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ORIGINAL PAPER

An efficient and facile synthesis of functionalized flavones from flavanones

Dasharath Kondhare[1] · Anjaneyulu Kasa[1] · Balaji Totawar[2] · Venkat Bhadke[3] · Harshad Lade[4]

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Abstract
A mild and efficient scheme for the synthesis of 3-substituted functionalized flavones was developed. The reaction of flavanone and glyoxylic acid in ethanol in the presence of the catalytic amount of sulphuric acid at reflux temperature for 2–3 h yielded good to excellent functionalized flavones. As per present scenario for the synthesis of different substituted flavones, this method represents mild reaction conditions, low-cost catalyst, broad substrate scope along with high yields, which makes it more credible and handy synthetic strategy.

Keywords C-3-substituted flavone · Facile synthesis · Claisen–Schmidt condensation · Functional group interconversion

Introduction

Flavonoids represent the class of natural products which are widely present in diversified fruits and vegetables [1, 2]. Flavonoids seized the attraction of chemists worldwide as its varied derivatives exhibit an array of pharmacological activities. The most promising pharmacological activities include antibacterial [3], antifungal [4], antimalarial [5], anticancer [6] antioxidant [7], antidiabetic [8], anti-HIV [9], anti-tubercular [10], anti-inflammatory [11], immune-stimulatory [12], and wound healing [13] as shown in (Fig. 1).

The literature search suggests that in the basic common natural flavonoids, the C-3 position is unsubstituted and because of this several reports concluded that the C-3 position is alkylated or oxygenated to get the comprehensive new spectrum of flavones for various pharmacological activities (Fig. 2) [14, 15].

There are several synthetic approaches have been developed over the last decade [16–19]. However, the direct functionalization of earlier reported or flavonoid from natural sources has been less studied [20, 21]. The synthesis of these functionalized C-3 flavones ring system has special importance as numerous flavonoids could be extracted in gram scale from their natural sources. This might give quick access to libraries of diverse flavonoid scaffolds in the field of organic chemistry. For the functionalization goal, limited methods for the alkylation at C-3 position are available [22, 23]. Earlier, Detty and McGarry [24, 25] showed a direct alkylation at C-3 via lithiation with lithium diisopropylamide (LDA). Additionally, there are some reports which proved the establishment of an alkyl substituent at C-3 could be accomplished through a palladium-mediated cross-coupling process using 3-haloflavones basic building block [26–28]. Furthermore, numerous strategies are available in the literature for the efficient and novel substitution at the 3-position of flavones [29, 30]. To date, for the functionalization at the C-3 position of flavanone, first hydroxyl group need to convert into a good leaving group such as triflate or halogen in palladium-mediated reactions. However, to perform this reaction, use strong basic conditions and expensive transition metal complexes are required [31–33].

By considering all these observations, we pondered if the flavanone ring frame (**1**) could be selectively functionalized

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✉ Harshad Lade
harshadlade@gmail.com

[1] School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded, MS 431606, India

[2] Gramin Science (Vocational) College, Vishnupuri, Nanded, MS 431606, India

[3] Unisynaxis Laboratories Private Limited, IDA Mallapur, Hyderabad 500076, India

[4] Department of Environmental Engineering, Konkuk University, Seoul 05029, Korea

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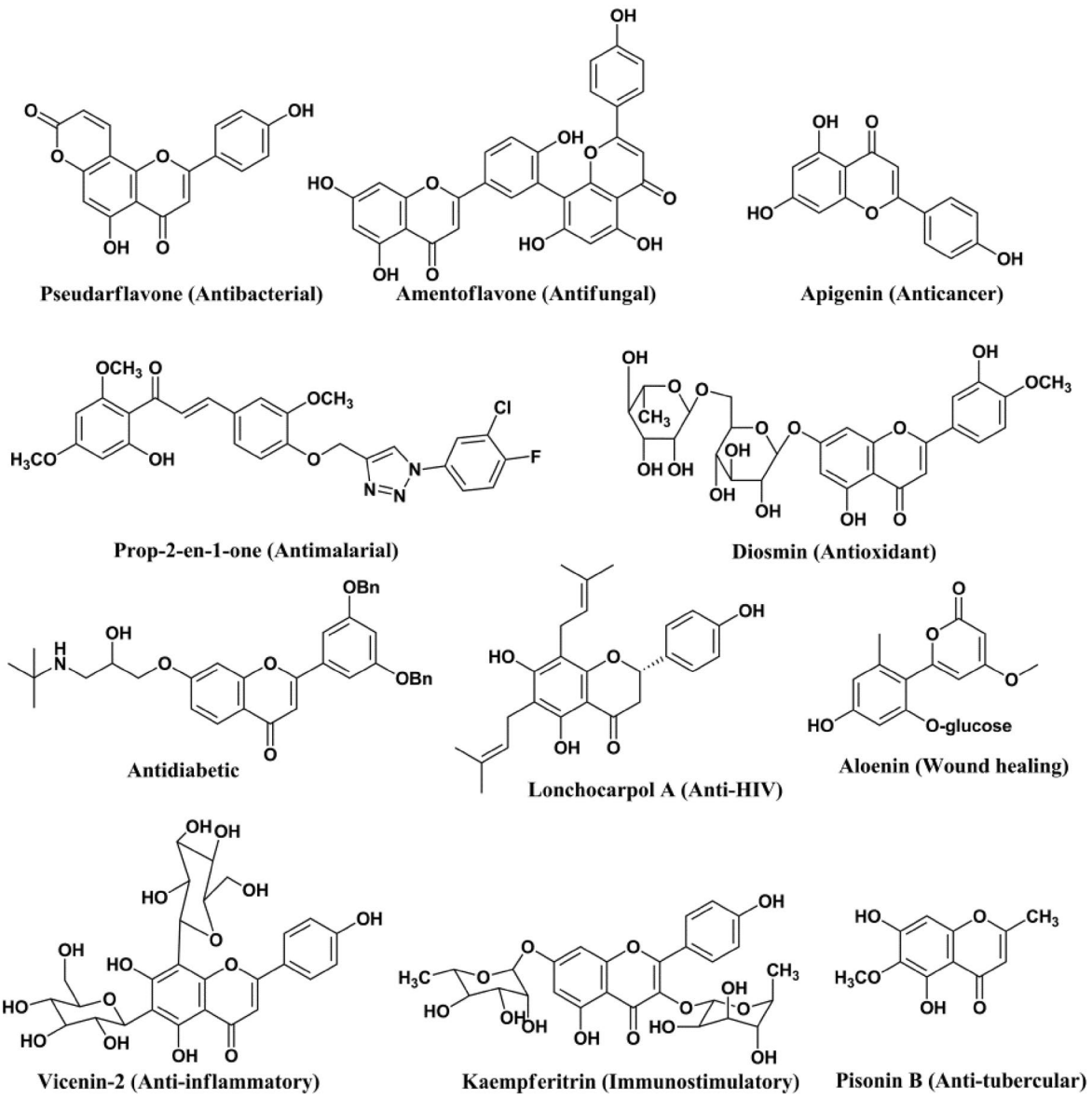


Fig. 1 Pharmacologically active flavanones

at C-3 position using a milder addition process to get the corresponding flavones (Scheme 1). In this context, we explore a metal-free alternative approach for the construction of the flavone ring framework with functionalization at the C3 position.

Experimental

All chemicals were purchased from Merck (Darmstadt, Germany) and Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. Reactions during synthesis were monitored by thin-layer chromatography (TLC) on precoated silica gel 60F254 (mesh), and spots were visualized under UV light or iodine chamber. Silica gel (100–200 mesh) (Merck, Darmstadt, Germany) was used for the column chromatography separations. The melting points (mp) were determined by the open capillary method and reported uncorrected. The spectra were collected on EOL GS-400 model FT-NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C NMR spectra) in DMSO-d_6 and $CDCl_3$. Chemical shift values were reported in parts per million (ppm) on the delta (δ) scale using tetramethylsilane (TMS) as the internal standard, and coupling constants were expressed in hertz. Infrared (IR) spectra were recorded at room temperature on Nicolet iS 10 spectrometer(Thermo Fisher Scientific, Waltham, MA, USA) using KBr pellets in the range of 4000–500 cm^{-1}. The mass spectral data were

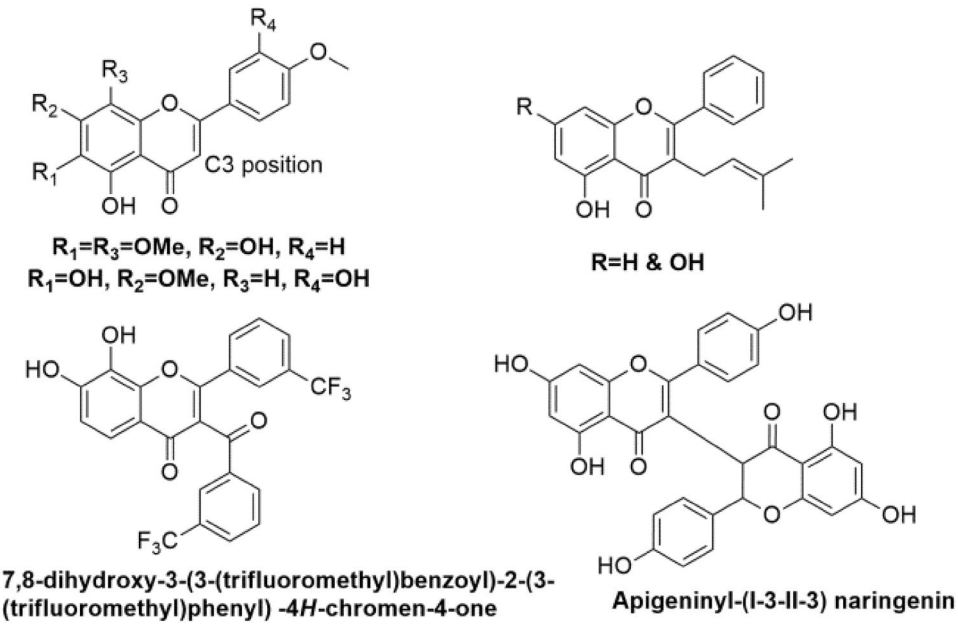
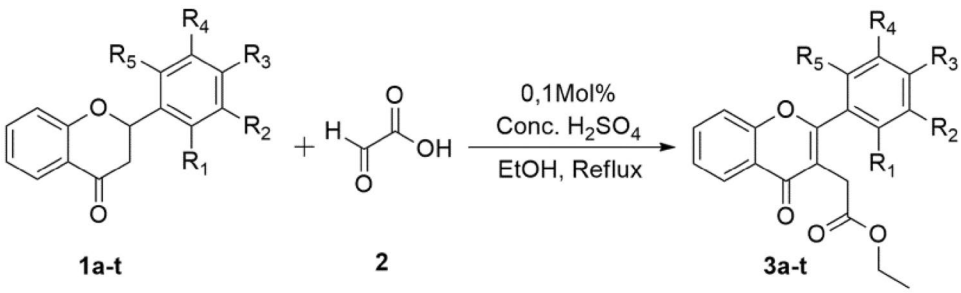


Fig. 2 Leading examples of C3 flavanoids



Scheme 1 Synthesis of 3-substituted flavone derivatives

obtained using Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS mass spectrometer. Elemental CHN analysis was performed on a Perkin-Elmer Model 240B automatic analyser.

Synthesis of 3-substituted flavones

A mixture of glyoxylic acid **2** (1.0 mmol) and flavanone [38] **1(a–t)** (1.0 mmol) in ethanol (2 mL) was prepared at room temperature, and concentrated sulphuric acid (0.1 mol%) was added. The reaction mixture was slowly heated to reflux for 2–3 h. After the starting material completion as monitored by TLC, the solvent was removed under reduced pressure. The resulted residue was dissolved in CH_2Cl_2 (20 mL) followed by an ice-water wash to remove the residual acid stresses. Then, the aqueous layer was washed with CH_2Cl_2 (2* 20 mL) and the combined organic layer with brine solution (30 mL) followed by concentration under reduced pressure to afford a crude product. This was then purified by silica column chromatography with an eluent of hexane/ethyl acetate (9:1) to get 3-substituted flavones **3a–t** (Fig. 3).

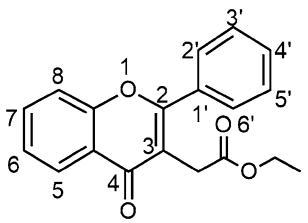


Fig. 3 General numbering of flavone

Ethyl 2-(4-oxo-2-phenyl-4H-chromen-3-yl)acetate (3a)

White powder, mp. 102–103 °C. IR (neat) V_{max}/cm^{-1} 698, 711, 765, 940, 963, 1033, 1123, 1170, 1193, 1333, 1390, 1464, 1574, 1635, 1731, 2904, 2968, 2981, 3444. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25–1.30 (3H, t) 3.56 (2H, s), 4.16–4.23 (2H, q), 7.39–7.55 (5H, m), 7.69–7.71 (3H, m), 8.23–8.26 (1H, dd,J = 1.70, 8.12). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 32.1, 60.9, 115.9, 117.9, 122.6, 124.3, 125.0, 125.9, 128.6, 130.6, 132.7, 133.6, 156.2, 163.2,

171.2, 177.8. EI MS: *m/z* (rel. abund.%) M^{+1}: 309 (100) 263 (35). Anal. Calcd. for $C_{19}H_{l6}O_4$ (308.33): C, 74.01; H, 5.23. Found: C, 74.06; H, 5.20%.

Ethyl 2-(2-(4-chlorophenyl)-4-oxo-4H-chromen-3-yl)acetate (3b)

Off-white solid, mp. 213–216 °C. IR (neat) V_{max}/cm^{-1} 693, 713, 748, 950, 1133, 1140, 1168, 1195, 1350, 1387, 1465, 1575, 1645, 1740, 2910, 2975, 2985, 3445. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–1.31 (3H, t) 3.53 (2H, s), 4.16–4.23 (2H, q) 7.40–7.52 (4H, m) 7.61–7.72 (3H, m), 8.22–8.25 (dd, 1H, $J = 1.51$, 7.93) ^{13}C NMR (100 MHz, CDCl3): δ 13.9, 33.6, 61.3, 117.2, 118.0, 121.3, 125.6, 126.0, 127.9, 128.6, 133.5, 134.1, 136.4, 155.2, 165.2, 175.2, 178.8. EI MS: *m/z* (rel. abund.%) M^{+1}: 344.06 (33), 343.07 (20.9), 345.07 (6.8), 344.07 (2.9) Anal. Calcd. for $C_{19}H_{15}ClO_4$ (342.07): C, 66.58; H, 4.41 Found: C, 66.55; H, 4.45%.

Ethyl 2-(4-oxo-2-p-tolyl-4H-chromen-3-yl)acetate (3c)

Pale yellow solid, mp. 197–199 °C. IR (KBr) V_{max}/cm^{-1} 690, 715, 751, 953, 1131, 1143, 1171, 1193, 1356, 1390, 1471, 1581, 1635, 1730, 2923, 2985, 2995, 3451. ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, t), 2.42 (3H, s), 3.57 (2H, s), 4.18 (2H, q), 7.02–7.05 (m, 2H), 7.25 (2H, d, $J = 7.81$ Hz), 7.35 (2H, d, $J = 7.81$ Hz), 7.52 (1H, m), 7.90 (1H, dd, $J = 8.08$, 1.76 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 32.3, 21.4, 59.6, 113.1, 112.4, 116.9, 123.6, 125.2, 126.9, 127.3, 131.4, 135.2, 157.4, 162.1, 165.1, 173.5, 176.9. EI MS: *m/z* (rel. abund.%) = M^{+1}: 322.12 (100.0), 323.12 (21.8), 324.13 (2.3). Anal. Calcd. for $C_{20}H_{18}O_4$ (322.12): C, 74.52; H, 5.63; Found: C, 74.65; H, 5.57%.

Ethyl 2-(2-(4-methoxyphenyl)-4-oxo-4H-chromen-3-yl) acetate (3d)

Pale yellow solid, mp. 219–221 °C. IR (KBr) V_{max}/cm^{-1} 675, 725, 748, 963, 1138, 1145, 1170, 1189, 1367, 1432, 1458, 1567, 1623, 1720, 2848, 2935, 2985, 3068. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, 3H), 3.58 (s, 2H), 3.86 (s, 3H), 4.21 (q, 2H), 7.02 (d, 2H, $J = 9.0$), 7.43 (m, 2H, $J = 7.4$), 7.65 (m, 3H), 8.23 (m, 3H, $J = 1.6$, 7.8). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 33.4, 56.3, 62.3, 115.1, 116.2, 119.1, 124.1, 125.8, 127.0, 128.9, 132.3, 135.6, 157.2, 160.1, 162.5, 172.5, 176.8 EI MS: *m/z* (rel. abund.%) = M^+: 338.12 (100.0), 339.12 (22.0), 340.12 (3.3). Anal. Calcd. for $C_{20}H_{18}O_5$ (338.12): C, 70.99; H, 5.36; Found: C, 70.94; H, 5.38%.

Ethyl 2-(2-(4-bromophenyl)-4-oxo-4H-chromen-3-yl) acetate (3e)

Yellow solid, mp. 241–242 °C. IR (KBr) V_{max}/cm^{-1} 678, 750, 758, 973, 1140, 1152, 1172, 1191, 1370, 1435, 1460, 1572, 1628, 1731, 2849, 2945, 2995, 3070. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26–1.32 (3H, t), 3.53 (2H, s), 4.18–4.25 (2H, q), 7.05 (2H, d), 7.35 (2H, dd, $J = 8.4$, 1.6 Hz), 7.55 (1H, td, $J = 8.4$, 1.6 Hz), 7.56 (2H, dd, $J = 8.4$, 2.0 Hz), 7.95 (1H, dd, $J = 8.0$, 2.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 32.0, 61.1, 116.2, 117.8, 122.5, 125.1, 125.5, 126.2, 130.3, 131.6, 132.1, 132.3, 134.1, 156.1, 162.4, 171.2, 177.6. EI MS: *m/z* (rel. abund.%) = M^{+1}: 388.01 (97.3). Anal. Calcd. for $C_{19}H_{15}BrO_4$ (386.02):C, 58.93; H, 3.90 Found: C, 58.95; H, 3.88%.

Ethyl 2-(2-(4-nitrophenyl)-4-oxo-4H-chromen-3-yl)acetate (3f)

Yellow solid, mp. 303–304 °C. IR (KBr) V_{max}/cm^{-1} 676, 756, 763, 970, 1143, 1155, 1168, 1193, 1371, 1438, 1464, 1575, 1630, 1733, 2842, 2946, 2989, 3075. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23–1.26 (3H, t), 3.48 (2H, s), 4.17–4.26 (2H, q), 7.10 (2H, m), 7.48 (1H, td, $J = 8.4$, 1.6 Hz), 7.65 (2H, dd, $J = 8.4$, 2.0 Hz), 7.92 (1H, dd, $J = 8.0$, 2.0 Hz), 8.31 (2H, dd, $J = 8.8$, 2.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 32.3, 61.2, 116.7, 116.5, 123.5, 124.8, 126.5, 127.2, 129.3, 130.8, 132.7, 133.4, 135.2, 157.3, 165.4, 173.2, 176.1. EI MS: *m/z* (rel. abund.%) = M^{+1}: 354.09. Anal. Calcd. for $C_{19}H_{15}NO_6$ (353.09):C, 64.59; H, 4.28; N, 3.96 Found: C, 64.55; H, 4.33; N, 3.97%.

Ethyl 2-(2-(4-fluorophenyl)-4-oxo-4H-chromen-3-yl)acetate (3g)

Off-white solid, mp. 176–177 °C. IR (KBr) V_{max}/cm^{-1} 695, 724, 735, 945, 1148, 1153, 1178, 1204, 1335, 1390, 1471, 1565, 1655, 1745, 2925, 2995, 3048, 3455. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20–1.23 (3H, t), 3.45 (2H, s), 4.18–4.25 (2H, q), 7.11 (4H, m), 7.45 (2H, m), 7.55 (1H, td, $J = 8.4$, 1.6 Hz), 7.97 (1H, dd, $J = 8.0$, 2.0 Hz).^{13}C NMR (CDCl3, 100 MHz): δ 14.4, 32.6, 61.4, 116.3, 117.6, 124.6, 125.4, 125.2, 126.9, 130.1, 131.2, 132.3, 133.1, 134.5, 158.7, 164.7, 172.3, 176.7. EI MS: *m/z* (rel. abund.%) = M^{+1}: 327.10. Anal. Calcd. for $C_{19}H_{15}FO_4$ (326.10): C, 69.93; H, 4.63 Found: C, 69.90; H, 4.65%.

Ethyl 2-(2-(2-methoxyphenyl)-4-oxo-4H-chromen-3-yl) acetate (3h)

Pale yellow solid, mp. 147–148 °C. IR (KBr) V_{max}/cm^{-1} 676, 728, 743, 965, 1140, 1142, 1177, 1199, 1376, 1438, 1463, 1572, 1630, 1731, 2850, 2923, 2967, 2995, 3038. ^{1}H NMR

($CDCl_3$, 400 MHz): δ 1.27–133 (3H, t), 3.58 (2H, s), 3.81 (3H, s), 4.18–4.30 (2H, q), 7.01–7.04 (1H, d, $J=8.3$ Hz), 7.06–7.08 (3H, m), 7.33–7.36 (1H, m), 7.47–7.53 (1H, m), 7.62 (1H, dd, $J=0.8$, 7.5 Hz), 7.92 (1H, dd, $J=1.36$, 7.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 32.1, 57.3, 65.1, 114.1, 115.2, 118.2, 120.1, 123.2, 126.3, 127.3, 128.0, 133.3, 134.6, 154.3, 156.2, 161.3, 162.4, 173.3, 175.8. EI MS: *m/z* (rel. abund.%) = M^{+1}: 339.12. Anal. Calcd. for $C_{20}H_{18}O_5$ (338.12): C, 70.99; H, 5.36 Found: C, 70.96; H, 5.38%.

Ethyl 2-(2-(2-fluorophenyl)-4-oxo-4H-chromen-3-yl)acetate (3i)

Colourless gummy solid, IR (KBr) V_{max}/cm^{-1} 675, 715, 745, 958, 1168, 1176, 1189, 1214, 1352, 1408, 1468, 1562, 1652, 1743, 2921, 2996, 3058, 3415. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23–1.26 (3H, t), 3.47 (2H, s), 4.07–4.13 (2H, q), 7.02–7.13 (3H, m), 7.22–7.25 (1H, m), 7.34–7.39 (1H, m), 7.49–7.53 (1H, m), 7.64–7.72 (1H, m), 7.96 (1H, dd, $J=8.56$, 1.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.5, 29.6, 58.3, 115.1, 116.4, 117.6, 123.6, 126.2, 126.8, 127.6, 130.6, 131.5, 132.8, 133.2, 135.5, 158.7, 164.7, 172.3, 176.7. EI MS: *m/z* (rel. abund.%) = M^{+1}: 327.10. Anal. Calcd. for $C_{19}H_{15}FO_4$ (326.10): C, 69.93; H, 4.63 Found: C, 69.89; H, 4.64%.

Ethyl 2-(2-(2-nitrophenyl)-4-oxo-4H-chromen-3-yl)acetate (3j)

Pale yellow solid, mp. 177–179 °C. IR (KBr) V_{max}/cm^{-1} 678, 761, 773, 976, 1145, 1159, 1172, 1215, 1375, 1442, 1465, 1578, 1637, 1738, 2846, 2950, 2995, 3070. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20–1.24 (3H, t), 3.51 (2H, s), 4.04–4.06 (2H, q), 6.09 (1H, dd, $J=13.12$, 2.6 Hz), 7.03 (1H, d, $J=8.0$ Hz), 7.06–7.13 (1H, m), 7.48–7.56 (1H, m), 7.76 (1H, m), 7.97 (1H, dd, $J=7.8$, 1.6 Hz), 8.03 (1H, d, $J=8.20$ Hz), 8.08 (1H, dd, $J=8.20$, 1.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 31.1, 58.5, 115.2, 116.7, 118.7, 123.9, 124.6, 126.1, 127.8 130.1, 130.9, 132.7, 133.5, 135.7, 156.9, 166.7, 172.4, 175.7. EI MS: *m/z* (rel. abund.%) = M^{+1}: 354.09. Anal. Calcd. for $C_{19}H_{15}NO_6$ (353.09): C, 64.59; H, 4.28; N, 3.96 Found: C, 64.62; H, 4.25; N, 4.01%.

Ethyl 2-(2-(2-chlorophenyl)-4-oxo-4H-chromen-3-yl)acetate (3k)

Off-white solid, mp. 164–166 °C. IR (KBr) V_{max}/cm^{-1} 695, 715, 750, 958, 1125, 1145, 1172, 1190, 1355, 1390, 1470, 1584, 1655, 1748, 2920, 2978, 2992, 3450. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20–1.24 (3H, t) 3.49 (2H, s), 4.08–4.15 (2H, q) 7.38–7.7.49 (4H, m) 7.51–7.57 (2H, m), 7.67–7.73 (1H, m), 8.25–8.28 (7.54, dd, 1H, $J=1.51$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 28.4, 59.5, 116.2, 117.5, 118.1, 123.1, 123.9, 126.9, 127.9, 129.1, 131.9, 132.7, 133.6, 135.5, 155.9, 166.6, 173.4, 176.7. EI MS: *m/z* (rel. abund.%) = M^{+1}: 343.07. Anal. Calcd. for $C_{19}H_{15}ClO_4$ (342.07): C, 66.58; H, 4.41 Found: C, 66.60; H, 4.39%.

Ethyl 2-(2-(3-methoxyphenyl)-4-oxo-4H-chromen-3-yl) acetate (3l)

Yellow solid, mp. 127–129 °C. IR (KBr) V_{max}/cm^{-1} 675, 730, 745, 970, 1138, 1145, 1176, 1210, 1335, 1367, 1428, 1453, 1562, 1603, 1670, 1735, 2867, 2920, 2962, 2990, 3018. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.25 (3H, t), 3.48 (2H, s), 3.84 (3H, s), 4.11–4.13 (2H, q), 6.87–6.91 (1H, m), 7.01–7.01 (4H, m), 7.35 (1H, t, $J=8.4$ Hz), 7.47–7.51 (1H, m), 7.93 (1H, dd, $J=8.24$, 1.64 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 32.5, 56.5, 65.8, 114.7, 115.8, 117.9, 120.6, 124.1, 126.8, 127.7, 127.9, 132.1, 133.5, 153.8, 155.7, 164.5, 165.6, 173.1, 175.8. EI MS: *m/z* (rel. abund.%) = M^{+1}: 339.12. Anal. Calcd. for $C_{20}H_{18}O_5$ (338.12): C, 70.99; H, 5.36 Found: C, 70.96; H, 5.38%.

Ethyl 2-(2-(3-nitrophenyl)-4-oxo-4H-chromen-3-yl)acetate (3m)

Pale yellow solid, mp. 182–184 °C. IR (KBr) V_{max}/cm^{-1} 670, 757, 771, 975, 1135, 1145, 1190, 1235, 1360, 1462, 1474, 1575, 1640, 1732, 2848, 2918, 2989 3170.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28–1.31 (3H, t) 3.54 (2H, s), 4.20–4.24 (2H, q) 7.44–7.47 (1H, t) 7.50–7.52 (2H, m), 7.67–7.73 (1H, d, $J=8.99$), 7.71–7.75 (2H, m), 8.04–8.05 (1H, d, $J=7.99$), 8.25–8.27 (dd, 1H, $J=2.00$, 7.99), 8.40–8.45 (1H, d, $J=7.99$), 8.58 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.6, 28.5, 62.4, 116.2, 118.9, 120.9, 123.2, 124.8, 126.3, 127.5, 127.8, 128.2, 131.9, 134.5, 148.7, 163.5, 164.6, 170.1, 176.6. EI MS: *m/z* (rel. abund.%) = M^{+1}: 354.09. Anal. Calcd. for $C_{19}H_{15}NO_6$ (353.09): C, 64.59; H, 4.28; N, 3.96 Found: C, 64.55; H, 4.30; N, 3.95%.

Ethyl 2-(2-(2,4-dichlorophenyl)-4-oxo-4H-chromen-3-yl) acetate (3n)

Off-white solid, mp. 134–136 °C. IR (KBr) V_{max}/cm^{-1}675, 741, 761, 860, 970, 1047, 1118, 1251, 1323, 1465, 1575, 1685, 1948, 2862, 2975, 3130, 3325. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.24 (3H, t) 3.36 (2H, s), 4.10–4.14 (2H, q), 7.39–7.7.45 (3H, m) 7.50–7.52 (1H, d, m, $J=7.99$), 7.57 (1H, s), 7.67–7.71 (1H, t), 8.24–8.26 (1H, d, $J=7.99$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 27.8, 58.9, 117.4, 121.4, 121.7, 127.2, 127.6, 128.8, 130.5, 133.1, 133.8, 134.7, 135.7, 160.4, 162.3, 170.3, 176.1. EI MS: *m/z* (rel. abund.%) = M^{+1}: 377.03. Anal. Calcd. for $C_{19}H_{14}Cl_2O_4$ (376.03): C, 60.50; H, 3.74 Found: C, 60.56; H, 3.71%.

Ethyl 2-(2-(2,4-dimethylphenyl)-4-oxo-4H-chromen-3-yl) acetate (3o)

Pale yellow solid, mp. 207–209 °C. IR (KBr) V_{max}/cm^{-1}: 668, 757, 781, 865, 967, 1147, 1255, 1322, 1475, 1525, 1630, 1690, 1835, 1925, 2873, 2895, 2963, 3135, 3349. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19–1.22 (3H, t), 2.33 (6H, s), 3.42 (2H, s), 4.09–4.12 (2H, q), 7.03–7.06 (2H, m), 7.11–7.13 (2H, d), 7.18–7.20 (1H, m), 7.24 (1H, d, J = 7.81 Hz), 7.48 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 18.7, 20.8, 27.2, 59.9, 115.9, 119.7, 120.2, 123.6, 125.6, 126.8, 127.8, 131.3, 133.1, 134.6, 136.7, 137.3, 161.5 163.3, 171.3, 177.1. EI MS: m/z (rel. abund.%) = M^{+1}: 337.14. Anal. Calcd. for $C_{21}H_{20}O_4$ (336.14): C, 74.98; H, 5.99 Found: C, 74.95; H, 6.00%.

Ethyl 2-(2-(3,4-dimethylphenyl)-4-oxo-4H-chromen-3-yl) acetate (3p)

Pale yellow solid, mp. 136–138 °C. IR (KBr) V_{max}/cm^{-1}: 671, 755, 775, 855, 957, 1137, 1215, 1352, 1480, 1535, 1628, 1685, 1850, 1930, 2872, 2965, 3125, 3350. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23–1.26 (3H, t), 2.38 (6H, s), 3.45 (2H, s), 4.13–4.15 (2H, q), 7.03–7.10 (2H, m), 7.11–7.13 (2H, d), 7.20 (1H, s), 7.42–7.45 (1H, m), 7.80–7.85 (1H, dd, J = 8.65, 1.76 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.7, 19.8, 27.8, 61.2, 116.9, 120.9, 122.3, 123.6, 125.6, 126.8, 127.8, 132.3, 133.1, 134.6, 136.7, 137.9, 159.5 160.7, 170.3, 176.1. EI MS: m/z (rel. abund.%) = M^{+1}: 337.14. Anal. Calcd. for $C_{21}H_{20}O_4$ (336.14): C, 74.98; H, 5.99 Found: C, 74.95; H, 6.00%.

Ethyl 2-(2-(2,5-dimethoxyphenyl)-4-oxo-4H-chromen-3-yl) acetate (3q)

Yellow solid, mp. 214, 216 °C. IR (KBr) V_{max}/cm^{-1}: 673, 764, 785, 868, 982, 1037, 1190, 1263, 1374, 1468, 1560, 1623, 1690, 1965, 2865, 2938, 3125. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–1.29 (3H, t), 2.39 (6H, s) 3.55 (2H, s), 4.17–4.22 (2H, q) 7.17 (1H, s) 7.24 (2H, s), 7.40–7.43 (1H, t), 7.47–7.49 (1H, d, J = 7.99), 7.66–7.69 (1H, t), 8.24–8.25 (1H, d, J = 7.99). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 27.3, 54.7, 55.2, 60.4, 110.7, 111.5, 115.2, 115.7, 118.7, 122.3, 123.8, 127.6, 128.7, 133.4, 148.3, 152.7, 159.5 160.7, 170.3, 176.1. EI MS: m/z (rel. abund.%) = M^{+1}: 369.13. Anal. Calcd. for $C_{21}H_{20}O_6$ (368.13): C, 68.47; H, 5.47 Found: C, 68.45; H, 5.48%.

Ethyl 2-(2-(3,5-dimethoxyphenyl)-4-oxo-4H-chromen-3-yl) acetate (3r) [37]

Pale yellow solid, mp. 103–105 °C. IR (KBr) V_{max}/cm^{-1}: 675, 760, 765, 850, 962, 1047, 1183, 1265, 1379, 1420, 1560, 1608, 1635, 1708, 1750, 2830, 2945, 3094. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (t, 3H), 3.40 (s, 2H), 3.79 (s, 3H), 3.88 (s, 3H), 4.12 (q, 2H), 6.58 (m, 2H), 7.41 (m, 3H), 7.65 (m, 1H, J = 1.6, 7.7), 8.25 (m, 1H, J = 1.6, 7.8). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 29.1, 55.4, 60.3, 98.7, 104.8, 115.5, 117.7, 117.9, 123.0, 124.3, 125.6, 131.2, 133.3, 156.6, 158.2, 161.3, 162.9, 171.1, 177.8. EI MS: m/z (rel. abund.%) = M^{+1}: 369.13. Anal. Calcd. for $C_{21}H_{20}O_6$ (368.13): C, 68.47; H, 5.47 Found: C, 68.45; H, 5.48%.

Ethyl 2-(4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3 -yl)acetate (3s) [37]

Off-white solid, mp. 122–124 °C. IR (KBr) V_{max}/cm^{-1}: 672, 735, 742, 855, 945, 1030, 1047, 1153, 1180, 1268, 1374, 1423, 1442, 1538, 1608, 1685, 1728, 1750, 2831, 2935, 3005, 3109. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (t, 3H), 3.59 (s, 2H), 3.90 (s, 6H), 3.93 (s, 3H), 4.20 (q, 2H), 6.93 (s, 2H), 7.45 (m, 2H), 7.69 (m, 1H, J = 1.8, 7.7), 8.24 (m, 1H, J = 1.5, 7.8). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 28.3, 56.2, 60.3, 61.3, 105.1, 115.7, 117.9, 125.2, 125.8, 127.4, 132.6, 134.6, 138.3, 153.7, 159.0, 161.4, 170.9, 176.7. EI MS: m/z (rel. abund.%) = M^{+1}: 399.14. Anal. Calcd. for $C_{22}H_{22}O_7$, (398.14): C, 66.32; H, 5.57 Found: C, 66.35; H, 5.55%.

Ethyl 2-(2-(naphthalen-2-yl)-4-oxo-4H-chromen-3-yl) acetate (3t)

Off-white solid, mp. 163–165 °C. IR (KBr) V_{max}/cm^{-1}: 648, 765, 878, 948, 1087, 1147, 1268, 1289, 1370, 1403, 1482, 1540, 1638, 1689, 1738, 2848, 2939, 3075, 3149. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.27 (3H, t) 3.35 (2H, s), 4.15–4.18 (2H, q) 7.05 (m, 2H), 7.07–7.10 (m, 2H), 7.55–7.60 (m, 4H), 7.90–7.95 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 28.1, 61.9, 115.9, 121.9, 122.6, 123.8, 124.3, 125.0, 125.9, 128.6, 130.6, 132.7, 133.1, 134.9, 135.8, 158.4, 160.6, 170.3, 176.7. EI MS: m/z (rel. abund.%) = M^{+1}: 359.12. Anal. Calcd. for $C_{23}H_{18}O_4$ (358.12): C, 77.08; H, 5.06 Found: C, 77.05; H, 5.07%.

Results and discussion

To introduce active ester functionality at the 3-positions of the flavones using flavanone as a precursor, conventional Claisen–Schmidt condensation chemistry was used for flavones preparation. The initial optimization was performed using a model reaction of flavanone and glyoxalic acid with a catalytic amount of sulphuric acid in ethanol at room temperature. The reaction was too slow and took more than 7 h to get the poorly yielded product. However, TLC substantiated clean product formation with unreacted starting

material without any side-product formation. To promote the reaction further, heat energy was provided. When the reaction was performed at a refluxed temperature, complete conversion of flavanone to flavones was observed on TLC. With this optimized condition, the scope of substituted aryl rings was investigated. For this reaction to proceed, a catalytic amount of sulphuric acid is required. However, with optimized results in our hands, this reaction proved an easy and reliable addition of ester at 3-position, and the plausible mechanism of reaction pathway is demonstrated in Fig. 4. The formation of C-3-substituted flavones from flavanone and glyoxalic acid is proposed via acid-catalysed Claisen–Schmidt condensation. A plausible mechanistic proposal could involve initially protonation of flavanone leading to the formation of enol-type intermediate (I); later intermediate (II) was formed through resonance stabilization. Here we assume that the intermediate II attacks on the carbonyl carbon of glyoxalic acid which results into formation of intermediate III. Subsequently, dehydration gave intermediate IV. To render stability, the intermediate IV converted to V. With this idea in mind, we proposed that the intermediate VI was formed through proton exchange. Now the electrophilicity of VI has been increased. The compound VI on nucleophilic addition gave intermediate VII. Followed by deprotonation, an unstable intermediate VIII was formed which on dehydration results into final C-3 functionalized flavones.

Here we developed an excellent strategy for the direct ester functionality at 3-position of flavone which comes from flavanones under mild reaction conditions, having an inexpensive catalyst, broad substrate scope along with high yields. Hence, we believe that this methodology will

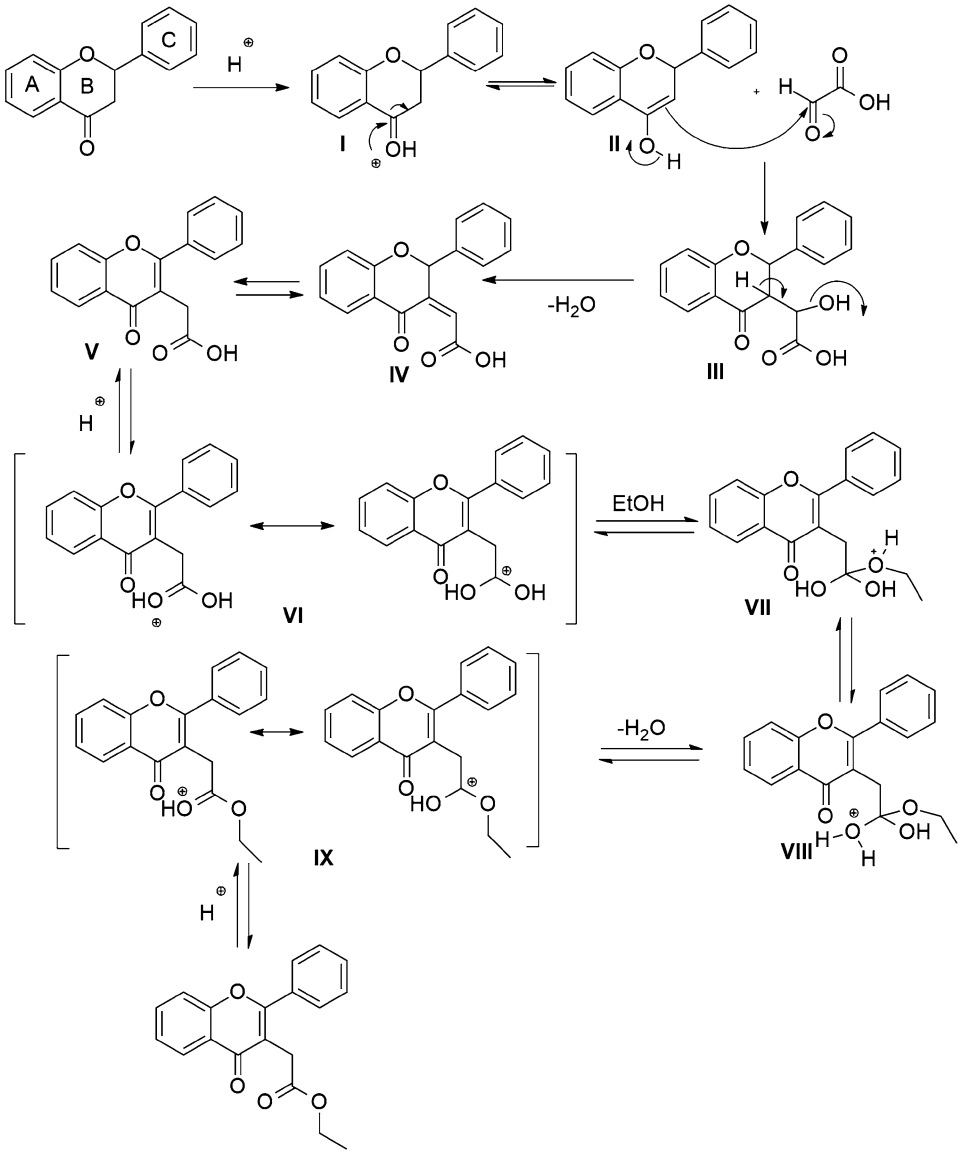


Fig. 4 A plausible mechanism based on the Claisen–Schmidt condensation for the synthesis of 3-substituted flavones

Table 1 Synthesis of novel 3-substituted flavones derivative

Entry	R_1	R_2	R_3	R_4	R_5	Time (h)	Yield (%)
3a	H	H	H	H	H	2	97
3b	H	H	Cl	H	H	1.5	95
3c	H	H	Me	H	H	2.5	98
3d	H	H	OMe	H	H	1.5	93
3e	H	H	Br	H	H	2	90
3f	H	H	NO_2	H	H	1.5	91
3g	H	H	F	H	H	1.5	90
3h	OMe	H	H	H	H	2	92
3i	F	H	H	H	H	2	90
3j	NO_2	H	H	H	H	1.5	85
3k	Cl	H	H	H	H	2	85
3l	H	OMe	H	H	H	2.5	80
3m	H	NO_2	H	H	H	1.5	80
3n	Cl	H	Cl	H	H	2	83
3o	Me	H	Me	H	H	1.5	92
3p	H	Me	Me	H	H	2	85
3q	OMe	H	H	OMe	H	2	80
3r	H	OMe	H	OMe	H	2.5	85
3s	H	OMe	OMe	OMe	H	2.5	88
3t	Naphthyl flavanone					2.5	90

be more compliant over conventional methods. Stille and Heck's reactions were often applied for the introduction of varied substituents in the 3-positions, whereas Sonogashira and Suzuki reactions were only applied in the 8-position [34–37].

The Stille reaction is widely used to introduce either an allyl or benzyl substituents. The allyl substituent can be functionalized through various reactions, for instance, hydroxylation followed by further oxidation to an aldehyde or a carboxylic acid. The Heck reaction, which is widely applied to introduce an α,β-unsaturated ester functionality, can be modified by additional reactions. The similar advantage of our protocol is that this reaction gives directly a versatile ester functional group at 3-positions of flavones which will be easily converted to another functional group that will help to develop further useful building blocks for flavonoids chemistry (Table 1).

The scope of this acid-catalysed Claisen–Schmidt reaction was examined under optimized conditions. In all the tested case, the desired C-3 functionalization reaction proceeded smoothly. In general, the reaction performed on various para-, ortho-, meta- as well as disubstituted flavanones (**1a–t**), thus giving the corresponding C-3 functionalized flavones (**3a–t**) with 80–97% yields. Various valuable functional groups at various positions on flavanone ring were tolerated, such as trimethoxy, chloro, fluro, bromo, methyl, nitro, dichloro, dimethyl, and naphthyl (Table 1). These results indicate that the electron-withdrawing or electron-donating properties in the aryl rings do not affect the reactivity. Thus, the process which omits strong basic conditions, cessation of expensive transition metal complexes, and pre-functionalized starting material will be a more beneficial and straightforward synthetic strategy for the preparation of exclusively useful flavone derivatives. Therefore, in this work, structural modifications on the C ring of flavanones **1a**–**1t**, leading to compounds **3a**–**3t**, respectively, were reported.

Conclusions

A simple synthetic strategy for 3-functionalized flavones was developed starting from a variety of flavanone. This approach allows the introduction of different substituents or functionalities at the 3-positions of flavones using FGI strategy. Results show that the choice of a substituent on aryl rings does not influence the reactivity at the other positions of the flavones ring system. Hence, these protocols would be a good inclusion to the environmentally benign methods reported for the said category of flavonoids synthesis.

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