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Synthesis of Novel Substituted Pyrano Annulated Flavones[1]

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Abstract—A simple and efficient one pot method has been developed for the synthesis of some new functionalized pyrano fused flavone derivatives, alkyl 4,8-dioxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-10-carboxylates and dialkyl 4-oxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-8,9-dicarboxylates, from 7-hydroxy flavones and 7-hydroxy 8-formyl flavones using dialkylacetalynedicarboxylates in the presence of triphenyl phosphine. The structures of all synthesized compounds were elucidated by FT-IR, ^{1}H and ^{13}C NMR and Mass spectral analysis.

Keywords: 7-hydroxy flavones, 7-hydroxy 8-formyl flavones, dialkyl acetylenedicarboxylates, Wittig reaction, pyrano flavones

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INTRODUCTION

Flavonoids make a group of polyphenolic compounds abundant in plants and mainly found in dietary components, including vegetables, fruits, tea, olive oil, and red wine [1]. Flavonoids are important in many biological processes that are beneficial for humans due to interacting with a large number of cellular targets involved in critical cell signaling processes in the body [2]. Various derivatives of flavones have been synthesized and evaluated for different biological activities such as antioestrogenic, anti-inflammatory, antimicrobial [3], anti-allergic, antioxidant, cytotoxic, and antitumor [4]. Thus, flavone moiety can be taken as a lead compound for the synthesis of semi- and purely synthetic flavone derivatives with different functional groups at different positions of its scaffold.

Coumarins constitute an important class of benzopyrones exhibiting a broad range of biological activities like anticoagulants [5], antimicrobial [6], antibacterial [7], anticancer [8, 9], and anti-HIV [10, 11]. They are also widely used in fragrances, agrochemicals, insecticides, and in food and cosmetics. Coumarins are important dyes in laser technology, optical brighteners, fluorescent indicators and photo sensitizers [12].

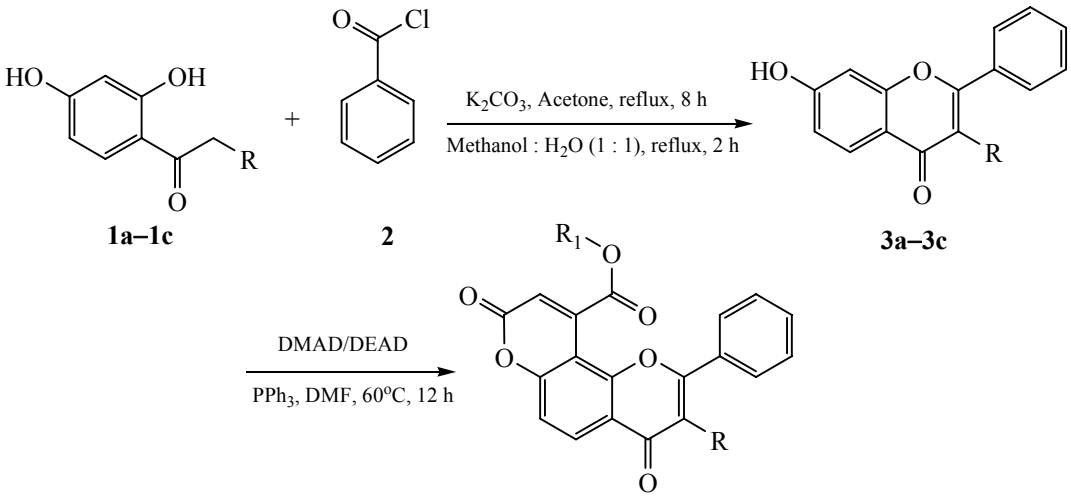
2*H*-1-Benzopyrans (2*H*-chromenes) are important intermediates in the synthesis of many natural products and medicinal entities [13–16]. The chromene units have elicited thereptical interest as structural elements in drug-like compounds. These biological activities of flavones and coumarin derivatives initiated our interest in developing alkyl 4,8-dioxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-10-carboxylate **4a–4f** and dialkyl 4-oxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-8,9-dicarboxylate **6a–6f** from hydroxy flavones **3a–3c** and dialkyl acetylenedicarboxylates with PPh_3. This methodology is the convenient approach to the synthesis of ester functionalized coumarins from phenols and vinyl triphenylphosphonium salts.

RESULTS AND DISCUSSION

The reaction of substituted resacetophenones **1a–1c** with benzoyl chloride **2** under refluxing in acetone/K_2CO_3 medium gave 7-hydroxy flavones **3a–3c** [17]. Refluxing of compounds **3a–3c** with dialkyl acetylenedicarboxylate (DMAD/DEAD) in the presence of triphenyl phosphine in CH_2Cl_2 for 18h led to low yield (18%) of the desired product. Reaction of the same compounds carried out in the polar solvent, DMF, at 60°C for 12 h gave alkyl 4,8-dioxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-10-carboxylates **4a–4f** in moderate to high yields (68–82%) (Scheme 1). The characteristic feature of DMAD/DEAD is in situ

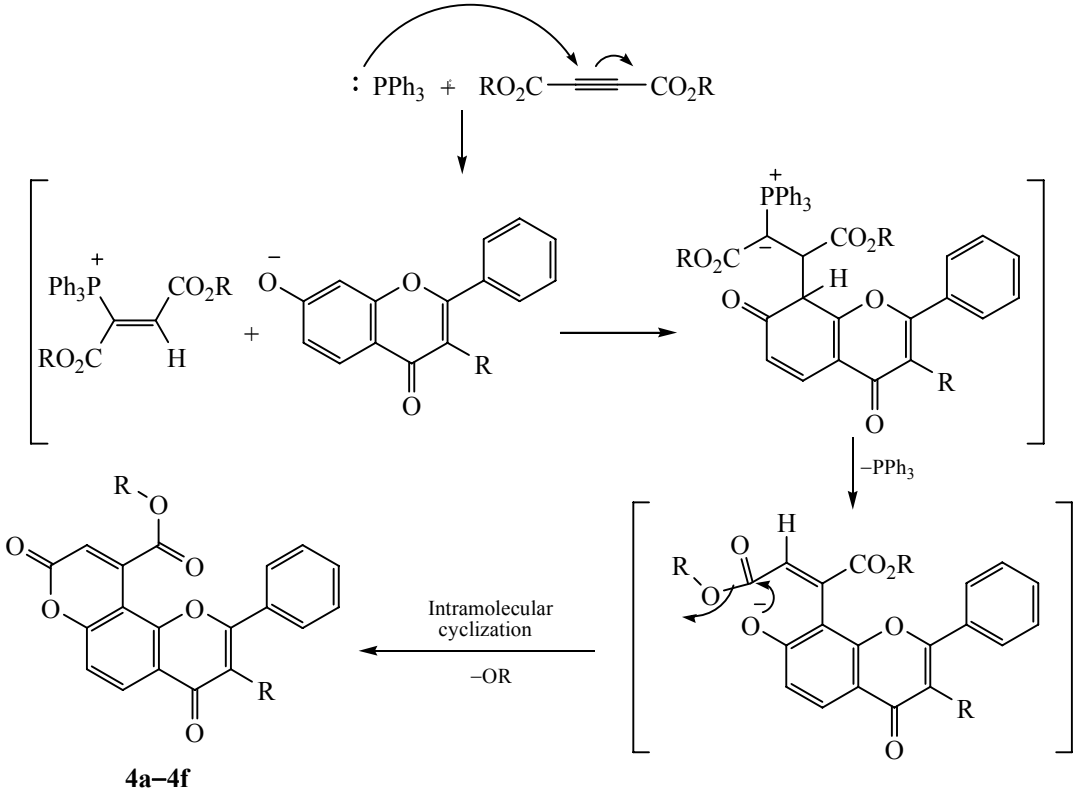
[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of coumarin-flavone esters **4a–4f**.



1: R = H (**a**), Me (**b**), Et (**c**); **4**: R = H, R_1 = Me (**a**), R = H, R_1 = Et (**b**), R = Me, R_1 = Me (**c**), R = Me, R_1 = Et (**d**), R = Et, R_1 = Me (**e**), R = Et, R_1 = Et (**f**).

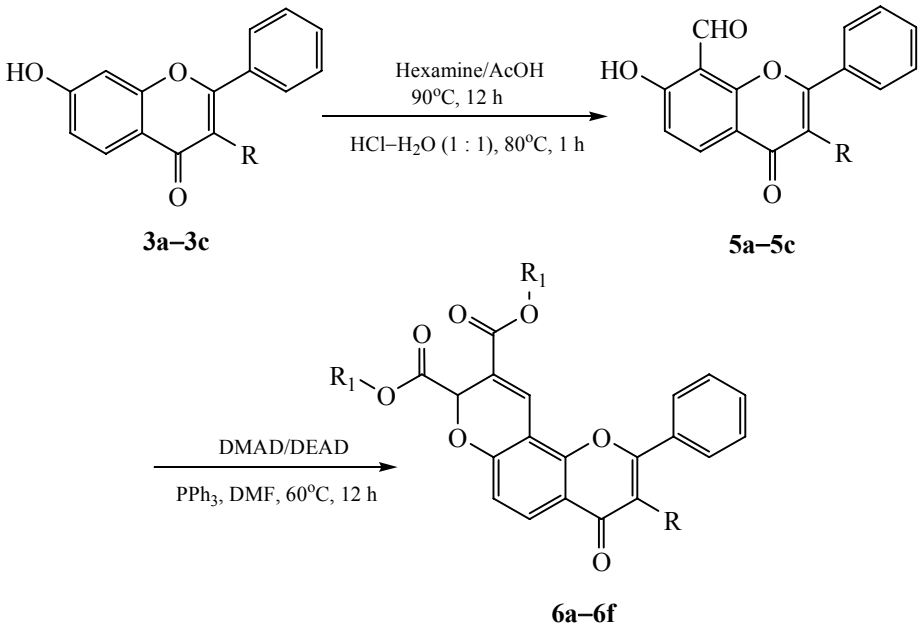
Scheme 2. Proposed mechanism of the synthesis of **4a–4f**.



generation of electrophelic vinyl tryphenyl phosphonium cation in the reaction with PPh_3. The products are probably formed by regioselective aromatic electrophilic attack of vinyl tryphenylphosphonium cation at the 8 position of the aromatic ring rather than the 6 position involving intramolecular lactonization from diesters (Scheme 2).

The structures of **4a–4f** were deduced from spectral analysis. In FT-IR spectrum of **4a** carbonyl bands were

Scheme 3. Synthesis of diesters of pyrano flavones **6a–6f**.



3: R = H (**a**), Me (**b**), Et (**c**); **6**: R = H, R_1 = Me (**a**), R = H, R_1 = Et (**b**), R = Me, R_1 = Me (**c**), R = Me, R_1 = Et (**d**), R = Et, R_1 = Me (**e**), R = Et, R_1 = Et (**f**).

recorded at 1626 and 1734 cm^{-1}. Its ^1H NMR spectrum exhibited characteristic signals at 3.71 ppm (s, $–OCH_3$) and 6.58 ppm (s, coumarin –CH). The structure of **4a** was supported by ^{13}C NMR spectrum.

The next step of the present study was preparation of dialkyl 4-oxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-8,9-dicarboxylates **6a–6f** from bifunctional 7-hydroxy-8-formyl flavones [18]. 7-Hydroxy flavones **3a–3c** introduced in the Duff reaction [19] with hexamethylenetetramine (HMT) in AcOH gave 8-formyl-7-hydroxyflavones **5a–5c,** that reacted with dialkyl acetylenedicarboxylate (DMAD/DEAD) in the presence of triphenyl phosphine in DMF at 60°C for 12 h to give **6a–6f** in high yields (72–85%) (Scheme 3). Mechanism of the reaction involved the initial formation of phosphorane ylide followed by the intramolecular Wittig cyclisation [20, 21] (Scheme 4).

The structures of compounds **6a–6f** were elucidated by FT-IR, ^1H and ^{13}C NMR and mass spectra as well as elemental analyses. FT-IR spectrum of **6a** demonstrated bands of the carbonyl bonds at 1610, 1632, and 1710 cm^{-1}. ^1H NMR spectrum of **6a** exhibited two single sharp lines at 3.72 and 3.93 ppm, characteristic for ester methyl protons, 2*H*-chromene proton and H^4 proton appeared at 5.99 ppm and 8.09 ppm as singlets. In ^{13}C NMR spectrum of **6a** signals of ester carbonyls carbons were recorded at 168.7 and 164.9 ppm.

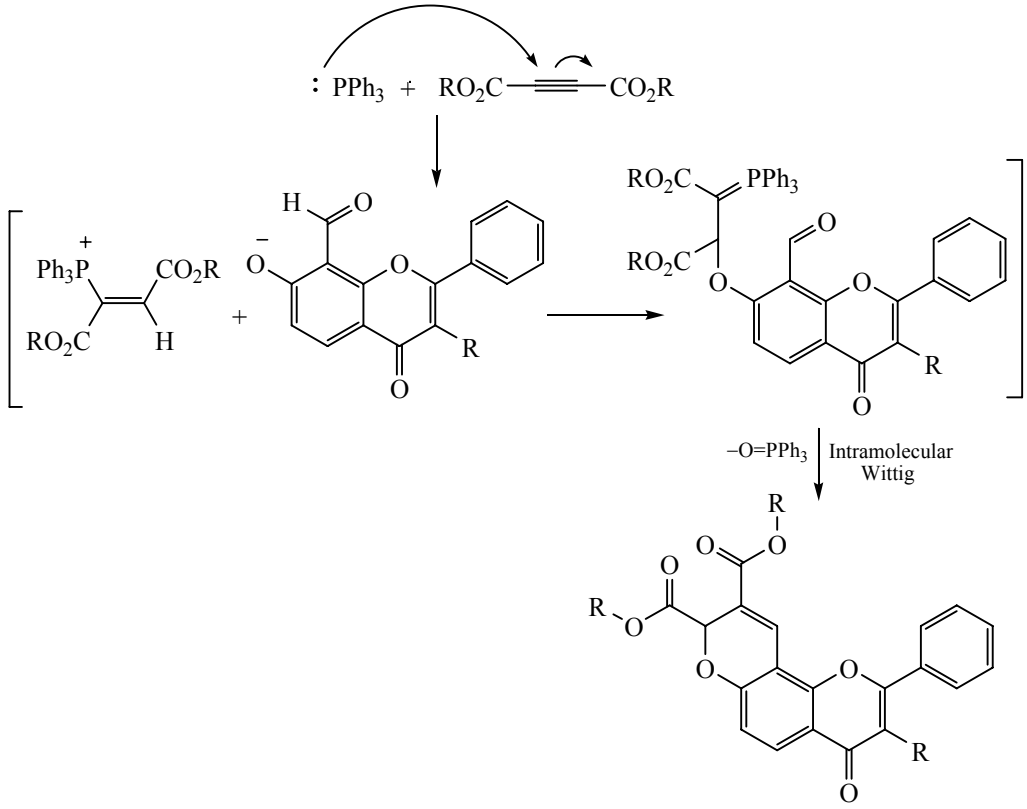
In conclusion, we have developed the simple and efficient one-pot synthesis of alkyl 4,8-dioxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-10-carboxylate **4a–4f** and dialkyl 4-oxo-2-phenyl-4,8-dihydropyrano-[2,3-*f*]chromene-8,9-dicarboxylate **6a–6f**, which cannot be obtained easily or as the sole products by other methods. 4-Ester and 2,3-diester derivatives may be useful precursors in preparation of many other heterocycles.

EXPERIMENTAL

Melting points were determined in open capillaries. Purity of all compounds was routinely tested by TLC on silica gel. IR spectra were recorded in KBr pellets on a Perkin Elmer 2000 spectrophotometer. ^1H NMR spectra were measured on a Bruker 400 MHz with TMS as the internal standard. Mass spectra were measured on a Hewelett Packard mass spectrometer operating at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

General procedure for the synthesis of alkyl 4,8-dioxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-10-carboxylate (4a–4f). A mixture of 7-hydroxy

Scheme 4. Proposed mechanism of the synthesis of **6a–6f**.



6a–6f

flavones **3a–3c** (1mmol) and PPh_3 (1.5 mmol) in DMF (8 mL) was stirred at room temperature for 10 min. Dialkylacetalynedicarboxylate (1.5 mmol) in DMF was added drop wise in 10 min. The brown solution thus obtained was heated at 60°C for 12 h. Then the reaction mixture was diluted with ice cold water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude mass. The product was isolated by silica gel (100–200 mesh) column chromatography using EtOAc–Petrolium ether (2 : 8) as an eluent, giving pure solid products **4a–4f** (65–82%).

Methyl 4,8-dioxo-2-phenyl-4,8-dihydropyrano-[2,3-*f*]chromene-10-carboxylate (4a). Yield 69%, mp 209–211°C. IR spectrum, ν, cm^{-1}: 1626 (C=O) and 1734 (C=O). ^1H NMR spectrum, δ, ppm: 8.46 d (1H, *J* = 8.78 Hz), 7.78 m (2H), 7.59 m (3H), 7.44 d (1H, *J* = 8.78 Hz), 6.77 s (1H), 6.58 s (1H), 3.71 s (3H). ^{13}C NMR spectrum, δ, ppm: 176.2, 165.6, 164.7, 158.1, 157.8, 152.2, 143.2, 132.0, 131.5, 130.1, 129.1, 129.1, 127.1, 127.1, 120.5, 116.2, 115.3, 109.6, 106.2, 53.3. ESI-MS: *m/z* 349 $[M + H]^+$. Found, %: C 68.89, H 3.44. $C_{20}H_{12}O_6$. Calculated, %: C 68.97, H 3.47.

Ethyl 4,8-dioxo-2-phenyl-4,8-dihydropyrano-[2,3-*f*]chromene-10-carboxylate (4b). Yield 66%, mp 196–198°C. IR spectrum, ν, cm^{-1}: 1620 (C=O), 1732 (C=O). ^1H NMR spectrum, δ, ppm: 8.46 d (1H, *J* = 8.78 Hz), 7.78 m (2H), 7.58 m (3H), 7.44 d (1H, *J* = 8.78 Hz), 6.77 s (1H), 6.57 s (1H), 4.19 q (2H), 1.11 t (3H). ^{13}C NMR spectrum, δ, ppm: 176.2, 165.2, 164.7, 158.2, 157.9, 152.2, 143.6, 132.1, 131.6, 130.0, 129.2, 129.2, 127.0, 127.0, 120.0, 116.1, 115.2, 109.6, 106.9, 62.8, 13.7. ESI-MS: *m/z* 363 $[M + H]^+$. Found, %: C 69.52, H 3.81. $C_{21}H_{14}O_6$. Calculated, %: C 69.61, H 3.89.

Methyl 3-methyl-4,8-dioxo-2-phenyl-4,8-dihydro-pyrano[2,3-*f*]chromene-10-carboxylate (4c). Yield 81%, mp 204–206°C. IR spectrum, ν, cm^{-1}: 1618 (C=O), 1736 (C=O). ^1H NMR spectrum, δ, ppm: 8.47 d (1H, *J* = 8.78 Hz), 7.57 m (5H), 7.40 d (1H, *J* = 8.78 Hz), 6.46 s (1H), 3.28 s (3H), 2.13 s (3H). ^{13}C NMR spectrum, δ, ppm: 176.9, 165.2, 161.1, 158.3, 157.6, 151.7, 143.5, 132.1, 130.7, 130.4, 129.2, 129.2,

128.6, 128.5, 119.0, 118.9, 115.2, 114.8, 105.4, 52.6, 11.4. ESI-MS: *m/z* 363 $[M + H]^+$. Found, %: C 69.48, H 3.83. $C_{21}H_{14}O_6$. Calculated, %: C 69.61, H 3.89.

Ethyl 3-methyl-4,8-dioxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-10-carboxylate (4d). Yield 76%, mp 186–188°C. IR spectrum, ν, cm^{-1}: 1622 (C=O), 1740 (C=O). ^1H NMR spectrum, δ, ppm: 8.47 d (1H, *J* = 9.03 Hz), 7.56 m (5H), 7.40 d (1H, *J* = 9.03 Hz), 6.45 s (1H), 3.71 q (2H), 2.13 s (3H), 0.95 t (3H). ^{13}C NMR spectrum, δ, ppm: 176.8, 165.0, 161.2, 158.3, 157.6, 151.7, 143.5, 132.0, 130.4, 130.1, 129.1, 129.0, 128.8, 128.7, 119.0, 118.8, 115.4, 114.5, 105.8, 61.8, 13.9, 11.3. ESI-MS: *m/z* 377 $[M + H]^+$. Found, %: C 70.12, H 4.21. $C_{22}H_{16}O_6$. Calculated, %: C 70.21, H 4.29.

Methyl 3-ethyl-4,8-dioxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-10-carboxylate (4e). Yield 78%, mp 162–164°C. IR spectrum, ν, cm^{-1}: 1606 (C=O), 1728 (C=O). ^1H NMR spectrum, δ, ppm: 8.46 d (1H, *J* = 9.03 Hz), 7.56 m (5H), 7.39 d (1H, *J* = 9.03 Hz), 6.44 s (1H), 3.22 s (3H), 2.54 q (2H), 1.16 t (3H). ^{13}C NMR spectrum, δ, ppm: 181.1, 166.4, 162.3, 159.6, 158.2, 153.0, 145.2, 133.2, 131.0, 130.6, 129.8, 129.8, 129.0, 128.9, 120.1, 119.3, 115.9, 115.1, 104.8, 52.1, 14.9, 11.1. ESI-MS: *m/z* 377 $[M + H]^+$. Found, %: C 70.08, H 4.34. $C_{22}H_{16}O_6$. Calculated, %: C 70.21, H 4.29.

Ethyl 3-ethyl-4,8-dioxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-10-carboxylate (4f). Yield 71%, mp 153–155°C. IR spectrum, ν, cm^{-1}: 1612 (C=O) and 1730 (C=O). ^1H NMR spectrum, δ, ppm: 8.46 d (1H, *J* = 8.78 Hz), 7.56 m (5H), 7.39 d (1H, *J* = 8.78 Hz), 6.43 s (1H), 3.62 q (2H), 2.54 q (2H), 1.15 t (3H), 0.95 t (3H). ^{13}C NMR spectrum, δ, ppm: 179.9, 166.2, 162.0, 159.5, 158.2, 153.2, 145.1, 133.0, 131.1, 130.8, 129.9, 129.9, 129.1, 129.1, 120.6, 119.8, 115.6, 115.8, 104.9, 62.2, 14.8, 14.2, 11.3. ESI-MS: *m/z* 391 $[M + H]^+$. Found, %: C 70.68, H 4.59. $C_{23}H_{18}O_6$. Calculated, %: C 70.76, H 4.65.

General procedure for the synthesis of dialkyl 4-oxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-8,9-dicarboxylate (6a–6f). A solution of 7-hydroxy 8-formyl flavones **5a–5c** (1 mmol) and PPh_3 (1.5 mmol) in DMF (8 mL) was stirred at room temperature for 10 min. A solution of dialkylacetalynedicarboxylate (1.5 mmol) in DMF was added drop wise in 10min, and the brown solution was heated at 60°C for 12 h. Then the reaction mixture was diluted with ice cold water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude mass. The product was isolated by silica gel (60–120 mesh) column chromatography using a mixture of EtOAc-petrolium ether (1.5 : 8.5) as an eluent giving pure solid products **6a–6f** (72–88%).

Dimethyl 4-oxo-2-phenyl-4,8-dihydropyrano-[2,3-*f*]chromene-8,9-dicarboxylate (6a). Yield 73%, mp 144–146°C. IR spectrum, ν, cm^{-1}: 1610 (C=O), 1632 (C=O), 1710 (C=O). ^1H NMR spectrum, δ, ppm: 8.20 d (1H, *J* = 8.78 Hz), 8.09 s (1H), 7.90 m (2H), 7.55–7.69 m (3H), 7.12 d (1H, *J* = 8.78 Hz), 6.79 s (1H), 5.99 s (1H), 3.93 s (3H), 3.72 s (3H). ^{13}C NMR spectrum, δ, ppm: 177.0, 168.7, 164.9, 163.0, 158.1, 153.4, 132.9, 132.1, 132.0, 131.9, 129.2, 128.5, 128.4, 126.6, 126.2, 120.5, 118.9, 114.8, 108.0, 71.9, 52.9, 52.5. ESI-MS: *m/z* 393 $[M + H]^+$. Found, %: C 67.28, H 4.06. $C_{22}H_{16}O_7$. Calculated, %: C 67.35, H 4.11.

Diethyl 4-oxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]-chromene-8,9-dicarboxylate (6b). Yield 76%, mp 140–142°C. IR spectrum, ν, cm^{-1}: 1601 (C=O), 1630 (C=O), 1705 (C=O). ^1H NMR spectrum, δ, ppm: 8.18 d (1H, *J* = 8.78 Hz), 8.09 s (1H), 7.92 m (2H), 7.48–7.69 m (3H), 7.02 d (1H, *J* = 8.78 Hz), 6.83 s (1H), 5.96 s (1H), 4.38 q (2H), 4.15 q (2H), 1.40 t (3H), 1.22 t (3H). ^{13}C NMR spectrum, δ, ppm: 177.0, 168.2, 163.7, 162.9, 158.1, 153.3, 134.6, 132.8, 132.0, 131.9, 129.2, 128.5, 128.4, 126.1, 126.0, 121.2, 118.8, 114.7, 108.3, 72.1, 62.0, 61.5, 14.2, 13.9. ESI-MS: *m/z* 421 $[M + H]^+$. Found, %: C 68.51, H 4.77. $C_{24}H_{20}O_7$. Calculated, %: C 68.57, H 4.80.

Dimethyl 3-methyl-4-oxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-8,9-dicarboxylate (6c). Yield 80%, mp 190-192°C. IR spectrum, ν, cm^{-1}: 1596 (C=O), 1628 (C=O), 1722 (C=O). ^1H NMR spectrum, δ, ppm: 8.24 d (1H, *J* = 8.78 Hz), 7.95 s (1H), 7.57–7.66 m (5H), 7.11 d (1H, *J* = 8.53 Hz), 5.97 s (1H), 3.89 s (3H), 3.73 s (3H), 2.16 s (3H). ^{13}C NMR spectrum, δ, ppm: 177.9, 168.8, 163.9, 160.5, 157.9, 153.6, 133.8, 131.0, 130.3, 130, 129.4, 129.0, 128.5, 126.9, 121.6, 118.0, 117.4, 114.8, 108.2, 72.0, 52.6, 52.1, 12.2. ESI-MS: *m/z* 407 $[M + H]^+$. Found, %: C 67.89, H 4.34. $C_{23}H_{18}O_7$. Calculated, %: C 67.98, H 4.46.

Diethyl 3-methyl-4-oxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-8,9-dicarboxylate (6d). Yield 75%, mp 138–140°C. IR spectrum, ν, cm^{-1}: 1608 (C=O), 1622 (C=O), 1690 (C=O). ^1H NMR spectrum, δ, ppm: 8.20 d (1H, *J* = 8.78 Hz), 7.92 s (1H), 7.65 m (2H),

7.55 m (3H), 7.08 d (1H, J = 8.78 Hz), 5.92 s (1H), 4.34 q (2H), 4.15 q (2H), 2.15 s (3H), 1.33 t (3H), 1.21 t (3H). ^{13}C NMR spectrum, δ, ppm: 177.7, 168.4, 163.8, 160.4, 157.9, 153.3, 133.0, 131.2, 130.3, 129.9, 129.2, 128.9, 128.6, 126.5, 120.7, 117.9, 117.5, 114.5, 108.7, 72.1, 61.9, 61.4, 14.2, 13.9, 11.6. ESI-MS: *m/z* 435 $[M + H]^+$. Found, %: C 69.06, H 5.08. $C_{25}H_{22}O_7$. Calculated, %: C 69.12, H 5.10.

Dimethyl 3-ethyl-4-oxo-2-phenyl-4,8-dihydropyrano[2,3-*f*]chromene-8,9-dicarboxylate (6e). Yield 78%, mp 157–159°C. IR spectrum, ν, cm^{-1}: 1610 (C=O), 1620 (C=O), 1698 (C=O). ^{1}H NMR spectrum, δ, ppm: 8.22 d (1H, J = 8.78 Hz), 7.90 s (1H), 7.55–7.65 m (5H), 7.08 d (1H, J = 8.78 Hz), 5.94 s (1H), 3.86 s (3H), 3.70 s (3H), 2.55 q (2H), 1.16 t (3H). ^{13}C NMR spectrum, δ, ppm: 179.7, 168.6, 163.9, 160.4, 157.8, 153.6, 133.1, 131.0, 130.4, 129.8, 128.9, 128.8, 126.6, 120.4, 117.8, 116.9, 114.6, 107.8, 72.0, 52.3, 51.9, 14.6, 11.2. ESI-MS: *m/z* 421 $[M + H]^+$. Found, %: C 68.50, H 4.72. $C_{24}H_{20}O_7$. Calculated, %: C 68.57, H 4.80.

Diethyl 3-ethyl-4-oxo-2-phenyl-4,8-dihydropyrano-[2,3-*f*]chromene-8,9-dicarboxylate (6f). Yield 72%, mp 150–153°C. IR spectrum, ν, cm^{-1}: 1603 (C=O), 1630 (C=O), 1708 (C=O). ^{1}H NMR spectrum, δ, ppm: 8.20 d (1H, J = 8.78 Hz), 7.89 s (1H), 7.55–7.64 m (5H), 7.08 d (1H, J = 8.78 Hz), 5.92 s (1H), 4.32 q (2H), 4.15 q (2H),2.56 q (2H), 1.34 t (3H), 1.21 t (3H), 1.17 t (3H). ^{13}C NMR spectrum, δ, ppm: 179.5, 168.4, 163.8, 160.1, 157.8, 153.8, 133.0, 131.4, 130.1, 129.6, 128.6, 128.5, 126.1, 120.8, 117.9, 116.6, 114.5, 107.9, 72.3, 62.3, 61.9, 14.8, 14.6 , 14.3, 11.4. ESI-MS: *m/z* 449 $[M + H]^+$. Found, %: C 69.56, H, 5.32. $C_{26}H_{24}O_7$. Calculated, %: C 69.63, H 5.39.

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