the product was extracted by DCM (15 mL \times 3). The combined organic layer was then dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography to give the desired compound 3.

4.2.1. 2,4,4-Trimethyl-2-(piperidin-1-yl)-3,4-dihydropyrano[3,2-*c*]chromen-5(2*H*)-one (3a). $R_f = 0.6$ (15% EtOAc/hexanes); white solid; 205 mg; yield 63%; mp 148–149 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.81 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.47 (td, $J = 8.0, 1.6$ Hz, 1H), 7.28 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.24 (td, $J = 8.0, 1.2$ Hz, 1H), 2.62–2.61 (m, 4H), 1.68 (bs, 1H), 1.61–1.45 (m, 7H), 1.48 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 161.3, 156.9, 152.6, 131.1, 123.5, 122.9, 116.22, 116.20, 109.5, 92.6, 47.0, 45.2, 30.6, 28.6, 26.8, 25.9, 24.8, 18.9; IR ν (ATR) 2932, 1664, 1616, 1452, 1369, 983, 757 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_3$ [M^+] 327.1834 found 327.1836.



4.2.2. 2-(Butylamino)-2,4,4-trimethyl-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3b). $R_f = 0.7$ (15% EtOAc/hexanes); yellow viscous liquid; 225 mg; yield 71%; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.80 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.48 (td, $J = 8.0, 1.2$ Hz, 1H), 7.30–7.22 (m, 2H), 2.84 (t, $J = 7.2$ Hz, 2H), 2.12 (bs, 1H), 2.04 (s, 2H), 1.59 (s, 3H), 1.52 (s, 6H), 1.44 (quintet, $J = 7.2$ Hz, 2H), 1.33 (sextet, $J = 7.2$ Hz, 2H), 0.88 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 161.4, 158.1, 152.6, 131.2, 123.5, 123.1, 116.4, 116.1, 107.7, 92.6, 48.9, 40.8, 32.6, 31.0, 28.8, 24.7, 20.3, 13.8; IR ν (ATR) 3345, 2956, 1705, 1611, 1567, 1373, 1103, 985, 755 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_3$ [M^+] 315.1834 found 315.1830.

4.2.3. 2,4,4-Trimethyl-2-((2-nitrobenzyl)amino)-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3c). $R_f = 0.5$ (15% EtOAc/hexanes); yellow viscous liquid; 285 mg; yield 72%; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.91 (dd, $J = 7.6, 0.8$ Hz, 1H), 7.66 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.61 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.56 (td, $J = 7.6, 1.2$ Hz, 1H), 7.48 (td, $J = 7.6, 1.6$ Hz, 1H), 7.39 (td, $J = 7.6, 1.6$ Hz, 1H), 7.27 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.21 (td, $J = 7.6, 0.8$ Hz, 1H), 4.41, 4.21 (ABdq, $J = 14.4, 6.8$ Hz, 1H each), 2.90 (t, $J = 6.8$ Hz, 1H), 2.12, 2.02 (ABq, $J = 14.4$ Hz, 1H each), 1.63 (s, 3H), 1.52 (s, 3H), 1.51 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 161.3, 157.8, 152.5, 148.8, 135.8, 133.4, 131.3, 131.1, 128.1, 124.8, 123.5, 123.1, 116.2, 116.0, 107.9, 91.9, 48.8, 43.1, 31.0, 29.2, 28.4, 24.8; IR ν (ATR) 3353, 2957, 1698, 1611, 1524, 1373, 987, 755 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5$ [M^+] 394.1529 found 394.1526.

4.2.4. 8-Methoxy-2,4,4-trimethyl-2-(piperidin-1-yl)-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3d). $R_f = 0.6$ (15% EtOAc/hexanes); white solid; 162 mg; yield 45%; mp 109–110 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.69 (d, $J = 8.8$ Hz, 1H), 6.81 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.77 (d, $J = 2.4$ Hz, 1H), 3.85 (s, 3H), 2.61–2.60 (m, 4H), 1.60 (s, 3H), 1.48–1.41 (m, 8H), 1.41 (s, 6H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 162.2, 161.7, 157.4, 154.3, 123.9, 111.8, 109.5, 106.8, 99.9, 92.5, 55.7, 46.9, 45.2, 30.3, 28.6, 26.8, 25.9, 24.8, 18.9; IR ν (ATR) 2932, 1702, 1615, 1389, 1212, 1108, 1003 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_4$ [M^+] 357.1940 found 357.1941.

4.2.5. 2,4,4,7,7-Pentamethyl-2-(piperidin-1-yl)-3,4,7,8-tetrahydro-2H-chromen-5(6H)-one (3e). $R_f = 0.6$ (10% EtOAc/hexanes); white solid; 260 mg; yield 86%; mp 67–68 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 2.63–2.47 (m, 4H), 2.27, 2.20 (ABq, $J = 16.4$ Hz, 1H each), 2.20 (s, 2H), 2.03, 1.55 (ABq, $J = 14.4$ Hz, 1H each), 1.58–1.48 (m, 4H), 1.46–1.42 (m, 2H), 1.37 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.03 (s, 6H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 197.7, 166.5, 117.7, 91.5, 52.5, 46.7, 45.6, 43.3, 31.5, 29.9, 29.0, 28.2, 27.9, 26.0, 24.9, 19.2; IR ν (ATR) 2934, 1737, 1716, 1607, 1367, 1217, 1071 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{19}\text{H}_{31}\text{NO}_2$ [M^+] 305.2355 found 305.2348.

4.2.6. 8-(Dimethylamino)-2,4,4-trimethyl-2-(piperidin-1-yl)-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3f). $R_f = 0.5$ (25% EtOAc/hexanes); light yellow solid; 295 mg; yield 80%; mp 154–155 °C; $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.60 (d, $J = 8.8$ Hz, 1H), 6.59 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.47 (d, $J = 2.4$ Hz, 1H), 3.02 (s, 6H), 2.67–2.53 (m, 4H), 2.27, 1.73 (ABq, $J = 14.4$ Hz, 1H each), 1.53 (s, 3H), 1.53–1.40 (m, 6H), 1.40 (s, 6H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz)

δ 162.3, 158.0, 154.6, 152.6, 123.6, 108.5, 105.3, 104.8, 97.6, 92.1, 46.9, 45.3, 40.2, 30.2, 28.8, 27.0, 25.9, 24.9, 18.9; IR ν (ATR) 2925, 1695, 1603, 1456, 1377, 1217, 1112 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_3$ [M^+] 370.2256 found 370.2253.

4.2.7. 2-(Butylamino)-8-(dimethylamino)-2,4,4-trimethyl-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3g). $R_f = 0.7$ (25% EtOAc/hexanes); brown viscous liquid; 313 mg; yield 88%; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.58 (d, $J = 8.8$ Hz, 1H), 6.58 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.46 (d, $J = 2.4$ Hz, 1H), 3.03 (s, 6H), 2.81 (t, $J = 7.2$ Hz, 2H), 2.13 (bs, 1H), 2.00 (s, 2H), 1.56 (s, 3H), 1.49 (s, 6H), 1.42 (quintet, $J = 7.2$ Hz, 2H), 1.31 (sextet, $J = 7.2$ Hz, 2H), 0.88 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 162.4, 159.1, 154.6, 152.7, 123.7, 108.5, 105.4, 103.2, 97.4, 91.8, 49.2, 40.9, 40.1, 32.7, 30.6, 29.1, 24.8, 20.3, 13.9; IR ν (ATR) 3341, 2955, 1697, 1595, 1520, 1380, 1106, 916, 731 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_3$ [M^+] 358.2256 found 358.2250.

4.2.8. 8-(Dimethylamino)-2,4,4-trimethyl-2-((2-nitrobenzyl)amino)-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3h). $R_f = 0.5$ (25% EtOAc/hexanes); yellow solid; 370 mg; yield 85%; mp 142–143 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.92 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.63 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.56 (td, $J = 8.4, 1.2$ Hz, 1H), 7.49 (d, $J = 7.2$ Hz, 1H), 7.39 (td, $J = 8.4, 1.2$ Hz, 1H), 6.57 (dd, $J = 7.2, 2.4$ Hz, 1H), 6.46 (d, $J = 2.4$ Hz, 1H), 4.40, 4.19 (ABdq, $J = 14.8, 6.4$ Hz, 1H each), 3.03 (s, 6H), 2.84 (t, $J = 6.4$ Hz, 1H), 2.08, 1.99 (ABq, $J = 14.4$ Hz, 1H each), 1.59 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 162.3, 158.8, 154.6, 152.8, 148.9, 136.0, 133.3, 131.0, 128.0, 124.8, 123.7, 108.5, 105.2, 103.4, 97.5, 91.1, 49.0, 42.9, 40.2, 30.6, 29.5, 28.6, 24.9; IR ν (ATR) 3394, 2970, 1739, 1619, 1366, 1217 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_5$ [M^+] 437.1951 found 437.1950.

4.2.9. 8-(Dimethylamino)-2-((4-methoxyphenyl)amino)-2,4,4-trimethyl-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3i). $R_f = 0.6$ (25% EtOAc/hexanes); light pink solid; 275 mg; yield 67%; mp 90–91 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.59 (d, $J = 8.8$ Hz, 1H), 6.96 (dd, $J = 6.8, 2.0$ Hz, 2H), 6.78 (dd, $J = 6.8, 2.0$ Hz, 2H), 6.60 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.47 (d, $J = 2.4$ Hz, 1H), 4.11 (bs, 1H), 3.77 (s, 3H), 3.03 (s, 6H), 2.16, 2.06 (ABq, $J = 14.4$ Hz, 1H each), 1.63 (s, 3H), 1.57 (s, 3H), 1.51 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 162.3, 158.5, 155.6, 154.7, 152.8, 135.7, 124.5, 123.9, 114.1, 108.6, 105.2, 103.6, 97.5, 89.9, 55.5, 49.6, 40.2, 30.6, 29.1, 28.8, 25.4; IR ν (ATR) 3342, 2946, 1688, 1595, 1509, 1378, 1235, 823 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_4$ [M^+] 408.2049 found 408.2044.

4.2.10. 8-(Dimethylamino)-2,4,4-trimethyl-2-((thiophen-2-ylmethyl)amino)-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3j). $R_f = 0.4$ (25% EtOAc/hexanes); yellow viscous liquid; 308 mg; 77%; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.59 (d, $J = 8.8$ Hz, 1H), 7.19 (dd, $J = 4.8, 1.2$ Hz, 1H), 6.93–6.89 (m, 2H), 6.60 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.47 (d, $J = 2.4$ Hz, 1H), 4.24, 4.18 (ABq, $J = 14.0$ Hz, 1H each), 3.04 (s, 6H), 2.59 (bs, 1H), 2.09, 2.01 (ABq, $J = 14.4$ Hz, 1H each), 1.62 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 162.3, 158.9, 154.6, 152.8, 143.9, 126.8, 124.7, 124.5, 123.8, 108.6, 105.2, 103.4, 97.4, 91.2, 48.9, 40.6, 40.2, 30.7, 29.5, 28.6, 24.9; IR ν (ATR) 3336, 2926, 1697, 1595, 1520, 1380, 1231, 915 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$ [M^+] 398.1664 found 398.1665.



4.2.11. 2-(3,4-Dihydroisoquinolin-2(1H)-yl)-8-(dimethylamino)-2,4,4-trimethyl-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3k). $R_f = 0.5$ (25% EtOAc/hexanes); light orange solid; 263 mg; 63%; mp 155–156 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.60 (d, $J = 8.8$ Hz, 1H), 7.11–7.05 (m, 3H), 6.99 (dd, $J = 7.2$, 2.0 Hz, 1H), 6.59 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.46 (d, $J = 2.4$ Hz, 1H), 3.96, 3.87 (ABq, $J = 14.4$ Hz, 1H each), 3.07–3.01 (m, 1H), 3.03 (s, 6H), 2.98–2.84 (m, 2H), 2.80–2.73 (m, 1H), 2.39, 1.85 (ABq, $J = 14.4$ Hz, 1H each), 1.54 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 162.1, 158.0, 154.6, 152.7, 134.7, 134.6, 128.6, 126.7, 126.1, 125.5, 123.5, 108.6, 105.1, 104.7, 97.6, 92.1, 48.8, 45.4, 43.7, 40.2, 30.4, 29.4, 28.7, 27.6, 19.4; IR ν (ATR) 2901, 1700, 1602, 1523, 1389, 1075, 737 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_3$ [M^+] 418.2256 found 418.2253.

4.2.12. 8-(Dimethylamino)-2,4,4-trimethyl-2-(methylphenylamino)-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3l). $R_f = 0.6$ (25% EtOAc/hexanes); light yellow solid; 255 mg; 65%; mp 138–139 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.62 (d, $J = 8.8$ Hz, 1H), 7.33–7.27 (m, 4H), 7.20–7.16 (m, 1H), 6.62 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.48 (d, $J = 2.4$ Hz, 1H), 3.04 (s, 6H), 3.01 (s, 3H), 2.28, 1.82 (ABq, $J = 14.4$ Hz, 1H each), 1.54 (s, 3H), 1.52 (s, 3H), 1.39 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 162.4, 159.5, 154.6, 152.7, 149.3, 128.7, 128.6, 125.7, 123.9, 108.5, 105.5, 103.3, 97.5, 94.3, 46.9, 40.2, 38.0, 31.4, 30.2, 27.4, 22.9; IR ν (ATR) 2926, 1717, 1600, 1441, 1365, 1217, 1009 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_3$ [M^+] 392.2100 found 392.2107.

4.2.13. 8-(Dimethylamino)-2-((4-methoxybenzyl)amino)-2,4,4-trimethyl-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3m). $R_f = 0.5$ (25% EtOAc/hexanes); light orange solid; 266 mg; 63%; mp 116–117 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.60 (d, $J = 8.8$ Hz, 1H), 7.19 (dd, $J = 6.4$, 2.0 Hz, 2H), 6.83 (d, $J = 6.4$, 2.0 Hz, 2H), 6.60 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.48 (d, $J = 2.4$ Hz, 1H), 3.93 (s, 2H), 3.78 (s, 3H), 3.04 (s, 6H), 2.37 (bs, 1H), 2.07 (s, 1H), 2.02 (s, 1H), 1.62 (s, 3H), 1.48 (s, 6H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 162.4, 159.0, 158.7, 154.6, 152.8, 132.2, 129.1, 123.7, 114.0, 108.5, 105.4, 103.5, 97.5, 91.6, 55.3, 49.1, 45.1, 40.2, 30.7, 29.5, 28.6, 25.0; IR ν (ATR) 3406, 2955, 1739, 1682, 1591, 1378, 1233, 1008 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_4$ [M^+] 422.2206 found 422.2211.

4.2.14. 8-(Dimethylamino)-2,4,4-trimethyl-2-(phenylamino)-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3n). $R_f = 0.6$ (25% EtOAc/hexanes); light pink solid; 247 mg; 65%; mp 118–119 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.65 (d, $J = 8.8$ Hz, 1H), 7.20 (td, $J = 8.4$, 0.8 Hz, 2H), 6.97 (dd, $J = 8.4$, 0.8 Hz, 2H), 6.88 (td, $J = 8.4$, 0.8 Hz, 1H), 6.61 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.46 (d, $J = 2.4$ Hz, 1H), 4.36 (bs, 1H), 3.02 (s, 6H), 2.23, 2.07 (ABq, $J = 14.4$ Hz, 1H each), 1.76 (s, 3H), 1.61 (s, 3H), 1.51 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 162.3, 158.2, 154.6, 152.8, 143.2, 129.0, 123.8, 120.7, 119.3, 108.7, 105.1, 103.8, 97.6, 88.7, 49.8, 40.2, 30.4, 29.0, 28.8, 25.4; IR ν (ATR) 3352, 2947, 1686, 1597, 1518, 1379, 1108, 752 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$ [M^+] 378.1943 found 378.1937.

4.2.15. 8-(Dimethylamino)-2,4,4-trimethyl-2-(1H-pyrrol-2-yl)-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (3o). $R_f = 0.7$ (30% EtOAc/hexanes); light pink solid; 125 mg; yield 36%; mp 122–123 °C; $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 8.11 (bs, 1H), 7.69 (d, $J = 8.7$ Hz, 1H), 6.70–6.68 (m, 1H), 6.62 (dd, $J = 8.7$, 2.4 Hz, 1H), 6.48 (d, $J = 2.7$ Hz, 1H), 6.13 (dd, $J = 6.3$, 2.7 Hz, 1H), 6.00–5.98 (m, 1H), 3.04 (s, 6H), 2.28, 2.12 (ABq, $J = 14.4$ Hz, 1H each), 1.77 (s, 3H), 1.48 (s, 3H), 1.05 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 162.0, 158.7, 154.5, 152.8, 134.5, 123.6, 116.8, 108.6, 104.8, 104.5, 104.2, 97.6, 77.5, 50.4, 40.2, 30.1, 29.2, 28.5, 27.3; IR ν (KBr) 3314, 2915, 1674, 1600, 1519, 1394, 1075 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3$ [M^+] 352.1787 found 352.1790.

4.3. 8-(Dimethylamino)-2,2,4-trimethylpyrano[3,2-c]chromen-5(2H)-one (4)

$R_f = 0.8$ (30% EtOAc/hexanes); yellow solid; $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.61 (d, $J = 9.0$ Hz, 1H), 6.59 (dd, $J = 9.0$, 2.4 Hz, 1H), 6.46 (d, $J = 2.4$ Hz, 1H), 5.13 (q, $J = 1.5$ Hz, 1H), 3.05 (s, 6H), 2.20 (d, $J = 1.5$ Hz, 3H), 1.46 (s, 6H); HRMS (EI) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_3$ [M^+] 285.1365 found 285.1367.

4.4. 3-(4-(Dimethylamino)-2-hydroxybenzoyl)-4,4-dimethyl-3,4-dihydro-2H-benzo[h]chromen-2-one (8)

$R_f = 0.5$ (30% EtOAc/hexanes); light pink solid; 193 mg; yield 50%; mp 103–104 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 12.50 (s, 1H), 8.31 (dd, $J = 8.8$, 1.2 Hz, 1H), 7.84 (dd, $J = 8.8$, 1.2 Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 1H), 7.66 (d, $J = 8.8$ Hz, 1H), 7.58–7.50 (m, 2H), 7.42 (d, $J = 8.8$ Hz, 1H), 6.25 (dd, $J = 9.2$, 2.4 Hz, 1H), 6.06 (d, $J = 2.4$ Hz, 1H), 4.62 (s, 1H), 3.06 (s, 6H), 1.54 (s, 3H), 1.49 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 194.1, 165.8, 165.6, 156.3, 145.2, 133.4, 132.4, 127.5, 126.7, 126.5, 125.3, 124.6, 123.4, 121.4, 121.2, 110.5, 104.5, 97.9, 56.1, 40.0, 37.8, 29.5, 24.2; IR ν (KBr) 2925, 1749, 1627, 1529, 1364, 1268, 1218, 1148, 812 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_4$ [M^+] 389.1627 found 389.1633.

4.5. General procedure for the synthesis of 11

To a mixture of 4-hydroxycoumarin (2.00 mmol, 1 equiv.) in acetone (20 mL) was added Et_3N (0.25 equiv.) and 3 Å molecular sieves (3.0 g) at room temperature. The resulting mixture was refluxed in acetone for 24 h. After cooled down to room temperature, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was re-dissolved in water (30 mL) and the product was extracted by DCM (15 mL \times 3). The combined organic layer was then dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography to give the desired compound 11.

4.5.1. 2-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2,4,4-trimethyl-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (11a). $R_f = 0.5$ (25% EtOAc/hexanes); white solid; 228 mg; 56%; mp 192–193 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 9.62 (s, 1H), 7.83 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.75 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.61–7.54 (m, 2H), 7.40–7.36 (m, 2H), 7.31–7.25 (m, 2H), 3.05, 2.39 (ABq, $J = 14.8$ Hz, 1H each), 2.00 (s, 3H), 1.55 (s, 3H), 1.39 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 160.8, 160.5, 160.1, 154.8, 152.5, 152.4, 132.7, 132.0, 124.4, 124.1, 123.8, 121.3, 117.0, 116.1, 115.6, 115.2, 112.1, 105.4, 86.3, 46.0, 30.6, 27.7, 26.9, 26.6; IR ν (ATR) 3367, 2932, 1688, 1610, 1563, 1367, 1218, 758 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{24}\text{H}_{20}\text{O}_6$ [M^+] 404.1260 found 404.1255.

4.5.2. 8-(Dimethylamino)-2-(7-(dimethylamino)-4-hydroxy-2-oxo-2H-chromen-3-yl)-2,4,4-trimethyl-3,4-dihydropyrano[3,2-



c]chromen-5(2H)-one (11b). $R_f = 0.4$ (25% EtOAc/hexanes); light pink solid; 380 mg; 77%; mp 222–223 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 9.59 (s, 1H), 7.60 (d, $J = 8.8$ Hz, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 6.68 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.58 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.51 (d, $J = 2.4$ Hz, 1H), 6.43 (d, $J = 2.4$ Hz, 1H), 3.06 (s, 6H), 3.04 (s, 6H), 2.99, 2.32 (ABq, $J = 14.4$ Hz, 1H each), 1.94 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 161.9, 161.6, 161.3, 156.0, 154.53, 154.49, 153.4, 152.9, 124.4, 122.1, 109.1, 108.9, 106.8, 104.4, 104.1, 101.0, 97.9, 96.9, 86.1, 46.3, 40.2, 40.1, 30.2, 27.9, 27.0, 26.8; IR ν (ATR) 3343, 2971, 1716, 1599, 1523, 1379, 1228, 771 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_6$ [M^+] 490.2104 found 490.2108.

4.5.3. 2-(4-Hydroxy-7-methoxy-2-oxo-2H-chromen-3-yl)-8-methoxy-2,4,4-trimethyl-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (11c). $R_f = 0.4$ (30% EtOAc/hexanes); white solid; 336 mg; 72%; mp 234–235 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 9.57 (s, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.63 (d, $J = 8.8$ Hz, 1H), 6.93 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.85–6.82 (m, 2H), 6.76 (d, $J = 2.4$ Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.01, 2.35 (ABq, $J = 14.8$ Hz, 1H each), 1.96 (s, 3H), 1.52 (s, 3H), 1.36 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 163.4, 162.9, 161.3, 161.0, 160.6, 155.3, 154.24, 154.21, 124.9, 122.4, 112.7, 112.5, 109.2, 108.7, 108.4, 102.9, 100.7, 99.7, 86.3, 55.83, 55.78, 46.1, 30.3, 27.8, 26.8, 26.7; IR ν (ATR) 3342, 2994, 1694, 1615, 1372, 1210, 1031, 770 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{26}\text{H}_{24}\text{O}_8$ [M^+] 464.1471 found 464.1476.

4.5.4. 2-(4-Hydroxy-6,7-dimethoxy-2-oxo-2H-chromen-3-yl)-8,9-dimethoxy-2,4,4-trimethyl-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (11d). $R_f = 0.4$ (30% EtOAc/hexanes); light yellow solid; 362 mg; 69%; mp 246–247 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 9.52 (s, 1H), 7.14 (s, 1H), 7.06 (s, 1H), 6.86 (s, 1H), 6.78 (s, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.11, 2.29 (ABq, $J = 14.8$ Hz, 1H each), 1.99 (s, 3H), 1.52 (s, 3H), 1.36 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 161.3, 160.72, 160.67, 155.2, 153.5, 153.0, 148.40, 148.39, 146.7, 146.3, 109.6, 107.5, 107.1, 103.7, 103.2, 101.8, 100.1, 99.0, 86.3, 56.7, 56.42, 56.39, 56.3, 46.1, 30.4, 27.8, 27.0, 26.5; IR ν (ATR) 3244, 2971, 1714, 1620, 1365, 1204, 969 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{28}\text{H}_{28}\text{O}_{10}$ [M^+] 524.1682 found 524.1680.

4.5.5. 9-Chloro-2-(6-chloro-4-hydroxy-2-oxo-2H-chromen-3-yl)-2,4,4-trimethyl-3,4-dihydropyrano[3,2-c]chromen-5(2H)-one (11e). $R_f = 0.4$ (25% EtOAc/hexanes); light yellow solid; 255 mg; 54%; mp 244–245 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 9.40 (s, 1H), 7.82 (d, $J = 2.4$ Hz, 1H), 7.69 (d, $J = 2.4$ Hz, 1H), 7.54 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.51 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.31 (d, $J = 8.8$ Hz, 1H), 7.25 (d, $J = 8.8$ Hz, 1H), 3.06, 2.34 (ABq, $J = 14.8$ Hz, 1H each), 1.99 (s, 3H), 1.53 (s, 3H), 1.35 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 160.3, 159.41, 159.35, 153.8, 150.8, 150.7, 132.8, 132.1, 130.0, 129.8, 123.5, 120.9, 118.5, 117.7, 116.6, 116.3, 113.1, 106.0, 86.5, 45.9, 30.7, 27.7, 26.7, 26.6; IR ν (ATR) 3391, 2926, 1717, 1608, 1567, 1357, 1229, 1112, 999 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{24}\text{H}_{18}\text{Cl}_2\text{O}_6$ [M^+] 472.0480 found 472.0483.

Conflicts of interest

There are no conflicts to declare.

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- 13 Crystallographic data (excluding structure factors) for **3a**, **3e**, **3h**, **4**, **8**, and **11b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-1853612, -1846223, -1846224, -1846226, -1853613, and -1846225, respectively.†

