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ORIGINAL PAPER

"On-water" organic synthesis: L-proline catalyzed synthesis of pyrimidine-2,4-dione-, benzo[*g*]- and dihydropyrano [2,3-*g*]chromene derivatives in aqueous media

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Abstract In this work, functionalized pyrimidine-2,4-dione-, benzo[*g*]-, and dihydropyrano[2,3-*g*]chromene derivatives have been synthesized via a Michael addition of 2-hydroxy-1,4-naphthoquinone or 2,5-dihydroxy-1,4-benzoquinone to the Knoevenagel condensation product of an aldehyde with Meldrum's acid, dimedone or barbituric acid in the presence of a catalytic amount of L-proline under refluxing conditions in water in good to excellent yields.

Keywords Pyrimidine-2,4-dione · Benzo[*g*]chromene · Dihydropyrano[2,3-*g*]chromene · Aqueous media

Introduction

Naturally occurring chromenes show a broad spectrum of biological activities. This moiety is core fragment of different natural products including pyranokunthone A and B, lambertellin B, β-lapachone C and α-xiloidone D [1–6]. Some derivatives of benzo[*g*]chromenes, such as compounds **E** and **F** have been isolated from marine actinomycete CNQ-525 bacteria (Fig. 1). These latter materials have shown significant anticancer and antibiotic activities [7]. Because of broad pharmacological activities of benzo[*g*]chromenes, different synthetic methods have been introduced by research groups [8–12]. Usually, these synthetic approaches are including a multi-step procedure. A semi-synthetic method has also been introduced [13].

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Within the previous decade, green chemistry has achieved the status of a major scientific discipline [14–17]. Cleaner and more benign chemical processes have been developed using green chemistry philosophy and many new technologies have been developed each year. Among the 12 principles of green chemistry, utilizing "safer solvents" and to "design for energy efficiency" can be considered the most important ones for the synthetic chemists. Although there is widespread argument over the relative "greenness" of many reaction media, water can undoubtedly be considered as the cleanest solvent available; therefore, the use and release of clean water will have the least dreadful impact to the environment. For biological chemistry, water is a green solvent that has been used by nature; it is nonflammable and nontoxic. After the masterful use of concept and language of "on-water" reactions for cases where the reactants are insoluble in water by Sharpless et al., the use of water as a reaction media for organic synthesis has attracted many attractions [18, 19].

The use of aqueous media in organic reactions has attracted a great deal of interest not only because of significant environmental advantages, but also different beneficial such as low cost and safety. Revolutionary studies of organic reactions in aqueous media established that Claisen rearrangement and Diels–Alder reactions of hydrophobic reactants are accelerated in aqueous media. In addition to these findings, higher reactivity and selectivity in aqueous environments have been reported as well. Therefore, many versatile and well-organized organic reactions have been developed [19–34].

Small organic molecules like cinchona alkaloids, L-proline and its derivatives are readily commercially available catalysts and have been used in various transformations in good yields [35, 36]. L-Proline has been found to be very effective in enamine-based direct catalytic

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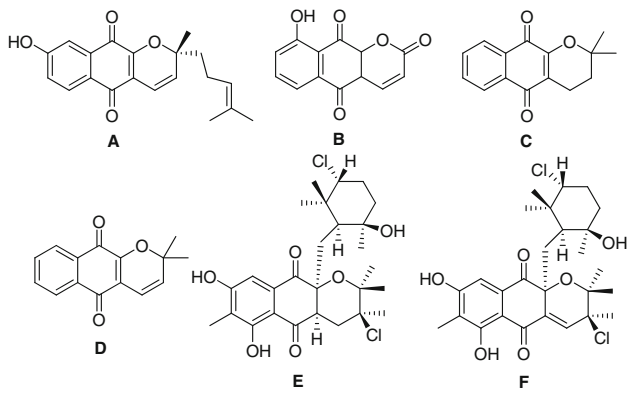


Fig. 1 Examples of biologically active benzo[*g*]chromene derivatives

asymmetric aldol [37], Mannich [38, 39], Michael [40–42], Diels–Alder [43], α-amination reactions [44], Knoevenagel type reactions [45], and asymmetric Biginelli reactions [46, 47]. More recently, L-proline and its derivatives have been used in multicomponent reactions [48–53].

Experiment

Materials

Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu GCMS-QP1100EX mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer 300.13 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR spectra are reported in order: number of protons, multiplicity and approximate coupling constant (*J* value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad signal) and Ar (aryl). The ^{13}C NMR spectra were recorded at 75.47 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. All the products are new compounds (except **8a–f** and **19a–e**), which were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra and mass spectral data.

Typical procedure for the synthesis of 3,3-dimethyl-12-phenyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (**4a**) A solution of 2-hydroxynaphthalene-1,4-dione (0.17 g, 1.0 mmol), benzaldehyde (0.11 g, 1.0 mmol), 5,5-dimethylcyclohexane-1,3-dione (0.14 g, 1.0 mmol) and L-proline (10 mol %) in refluxing water (5 ml) was stirred for 4 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and washed with water and crystallized from EtOH/H_2O (v:v = 1:3) to afford pure product **4a**. Yellow powder. m.p. 228–230 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,451, 3,075, 2,956, 2,861, 1,664, 1,618, 1,586, 1,461, 1,366. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.95 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.10–2.50 (4H, m, $2CH_2$), 4.89 (1H, s, CH), 7.00–8.10 (9H, m, H–Ar); MS (*m*/*z*, %): 384 (M^+, 80), 327 (10), 307 (65), 273 (30), 251 (45), 215 (50), 139 (70), 105 (30), 77 (100), 41 (70). Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 78.08; H, 5.14.

Typical procedure for the synthesis of 7,14-*bis*(2,4-dimethoxyphenyl)-3,3,10,10-tetramethyl-3,4,10,11-tetrahydrochromeno[2,3-*b*]xanthene-1,6,8,13(2*H*,7*H*,9*H*,14*H*)-tetraone (**6b**) A solution of 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (0.17 g, 1.0 mmol), 2,4-dimethoxybenzaldehyde (0.33 g, 2.0 mmol), 5,5-dimethylcyclohexane-1,3-dione (0.28 g, 2.0 mmol) and L-proline (10 mol %) in refluxing water (5 ml) was stirred for 8 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and then crystallized from ethanol to give **6b** as pure products. Orange powder. m.p. 189–191 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,390, 2,969, 2,838, 1,716, 1,639, 1,603. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.08 (12H, br s, $4CH_3$), 1.99–2.22 (8H, m, $4CH_2$), 2.98 (1H, s, CH), 3.5 (12H, br s, 4OMe), 4.42 (2H, s, 2CH), 6.28–6.76 (6H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.0, 27.6, 28.1, 29.9, 31.7, 32.6, 33.1, 40.7, 42.7, 49.2, 50.9, 53.3, 55.4, 55.7, 97.9, 101.6, 104.0, 110.0, 115.6, 123.8, 129.9, 157.2, 158.7, 162.4, 167.2, 196.0, 205.5. MS (*m*/*z*, %): 680 (M^+, 8), 678 (10), 606 (25), 577 (75), 565 (58), 551 (100), 537 (67), 523 (54), 500 (58). Anal. Calcd for $C_{40}H_{40}O_{10}$: C, 70.57; H, 5.92; O, 23.50. Found: C, 70.47; H, 5.83; O, 23.40.

Typical procedure for the synthesis of 4,9-dio-tolyl-3,4,8,9-tetrahydropyrano[2,3-*g*]chromene-2,5,7,10-tetraone (**19b**) To a magnetically stirred solution of 2-hydroxynaphthalene-1,4-dione (0.17 g, 1.0 mmol), 4-methylbenzaldehyde (0.24 g, 2.0 mmol), Meldrum's acid (0.28 g, 2.0 mmol) and L-proline (10 mol %) in refluxing water (5 ml) was stirred for 4 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and washed with 5 mL of *n*-hexane. The desired product was obtained as a yellow powder. m.p. 300 °C. IR (KBr) (cm^{-1}): 2,938, 1,792, 1,673, 1,633. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.32 (6H, s, $2CH_3$), 2.87–3.06 (4H, m, CH_2), 4.67 (2H, t, ^{3}J = 8 Hz, 2CH), 7.02–7.40 (8H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 18.0 (CH_3), 29.7 (CH_2), 32.1 (CH), 106.1, 118.1, 119.5, 120.2, 126.3, 126.5, 130.8, 131.3 (C-alkene and aromatic), 157.1, 181.4 (C=O). MS (*m*/*z*, %): 430 (M+2, 11), 386 (4), 368 (7), 257 (25), 236 (21), 196 (11),

149 (61), 83 (65), 69 (86), 57 (96), 43 (100). Anal. Calcd for $C_{26}H_{20}O_6$: C, 72.89; H, 4.71. Found: C, 72.79; H, 4.70.

3,3-Dimethyl-12-phenyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (**4a**) Yellow powder. m.p. 228–230 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,451, 3,075, 2,956, 2,861, 1,664, 1,618, 1,586, 1,461, 1,366. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.95 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.10–2.50 (4H, m, $2CH_2$), 4.89 (1H, s, CH), 7.00–8.10 (9H, m, H–Ar); MS (*m*/*z*, %): 384 (M^+, 80), 327 (10), 307 (65), 273 (30), 251 (45), 215 (50), 139 (70), 105 (30), 77 (100), 41 (70). Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 78.08; H, 5.14.

3,3-Dimethyl-12-*p*-tolyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (**4b**) Brown powder. m.p. 170–172 °C. IR (KBr) (ν_{max}/cm^{-1}): 3,435, 3,070, 2,958, 2,866, 1,732, 1,675, 1,590, 1,464, 1,372. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.94–1.26 (9H, m, $3CH_3$), 2.00–2.50 (4H, m, $2CH_2$), 4.29 (1H, s, CH), 6.90–8.10 (8H, m, H–Ar). MS (*m*/*z*, %): 398 (M^+, 1), 349 (1), 330 (1), 308 (1), 192 (10), 174 (50), 146 (20), 105 (100), 77 (60), 41 (70). Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.30; H, 5.47.

12-(2-Hydroxyphenyl)-3,3-dimethyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (**4c**) Yellow powder. m.p. 237–239 °C. IR (KBr) (ν_{max}/cm^{-1}): 3,430, 3,188, 2,953, 2,866, 1,677, 1,635, 1,580, 1,490, 1,369. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.96 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.16 (2H, ABq, $J = 16.0$, CH_2), 2.50 (2H, ABq, $J = 17.4$, CH_2), 5.34 (1H, s, CH), 6.90–8.10 (8H, m, H–Ar), 11.35 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 26.6, 26.8, 32.2, 50.6, 110.1, 116.4, 125.2, 126.1, 128.3, 129.2, 130.2, 132.1, 133.7, 135.2, 149.8, 155.3, 166.0, 181.9, 183.8, 196.5. MS (*m*/*z*, %): 400 (M^+, 10), 316 (65), 282 (30), 244 (10), 277 (100), 211 (40), 171 (70), 152 (10), 115 (80), 77 (50), 41 (40). Anal. Calcd for $C_{25}H_{20}O_5$: C, 74.99; H, 5.03. Found: C, 74.89; H, 5.00.

3,3-Dimethyl-12-(3-nitrophenyl)-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (**4d**) Brown powder. m.p. 231–233 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,348, 3,082, 2,961, 2,870, 1,668, 1,587, 1,526, 1,467, 1,349. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.93 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.10–2.50 (4H, m, $2CH_2$), 6.09 (1H, s, CH), 7.00–8.20 (8H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 26.6, 28.6, 32.2, 33.1, 50.2, 109.6, 112.8, 113.4, 117.3, 121.0, 122.2, 122.8, 123.8, 126.4, 129.8, 131.0, 131.4, 134.4, 134.7, 135.8, 148.0, (158.1, 158.6, 159.1, 159.6, CF_3), 163.8, 175.4, (183.2), 196.3. MS (*m*/*z*, %): 429 (M^+, 2), 412 (10), 395 (4), 378 (60), 348 (25), 307 (10), 273 (75), 217 (30), 161 (40), 105 (65), 77 (60), 41 (100). Anal. Calcd for $C_{25}H_{19}NO_6$: C, 69.92; H, 4.46; N, 3.26. Found: C, 69.90; H, 4.36; N, 3.20.

3,3-Dimethyl-12-(4-nitrophenyl)-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (**4e**) Yellow powder. m.p. 238–240 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,432, 3,075, 2,960, 2,866, 1,664, 1,606, 1,518, 1,348. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.90 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.10–2.70 (4H, m, $2CH_2$), 4.96 (1H, s, CH), 7.00–8.10 (8H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.0, 28.8, 32.8, 33.3, 50.3, 122.8, 123.7, 126.3, 126.5, 130.6, 131.0, 131.4, 134.7, 135.1, 146.7, 150.0, 150.6, 163.9, 177.4, 196.4. MS (*m*/*z*, %): 429 (M^+, 25), 412 (30), 382 (25), 348 (15), 307 (60), 273 (80), 251 (60), 213 (40), 195 (25), 165 (25), 139 (85), 105 (25), 76 (70), 41 (100). Anal. Calcd for $C_{25}H_{19}NO_6$: C, 69.92; H, 4.46; N, 3.26. Found: C, 69.87; H, 4.38; N, 3.19.

12-(4-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (**4f**) Pink powder. m.p. 225–227 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,391, 2,965, 2,835, 1,716, 1,641, 1,611. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.94 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.00–2.50 (4H, m, $2CH_2$), 4.88 (1H, s, CH), 7.00–8.10 (8H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.0, 28.9, 32.3, 33.5, 50.4, 113.3, 114.4, 123.6, 126.3, 126.5, 128.3, 128.6, 130.4, 131.0, 131.5, 131.9, 134.7, 135.1, 142.2, 163.6, 177.5, 196.5, 196.6. MS (*m*/*z*, %): 420 (M^+, ^{37}Cl, 20), 418 (M^+, ^{35}Cl, 60), 383 (20), 327 (10), 307 (75), 271 (25), 251 (70), 215 (50), 195 (25), 176 (25), 139 (100), 111 (65), 76 (80), 71 (80). Anal. Calcd for $C_{25}H_{19}ClO_4$: C, 71.69; H, 4.57. Found: C, 71.59; H, 4.47.

12-Phenyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (**4g**) Yellow powder. m.p. 234–236 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,446, 3,033, 2,948, 2,882, 1,664, 1,618, 1,586, 1,456, 1,368. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.50–2.70 (6H, m, $3CH_2$), 4.91 (1H, s, CH), 7.00–8.10 (9H, m, H–Ar). MS (*m*/*z*, %): 356 (M^+, 60), 299 (8), 280 (25), 279 (100), 215 (27), 189 (10), 165 (20), 139 (40), 104 (20), 77 (60), 51 (40). Anal. Calcd for $C_{23}H_{16}O_4$: C, 77.52; H, 4.53. Found: C, 77.48; H, 4.43.

3,3,10,10-Tetramethyl-7,14-diphenyl-3,4,10,11-tetrahydrochromeno[2,3-*b*]xanthene-1,6,8,13(2*H*,7*H*,9*H*,14*H*)-tetraone (**6a**) Orange powder. m.p. 228–230 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,392, 2,971, 2,851, 1,720, 1,642, 1,615; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.86 (6H, bs, $2CH_3$), 0.99 (6H, bs, $2CH_3$), 2.13 (4H, bs, $2CH_2$), 2.25 (4H, bs, $2CH_2$), 5.70 (H, s, CH), 6.03 (H, s, CH), 6.84–7.17 (10H, m, H–Ar). Anal. Calcd for $C_{36}H_{32}O_6$: C, 77.12; H, 5.75. Found: C, 77.04; H, 5.65.

7,14-*Bis*(2,4-dimethoxyphenyl)-3,3,10,10-tetramethyl-3,4,10,11-tetrahydrochromeno[2,3-*b*]xanthene-1,6,8,13(2*H*,7*H*,9*H*,14*H*)-tetraone (**6b**) Orange powder (yield 65 %). m.p. 189–191 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,390, 2,969, 2,838, 1,716, 1,639, 1,603. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H

(ppm) 1.08 (12H, br s, $4CH_3$), 1.99–2.22 (8H, m, $4CH_2$), 2.98 (1H, s, CH), 3.5 (12H, br s, 4OMe), 4.42 (2H, s, 2CH), 6.28–6.76 (6H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.0, 27.6, 28.1, 29.9, 31.7, 32.6, 33.1, 40.7, 42.7, 49.2, 50.9, 53.3, 55.4, 55.7, 97.9, 101.6, 104.0, 110.0, 115.6, 123.8, 129.9, 157.2, 158.7, 162.4, 167.2, 196.0, 205.5. MS (*m*/*z*, %): 680 (M^+, 8), 678 (10), 606 (25), 577 (75), 565 (58), 551 (100), 537 (67), 523 (54), 500 (58). Anal. Calcd for $C_{40}H_{40}O_{10}$: C, 70.57; H, 5.92; O, 23.50. Found: C, 70.47; H, 5.83; O, 23.40.

7,14-*Bis*(5-bromo-2-hydroxyphenyl)-3,3,10,10-tetramethyl-3,4,10,11-tetrahydrochromeno[2,3-*b*]xanthene-1,6,8,13(2*H*,7*H*,9*H*,14*H*)-tetraone (**6c**) Orange powder. m.p. >260 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,389, 2,962, 2,846, 1,721, 1,642, 1,612; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.02 (12H, bs, $4CH_3$), 2.94 (8H, m, $4CH_2$), 5.00 (2H, s, 2CH), 6.90–725 (8H, m, H–Ar and 2OH). Anal. Calcd for $C_{36}H_{30}Br_2O_8$: C, 57.62; H, 4.03. Found: C, 57.55; H, 3.93.

3,3,10,10-Tetramethyl-7,14-*bis*(3-nitrophenyl)-3,4,10,11-tetrahydrochromeno[2,3-*b*]xanthene-1,6,8,13(2*H*,7*H*,9*H*,14*H*)-tetraone (**6d**) Orange powder. m.p. >260 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,392, 2,966, 2,838, 1,718, 1,642, 1,612; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.03 (12H, bs, $4CH_3$), 2.29 (8H, bs, $4CH_2$), 5.72 (2H, s, 2CH), 7.49–7.98 (8H, m, H–Ar); Anal. Calcd for $C_{36}H_{30}N_2O_{10}$: C, 66.46; H, 4.65; N, 4.31. Found: C, 66.46; H, 4.55; N, 4.22.

3,3,10,10-Tetramethyl-7,14-*bis*(4-nitrophenyl)-3,4,10,11-tetrahydrochromeno[2,3-*b*]xanthene-1,6,8,13(2*H*,7*H*,9*H*,14*H*)-tetraone (**6e**) Brown powder. m.p. >260 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,316, 3,112, 3,075, 2,960, 2,874, 1,671, 1,601, 1,522, 1,462, 1,350. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.89 (6H, s, $2CH_3$), 1.02 (6H, s, $2CH_3$), 2.17 (4H, ABq, $J = 16.0$, $2CH_2$), 2.55 (4H, ABq, $J = 14.4$, $2CH_2$), 4.62 (2H, s, 2CH), 7.40–7.80 (8H, H–Ar); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.0, 29.0, 32.3, 50.3, 113.8, 123.6, 124.7, 130.0, 131.1, 146.4, 152.3, 163.9, 196.5. MS (*m*/*z*, %): 395 (M^+-255, 5), 378 (8), 348 (5), 273 (100), 217 (30), 178 (5), 161 (30), 133 (15), 115 (10), 77 (30), 55 (65). Anal. Calcd for $C_{36}H_{30}N_2O_{10}$: C, 66.46; H, 4.65; N, 4.31. Found: C, 66.36; H, 4.61; N, 4.31.

7,14-Diphenyl-3,4,10,11-tetrahydrochromeno[2,3-*b*]xanthene-1,6,8,13(2*H*,7*H*,9*H*,14*H*)-tetraone (**6f**) Dark brown powder. m.p. 262–264 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,435, 2,946, 2,877, 1,659, 1,615, 1,494, 1,454. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.00–2.50 (12H, m, $6CH_2$), 4.48 (2H, s, 2CH), 7.00–8.00 (10H, m, H–Ar). MS (*m*/*z*, %): 504 (M^+, 1), 429 (1), 294 (25), 217 (100), 152 (8), 115 (8), 77 (25), 55 (25). Anal. Calcd for $C_{32}H_{24}O_6$: C, 76.18; H, 4.79. Found: C, 66.18; H, 4.70.

7,14-*Bis*(4-chlorophenyl)-3,4,10,11-tetrahydrochromeno[2,3-*b*]xanthene-1,6,8,13(2*H*,7*H*,9*H*,14*H*)-tetraone (**6g**) Dark powder. m.p. >290 °C; IR (KBr) (ν_{max}/cm^{-1}): 3,436, 2,945, 2,913, 2,877, 1,664, 1,529, 1,487, 1,441, 1,360. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.80–2.00 (4H, m, $2CH_2$), 2.26 (4H, m, $2CH_2$), 2.64 (4H, m, $2CH_2$), 4.54 (2H, s, 2CH), 7.00–7.30 (8H, m, H–Ar). MS (*m*/*z*, %): 328 (M^+-244, 20), 293 (25), 217 (100), 152 (5), 111 (5), 55 (20). Anal. Calcd for $C_{32}H_{22}Cl_2O_6$: C, 67.03; H, 3.87. Found: C, 67.03; H, 3.77.

4-(3-Methoxyphenyl)-3,4-dihydro-2*H*-benzo[*g*]chromene-2,5,10-trione (**8a**) Yellow powder. m.p. 191–192 °C; IR (KBr) (cm^{-1}): 2,990, 2,933, 1,792, 1,645, 1,582. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.89 (2H, bs, CH_2), 3.70 (3H, s, OCH_3), 4.55 (1H, bs, CH), 6.84–8.08 (8H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 34.9 (CH_2), 36.2 (CH), 55.1 (OCH_3), 113.1, 113.5, 119.2, 125.1, 126.4, 126.6, 130.6, 131.5, 134.7, 134.9, 141.5, 152.6, 160.1 (C-alkene and aromatic), 165.9, 177.5, 183.2 (3C=O). MS (*m*/*z*, %): 334 (M^+, 100), 306 (40), 291 (14), 227 (38), 263 (27), 247 (20), 237 (19), 165 (18), 134 (35), 104 (32), 57 (40). Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22; Found: C, 71.72; H, 4.19.

4-(4-Methoxyphenyl)-3,4-dihydro-2*H*-benzo[*g*]chromene-2,5,10-trione (**8b**) Yellow powder. m.p. 191–192 °C; IR (KBr) (cm^{-1}): 2,993, 2,930, 1,792, 1,648, 1,583. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.85 (1H, d, $^2J_{HH} = 15$ Hz, CH_2), 3.36 (1H, dd, $^2J_{HH} = 15$ Hz, $^3J_{HH} = 7$ Hz, CH_2), 3.70 (3H, s, OCH_3), 4.53 (1H, d, $^3J_{HH} = 7$ Hz, CH), 6.86 (2H, d, $^3J_{HH} = 8.5$ Hz, H–Ar), 7.21 (2H, d, $^3J_{HH} = 8.5$ Hz, H–Ar), 7.82–8.11 (4H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 34.1 (CH_2), 36.4 (CH), 55.5 (OCH_3), 114.8, 125.7, 126.4, 126.6, 128.5, 131.4, 131.5, 131.7, 134.8, 135.0, 152.3, 159.0 (C-alkene and aromatic), 166.1, 177.6, 183.2 (3C=O). Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22; Found: C, 71.91; H, 4.26.

4-(4-Hydroxyphenyl)-3,4-dihydro-2*H*-benzo[*g*]chromene-2,5,10-trione (**8c**) Yellow powder. m.p. 246–248 °C; IR (KBr) (cm^{-1}): 3,442, 3,095, 1,787, 1,666, 1,645, 1,603, 1,519. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.85 (1H, d, $^2J_{HH} = 16$ Hz, CH_2), 3.29–3.36 (1H, m, CH_2), 4.47 (1H, d, $^3J_{HH} = 6.32$ Hz, CH), 6.68–8.01 (8H, m, aromatic), 9.48 (1H, bs, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 34.11 (CH_2), 36.46 (CH), 116.1, 125.9, 126.4, 126.5, 128.4, 129.9, 131.3, 131.4, 134.7, 135.0, 152.1, 157.1 (C-alkene and H–Ar), 166.1, 177.5, 183.1 (3C=O). MS (*m*/*z*, %): 320 (M^+, 83), 292 (100), 263 (77), 249 (35), 222 (11), 165 (27), 120 (19), 104 (31), 76 (40), 50 (15). Anal. Calcd for $C_{19}H_{12}O_5$: C, 71.25; H, 3.78; Found: C, 71.31; H, 3.70.

4-(2-Hydroxyphenyl)-3,4-dihydro-2*H*-benzo[*g*]chromene-2,5,10-trione (**8d**) Yellow powder. m.p. 208–209 °C; IR (KBr) (cm^{-1}): 3,448, 3,195, 1,757, 1,677, 1,635. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.49–2.96 (1H, m, CH_2), 3.12–3.20 (1H, m, CH_2), 4.85 (1H, bs, CH), 7.03–7.99 (8H, m, H–Ar), 11.71 (1H, bs, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 29.7 (CH_2), 32.4 (CH), 116.8, 123.5, 124.5, 126.1, 126.3, 128.5, 130.4, 132.2, 133.7, 135.1, 151.6, 156.6 (C-alkene and aromatic), 167.1, 181.4, 184.3 (3C=O). Anal. Calcd for $C_{19}H_{12}O_5$: C, 71.25; H, 3.78; Found: C, 71.31; H, 3.69.

4-(2-Hydroxy-3-methoxyphenyl)-3,4-dihydro-2*H*-benzo[*g*]chromene-2,5,10-trione (**8e**) Yellow powder. m.p. 252–254 °C; IR (KBr) (cm^{-1}): 3,357, 3,012, 2,922, 1,761, 1,649, 1,587. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.92 (1H, dd, $^2J_{HH} = 16.0$ Hz, $^3J_{HH} = 8.45$ Hz CH_2), 3.15 (1H, dd, $^2J_{HH} = 16$ Hz, $^3J_{HH} = 8.45$ Hz, CH_2), 3.81 (3H, s, OCH_3), 4.83 (1H, dd, $^3J_{HH} = 8.45$ Hz, $^3J_{HH} = 8.45$ Hz, CH), 6.69–7.99 (7H, m, H–Ar), 11.60 (1H, bs, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 29.9 (CH_2), 32.3 (CH), 56.1 (OCH_3), 111.3, 119.7, 123.5, 124.1, 124.2, 126.2, 126.3, 130.4, 132.2, 133.7, 135.1, 140.8, 147.4, 156.5 (C-alkene and aromatic), 166.8, 181.4, 184.3 (3C=O). Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.57; H, 4.03; Found: C, 68.48; H, 4.15.

4-(5-Bromo-2-hydroxyphenyl)-3,4-dihydro-2*H*-benzo[*g*]chromene-2,5,10-trione (**8f**) Yellow powder. m.p. 279–281 °C; IR (KBr) (cm^{-1}): 3,345, 2,927, 2,859, 1,781, 1,651. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.91–2.96 (1H, m, CH_2), 3.09–3.33 (1H, m, CH_2), 4.84 (1H, bs, CH), 7.24–7.97 (7H, m, H–Ar), 11.65 (1H, bs, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 29.7 (CH_2), 32.1 (CH), 116.1, 119.1, 122.4, 126.2, 126.3, 130.7, 130.9, 131.3, 132.4, 133.7, 134.9, 151.0, 157.1 (C-alkene and aromatic), 166.7, 181.4, 184.3 (3C=O). MS (*m*/*z*, %): 399 (M^+, ^{81}Br, 10), 397 (M^+, ^{79}Br, 10), 396 (25), 388 (12), 386 (98), 371 (46), 368 (89), 353 (50), 351 (22), 343 (15), 341 (100). Anal. Calcd for $C_{19}H_{11}BrO_5$: C, 57.17; H, 2.78; Found: C, 57.32; H, 2.83.

4,9-*Bis*(2,4-dimethoxyphenyl)-3,4,8,9-tetrahydropyrano[2,3-*g*]chromene-2,5,7,10-tetraone (**19a**) Brown powder. m.p. 180 °C; IR (KBr) (cm^{-1}): 3,343, 3,001, 2,938, 2,838, 1,792, 1,650, 1,608, 1,588; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.94 (4H, bs, $2CH_2$), 3.54–3.92 (14H, m, 2CH and 4OMe), 6.01–7.28 (6H, m, H–Ar). Anal. Calcd for $C_{28}H_{24}O_{10}$: C, 57.17; H, 2.78; Found: C, 57.32; H, 2.83. Anal. Calcd for $C_{28}H_{24}O_{10}$: C, 64.61; H, 4.65; Found: C, 64.61; H, 4.55.

4,9-*Dio*-tolyl-3,4,8,9-tetrahydropyrano[2,3-*g*]chromene-2,5,7,10-tetraone (**19b**) Yellow powder. m.p. 300 °C. IR (KBr) (cm^{-1}): 2,938, 1,792, 1,673, 1,633. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.32 (6H, s, $2CH_3$), 2.87–3.06 (4H, m, CH_2), 4.67 (2H, t, $^3J = 8$ Hz, 2CH), 7.02–7.40 (8H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 18.0 (CH_3), 29.7 (CH_2), 32.1 (CH), 106.1, 118.1, 119.5, 120.2, 126.3, 126.5, 130.8, 131.3 (C-alkene and aromatic), 157.1, 181.4 (C=O). MS (*m*/*z*, %): 430 (M+2, 11), 386 (4), 368 (7), 257 (25), 236 (21), 196 (11), 149 (61), 83 (65), 69 (86), 57 (96), 43 (100). Anal. Calcd for $C_{26}H_{20}O_6$: C, 72.89; H, 4.71. Found: C, 72.79; H, 4.70.

4,9-*Bis*(3-bromophenyl)-3,4,8,9-tetrahydropyrano[2,3-*g*]chromene-2,5,7,10-tetraone (**19c**) Brown powder. m.p. 193–196 °C; IR (KBr) (cm^{-1}): 3,059, 2,985, 2,922, 2,854, 1,723, 1,640, 1,566; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.07 (2H, bs, $2CH_2$), 2.88 (2H, bs, $2CH_2$), 4.49 (2H, bs, CH), 7.26–7.44 (8H, m, H–Ar)**.** Anal. Calcd for $C_{24}H_{14}Br_2O_6$: C, 51.64; H, 2.53; Found: C, 51.54; H, 2.62.

4,9-*Bis*(2-hydroxy-3-methoxyphenyl)-3,4,8,9-tetrahydropyrano[2,3-*g*]chromene-2,5,7,10-tetraone (**19d**) Pink powder. m.p. 193 °C; IR (KBr) (cm^{-1}): 3,427, 2,927, 2,854, 1,747, 1,645, 1,540; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.66 (2H, dd, $^2J_{HH} = 16.35$ HZ, $^3J_{HH} = 4$ Hz, CH_2), 2.88 (2H, t, $^2J_{HH} = 8$ Hz, CH_2), 4.50 (2H, bs, CH), 6.61–6.95 Hz (6H, m, H–Ar), 11.60 (1H, bs, OH). Anal. Calcd for $C_{26}H_{20}O_{10}$: C, 63.42; H, 4.09; Found: C, 63.51; H, 4.14.

4,9-*Bis*(5-bromo-2-hydroxyphenyl)-3,4,8,9-tetrahydropyrano[2,3-*g*]chromene-2,5,7,10-tetraone (**19e**) Brown powder. m.p. 332–334 °C. IR (KBr) (cm^{-1}): 3,253, 2,912, 1,760, 1,623, 1,427. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.87 (2H, bs, CH_2), 3.08 (2H, bs, CH_2), 4.59 (2H, bs, CH), 7.01–7.41 (6H, m, H–Ar), 11.55 (1H, bs, OH). MS (*m*/*z*, %): 588 (M^+, 9), 580 (32), 577 (44), 565 (50), 262 (25), 551 (100), 548 (36), 537 (90), 534 (14), 523 (82), 521 (34), 368 (25), 326 (35), 85 (100), 57 (80). Anal. Calcd for $C_{24}H_{14}Br_2O_8$: C, 48.84; H, 2.39; Found: C, 48.70; H, 2.45.

Product **21a** Brownish powder. m.p. 217–219 °C. IR (KBr) (cm^{-1}): 3,443, 1,683, 1,634, 1,600, 1,573. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.47 (3H, s, OCH_3), 6.22 (1H, s, CH), 6.75–7.95 (8H, m, H–Ar), 9.90 (1H, s, NH), 9.95 (1H, s, NH). ^{13}CNMR (75 MHz, DMSO-d_6): δ_H (ppm) 29.3 (CH), 55.7 (OCH_3), 88.4, 111.2, 119.8, 125.5, 126.1, 126.6, 129.5, 131.3, 132.0, 132.3, 133.2, 133.7, 134.2, 151.5, 157.6, 165.5, 184.3, 184.8. Anal. Calcd for $C_{22}H_{14}N_2O_6$: C, 65.67; H, 3.51; N, 6.96; Found: C, 65.60; H, 3.53; N, 6.89.

Product **21b** Brownish powder. m.p. 198–200 °C. IR (KBr) (cm^{-1}): 3,409, 1,737, 1,695, 1,654, 1,617. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 6.07 (1H, s, CH), 7.24–8.81 (8H, m, H–Ar), 11.25 (1H, s, NH), 11.50 (1H, s, NH). ^{13}CNMR (75 MHz, DMSO-d_6): δ_H (ppm) 29.2 (CH),

90.8, 120.9, 123.6, 124.5, 126.5, 130.6, 130.8, 131.1, 132.1, 134.2, 138.0, 146.7, 150.7, 151.2, 152.9, 161.6, 162.8, 164.7. Anal. Calcd for $C_{21}H_{11}N_3O_7$: C, 60.44; H, 2.66; N, 10.07; Found: C, 60.48; H, 2.57; N, 10.11.

Product **21c** Brownish red powder. m.p. 221–223 °C. IR (KBr) (cm^{-1}): 3,437, 1,686, 1,606, 1,468. ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 6.42 (1H, s, CH), 7.13–8.00 (8H, m, H–Ar), 9.37 (1H, s, NH), 10.81 (1H, s, NH). Anal. Calcd for $C_{21}H_{11}ClN_2O_5$: C, 62.01; H, 2.73; N, 6.89; Found: C, 62.14; H, 2.70; N, 6.81.

Product **21d** Red powder. m.p. 217–219 °C. IR (KBr) (cm^{-1}): 3,569, 3,474, 1,698, 1,614, 1,572. ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 4.91 (1H, bs, CH), 7.16–8.60 (7H, m, H–Ar), 10.94 (1H, s, NH), 11.21 (2H, s, NH and OH). Anal. Calcd for $C_{21}H_{11}BrN_2O_6$: C, 53.98; H, 2.37; N, 6.00; Found: C, 53.91; H, 2.30; N, 6.12.

Result and discussion

In view of our present study [54–60], and because of high importance of pyrimidine-2,4-dione-, benzo[*g*]- and dihydropyrano[2,3-*g*]chromene from pharmacological and biological point of view, we wish to introduce a synthetic method for the synthesis of these groups of compounds via Michael addition of 2-hydroxy-1,4-naphthoquinone or 2,5-dihydroxy-1,4-benzoquinone to the Knoevenagel condensation product of an aldehyde with Meldrum's acid, dimedone or barbituric acid in the presence of a catalytic amount of L-proline (10 mol %) under refluxing conditions in water in good to excellent yields (Scheme 1).

The procedure is very simple and clean. Products are separated from the reaction media with a simple filtration and no more purification is needed. H_2O use as a green solvent increases the environment-friendly aspects of the reaction.

The effect of solvents in the reaction has been investigated (Table 1). As indicated in Table 1, the reaction could be progressed very efficiently in H_2O and EtOH; by considering environmental aspects, H_2O has been chosen as a green solvent for the synthesis.

The effect of L-proline derivatives as catalysts in the reaction has been investigated (Table 2). As indicated in Table 2, the reaction could be progressed very efficiently in the presence of a catalytic amount of L-proline in water.

In a pilot experiment, reaction between a mixture of 2-hydroxynaphthalene-1,4-dione **1**, aldehydes **2**, 5,5-dimethylcyclohexane-1,3-dione or cyclohexane-1,3-dione **3** in the presence of a catalytic amount of L-proline as an inexpensive and readily available catalyst proceeded smoothly in water under reflux conditions for 2 h (Scheme 2). After completion of the reaction (monitored by TLC), the reaction mixture was filtered and the obtained precipitate was washed with water and crystallized from EtOH/H_2O (v:v = 1:3) to afford pure 2*H*-benzo[*b*]xanthene-triones **4a–g**.

To explore the scope and limitations of this reaction, various aldehydes with electron withdrawing and electron donating groups were employed under similar circumstances and the results have been shown in Fig. 2. These reactions proceeded very cleanly under mild reaction conditions and no undesirable side reactions were observed.

To extend the chemical library, 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione **5** has been used instead of compound **1**. The reactions proceed efficiently and led to the formation of the desired products **6a–g** by a pathway similar to the previously mentioned pathway (Scheme 3). The results shown in Fig. 3 clearly indicate the scope and limitations of the reaction.

In order to investigate the scope and limitations of this reaction further, we decided to extend it to Meldrum's acid **7** instead of 5,5-dimethylcyclohexane-1,3-dione or cyclohexane-1,3-dione **3**. In a pilot experiment (Scheme 4), a mixture of 3-methoxybenzaldehyde **2** and Meldrum's acid **7** in EtOH was stirred in the presence of a catalytic amount of L-proline at room temperature for 1 h, then 2-hydroxy-1,4-naphthoquinone **1** was added to the reaction mixture. After completion of the reaction (after 24 h, monitored by TLC), the precipitated product was separated from the

Scheme 1 Synthesis of pyrimidine-2,4-dione-, benzo[*g*]-, and dihydropyrano[2,3-*g*]chromene derivatives

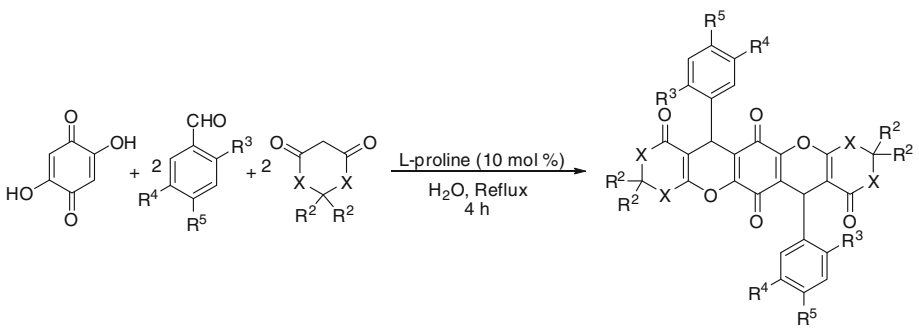


Table 1 Effect of solvents

Entry	Solvent	Time (h)	Yield (%)
1	$PhCH_3$	2	25
2	CH_2Cl_2	2	32
3	CH_3CN	2	40
4	EtOH	2	70
5	H_2O	2	70

5,5-Dimethylcyclohexane-1,3-dione (1 mmol), benzaldehyde (1 mmol), 2-hydroxynaphthalene-1,4-dione (1 mmol) in the presence of L-proline (10 mol %), under reflux conditions

Table 2 Effect of catalysts

Entry	Catalysts	Time (h)	Yield (%)
1	3,4-Dehydro-L-proline[a]	2	25
2	4-Hydroxy-L-proline[a]	2	32
3	L-Proline[a]	2	70
4	L-Proline[b]	24	–
5	–	24	–

[a] 5,5-Dimethylcyclohexane-1,3-dione (1 mmol), benzaldehyde (1 mmol), 2-hydroxynaphthalene-1,4-dione (1 mmol) in the presence of catalyst (10 mol %), under reflux conditions in water

[b] Room temperature

reaction mixture by filtration and washed with *n*-hexane (5 mL) to afford product **8a** in 78 % yield (Fig. 4).

As indicated in Fig. 4, various aldehydes with electron withdrawing and electron donating groups have been used. The reactions are very efficient and the corresponding functionalized products could be obtained with good yields under mild reaction conditions.

Although the mechanism of the reaction has not been studied experimentally, at first, the initial formation of iminium ion **10** in a reversible reaction between aldehydes **2** and L-proline **9** could be assumed, which finally lead to the intermediate **13** after attack of Meldrum's acid or intermediate **14** through the attack of 5,5-dimethylcyclohexane-1,3-dione or cyclohexane-1,3-dione. Then, **13** or **14** is attacked via a Michael-type addition reaction by the 2-hydroxynaphthalene-1,4-dione **1**, which leads to the intermediate **15** or **16**, respectively. In the case of intermediate **15**, an intramolecular cyclization reaction generates intermediate **17**, which undergoes decarboxylation and tautomerization under the reaction conditions to produce the fused heterocyclic systems **8a–f**. Intermediate **16** could be converted to the appropriate products **4a–g** via intramolecular cyclization (Scheme 5) [45].

To extend the chemical library, 2,5-dihydroxy-1,4-benzoquinone **5** has was instead of compound **1**. As

Scheme 2 Synthesis of 2*H*-benzo[*b*]xanthene-triones **4a–g**

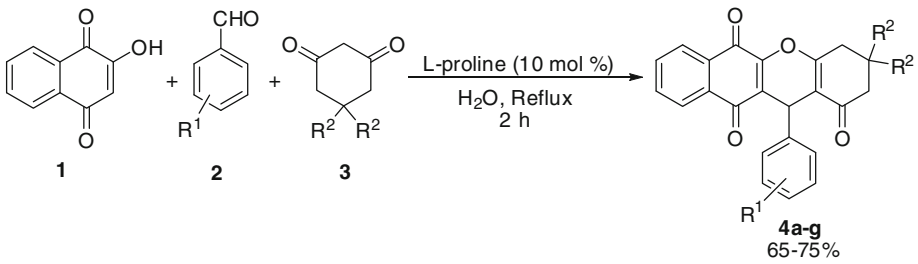
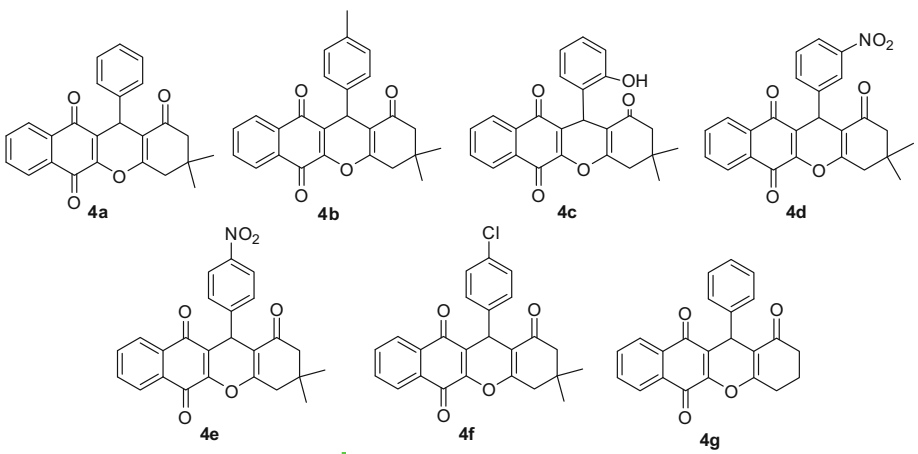


Fig. 2 The structure of 2*H*-benzo[b]xanthene-triones **4a–g**



Product	4a	4b	4c	4d	4e	4f	4g
Yield/%	70	68	75	70	72	73	65

Scheme 3 Synthesis of dodecahydrochromeno[2,3-*b*] xanthene-1,6,8,13-tetraones **6a–g**

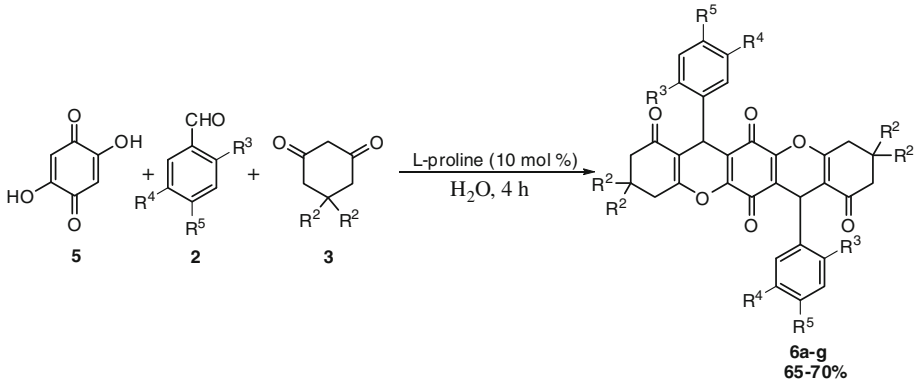
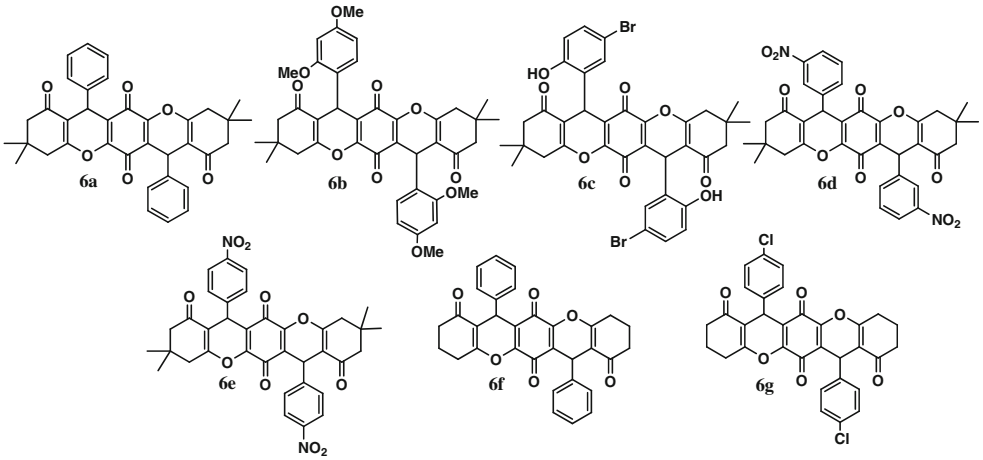
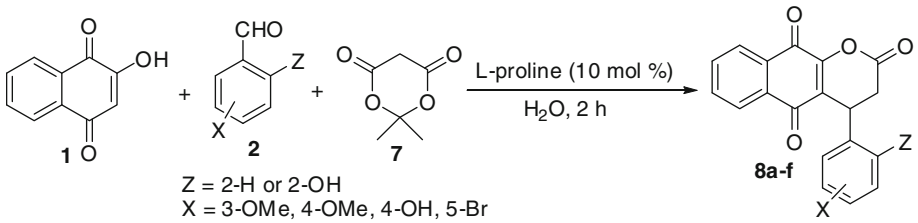


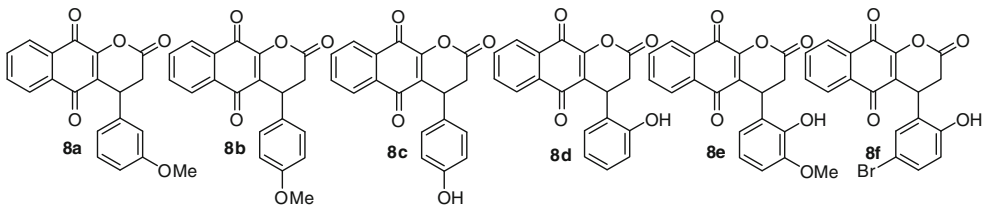
Fig. 3 The structure of dodecahydrochromeno[2,3-*b*] xanthene-1,6,8,13-tetraones **6a–g**



Product	6a	6b	6c	6d	6e	6f	6g
Yield/%	70	65	67	70	70	65	65

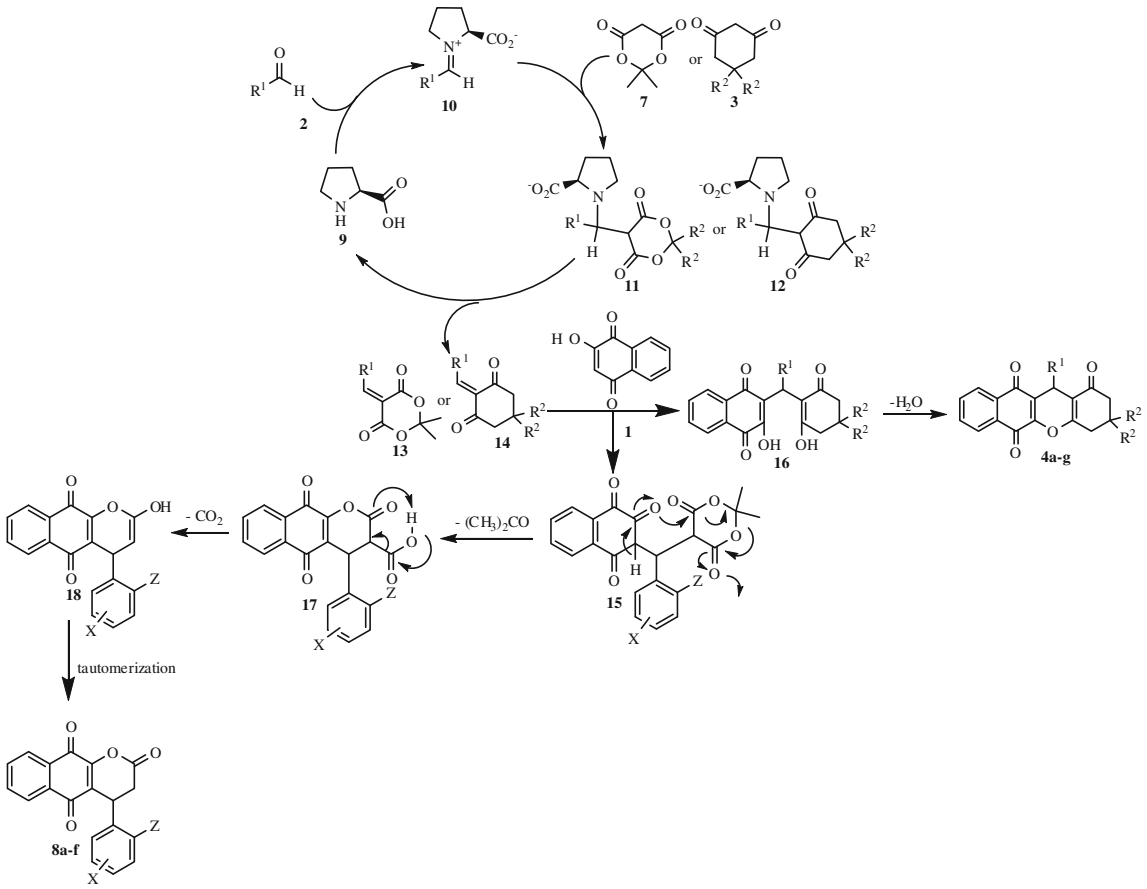
Scheme 4 Synthesis of the products **8a–f**





Product	8a	8b	8c	8d	8e	8f
Yield/%	78	64	80	73	61	80

Fig. 4 Products **8a–f**

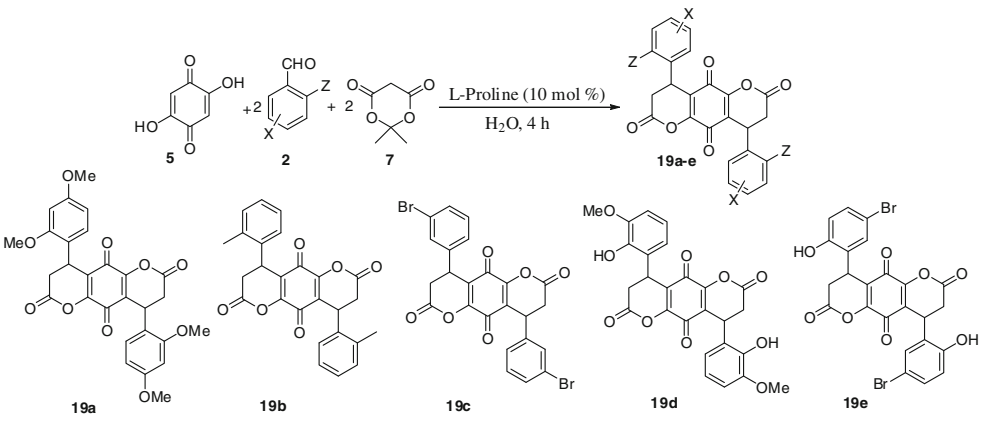


Scheme 5 Proposed pathway for the formation of the products **4a–g** and **8a–f**

indicated in Fig. 5, the reactions proceed efficiently and led to the formation of the desired products **19a–e**.

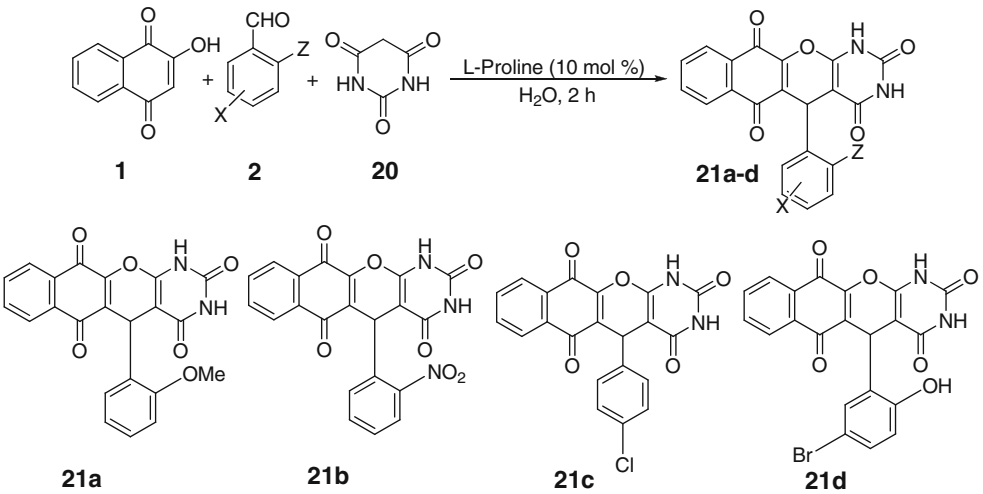
The use of the barbituric acid in the proposed procedure has also been investigated. In this case, similar to the previous reactions, the desired product could be produced via the reaction between barbituric acid **20**, an aldehyde, and 2-hydroxy-1,4-naphthoquinone (Fig. 6). The product of this procedure contains a pyrimidine-2,4-dione moiety which introduces a variety of potential new biological activities to the products. These potential pharmacological activities merit further investigation. It is important to note that some compounds which contain a pyrimidine-2,4-dione

Fig. 5 Products **19a–e**



Product	19a	19b	19c	19d	19e
Yield/%	67	70	83	76	68

Fig. 6 Products **21a–d**



Product	21a	21b	21c	21d
Yield/%	70	74	80	65

moiety have anti-viral properties and these kinds of compounds are very valuable from pharmacological point of view [61].

All the compounds are new (except **8a–f** and **19a–e**) and their structures have been deduced from IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Because of very low solubility of some of the products, we were not able to obtain ^{13}C NMR spectra of them.

Conclusions

In conclusion, we have developed a green and efficient organocatalyzed multicomponent reaction for the synthesis of pyrimidine-containing chromene, benzo[*g*]-, and dihydropyrano[2,3-*g*]chromene derivatives via a domino Knoevenagel/Michael/cyclization sequence from readily available substrates in the presence of a catalytic amount of L-proline in water in moderate to good yields. L-Proline is a very useful organocatalyst and forms imine intermediates through which the reaction proceeded in a more favorable manner. Very simple reaction procedure, good functional group tolerance and easy work-up are some of the advantages of above-mentioned process. Because of structural similarity between synthesized libraries with biologically active chromenes, we hope that these compounds provide promising candidates for chemical library and drug discovery.

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