Synthesis and transformations of 4*H*-chromene 4-hydroxy-2*H*-pyran-2-one and 4*H*-chromene 4-hydroxycoumarin conjugates

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MS received 3 January 2013; revised 6 March 2013; accepted 5 April 2013

Abstract. The reaction of *N*-methyl-4-(methylthio)-3-nitro-4*H*-chromen-2-amine and its derivatives with 4-hydroxy-6-methyl-2*H*-pyran-2-one in EtOH reflux for 5 min furnish 4-hydroxy-6-methyl-3-(2-(methylamino)-3-nitro-4*H*-chromen-4-yl)-2*H*-pyran-2-ones in quantitative yield. By extending EtOH reflux for 2 h, the 4*H*-chromene 4-hydroxy-2-pyranone conjugates get converted into acetoacetyl coumarins. Similar reaction of *N*-methyl-4-(methylthio)-3-nitro-4*H*-chromen-2-amine and its derivatives with 4-hydroxycoumarin in EtOH reflux furnish 4-hydroxy-2'-(methylamino)-3'-nitro-2*H*,4'*H*-3,4'-bichromen-2-ones. In contrast to earlier system, prolonging reflux in EtOH or in *n*-PrOH reflux the product gets transformed into *trans*-ethyl 3-(2-hydroxyaryl)-4-oxo-3,4-dihydro-2*H*-furo[3,2-*c*]chromene-2-carboxylates. Thus, facile synthesis and characterization of 4*H*-chromene 4-hydroxy-2-pyrone, 4*H*-chromene 4-hydroxycoumarin conjugates, acetoacetyl coumarins and *trans*2,3-disubstituted dihydrofuro[3,2-*c*]coumarins is described.

Keywords. 4*H*-Chromenes; 4-hydroxy-2*H*-pyran-2-ones; hydroxycoumarins; furo[3,2-*c*]coumarins.

1. Introduction

Unlike chroman (benzodihydropyran), the heterocyclic scaffold 4*H*-chromene (4*H*-1-benzopyran) is not widely distributed in nature.¹ It has, however, emerged as a 'privileged medicinal scaffold' owing to rigid hetero-ring system, ease of synthesis and many possibilities to place functional groups for binding to specific sites in the target.² Among 4*H*-chromenes, 2-amino-4-aryl-4*H*-chromenes have been identified for inducing apoptosis, thus, useful for treatment of cancer.³ We have recently described a facile, high yielding, atom-economic synthesis of 4-methylsulphanyl-4*H*-chromenes **3** from readily available 2-hydroxybenzaldehydes (salicylaldehydes) **1** and nitroketene *N,S*-acetals **2** (scheme 1).⁴ Reaction of **3** with thiophenols lead to facile substitution of labile C4SMe to provide 4*H*-chromenes **4** having aryl thioether group (scheme 1). The reactions of **3** with phenols, on the other hand, lead to exclusive substitution at *ortho*-position in phenol to provide 4-aryl-4*H*-chromenes **5** (scheme 1).⁵ The C4SMe group in **3** could be replaced with electron-rich aromatics enroute to some interesting and biologically relevant amino acids.⁶ In continuation of these studies, we formulated

reactions of **3** and its siblings with 4-hydroxy-6-methyl-2*H*-pyran-2-one **6** to realize pyrone-4*H*-chromene conjugates, e.g., **7** (scheme 1). Similarly, reactions of **3** and its siblings with 4-hydroxycoumarin **8** could provide coumarin 4*H*-chromene conjugates **9**. Molecules like **7** and **9** incorporate structural features of bioactive heterocycles like 4*H*-chromene and pyrone or 4*H*-chromene and coumarin. Such conjugates are expected to show unique properties attributable to both the motifs. Here we describe facile synthesis of chromene–pyrone conjugates **7** and chromene–coumarin conjugates **9**. Furthermore, we describe transformation of the chromene–pyrone conjugates **7** to acetoacetyl coumarins and the chromene–coumarin conjugates **9** to 2,3-disubstituted 2,3-dihydrofuro[3,2-*c*]coumarins.

2. Experimental

2.1 General methods

Melting points were recorded using open-ended capillary tubes on VEEGO VMP-DS instrument. The progression of all the reactions was monitored by TLC using a mixture of hexanes (60–80°C boiling mixture) and ethyl acetate. Column chromatography was performed on silica gel (100–200 mesh, SRL Chemicals) using increasing percentage of ethyl acetate in hexanes.

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Scheme 1. Synthesis of 4-methylsulphonyl-4H-chromene **3** and its further transformations.

^1H NMR spectra (400 MHz) and ^{13}C NMR (100 MHz) and DEPT –135 spectra were recorded for DMSO- D_6 + CCl_4 (2:1) solutions on a Bruker –400 spectrometer with tetramethylsilane (TMS) as internal standard; J values are given in Hz. IR spectra were recorded as KBr solid solution on a Nicolet-6700 spectrometer. High resolution mass spectra were recorded on a Waters Micro-mass Q-TOF micro mass spectrometer using electron spray ionization mode. Organic solvents were distilled and dried before use. Melting points were measured in open capillary tubes and are uncorrected. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

2.2 General procedure for synthesis of 4H-chromenyl-2H-pyran-2-ones

2.2a 4-Hydroxy-6-methyl-3-(2-(methylamino)-3-nitro-4H-chromen-4-yl)-2H-pyran-2-one (7a): The solution of *N*-methyl-*N*-[4-(methylsulphonyl)-3-nitro-4H-2-chromenyl]amine **3a** (50 mg, 31 mmol) and 4-hydroxy-6-methyl-2H-pyran-2-one **6** (38 mg, 0.31 mmol) in ethanol (15 mL) was heated to reflux for 5 min by which time the reaction was complete (TLC; hexanes : EtOAc, 6:4). The solid formed was washed with EtOH (5 mL). Analytical samples were obtained through recrystallization from EtOH. Product obtained as colourless crystalline solid. Yield = 98%, mp 149°C; IR (KBr) ν_{max} 3144, 2628, 1698, 1585, 1461, 1405, 1123, 1175, 1060, 988, 866, 761 cm^{-1} ; ^1H NMR (400 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 11.63 (s, 1H), 10.51 (br s, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 4.8 Hz, 2H),

7.14 (d, J = 7.6 Hz, 1H), 5.97 (s, 1H), 5.58 (s, 1H), 3.14 (d, J = 5.2 Hz, 3H), 2.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 165.6 (C), 161.0 (C), 160.5 (C), 160.3 (C), 148.1 (C), 128.4 (CH), 128.2 (CH), 125.5 (CH), 123.6 (C), 115.8 (CH), 105.7 (C), 103.8 (C), 100.4 (CH), 30.9 (CH), 28.1 (CH_3), 19.6 (CH_3) ppm. Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_6$: C, 58.18; H, 4.27; N, 8.48; Found C, 58.16; H, 4.25; N, 8.47.

2.2b 3-(6-Chloro-2-(methylamino)-3-nitro-4H-chromen-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (7b): Colourless crystalline solid, yield 89%, mp 143°C; IR (KBr) ν_{max} 3144, 2628, 1698, 1585, 1461, 1405, 1123, 1175, 1060, 988, 866, 761 cm^{-1} ; ^1H NMR (400 MHz, DMSO- D_6) δ 11.70 (s, 1H), 10.48 (br s, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.12 (s, 1H), 5.98 (s, 1H), 5.57 (s, 1H), 3.14 (d, J = 5.2 Hz, 3H), 2.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- D_6) δ 165.2 (C), 162.3 (C), 160.3 (C), 159.5 (C), 146.7 (C), 128.6 (C), 128.0 (CH), 127.3 (CH), 125.6 (C), 117.7 (CH), 105.3 (C), 103.0 (C), 100.0 (CH), 30.5 (CH), 27.8 (CH_3), 19.2 (CH_3) ppm; Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}_6$: C, 52.69; H, 3.59; N, 7.68; Found C, 52.66; H, 3.52; N, 7.69.

2.2c 3-(6-Bromo-2-(methylamino)-3-nitro-4H-chromen-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (7c): Colourless crystalline solid, yield 94%, mp 151°C; IR (KBr) ν_{max} 3144, 2628, 1698, 1585, 1461, 1405, 1123, 1175, 1060, 988, 866, 761 cm^{-1} ; ^1H NMR (400 MHz, DMSO- D_6) δ 11.70 (s, 1H), 10.48 (br s, 1H), 7.34 (d,

$J = 8.8$ Hz, 1H), 7.27 (d, $J = 8.8$ Hz, 1H), 7.12 (s, 1H), 5.98 (s, 1H), 5.57 (s, 1H), 3.14 (d, $J = 5.2$ Hz, 3H), 2.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- D_6) δ 165.2 (C), 161.2 (C), 159.5 (C), 159.1 (C), 146.7 (C), 128.6 (C), 128.0 (CH), 127.3 (CH), 125.6 (C), 117.7 (CH), 105.1 (C), 103.0 (C), 100.0 (CH), 27.9 (CH), 19.3 (CH₃), 18.5 (CH₃) ppm; Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{BrN}_2\text{O}_6$: C, 46.96; H, 3.20; N, 6.85; Found C, 46.94; H, 3.24; N, 6.83.

2.2d 4-Hydroxy-3-(8-methoxy-2-(methylamino)-3-nitro-4H-chromen-4-yl)-6-methyl-2H-pyran-2-one (**7d**): Colourless crystalline solid, yield 96%, mp 149°C; IR (KBr) ν_{max} 3217, 3078, 2946, 1697, 1648, 1581, 1464, 1397, 1366, 1303, 1243, 1221, 1185, 1064, 986, 893, 867, 775, 635, 604, 553, 511 cm^{-1} ; ^1H NMR (400 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 11.45 (s, 1H), 10.46 (br s, 1H), 7.03 (t, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 7.2$ Hz, 1H), 6.75 (d, $J = 7.6$ Hz, 1H), 5.94 (s, 1H), 5.55 (s, 1H), 3.86 (s, 3H), 3.17 (d, $J = 5.2$ Hz, 3H), 2.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 164.9 (C), 160.3 (C), 159.5 (C), 146.6 (C), 137.5 (C), 137.3 (C), 124.7 (CH), 124.2 (CH), 119.0 (C), 110.4 (CH), 105.0 (C), 103.3 (C), 99.9 (CH), 55.8 (CH₃), 30.5 (CH), 27.7 (CH₃), 19.2 (CH₃) ppm. Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_7$: C, 56.67; H, 4.48; N, 7.77; Found C, 56.64; H, 4.54; N, 7.73.

2.2e 3-(8-Ethoxy-2-(methylamino)-3-nitro-4H-chromen-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (**7e**): Colourless crystalline solid, yield 95%, mp 152°C; IR (KBr) ν_{max} 3172, 2983, 2935, 1670, 1637, 1606, 1503, 1463, 1404, 1372, 1342, 1269, 1211, 1182, 1064, 1024, 958, 812, 774, 724 cm^{-1} ; ^1H NMR (400 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 11.45 (s, 1H), 10.42 (br s, 1H), 6.99 (t, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 7.2$ Hz, 1H), 6.74 (d, $J = 7.6$ Hz, 1H), 5.95 (s, 1H), 5.56 (s, 1H), 4.09 (q, $J = 3.6$ Hz, 2H), 3.18 (d, $J = 4.8$ Hz, 3H), 2.10 (s, 3H), 1.42 (t, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 164.8 (C), 160.3 (C), 159.5 (C), 145.9 (C), 137.5 (C), 124.7 (CH), 124.2 (CH), 121.1 (C), 119.1 (C), 111.5 (CH), 105.0 (C), 103.3 (C), 99.4 (CH), 64.0 (CH₂), 30.6 (CH), 27.5 (CH₃), 19.2 (CH₃), 14.5 (CH₃) ppm. Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_7$: C, 57.75; H, 4.85; N, 7.48; Found C, 57.72; H, 4.89; N, 7.49.

2.2f 4-Hydroxy-3-(6-methoxy-2-(methylamino)-3-nitro-4H-chromen-4-yl)-6-methyl-2H-pyran-2-one (**7f**): Colourless crystalline solid, yield 94%, mp 149°C; IR (KBr) ν_{max} 3217, 3078, 2946, 1697, 1648, 1581,

1464, 1397, 1366, 1303, 1243, 1221, 1185, 1064, 986, 893, 867, 775, 635, 604, 553, 511 cm^{-1} ; ^1H NMR (400 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 11.45 (s, 1H), 10.42 (br s, 1H), 7.03 (t, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 7.2$ Hz, 1H), 6.75 (d, $J = 7.6$ Hz, 1H), 5.94 (s, 1H), 5.55 (s, 1H), 3.86 (s, 3H), 3.17 (d, $J = 4.8$ Hz, 3H), 2.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 164.9 (C), 160.3 (C), 159.5 (C), 146.6 (C), 137.5 (C), 137.3 (C), 124.7 (CH), 124.2 (CH), 119.0 (C), 110.4 (CH), 105.0 (C), 103.3 (C), 99.9 (CH), 55.8 (C), 30.5 (CH), 27.7 (CH₃), 19.2 (CH₃) ppm. Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_7$: C, 56.67; H, 4.48; N, 7.77; Found C, 56.64; H, 4.50; N, 7.77.

2.2g 4-Hydroxy-6-methyl-3-(2-(methylamino)-3,6-dinitro-4H-chromen-4-yl)-2H-pyran-2-one (**7g**): Colourless crystalline solid, yield 98%, mp 151°C; IR (KBr) ν_{max} 3294, 3222, 3066, 2946, 1720, 1656, 1598, 1564, 1527, 1367, 1343, 1253, 1224, 1167, 1135, 1057, 746 cm^{-1} ; ^1H NMR (400 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 11.70 (s, 1H), 10.48 (br s, 1H), 7.34 (d, $J = 8.8$ Hz, 1H), 7.27 (d, $J = 8.8$ Hz, 1H), 7.12 (s, 1H), 5.98 (s, 1H), 5.57 (s, 1H), 3.14 (d, $J = 5.2$ Hz, 3H), 2.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 165.7 (C), 163.2 (C), 161.1 (C), 159.0 (C), 142.9 (C), 137.7 (C), 133.6 (C), 126.0 (CH), 123.1 (C), 123.0 (CH), 114.8 (CH), 106.5 (C), 102.4 (CH), 29.9 (CH), 27.0 (CH₃), 18.4 (CH₃) ppm; Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_8$: C, 51.21; H, 3.49; N, 11.20; Found C, 51.22; H, 3.48; N, 11.23.

2.2h 3-(6,8-Dichloro-2-(methylamino)-3-nitro-4H-chromen-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (**7h**): Colourless crystalline solid, yield 93%, mp 147°C; IR (KBr) ν_{max} 3217, 3078, 2946, 1697, 1648, 1581, 1464, 1397, 1366, 1303, 1243, 1221, 1185, 1064, 986, 893, 867, 775, 635, 604, 553, 511 cm^{-1} ; ^1H NMR (400 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 11.71 (s, 1H), 10.36 (br s, 1H), 7.39 (s, 1H), 7.06 (s, 1H), 5.98 (s, 1H), 5.57 (s, 1H), 3.19 (d, $J = 5.2$ Hz, 3H), 2.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- D_6 + CCl_4 , 2:1) δ 165.7 (C), 163.2 (C), 161.1 (C), 159.0 (C), 142.9 (C), 129.0 (C), 127.9 (C), 127.1 (CH), 126.4 (CH), 121.2 (C), 106.5 (C), 104.5 (C), 102.7 (CH), 30.9 (CH), 28.1 (CH₃), 19.4 (CH₃) ppm. Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_6$: C, 48.14; H, 3.03; N, 7.02; Found C, 48.11; H, 3.04; N, 7.03.

2.2i 3-(8-bromo-6-chloro-2-(methylamino)-3-nitro-4H-chromen-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (**7i**): Colourless crystalline solid, yield 92%, mp 142°C; IR (KBr) ν_{max} 3215, 3081, 2942, 2653, 1691, 1651, 1586,

1458, 1397, 1284, 1241, 1219, 1196, 1102, 1063, 1019, 990, 894, 869, 835, 811, 791, 777, 729 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-D}_6 + \text{CCl}_4$, 2:1) δ 11.81 (s, 1H), 10.34 (br s, 1H), 7.51 (s, 1H), 7.11 (s, 1H), 5.98 (s, 1H), 5.58 (s, 1H), 3.21 (d, $J = 5.2$ Hz, 3H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO-D}_6 + \text{CCl}_4$, 2:1) δ 165.7 (C), 163.2 (C), 161.1 (C), 158.9 (C), 142.9 (C), 129.0 (C), 127.9 (C), 127.1 (CH), 126.4 (CH), 121.2 (C), 104.5 (C), 102.7 (C), 100.2 (CH), 30.9 (CH), 28.1 (CH_3), 19.4 (CH_3) ppm. Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{BrClN}_2\text{O}_6$: C, 43.32; H, 2.73; N, 6.31; Found C, 43.33; H, 2.70; N, 6.34.

2.2j 3-(6,8-Dibromo-2-(methylamino)-3-nitro-4H-chromen-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (**7j**): Colourless crystalline solid, yield 95%, mp 158°C; IR (KBr) ν_{max} 3205, 3085, 2981, 2690, 2639, 1644, 1491, 1404, 1370, 1338, 1215, 1179, 1119, 1086, 1026, 998, 965, 883, 842, 769, 742, 692 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-D}_6 + \text{CCl}_4$, 2:1) δ 11.79 (s, 1H), 10.34 (br s, 1H), 7.61 (s, 1H), 7.24 (s, 1H), 5.98 (s, 1H), 5.58 (s, 1H), 3.22 (d, $J = 5.2$ Hz, 3H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO-D}_6 + \text{CCl}_4$, 2:1) δ 165.5 (C), 163.0 (C), 160.9 (C), 159.0 (C), 144.3 (C), 133.1 (C), 129.8 (CH), 127.3 (CH), 116.7 (C), 110.2 (C), 104.5 (C), 102.7 (C), 100.1 (CH), 30.9 (CH), 28.2 (CH_3), 19.4 (CH_3) ppm. Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}_6$: C, 39.37; H, 2.48; N, 5.74; Found C, 39.34; H, 2.46; N, 5.75.

2.3 General procedure for synthesis of 3(Z)-3-(1-hydroxy-3-oxobut-1-enyl)-2H-chromen-2-ones **10a-j**

2.3a (Z)-3-(1-Hydroxy-3-oxobut-1-enyl)-2H-chromen-2-one (**10a**): The solution 4-hydroxy-6-methyl-3-(2-(methylamino)-3-nitro-4H-chromen-4-yl)-2H-pyran-2-one (**7a**) (0.050 g, 0.243 mmol) in ethanol (15 mL) was heated to reflux for 2 h by which time the reaction was complete (TLC; hexanes : EtOAc, 6:4). Reaction mixture was purified through column chromatography by eluting with hexanes and ethylacetates mixtures (7.5:2.5). Analytical samples were obtained through recrystallization from chloroform. Colourless crystalline solid, yield 93%, mp 132°C; IR (KBr) ν_{max} 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.73 (s, 1H), 8.53 (s, 1H), 7.77–7.16 (m, 4H), 6.98 (s, 1H), 2.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 200.2 (C), 171.1 (C), 157.5 (C), 153.3 (C), 144.0 (CH), 136.6 (C), 131.6 (CH), 125.1 (CH), 120.1 (CH), 118.4 (C), 117.6 (CH), 102.0 (CH), 27.8 (CH_3) ppm. Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{O}_4$: C, 67.82; H, 4.38; found C, 67.84; H, 4.37.

2.3b (Z)-6-Chloro-3-(1-hydroxy-3-oxobut-1-enyl)-2H-chromen-2-one (**10b**): Light yellow colour crystalline solid, yield 88%, mp 135°C; IR (KBr) ν_{max} 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.76 (s, 1H), 8.54 (s, 1H), 7.77 (s, 1H), 7.70 (d, $J = 8.6$ Hz, 1H), 7.24 (d, $J = 8.2$ Hz, 1H), 6.99 (s, 1H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 200.2 (C), 171.1 (C), 157.5 (C), 153.3 (C), 144.0 (CH), 136.6 (CH), 131.6 (CH), 126.2 (C), 120.1 (C), 118.4 (CH), 117.6 (C), 102.0 (CH), 27.8 (CH_3) ppm. Anal. Calcd for $\text{C}_{13}\text{H}_9\text{ClO}_4$: C, 59.00; H, 3.43; Found: C, 58.97; H, 3.44.

2.3c (Z)-6-Bromo-3-(1-hydroxy-3-oxobut-1-enyl)-2H-chromen-2-one (**10c**): Light yellow colour crystalline solid, yield 82%, mp 131°C; IR (KBr) ν_{max} 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.76 (s, 1H), 8.54 (s, 1H), 7.77 (s, 1H), 7.70 (d, $J = 8.6$ Hz, 1H), 7.24 (d, $J = 8.6$ Hz, 1H), 6.99 (s, 1H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 200.2 (C), 171.1 (C), 157.5 (C), 153.3 (C), 144.0 (CH), 136.6 (CH), 131.6 (CH), 121.8 (C), 120.1 (C), 118.4 (CH), 117.6 (C), 102.0 (CH), 27.8 (CH_3) ppm. Anal. Calcd for $\text{C}_{13}\text{H}_9\text{BrO}_4$: C, 50.51; H, 2.93; Found C, 50.53; H, 2.89.

2.3d (Z)-3-(1-Hydroxy-3-oxobut-1-enyl)-8-methoxy-2H-chromen-2-one (**10d**): Light yellow colour crystalline solid, yield 96%, mp 136°C; IR (KBr) ν_{max} 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.85 (s, 1H), 8.63 (s, 1H), 7.29–7.16 (m, 3H), 7.05 (s, 1H), 3.99 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 199.9 (C), 172.0 (C), 157.6 (C), 147.1 (C), 145.7 (CH), 144.2 (C), 124.9 (CH), 120.9 (CH), 120.8 (C), 119.3 (C), 115.5 (CH), 106.0 (C), 101.8 (CH), 56.4 (CH_3), 27.6 (CH_3) ppm. Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{O}_5$: C, 64.61; H, 4.65; Found C, 64.57; H, 4.59.

2.3e (Z)-8-Ethoxy-3-(1-hydroxy-3-oxobut-1-enyl)-2H-chromen-2-one (**10e**): Light yellow colour crystalline solid, yield 94%, mp 132°C; IR (KBr) ν_{max} 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.85 (s, 1H), 8.63 (s, 1H), 7.29–7.16 (m, 3H), 7.05 (s, 1H), 3.99 (q, $J = 4.2$ Hz, 2H), 2.27 (s, 3H), 2.13 (t, $J = 4.2$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 199.9 (C), 172.0 (C), 157.6 (C), 147.1 (C), 145.7 (C), 144.2 (CH), 124.9 (CH), 120.9 (C), 119.3 (CH), 115.5 (C), 106.0 (C), 101.8 (CH), 56.4 (CH_2), 27.6 (CH_3), 21.2 (CH_3) ppm.

Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15; Found C, 65.67; H, 5.13.

2.3f (Z)-3-(1-Hydroxy-3-oxobut-1-enyl)-6-methoxy-2H-chromen-2-one (**10f**): Light yellow colour crystalline solid, yield 92%, mp 121°C; IR (KBr) $\nu_{\max}$ 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.79 (s, 1H), 8.55 (s, 1H), 7.23–7.15 (m, 2H), 6.99 (s, 1H), 6.98 (s, 1H), 3.82 (s, 3H), 2.22 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 199.9 (C), 172.1 (C), 158.3 (C), 156.5 (C), 149.2 (C), 145.3 (CH), 122.6 (CH), 120.9 (C), 118.9 (CH), 117.0 (C), 110.7 (CH), 101.8 (CH), 56.0 (CH_3), 27.7 (CH_3) ppm. Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65; Found C, 64.60; H, 4.64.

2.3g (Z)-3-(1-Hydroxy-3-oxobut-1-enyl)-6-nitro-2H-chromen-2-one (**10g**): Yellow colour crystalline solid, yield 89%, mp 142°C; IR (KBr) $\nu_{\max}$ 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.71 (s, 1H), 8.70 (s, 1H), 8.58 (s, 1H), 8.49 (d, $J = 9.0$ Hz, 1H), 7.51 (d, $J = 9.1$ Hz, 1H), 6.98 (s, 1H), 2.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 200.2 (C), 171.1 (C), 157.5 (C), 153.3 (C), 144.0 (CH), 136.6 (CH), 131.6 (CH), 121.8 (C), 120.1 (C), 118.4 (CH), 117.6 (C), 102.0 (CH), 27.8 (CH_3) ppm. Anal. Calcd for $C_{13}H_9NO_6$: C, 56.73; H, 3.30; N, 5.09; Found C, 56.72; H, 3.28; N, 5.10.

Crystal data for 10g: Crystals obtained from CHCl_3 , Empirical formula, $C_{13}H_9NO_6$; formula weight, 275.21; crystal colour, habit: colourless, plate; crystal dimensions, $0.4 \times 0.32 \times 0.2 \text{ mm}^3$; Crystal system, triclinic; lattice type, primitive; lattice parameters $a = 7.4591(13) \text{ \AA}$, $b = 8.2178(19) \text{ \AA}$, $c = 10.0087(18) \text{ \AA}$; $\alpha = 85.202(17)^\circ$, $\beta = 77.346(15)^\circ$, $\gamma = 89.278(17)^\circ$; $V = 596.5(2) \text{ \AA}^3$, space group, $P-1$; $Z = 2$; $D_{\text{calcd}} = 1.532 \text{ g/cm}^3$; $F_{000} = 284.0$; $\lambda(\text{Mo K}\alpha) = 0.71073 \text{ \AA}$; $R(I > 2\sigma_1) = 0.0479$, $wR^2 = 0.1414$.

Crystallographic data (excluding structure factors) for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 904105. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

2.3h (Z)-6,8-Dichloro-3-(1-hydroxy-3-oxobut-1-enyl)-2H-chromen-2-one (**10h**): Light yellow colour crystalline solid, yield 91%, mp 144°C; IR (KBr) $\nu_{\max}$ 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060,

885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.71 (s, 1H), 8.52 (s, 1H), 7.66 (s, 1H), 7.53 (s, 1H), 6.99 (s, 1H), 2.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 200.5 (C), 170.4 (C), 156.4 (C), 148.7 (C), 143.6 (CH), 133.6 (CH), 130.2 (C), 127.1 (CH), 122.7 (C), 122.6 (C), 120.4 (C), 102.3 (CH), 27.9 (CH_3) ppm. Anal. Calcd for $C_{13}H_8Cl_2O_4$: C, 52.20; H, 2.70; Found C, 52.23; H, 2.69.

2.3i (Z)-8-Bromo-6-chloro-3-(1-hydroxy-3-oxobut-1-enyl)-2H-chromen-2-one (**10i**): Light yellow colour crystalline solid, yield 87%, mp 148°C; IR (KBr) $\nu_{\max}$ 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.71 (s, 1H), 8.50 (s, 1H), 7.81 (s, 1H), 7.57 (s, 1H), 6.98 (s, 1H), 2.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 200.5 (C), 170.3 (C), 156.5 (C), 149.8 (C), 143.6 (C), 136.5 (CH), 130.5 (CH), 127.8 (C), 122.5 (CH), 120.3 (C), 110.9 (C), 102.2 (CH), 27.9 (CH_3) ppm. Anal. Calcd for $C_{13}H_8BrClO_4$: C, 45.45; H, 2.35; Found C, 45.43; H, 2.36.

2.3j (Z)-6,8-Dibromo-3-(1-hydroxy-3-oxobut-1-enyl)-2H-chromen-2-one (**10j**): Light yellow colour crystalline solid, yield 88%, mp 149°C; IR (KBr) $\nu_{\max}$ 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 15.72 (s, 1H), 8.50 (s, 1H), 7.95 (s, 1H), 7.72 (s, 1H), 6.98 (s, 1H), 2.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 200.5 (C), 170.4 (C), 156.5 (C), 150.2 (C), 143.5 (CH), 139.1 (CH), 130.8 (CH), 122.6 (C), 120.8 (C), 117.5 (C), 111.2 (C), 102.3 (CH), 27.9 (CH_3) ppm. Anal. Calcd for $C_{13}H_8Br_2O_4$: C, 40.24; H, 2.08; Found C, 40.22; H, 2.06.

2.4 General procedure for synthesis of 4-hydroxy-2'-(methylamino)-3'-nitro-2H, 4'H-[3,4'-bichromen]-2-ones **9a-j**

2.4a 4-Hydroxy-2'-(methylamino)-3'-nitro-2H,4'H-[3,4'-bichromen]-2-one (**9a**): The solution of *N*-methyl-*N*-[4-(methylsulphonyl)-3-nitro-4H-2-chromenyl]amine **3a** (0.05 g, 0.308 mmol) and 4-hydroxy coumarin **9a** (0.077 g, 0.308 mmol) in ethanol (15 mL) was heated to reflux for 5 min by which time the reaction was complete (TLC; hexanes : EtOAc, 6:4). The solid formed was washed with EtOH (5 mL). Analytical samples were obtained through recrystallization from EtOH. Colourless crystalline solid, yield 97%, mp 121°C, IR (KBr) $\nu_{\max}$ 3229, 2939, 1708, 1567, 1463, 1352, 1159, 1102, 1065, 871, 761 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.87 (s, 1H), 10.58 (br s, 1H), 8.01

(d, $J = 5.2$ Hz, 1H), 7.49 (t, $J = 8.4$ Hz, 1H), 7.27 (t, $J = 9.2$ Hz, 2H), 7.22 (t, $J = 7.67$ Hz, 2H), 7.14 (d, $J = 7.6$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 5.91 (s, 1H), 3.24 (d, $J = 5.2$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- D_6) δ 161.3 (C), 160.0 (C), 159.7 (C), 152.0 (C), 148.1 (C), 132.1 (CH), 128.3 (CH), 128.2 (CH), 125.2 (CH), 124.0 (CH), 123.7 (CH), 122.8 (C), 116.17 (CH), 116.12 (CH), 115.3 (C), 106.4 (C), 105.0 (C), 31.5 (CH), 27.7 (CH_3) ppm; Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_6$: C, 62.30; H, 3.85; N, 7.65; Found: C, 62.28; H, 3.83; N, 7.62.

2.4b *6'-Chloro-4-hydroxy-2'-(methylamino)-3'-nitro-2H, 4'H-[3,4'-bichromen]-2-one (9b)*: Colourless crystalline solid, yield 97%, mp 143°C ; IR (KBr) ν_{max} 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, DMSO- $\text{D}_6 + \text{CCl}_4$, 2:1) δ 11.87 (s, 1H), 10.53 (br s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.51 (t, $J = 7.0$ Hz, 1H), 7.28 (t, $J = 7.4$ Hz, 1H), 7.23–7.14 (m, 4H), 5.89 (s, 1H), 3.21 (d, $J = 5.2$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- $\text{D}_6 + \text{CCl}_4$, 2:1) δ 165.6 (C), 164.6 (C), 157.4 (C), 152.2 (C), 136.6 (C), 134.1 (CH), 133.0 (CH), 132.8 (CH), 130.1 (CH), 129.1 (CH), 128.6 (CH), 127.7 (C), 122.4 (C), 121.1 (CH), 114.2 (C), 109.7 (C), 100.8 (C), 36.7 (CH), 33.0 (CH_3) ppm; Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{ClN}_2\text{O}_6$: C, 56.94; H, 3.27; N, 6.99; Found C, 56.89; H, 3.23; N, 6.97.

2.4c *6'-Bromo-4-hydroxy-2'-(methylamino)-3'-nitro-2H, 4'H-[3,4'-bichromen]-2-one (9c)*: Colourless crystalline solid, yield 95%; mp 143°C ; IR (KBr) ν_{max} 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm^{-1} ; ^1H NMR (400 MHz, DMSO- $\text{D}_6 + \text{CCl}_4$, 2:1) δ 11.8 (s, 1H), 10.53 (br s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.51 (t, $J = 7.0$ Hz, 1H), 7.28 (t, $J = 7.4$ Hz, 1H), 7.24–7.14 (m, 4H), 5.89 (s, 1H), 3.21 (d, $J = 5.2$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- $\text{D}_6 + \text{CCl}_4$, 2:1) δ 165.6 (C), 164.6 (C), 157.4 (C), 152.2 (C), 136.6 (CH), 134.1 (CH), 133.0 (CH), 132.8 (CH), 130.1 (CH), 129.1 (CH), 128.6 (CH), 128.5 (C), 122.4 (C), 121.1 (C), 114.2 (C), 109.7 (C), 100.8 (C), 36.7 (CH), 33.0 (CH_3) ppm; Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{BrN}_2\text{O}_6$: C, 51.26; H, 2.94; N, 6.29; Found C, 51.19, H, 2.91; N, 6.25.

2.4d *4-Hydroxy-8'-methoxy-2'-(methylamino)-3'-nitro-2H,4'H-[3,4'-bichromen]-2-one (9d)*: Colourless crystalline solid, yield 96%, mp 143°C ; IR (KBr) ν_{max} 3599, 3189, 2969, 2837, 1705, 1648, 1621, 1568, 1475, 1447, 1398, 1355, 1292, 1235, 1163, 1195, 1099, 1069, 961, 813, 771, 692 cm^{-1} ; ^1H NMR (400 MHz, DMSO-

$\text{D}_6 + \text{CCl}_4$, 2:1) δ 11.21 (s, 1H), 10.52 (br s, 1H), 7.96 (d, $J = 6.8$ Hz, 1H), 7.53–7.48 (m, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.21 (d, $J = 6.4$ Hz, 1H), 6.99 (t, $J = 6.4$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.72 (d, $J = 6.4$ Hz, 1H), 5.85 (s, 1H), 3.85 (s, 3H), 3.20 (d, $J = 4.2$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- $\text{D}_6 + \text{CCl}_4$, 2:1) δ 160.5 (C), 159.7 (C), 152.2 (C), 146.9 (C), 137.8 (CH), 131.8 (CH), 128.2 (CH), 127.7 (C), 125.1 (C), 124.7 (C), 123.8 (C), 122.8 (CH), 119.4 (CH), 116.4 (CH), 116.2 (CH), 110.9 (C), 104.1 (C), 56.1 (CH_3), 31.8 (CH), 28.0 (CH_3) ppm; Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_7$: C, 60.61; H, 4.07; N, 7.07; Found: C, 60.62; H, 4.06; N, 7.04.

2.4e *8'-Ethoxy-4-hydroxy-2'-(methylamino)-3'-nitro-2H, 4'H-[3,4'-bichromen]-2-one (9e)*: Colourless crystalline solid, yield 97%, mp 141°C ; IR (KBr) ν_{max} 3190, 3073, 2978, 2934, 2873, 1675, 1636, 1604, 1568, 1496, 1472, 1404, 1367, 1340, 1276, 1205, 1184, 1095, 1065, 959, 936, 819 cm^{-1} ; ^1H NMR (400 MHz, DMSO- $\text{D}_6 + \text{CCl}_4$, 2:1) δ 11.31 (s, 1H), 10.49 (br s, 1H), 7.98 (d, $J = 6.2$ Hz, 1H), 7.54–7.49 (m, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.21 (d, $J = 6.4$ Hz, 1H), 6.96 (t, $J = 6.4$ Hz, 1H), 6.86 (d, $J = 7.6$ Hz, 1H), 6.72 (d, $J = 7.6$ Hz, 1H), 5.84 (s, 1H), 4.08 (q, $J = 4.8$ Hz, 2H), 3.20 (d, $J = 5.2$ Hz, 3H), 1.41 (t, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- $\text{D}_6 + \text{CCl}_4$, 2:1) δ 160.4 (C), 159.7 (C), 152.2 (C), 146.2 (C), 131.8 (CH), 129.1 (CH), 128.2 (C), 128.0 (CH), 127.2 (CH), 126.1 (CH), 125.0 (CH), 123.9 (C), 123.8 (C), 119.4 (C), 116.4 (CH), 116.1 (C), 112.0 (C), 64.4 (CH_2), 31.8 (CH), 27.9 (CH_3), 14.8 (CH_3) ppm; Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_7$: C, 61.46; H, 4.42; N, 6.83; Found: C, 61.42; H, 4.39; N, 6.81.

2.4f *4-Hydroxy-6'-methoxy-2'-(methylamino)-3'-nitro-2H,4'H-[3,4'-bichromen]-2-one (9f)*: Colourless crystalline solid, yield 93%, mp 143°C ; IR (KBr) ν_{max} 3190, 3073, 2978, 2934, 2873, 1675, 1636, 1604, 1568, 1496, 1472, 1404, 1367, 1340, 1276, 1205, 1184, 1095, 1065, 959, 936, 819 cm^{-1} ; ^1H NMR (400 MHz, DMSO- $\text{D}_6 + \text{CCl}_4$, 2:1) δ 11.21 (s, 1H), 10.52 (br s, 1H), 7.96 (d, $J = 6.8$ Hz, 1H), 7.53–7.48 (m, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.21 (d, $J = 4.4$ Hz, 1H), 6.99 (t, $J = 6.4$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.72 (d, $J = 3.2$ Hz, 1H), 5.85 (s, 1H), 3.85 (s, 3H), 3.20 (d, $J = 4.2$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- $\text{D}_6 + \text{CCl}_4$, 2:1) δ 160.5 (C), 159.7 (C), 152.2 (C), 146.9 (C), 137.8 (C), 131.8 (CH), 128.2 (CH), 127.7 (C), 125.1 (C), 124.7 (CH), 123.8 (CH), 122.8 (CH), 119.4 (CH), 116.4 (C), 116.2 (CH), 110.9 (C), 104.1 (C), 56.1 (CH_3), 31.8 (CH), 28.0 (CH_3) ppm; Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_7$:

C, 60.61; H, 4.07; N, 7.07; Found: C, 60.62; H, 4.09; N, 7.04.

2.4g 4-Hydroxy-2'-(methylamino)-3',6'-dinitro-2H,4'H-[3,4'-bichromen]-2-one (**9g**): Colourless crystalline solid, yield 97%, mp 151°C IR (KBr) $\nu_{\max}$ 3184, 1692, 1621, 1566, 1462, 1377, 1260, 1179, 1060, 885, 765 cm⁻¹; ¹H NMR (400 MHz, DMSO-D₆ + CCl₄, 2:1) δ 11.80 (s, 1H), 10.53 (br s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.24–7.14 (m, 4H), 5.89 (s, 1H), 3.21 (d, *J* = 4.8 Hz, 3H) ppm; ¹³C NMR (100 MHz, DMSO-D₆ + CCl₄, 2:1) δ 165.6 (C), 164.6 (C), 157.4 (C), 152.2 (C), 136.6 (C), 134.1 (CH), 133.0 (CH), 132.8 (C), 130.1 (C), 129.1 (CH), 128.6 (CH), 127.3 (CH), 122.4 (CH), 121.1 (C), 109.7 (CH), 100.8 (C), 36.7 (CH), 33.0 (CH₃) ppm; Anal. Calcd for C₁₉H₁₃N₃O₈: C, 55.48; H, 3.19; N, 10.22; Found C, 55.42; H, 3.21; N, 10.19.

2.4h 6',8'-Dichloro-4-hydroxy-2'-(methylamino)-3'-nitro-2H,4'H-[3,4'-bichromen]-2-one (**9h**): Colourless crystalline solid, yield 93%, mp 145°C, IR (KBr) $\nu_{\max}$ 3178, 3085, 2940, 1662, 1629, 1572, 1497, 1457, 1403, 1364, 1289, 1168, 1107, 1064, 950, 813, 760 cm⁻¹; ¹H NMR (400 MHz, DMSO-D₆ + CCl₄, 2:1) δ 12.07 (s, 1H), 10.42 (br s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.58 (t, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 15.2 Hz, 1H), 7.16 (s, 1H), 5.93 (s, 1H), 3.24 (d, *J* = 4.8 Hz, 3H) ppm; ¹³C NMR (100 MHz, DMSO-D₆ + CCl₄, 2:1) δ 161.7 (C), 158.8 (C), 156.5 (C), 152.1 (C), 144.1 (C), 131.9 (CH), 130.1 (CH), 129.0 (C), 127.4 (C), 126.3 (CH), 125.5 (C), 123.8 (CH), 123.6 (CH), 116.0 (CH), 109.9 (C), 102.2 (C), 96.3 (C), 31.9 (CH), 28.2 (CH₃) ppm; Anal. Calcd for C₁₉H₁₂Cl₂N₂O₆: C, 52.43; H, 2.78; N, 6.44; Found C, 52.40; H, 2.74; N, 6.43.

2.4i 8'-bromo-6'-chloro-4-hydroxy-2'-(methylamino)-3'-nitro-2H,4'H-3,4'-bichromen-2-one (**9i**): Colourless crystalline solid, yield 92%, mp 158°C, IR (KBr) $\nu_{\max}$ 3170, 3089, 2912, 1660, 1633, 1555, 1437, 1444, 1403, 1363, 1281, 1118, 1107, 1064, 950, 813, 762 cm⁻¹; ¹H NMR (400 MHz, DMSO-D₆ + CCl₄, 2:1) δ 12.15 (s, 1H), 10.42 (br s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.57 (t, *J* = 8.4 Hz, 1H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.16 (s, 1H), 5.93 (s, 1H), 3.33 (d, *J* = 5.2 Hz, 3H) ppm; ¹³C NMR (100 MHz, DMSO-D₆ + CCl₄, 2:1) δ 160.7 (C), 158.8 (C), 156.4 (C), 152.1 (C), 144.1 (C), 131.9 (CH), 130.7 (CH), 129.2 (C), 129.0 (C), 127.0 (C), 126.3 (CH), 123.8 (CH), 123.6 (CH), 116.0 (CH), 109.9 (C),

103.3 (C), 94.2 (C), 31.9 (CH), 28.2 (CH₃) ppm; Anal. Calcd for C₁₉H₁₂BrClN₂O₆: C, 47.58; H, 2.52; N, 5.84; Found C, 47.46; H, 2.58; N, 5.82.

2.4j 6',8'-Dibromo-4-hydroxy-2'-(methylamino)-3'-nitro-2H,4'H-3,4'-bichromen-2-one (**9j**): Colourless crystalline solid, yield 95%, mp 158°C, IR (KBr) $\nu_{\max}$ 3178, 3082, 2946, 1662, 1630, 1569, 1497, 1455, 1404, 1365, 1279, 1231, 1200, 1108, 1065, 943, 794 cm⁻¹; ¹H NMR (400 MHz, DMSO-D₆ + CCl₄, 2:1) δ 12.13 (s, 1H), 10.42 (br s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.74 (s, 1H), 7.57 (t, *J* = 8.4 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 7.29–7.27 (m, 2H), 5.93 (s, 1H), 3.25 (d, *J* = 4.2 Hz, 3H) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆ + CCl₄, 2:1) δ 160.7 (C), 158.7 (C), 156.4 (C), 152.1 (C), 144.6 (C), 133.3 (CH), 131.9 (CH), 129.9 (C), 129.0 (C), 126.7 (C), 123.8 (CH), 123.6 (CH), 116.5 (CH), 116.0 (CH), 110.2 (C), 104.3 (C), 96.5 (C), 31.8 (CH), 28.2 (CH₃) ppm; Anal. Calcd C₁₉H₁₂Br₂N₂O₆: C, 43.54; H, 2.31; N, 5.34; Found C, 43.52; H, 2.39; N, 5.34.

2.5 General procedure for synthesis of trans-3-(2-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromen-2-yl butyrate **16a**

2.5a Trans-propyl 3-(2-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (**16a**): The solution of *N*-methyl-*N*-[4-(methylsulphonyl)-3-nitro-4H-2-chromenyl]amine **3a** (0.05 g, 0.308 mmol) and 4-hydroxy coumarin **9** (0.077 g, 0.308 mmol) in Propanol (15 mL) was heated to reflux for 30 min by which time the reaction was complete (TLC; hexanes : EtOAc, 7:3). Reaction mixture was purified through column chromatography by eluting with hexanes and ethylacetates mixtures (7.5:2.5). Analytical samples were obtained through recrystallization from chloroform. Colourless crystalline solid, Yield 69%, mp 139°C, IR (KBr) $\nu_{\max}$ 3528, 2968, 2835, 1723, 1650, 1610, 1481, 1449, 1405, 1280, 1203, 1082, 1022, 929, 752 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.13–7.10 (m, 2H), 6.9–6.8 (m, 2H), 5.51 (d, *J* = 4.5 Hz, 1H), 5.12 (d, *J* = 4.5 Hz, 1H), 4.23–4.19 (m, 2H), 1.70 (q, *J* = 6.0 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3 H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 169.4 (C), 167.0 (C), 161.3 (C), 155.1 (C), 154.1 (C), 133.2 (CH), 129.3 (CH), 126.7 (CH), 126.5 (C), 124.6 (CH), 123.2 (CH), 121.5 (CH), 118.4 (CH), 117.2 (CH), 112.3 (C), 105.0 (C), 88.1 (CH), 68.1 (CH₂), 44.2 (CH), 21.9 (CH₂), 10.3 (CH₃) ppm; HRMS (ESI, *m/z*) 389.1004. Calcd

for $C_{21}H_{18}O_6(M+Na)$ found 389.1006. Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95; Found: C, 68.82; H, 4.96.

2.5b *Trans-propyl 3-(5-chloro-2-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16b)*: Colourless crystalline solid, Yield 64%, mp 168°C, IR (KBr) $\nu_{\max}$ 3494, 3059, 2971, 2933, 1725, 1655, 1610, 1571, 1470, 1453, 1421, 1406, 1331, 1249, 1026, 990, 768, 655 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, $J = 7.6$ Hz, 1H), 7.82 (s, 1H), 7.67 (t, $J = 7.6$ Hz, 1H), 7.46 (d, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.02 (d, $J = 6.4$ Hz, 1H), 7.02 (d, $J = 6.4$ Hz, 1H), 6.95 (s, 1H), 6.69 (d, $J = 8.4$ Hz, 1H), 5.37 (d, $J = 4.4$ Hz, 1H), 5.12 (d, $J = 4.4$ Hz, 1H), 4.26–4.18 (m, 2H), 1.74–1.62 (m, 2H), 0.93 (t, $J = 4.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0 (C), 168.1 (C), 161.7 (C), 155.2 (C), 153.1 (C), 133.6 (CH), 129.0 (CH), 127.6 (C), 126.3 (CH), 125.6 (C), 124.9 (CH), 123.4 (CH), 118.8 (CH), 117.3 (CH), 112.1 (C), 104.1 (C), 88.5 (CH), 68.1 (CH_2), 43.6 (CH), 21.9 (CH_2), 10.3 (CH_3) ppm; HRMS (ESI, m/z) 423.0611 calcd for $C_{21}H_{17}ClO_6$ (M+Na) found 423.0611. Anal. Calcd for $C_{21}H_{17}ClO_6$: C, 62.93; H, 4.28; Found C, 62.90; H, 4.27.

2.5c *Trans-propyl 3-(5-bromo-2-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16c)*: Colourless crystalline solid, Yield 77%, mp 131°C, IR (KBr) $\nu_{\max}$ 3423, 2968, 2880, 1727, 1648, 1587, 1574, 1493, 1456, 1408, 1325, 1272, 1178, 1095, 1030, 993, 931, 899, 855, 805, 755, 622 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 7.66 (t, $J = 8.4$ Hz, 1H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.08 (d, $J = 8.4$ Hz, 1H), 7.02 (s, 1H), 6.53 (d, $J = 8.6$ Hz, 1H), 5.29 (d, $J = 8.6$ Hz, 1H), 5.15 (d, $J = 4.6$ Hz, 1H), 4.26–4.15 (m, 2H), 1.68 (q, $J = 7.0$ Hz, 2H), 0.93 (t, $J = 7.4$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (C), 168.0 (C), 161.6 (C), 155.1 (C), 153.5 (C), 133.5 (CH), 131.8 (CH), 129.0 (CH), 127.8 (C), 124.7 (CH), 123.3 (CH), 122.2 (C), 118.9 (CH), 117.2 (CH), 112.0 (C), 103.9 (C), 88.6 (CH), 67.9 (CH_2), 43.3 (CH_3), 21.8 (CH_2), 10.1 (CH_3) ppm; HRMS (ESI, m/z) 467.0106 calcd for $C_{21}H_{17}BrO_6$ (M+Na) found 467.0106. Anal. Calcd for $C_{21}H_{17}BrO_6$: C, 56.65; H, 3.85; Found: C, 56.63; H, 3.82.

2.5d *Trans-propyl 3-(2-hydroxy-3-methoxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16d)*: Colourless crystalline solid, Yield 77%, mp 143°C, IR (KBr) $\nu_{\max}$ 3534, 2967, 1722, 1654, 1606, 1484, 1407, 1341, 1271, 1341, 1209, 1079, 1033, 933,

756 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, $J = 8.4$ Hz, 1H), 7.59 (t, $J = 5.2$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 6.81 (dd, $J = 6.2$, 1.2 Hz, 2H), 6.73 (t, $J = 6.0$ Hz, 1H), 5.92 (s, 1H), 5.37 (d, $J = 5.2$ Hz, 1H), 5.08 (d, $J = 5.2$ Hz, 1H), 4.27–4.14 (m, 2H), 3.81 (s, 3H), 1.70 (d, $J = 7.2$ Hz, 2H), 0.95 (t, $J = 7.6$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C), 166.8 (C), 159.6 (C), 155.4 (C), 146.9 (C), 143.7 (C), 133.4 (CH), 133.1 (CH), 132.8 (CH), 124.7 (C), 124.1 (CH), 123.2 (CH), 122.2 (C), 120.1 (CH), 117.0 (CH), 112.4 (C), 104.1 (CH), 88.3 (CH), 67.7 (CH_2), 56.2 (CH_3), 45.4 (CH), 22.0 (CH_2), 10.3 (CH_3) ppm; HRMS (ESI, m/z) 419.1107 calcd for $C_{22}H_{20}O_7$ (M+Na) found 419.1105. Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09; Found: C, 66.63; H, 5.06.

2.5e *Trans-propyl 3-(3-ethoxy-2-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16e)*: Colourless crystalline solid, Yield 70%, mp 166°C, IR (KBr) $\nu_{\max}$ 3289, 2970, 2936, 2889, 1747, 1716, 1643, 1606, 1499, 1483, 1472, 1415, 1279, 1193, 1176, 1067, 1026, 949, 807 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, $J = 7.6$ Hz, 1H), 7.61 (t, $J = 1.08$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 6.81 (dd, $J = 4.2$, 1.2 Hz, 2H), 6.73 (t, $J = 6.2$ Hz, 1H), 5.92 (s, 1H), 5.37 (d, $J = 5.2$ Hz, 1H), 5.08 (d, $J = 5.2$ Hz, 1H), 4.27–4.14 (m, 2H), 4.08 (q, $J = 6.8$ Hz, 2H), 1.73–1.68 (m, 2H), 1.41 (t, $J = 6.9$ Hz, 3H), 0.97 (t, $J = 7.4$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C), 166.8 (C), 159.6 (C), 155.4 (C), 146.2 (C), 143.8 (C), 132.8 (CH), 124.7 (CH), 124.1 (C), 123.2 (CH), 120.6 (CH), 120.1 (CH), 117.0 (CH), 112.4 (C), 111.2 (CH), 104.1 (C), 88.4 (CH), 67.7 (CH_2), 64.7 (CH_2), 45.6 (CH), 22.0 (CH_2), 14.9 (CH_3), 10.3 (CH_3) ppm; HRMS (ESI, m/z) 433.1263 calcd for $C_{23}H_{22}O_7$ (M+Na) found 433.1266. Anal. Calcd for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40; Found C, 67.29; H, 5.41.

2.5f *Trans-propyl 3-(2-hydroxy-5-methoxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16f)*: Colourless crystalline solid, Yield 68%, mp 161°C, IR (KBr) $\nu_{\max}$ 3534, 3099, 2965, 1752, 1723, 1654, 1482, 1329, 1272, 1249, 1075, 1033, 980, 970, 760 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, $J = 8.4$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 6.81 (dd, $J = 5.6$, 1.2 Hz, 2H), 6.73 (t, $J = 6.0$ Hz, 1H), 5.92 (s, 1H), 5.37 (d, $J = 5.2$ Hz, 1H), 5.36 (d, $J = 5.2$ Hz, 1H), 5.08 (d, $J = 4.2$ Hz, 1H), 4.27–4.14 (m, 2H), 3.81 (s, 3H), 1.70 (d, $J = 7.2$ Hz, 2H), 0.95 (t, $J = 7.6$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C), 166.8 (C), 159.6 (C), 155.4 (C), 146.9 (C), 143.7 (C), 132.8 (CH), 124.7

(C), 124.1 (CH), 123.2 (CH), 122.9 (C), 120.6 (CH), 120.1 (CH), 117.0 (CH), 112.4 (C), 110.4 (CH), 88.3 (CH), 67.7 (CH₂), 56.2 (CH₃), 45.4 (CH), 22.0 (CH₂), 10.3 (CH₃) ppm; HRMS (ESI, m/z) 419.1107 calcd for C₂₂H₂₀O₇ (M+Na) found 419.1105. Anal. Calcd for C₂₂H₂₀O₇: C, 66.66; H, 5.09; Found C, 66.62; H, 5.11.

2.5g *Trans-propyl 3-(2-hydroxy-5-nitrophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16g)*: Colourless crystalline solid, Yield 61%, mp 195°C, IR (KBr) $\nu_{\max}$ 3310, 3079, 3120, 2978, 1746, 1691, 1642, 1564, 1591, 1525, 1497, 1437, 1340, 1287, 1245, 1156, 1049, 794, 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 5.29 (d, *J* = 8.6 Hz, 1H), 5.15 (d, *J* = 4.6 Hz, 1H), 4.26–4.15 (m, 2H), 1.68 (q, *J* = 7.2 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 169.4 (C), 168.6 (C), 162.1 (C), 160.6 (C), 155.3 (C), 141.1 (C), 134.2 (CH), 126.3 (C), 125.4 (CH), 125.3 (CH), 123.6 (CH), 123.3 (CH), 117.5 (CH), 116.4 (CH), 112.0 (C), 103.0 (C), 89.1 (CH), 68.3 (CH₂), 43.1 (CH), 21.9 (CH₂), 10.3 (CH₃) ppm; HRMS (ESI, m/z) 434.0852 calcd for C₂₁H₁₇NO₈ (M+Na) found 434.0857. Anal. Calcd for C₂₁H₁₇NO₈: C, 61.31; H, 4.17; N, 3.40; Found C, 61.29; H, 4.15; N, 3.44.

2.5h *Trans-propyl 3-(3,5-dichloro-2-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16h)*: Colourless crystalline solid, Yield 58%, mp 166°C, IR (KBr) $\nu_{\max}$ 3415, 2964, 2879, 1727, 1646, 1574, 1497, 1453, 1413, 1272, 1183, 1094, 1030, 990, 885, 756, 627 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.54 (t, *J* = 8.4 Hz, 1H), 7.30–7.28 (m, 2H), 7.10 (s, 1H), 6.86 (s, 1H), 5.45 (d, *J* = 8.7 Hz, 1H), 5.38 (d, *J* = 8.7 Hz, 1H), 4.17–4.13 (m, 2H), 1.67 (q, *J* = 6.8 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.6 (C), 164.9 (C), 163.0 (C), 154.0 (C), 153.0 (C), 132.6 (CH), 131.1 (C), 128.3 (CH), 126.4 (CH), 124.3 (CH), 123.8 (CH), 122.2 (CH), 116.8 (CH), 116.7 (C), 115.5 (CH), 101.8 (CH), 83.9 (C), 68.2 (CH₂), 43.6 (C), 29.8 (CH₂), 21.8 (CH₃) ppm; HRMS (ESI, m/z) 457.0224 calcd for C₂₁H₁₆Cl₂O₆ (M+Na) found 457.0221. Anal. Calcd for C₂₁H₁₆Cl₂O₆: C, 57.95; H, 3.71; Found C, 57.97; H, 3.72.

2.5i *Trans-propyl 3-(3-bromo-5-chloro-2-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16i)*: Colourless crystalline solid, Yield 51%, mp

168°C, IR (KBr) $\nu_{\max}$ 3534, 2967, 2846, 1722, 1653, 1609, 1484, 1407, 1346, 1272, 1210, 1078, 1034, 933, 893, 759, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.54 (t, *J* = 8.4 Hz, 1H), 7.30–7.28 (m, 2H), 7.10 (s, 1H), 6.86 (s, 1H), 5.45 (d, *J* = 8.7 Hz, 1H), 5.38 (d, *J* = 8.7 Hz, 1H), 4.17–4.13 (m, 2H), 1.67 (q, *J* = 6.9 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.6 (C), 165.9 (C), 163.6 (C), 156.1 (C), 153.0 (C), 133.3 (CH), 132.4 (CH), 131.8 (C), 125.6 (CH), 124.0 (CH), 117.2 (C), 116.7 (CH), 113.2 (C), 103.0 (C), 101.8 (C), 83.5 (C), 67.8 (CH₂), 43.8 (C), 21.8 (CH₂), 10.2 (CH₃) ppm; HRMS (ESI, m/z) 500.9719 calcd for C₂₁H₁₆BrClO₆ (M+Na) found 500.9716. Anal. Calcd for C₂₁H₁₆BrClO₆: C, 52.58; H, 3.36; Found C, 52.55; H, 3.39.

2.5j *Trans-propyl 3-(3,5-dibromo-2-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16j)*: Colourless crystalline solid, Yield 62%, mp 171°C, IR (KBr) $\nu_{\max}$ 3534, 2967, 2846, 1722, 1653, 1609, 1484, 1407, 1346, 1272, 1210, 1078, 1034, 933, 893, 759, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.52 (t, *J* = 8.2 Hz, 1H), 7.30–7.28 (m, 2H), 7.13 (s, 1H), 6.86 (s, 1H), 5.45 (d, *J* = 8.7 Hz, 1H), 5.38 (d, *J* = 8.7 Hz, 1H), 4.19–4.15 (m, 2H), 1.67 (q, *J* = 6.9 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.8 (C), 164.5 (C), 162.8 (C), 154.0 (C), 153.4 (C), 132.5 (CH), 131.4 (C), 128.3 (CH), 126.7 (CH), 124.4 (CH), 123.8 (CH), 122.4 (CH), 115.6 (CH), 116.8 (CH), 115.3 (C), 101.6 (C), 83.7 (CH), 68.0 (CH₂), 43.8 (CH), 21.6 (CH₂), 10.3 (CH₃) ppm; HRMS (ESI, m/z) 544.9214 calcd for C₂₁H₁₆Br₂O₆ (M+Na) found 544.9212. Anal. Calcd for C₂₁H₁₆Br₂O₆: C, 48.12; H, 3.08; Found C, 48.10; H, 3.05.

2.5k *Trans-ethyl 3-(2-hydroxyphenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-2-carboxylate (16k)*: Colourless crystalline solid, Yield 68%, mp 131°C, IR (KBr) $\nu_{\max}$ 3261, 2986, 1742, 1692, 1639, 1604, 1501, 1451, 1413, 1256, 1202, 1038, 940, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 6.8 Hz, 1H), 7.14 (m, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 5.52 (d, *J* = 8.8 Hz, 1H), 5.10 (d, *J* = 8.8 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 169.4 (C), 166.9 (C), 161.3 (C), 155.1 (C), 154.0 (C), 133.3 (CH), 129.4 (CH), 126.8 (CH), 126.7 (CH), 124.6 (CH), 123.3 (CH), 121.7 (CH), 118.6 (CH), 117.3 (CH), 112.3 (C), 105.1 (C), 88.0 (CH₂), 62.7 (CH), 44.2 (CH), 14.2

(CH₃) ppm; HRMS (ESI, *m/z*) 375.0845 calcd for C₂₀H₁₆O₆ (M+Na) found 375.0847. Anal. Calcd for C₂₀H₁₆O₆: C, 68.18; H, 4.58; Found C, 68.16; H, 4.61.

Crystal data for 16K: Crystals obtained from CHCl₃, Empirical formula, C₂₀H₁₆O₆; formula weight, 352.33; crystal colour, habit: colourless, plate; crystal dimensions, 0.4 × 0.3 × 0.25 mm³; crystal system, triclinic; lattice type, primitive; lattice parameters *a* = 7.8881(5) Å, *b* = 9.9292(7) Å, *c* = 12.2702(9) Å; *α* = 72.376(7), *β* = 87.677(6), *γ* = 70.882(7); *V* = 863.57(10) Å³, space group, *P*−1; *Z* = 2; *D*_{calcd} = 1.355 g/cm³; *F*₀₀₀ = 368.0; λ(Mo K_α) = 0.71073 Å; *R* (*I* > 2σ_{*i*}) = 0.0934, *wR*² = 0.2410.

Crystallographic data (excluding structure factors) for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 904106. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

3. Results and discussion

3.1 Reaction of 4*H*-chromene 3 with 4-hydroxypyran-2-one 6 and further transformations

The reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one 6 with 4-methylsulphanyl-4*H*-chromene 3a in ethanol reflux in a pre-heated oil-bath furnished 4*H*-chromene 4-hydroxy-2*H*-pyran-2-one conjugate 7a as a single regio-isomer within 5 min (scheme 2). The reaction did not provide even a trace of *O*-alkylation product.

The ¹H NMR spectrum of 7a showed two singlets located at δ 5.55 and 5.94 ppm for C4H of chromene and C5H of pyran-2-one rings, respectively. The ¹³C NMR spectrum displayed 16 signals out of which, as anticipated, three were located in the aliphatic region. Extending ethanol reflux of the reaction of 4*H*-chromene 3a with pyranone 6 for 30 min resulted in complete transformation of the intermediate 7a into known⁷ acetoacetyl coumarin 9a (scheme 2). Apart from the signals for two methyl groups, the ¹H NMR spectrum of 10a displayed a strong signal at about δ16 ppm for the enolic hydrogen. Integration ratio of relevant signals showed that entire population of 10a is present in enol form. In an independent run, we observed that refluxing of an ethanolic solution of 7a for 30 min provided 10a confirming that 7a is the principal intermediate in the reaction of 4*H*-chromene 3a and pyran-2-one 6. Substitution of C4SMe in 3a with pyran-2-one 6 to form 4*H*-chromene pyran-2-one conjugates 7a within 5 min of ethanol reflux was proved to be general. We reacted nine more 4*H*-chromene derivatives 3b–j with pyran-2-one 6 in ethanol reflux for 5 min to isolate pyran substituted 4*H*-chromenes 7b–j (scheme 1). On further heating, however, in each case the reaction provided acetoacetyl coumarins 10b–j. The 4*H*-chromene 4-hydroxy-2*H*-pyran-2-one conjugates 7b–j and acetoacetyl coumarins 10b–j were characterized by spectral and analytical means which compared well with the parent chromene 7a and coumarin 10a. Structure of hitherto unknown acetoacetyl coumarin 10f was further confirmed by X-ray crystal structure determination (figure 1). Reaction of 2-hydroxybenzaldehyde with 4-hydroxypyran-2-one 6 to form acetoacetyl coumarin 10 is a known reaction.⁸ Analysis of the NMR spectral and single crystal X-ray

Scheme 2. Synthesis of 4*H*-chromene 4-hydroxy-2*H*-pyran-2-one conjugates 7 and further transformation into acetoacetyl coumarins 10. Yield of the product is given in parenthesis.

Figure 1. X-ray crystal structure (*Z*)-3-(1-hydroxy-3-oxobut-1-enyl)-6-nitro-2*H*-chromen-2-one **10f** with crystallographic numbering.

crystallographic data shows that in both solution and in solid states, **10f** stabilizes in its enol form, directed by intramolecular hydrogen bonding interactions and extended conjugation of the enolic double bond to the coumarin ring.

Possible mechanism for formation of the chromene **7** and the coumarin **10** is depicted in scheme 3 in which only mile-stone intermediates are shown. Under the reaction conditions, the 4*H*-chromene **3** is expected to be in equilibrium with the benzpyrylium cation **11**, which gets quenched by 4-hydroxy-2*H*-pyran-2-one **6** to form the chromene–pyranone conjugate **7**. On prolonged ethanol reflux **7** disintegrates into Knoevenagel product **12** and *N*-methyl-2-nitroethynamine **13**. Intramolecular opening of the lactone ring in **7** with concomitant cyclization furnishes acetoacetyl coumarin **10**. Conjugate addition of ethanol to *N*-methyl-2-nitroethynamine **13** leads to nitroketene-*N*, *O*-acetal **14**. Formation of nitroketene *N*, *O*-acetal **14** as a side product was ascertained by its independent synthesis from corresponding *N*, *S*-acetal **15** and ethanol (scheme 3).

3.2 Reaction of 4*H*-chromene **3** with 4-hydroxycoumarin **8** and further transformations

4-Hydroxycoumarin **8** has structural ingredients of 4-hydroxy-6-methyl-2*H*-pyran-2-one **6** – both of them are 1,3-diketones. In analogy with the reaction of 4*H*-chromene **3** with 4-hydroxy-2-pyrone **6**, the reaction of **3** with 4-hydroxycoumarin **8** in EtOH reflux for 5 min provided chromene–coumarin conjugate **9a** in near quantitative yield (scheme 4). The ^1H NMR spectrum of **9a** displayed signals for C4H (δ 5.91, singlet) of the 4*H*-chromene portion and C5'H (δ 8.01, doublet) for coumarin portion. The ^{13}C NMR spectrum displayed 19 signals out of which two were in the aliphatic region (δ 31.5, 27.7). Continuation of the reaction of **3a** and **8** in ethanol reflux for 2 h provided 2,3-dihydrofuro[3,2-*c*]coumarin **16 k** as a single diastereomer in 68% yield (scheme 4). Ethanol reflux of the coumarin–chromene conjugate **9a** for 2 h also provided **16 k** in about 70% yield. Transformation of **3a** and **8** into **16a** or **9a** into **16a** in *n*-propanol reflux was faster (30 min) and cleaner than observed in ethanol reflux (2 h). The structure of **16 k** was confirmed on the basis of spectral (^1H NMR, ^{13}C NMR, DEPT, 2D NMR) and analytical data. Its ^1H NMR spectrum displayed double doublets at δ 5.52 and 5.10 assignable to C3H and C2H of the dihydro ring. Furthermore, the structure was established by single crystal X-ray crystal structure analysis (figure 2).

The furocoumarin derivatives are ubiquitous subunit in a variety of Natural Products particularly those belonging to sesquiterpene family.⁹ Owing to their highly potent biological activity and their applications from being synthetic materials, agrochemicals and pharmaceuticals, different approaches toward the synthesis of furocoumarins have been reported.¹⁰ However,

Scheme 3. Proposed mechanism for formation of the chromene **7** and acetoacetyl coumarin **10** and independent synthesis of *N*, *O*-acetal **13**.

Scheme 4. Synthesis of 4*H*-chromene 4-hydroxy-coumarin conjugates **9** and further transformation into 3-dihydrofuro[3,2-*c*]coumarins **16**.

access to 2,3-disubstituted furo[3,2-*c*]coumarins of the type **16** is limited.¹¹ Previously, they have been synthesized by base catalysed three-component cascade condensation between 4-hydroxycoumarin, aromatic aldehydes and α -halocarbonyl compounds.¹² The two-step method that we have now described for furocoumarins provides ample scope for variation of at least three locations namely; aromatic ring of 2-hydroxybenzaldehyde, aromatic ring of 4-hydroxycoumarin, and the alcohol that gets used to form ester.

Having discovered a facile condensation of 4*H*-chromene **3a** with 4-hydroxycoumarin **8** to form chromene–coumarin conjugate **9a** and subsequent transformation into dihydrofurocoumarin **16k** in chemoselective and diastereoselective manner, we

examined preparation of derivatives using nine more 4*H*-chromenes **3b–j** (scheme 4). First we subjected 4*H*-chromenes **3b–j** to condensation with 4-hydroxycoumarin **8** in EtOH reflux for 5 min in a pre-heated oil bath. On cooling chromene–coumarin conjugates **9b–j** precipitated. Each of the products **9b–j** were then taken in *n*-propanol and heated to reflux in a pre-heated oil bath to furnish dihydrofurocoumarins **16a–j** on cooling. Synthetic intermediates **9b–j** as well as the final products **16b–j** were well characterized by spectral and analytical means (scheme 4).

The proposed mechanism for the two stage cascade condensation of 4*H*-chromene **3a** and 4-hydroxycoumarin **8** to form **9a** initially followed by slide into **16k** is summarized in scheme 5, where only prominent intermediates, condensed form of multi-step cascades are depicted. Similar to 4-hydroxy-2-pyranone's nucleophilic attack on benzopyrylium cation **11** (scheme 3), the attack by 4-hydroxycoumarin proceeds to provide 4*H*-chromene 4-hydroxycoumarin conjugate **9a**. Intramolecular nucleophilic attack of C4OH of coumarin on to C3 of 4*H*-chromene ring in **17** provides dihydrofuran derivative **18**. In contrast to disintegration of **7** into **12** and **13** as given in scheme 3, in the present case intramolecular nucleophilic attack of C4OH of coumarin ring is the major pathway to provide intermediate **18**. Solvent-assisted elimination of MeNH₂, HNO₂ and release of lactone moiety in **18** proceed in cascade manner to provide final furanocoumarin **16**. Exclusive arrival of product **16** with *trans*-stereochemistry for COOEt and aryl ring can be attributed to diastereoselective protonation of the enolate tautomer of the ester that gets generated during transformation of **18** to **16**.

Figure 2. X-ray crystal structure of furocoumarin **16k** with crystallographic numbering.

Scheme 5. Proposed mechanism for formation of the chromene–coumarin conjugate **9** and dihydrofuranocoumarin **16**.

At a first glance, it looks strange that the 4*H*-coumarins **7** and **9** with similar structures provide two different products namely acetoacetyl coumarin **10** and dihydrofuranocoumarin **16**, respectively. Differential behaviour of **9** can be attributed to reluctance of participation of the styryl double bond in **9** to extrude *N*-methyl-2-nitroethynamine **13** owing to extended conjugation. Furthermore, the C4OH of 4-hydroxycoumarin portion in **9** is similar to phenolic hydroxyl group and it participates in intra-molecular attack on C3 carbon of 4*H*-chromene portion to initiate cascade process finally resulting in the formation of furan ring as seen in **16** with concomitant extrusion of HNO_2 and MeNH_2 .

4. Conclusion

In conclusion, we have shown that 4-methylsulphanyl-4*H*-chromenes are useful starting compounds for the synthesis of a range of 4*H*-chromene 4-hydroxy-2-pyrone and 4*H*-chromene 4-hydroxycoumarin conjugates. Furthermore, the 4*H*-chromene 4-hydroxy-2-pyrone conjugates were transformed into acetoacetylcoumarins and 4*H*-chromene 4-hydroxycoumarin conjugates into *trans*-2,3-disubstituted dihydrofuro[3,2-*c*]coumarins. As the products prepared in the present study possess structural characteristics of privileged medicinal scaffolds, we expect them to exhibit useful biological activities.

Supplementary information

The electronic supporting information can be seen in www.ias.ac.in/chemsci.

Acknowledgements

HSPR thanks the University grants Commission (UGC, UGC-SAP), the Council of Scientific and Industrial Research (CSIR) and DST-FIST for financial assistance. VST thanks CSIR for fellowship. Authors also thank the Indian Institute of Science (IISc), Bangalore for recording MS spectra.

References

- Lockhart I M 1977 in *Chromenes, chromanones and chromones* (ed) G P Ellis (London: John Wiley & Sons) p. 207
- (a) Ren Q, Siau W-Y, Du Z, Zhang K and Wang J 2011 *Chem. Eur. J.* **17** 7781; (b) Sabry N M, Mohamed H M, Khattab E S A E H, Motlaq S S and El-Agrody A M 2011 *Eur. J. Med. Chem.* **46** 765; (c) Fravel B W 2008 In *Comprehensive heterocyclic chemistry III*, **7** 701; (d) Green G R, Evans J M and Vong A K 1995 In *Comprehensive heterocyclic chemistry II*, **5** 469; (e) Hepworth J D 1984 In *Comprehensive heterocyclic chemistry I*, **2** 737
- (a) Mahdavi M, Davoodi J, Zali M R and Foroumadi A 2011 *Biomed. Pharm.* **65** 175; (b) Kemnitzer W, Drewe J, Jiang S, Zhang H, Crogan-Grundy C, Labreque D,

- Bubenick M, Attardo G, Denis R, Lamothe S, Gourdeau H, Tseng B, Kasibhatla S and Cai S X 2008 *J Med. Chem.* **51** 417; (c) Cai S X 2007 *Recent Pat. Anti-canc. Drug Discov.* **2** 79
4. (a) Rao H S P, Geetha K 2009 *Tetrahedron Lett.* **50** 3836–839; (b) Gayathri D, Velmurugan D, Ravikumar K, Geetha K and Rao H S P 2006 *Acta Crystallogr.* **E62** o1961
5. Rao H S P, Geetha K and Kamalraj M 2011 *Tetrahedron* **67** 8146
6. Rao H S P, Geetha K and Kamalraj M 2011 *RSC Adv.* **1** 1050
7. De March P, Moreno-Manas M and Roca J L 1984 *J. Het. Chem.* **21** 1371
8. Svetlík J, Pronayovo N and Hanus V 2000 *J. Het. Chem.* **37** 395
9. (a) Murray R D H, Mendez J and Brown S A 1982 *The natural coumarins, occurrence, chemistry, and biochemistry* (New York, NY: Wiley) pp. 214–225; (b) Gliszczyńska A and Brodelius P E 2012 *Phytochem. Rev.* **11** 77
10. (a) O’Kennedy R and Thornes R D 1997 *Coumarins: Biology, applications and mode of action*. Chichester: Wiley; (b) Zheng J C, Zhu Y C, Sun X L, Tang Y and Dai L X 2008 *J. Org. Chem.* **73** 6909; (c) Calo V, Scordari F, Nacci A, Schingaro E, D’Accolti L and Monopoli A 2003 *J. Org. Chem.* **68** 4406; (d) Xing C and Zhu S 2004 *J. Org. Chem.* **69** 6488; (e) Evans D A, Sweeney Z K, Rovis T and Tedrow J S 2001 *J. Am. Chem. Soc.* **123** 12095; (f) Zhong C, Liao T, Tuguldur O and Shi X 2010 *Org. Lett.* **12** 2064
11. Guillaume R, Marion R, Genevie B and Nuno M 2009 *Org. Lett.* **11** 5254
12. (a) Rajesh M S, Perumal S, Menéndez J C, Pandian S and Murugesan R 2012 *Tetrahedron* **68** 5631; (b) Altieri E, Cordaro M, Grassi G, Risitano F and Scala A 2010 *Tetrahedron* **66** 9493–9496; (c) Wang Q-F, Hou H, Hui L and Yan C-C 2009 *J. Org. Chem.* **74** 7403