Synthesis and Photooxygenation of Linear and Angular Furocoumarin Derivatives as a Hydroxyl Radical Source: Psoralen, Pseudopsoralen, Isopseudopsoralen, and Allopsoralen

Sameh Ramadan Elgogary,[a,b]* Neveen Mohamed Hashem,[a] and Mohamed Nabeel Khodeir[a]

[a]Chemistry Department, Faculty of Science, Damietta University, Egypt
[b]Chemistry Department, Faculty of Science (Jazan), Jazan University, Kingdom of Saudi Arabia
*E-mail: selgogary@gmail.com

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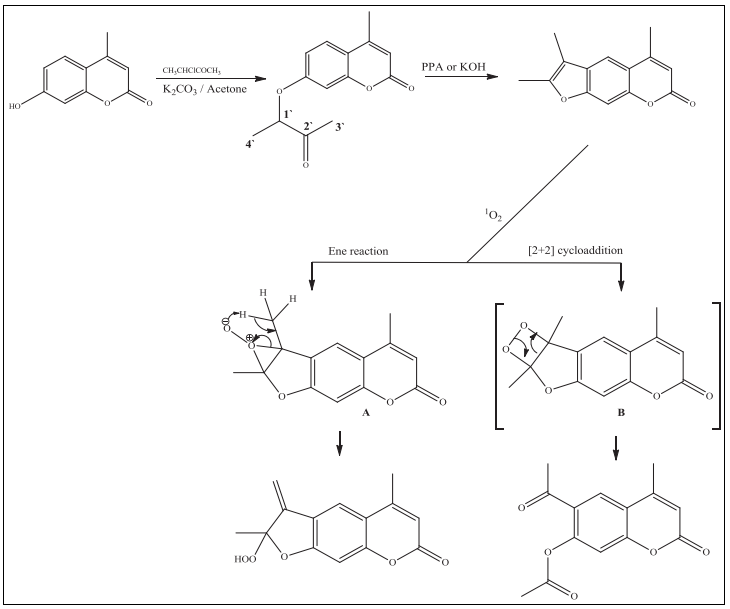

Synthesis of linear and angular furocoumarins with new skeleton structure of potential photobiological feature interest was carried out through Williamson reaction of hydroxycoumarins with 3-chloro-2-butanone followed by cyclization with polyphosphoric acid or by heating in a strongly alkaline solution. The photooxygenation reactions of synthesized furocoumarins were performed in chloroform and in the presence of tetraphenylporphyrin as singlet oxygen sensitizer ($^1O_2$). The photooxygenation reactions afforded the photocleaved product through [2 + 2] cycloaddition and the photooxygenated products through *ene* reaction and [4 + 2] cycloaddition. The photoproducts were isolated and fully characterized by spectral analyses.

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INTRODUCTION

Furocoumarins such as psoralens **1** are photoactive drugs, which are commonly used in the PUVA therapy (psoralen plus UVA radiation) for the treatment of human skin diseases [1]. The potency and effectiveness of these photochemotherapeutic agents depend on their photobinding ability with DNA. Although PUVA therapy proves to be very effective, some undesirable side effects are present such as a persistant erythema [2], genotoxicity [3], phototoxicity, and a possible risk of skin cancer [4]. These side effects are mostly attributed to psoralen interstrand cross-links with DNA rather than to monofunctional adducts [5], a consequence of their bifunctional nature (photoactive α-pyrone and furan sites).

To enhance the photobinding properties and reduce side effects, a wide range of structural modifications of psoralens have been attempted to obtain furocoumarins able to behave as essentially monofunctional agents [6]. To date, this has been accomplished in three different ways: (a) using angular furocoumarins such as angelicins **2**, which on account of their geometry cannot cross-link with DNA [7], (b) blocking of the photoreactive α-pyrone double bond by appropriate substituents [8] or by annelation of an additional aromatic ring [9], and (c) incorporating an additional benzene ring between active double bonds of the α-pyrone and furan moiety [10].

The differences of photobiological and mutagenic activities between psoralens and angelicins [7,11] indicate that the geometries of active double bonds of α-pyrone and furan moieties play a crucial role in their properties.

In the last decade, intensive investigations have been carried out on the chemical, biochemical, and biological aspects of DNA oxidations caused by reactive oxygen

species such as hydroxyl and alkoxyl radicals [12,13], singlet oxygen [14], and superoxide ion [13], which are involved in oxidative stress [15]. Among the reactive oxygen species, hydroxyl radicals are implicated as the key oxidizing reagents of DNA and other biological molecules [12,15,16]. The conventional chemical sources of hydroxyl radicals, for example H_2O_2/Fe^{2+} (Fenton reaction) [17] or radiolysis of aqueous solutions [18], are not properly suited for biochemical or biological investigations because they generate, besides hydroxyl radicals, other reactive oxygen species [18].

It has been reported that the furocoumarin hydroperoxides [19,20], which are readily available by photooxygenation of imperatorin or the alloimperatorin derivative, cause DNA damage through generation of hydroxyl radicals under photolytic conditions, and they intercalated into the DNA [21].

In this context, our strategy has been focused on synthesizing linear and angular furocoumarins and incorporating the photolabile hydroperoxide group into their skeleton through photooxygenation to provide an effective hydroxyl radical source.

RESULTS AND DISCUSSION

Construction of furan ring on the benzene ring of coumarin gives six possible structures of furocoumarins. The two possible linear geometry are 7*H*-furo[3,2-*g*]chromen-7-one (**psoralen, 1**) and 6*H*-furo[2,3-*g*]chromen-6-one (**pseudopsoralen, 3**), while the four angular structures are 2*H*-furo[2,3-*h*]chromen-2-one (**angelicin, 2**), 7*H*-furo [3,2-*f*]chromen-7-one (**isopseudopsoralen, 4**), 7*H*-furo [2,3-*f*]chromen-7-one (**allopsoralen, 5**), and 8*H*-furo[3,2-*h*]chromen-8-one (**pseudoisopsoralen, 6**) (Fig. 1). We prepared, successfully, new linear and angular furocoumarins with new skeleton structure and potentially interesting photobiological features.

Synthesis of linear and angular furocoumarin derivatives. The synthetic methodology for the preparation of the furocoumarins is displayed in Scheme 1. The first step was Pechmann condensation of resorcinol [22], quinol [23], and orcinol [15] with ethyl acetoacetate in sulfuric acid, affording the corresponding hydroxycoumarins **7**, **8**, and **9** in 95, 35, and 78% yields, respectively. Next, the

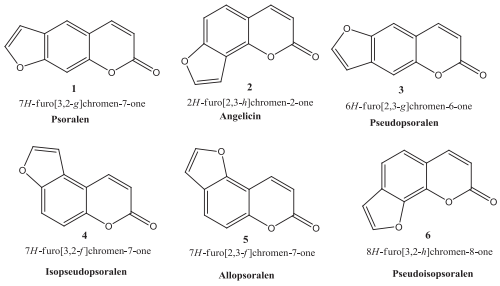
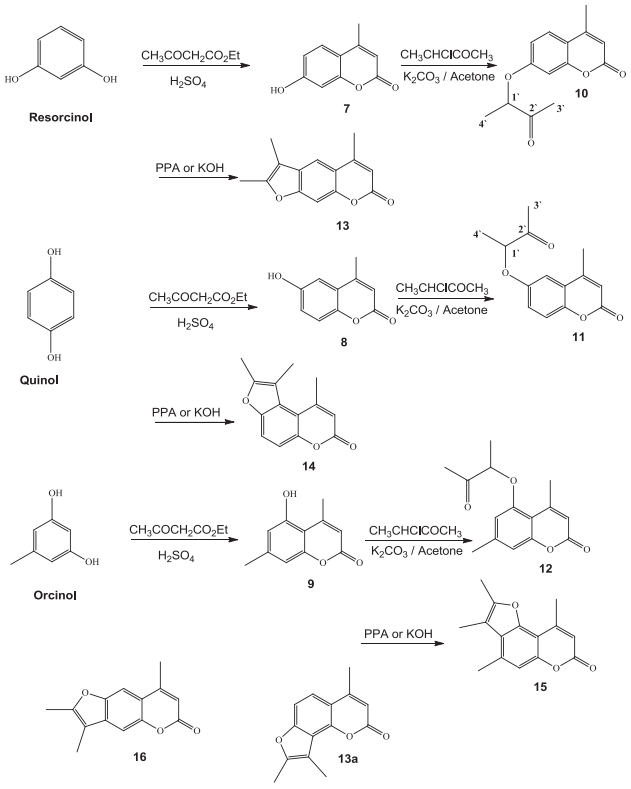


Figure 1. Structure of linear and angular furocoumarins (psoralens).

Scheme 1. Synthesis of linear and angular furocoumarin derivatives.



Williamson reaction of **7**, **8**, and **9** with 3-chloro-2-butanone in refluxing acetone and in the presence of K_2CO_3 for 24 h gave the keto ethers **10, 11**, and **12** in 51, 65, and 83% yields, respectively (Scheme 1).

The structure of keto ether **10**, for example, was confirmed by the disappearance of the hydroxyl group absorption band and appearance of the new absorption band related to carbonyl group at 1712.48 cm^{-1}. The ^1H NMR of this compound revealed that new signals corresponding to aliphatic protons resonates at δ 4.69 (q, $J = 6.9$ Hz), 2.19 (s), and 1.54 (d, $J = 6.9$ Hz) for 1′-H, 3′-H, and 4′-H respectively. Further confirmation of **10** was the detection of the molecular ion (M^+) at *m/z* 246 (M^+, 54%) in the mass spectrum.

Finally, compounds **10**, **11**, and **12** were cyclized by treatment with polyphosphoric acid (PPA) at 70°C for 5 h or by heating in a strongly alkaline solution (3% KOH) for 2 h.

Cyclization of **10** gave the linear furocoumarin **13** exclusively in 80% yield (psoralen type). The structure of **13** was established for the reaction product based on the spectral [IR, ^1H NMR, ^{13}C NMR, and mass spectroscopy (MS)] and elemental analyses, while the structure of angular furocoumarin **13a** was excluded.

^1H NMR spectrum of **13** showed two singlet signals for two aromatic protons (C-5 and C-8) at δ 7.49 and 7.28 ppm. The multiplicity of the aromatic protons (singlet signals),

and the absence of *ortho* coupling, confirmed the exclusive cyclization to the linear furocoumarin skeleton.

Compound **11** was cyclized with PPA to yield 1,2,9-trimethyl-7*H*-furo[3,2-*f*]chromen-7-one (**14**) (isopseudopsoralen type) and 2,3,8-trimethyl-6*H*-furo[2,3-*g*]chromen-6-one (**16**) (pseudopsoralen type) in 43 and 10% yields, respectively (Scheme 1). The structures of **14** and **16** were supported by spectral analyses. ^{1}H NMR spectrum of **14** showed separated two signals for two aromatic protons (H-7 and H-8) as doublet with coupling constant 9 Hz at δ 7.52 and 7.19 ppm (presence of *ortho* coupling). On the other hand, ^{1}H NMR spectrum of **16** showed two singlet signals for two aromatic protons (H-5 and H-8) at δ 7.54 and 7.31 ppm (absence of *ortho* coupling).

The cyclization of **12** gave the angular furocoumarin **15** (allopsoralen type) in 54% yield. The structure of **15** was confirmed by spectral (IR, ^{1}H NMR, ^{13}C NMR, and MS) and elemental analyses. ^{1}H NMR spectrum of **15** showed singlet signal for one aromatic proton at δ 6.89 ppm (C-8) and four singlet signals at δ 2.68, 2.64, 2.39, and 2.31 ppm assigned to four methyl groups (each signal integrating for three protons), with resonance at δ 22.0, 19.6, 11.7, and 10.5 ppm in ^{13}C NMR.

Photooxygenation reactions of furocoumarin derivatives 13–15. Our strategy to obtain an effective hydroxyl radical source has been oriented to incorporate the photolabile hydroperoxide group into an intercalating chromophore such as furocoumarins (**13–15**) through the photooxygenation reactions.

The photooxygenation of the linear furocoumarin derivative **13** in chloroform and in the presence of tetraphenylporphyrin (TPP) as singlet oxygen sensitizer at room temperature gave the stable allylic hydroperoxide **17** and 6-acetyl-4-methyl-2-oxo-2*H*-chromen-7-yl acetate (**18**) in 10 and 60% yields, respectively (Scheme 2).

The mechanism of the formation of the allylic hydroperoxide **17** was achieved by the reaction of singlet oxygen ($^1O_2$) with an olefin bearing allylic hydrogens in the so-called Schenck-ene reaction [24] through the ene mechanism from peroxirane transition state (**A**) that led to the formation of an allylic hydroperoxide. On the other hand, the formation of the dioxetane (**B**) was carried out by the [2 + 2] cycloaddition of singlet oxygen with the double bond of the furan moiety. The dioxetane (**B**) was photolized rapidly under the photooxygenation conditions to give **18** *via* broken O–O and C–C bond (Scheme 2).

The stable allylic hydroperoxide **17** was isolated and fully characterized by spectral analyses (cf. Experimental section). The most conspicuous features in ^{1}H NMR spectrum of stable allylic hydroperoxide were two distinct doublets that correspond to two olefinic protons at δ 6.33 and 6.19 ppm with a coupling constant of 1.2 Hz and a singlet peak at δ 12.62 ppm for OOH, which was exchangeable with D_2O. The IR spectrum of **17** showed that hydroperoxy stretching broad band was at 3500–3250 cm^{-1}.

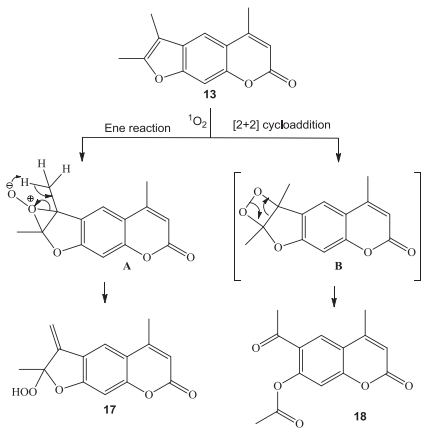
The structure of **18** was confirmed by the presence of new two bands at 1754.9 and 1685.48 cm^{-1} for two carbonyl moieties in IR and the three singlet signals of three methyl groups at δ 2.61, 2.49, and 2.40 ppm in ^{1}H NMR. Further confirmation of compound **18** was obtained through acid hydrolysis of compound **18** to afford 6-acetyl-7-hydroxy-4-methyl-2*H*-chromen-2-one (**20**), which was obtained through Fries rearrangement of **19** (Scheme 3).

Similarly, under the photooxygenation conditions (chloroform/TPP/$^1O_2$), the photooxygenation reaction of **14** gave the photooxygenated product **22** (allylic hydroperoxide) and the photocleaved product 5-acetyl-4-methyl-2-oxo-2*H*-chromen-6-yl acetate (**23**) in 6 and 55% yields, respectively (Scheme 4).

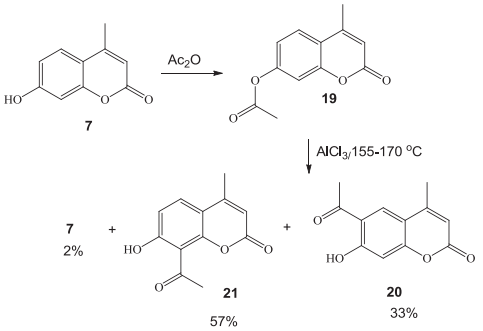
The IR spectrum of **22** showed the hydroperoxy (OOH) stretching broad band at 3600–3200 cm^{-1}. The most important signals in the ^{1}H NMR spectrum of **22** were two distinct doublets that attributed to two olefinic protons at δ 6.33 and 5.16 ppm with coupling constant $J = 0.9$ Hz and a singlet peak at δ 7.30 ppm for OOH, which was exchangeable with D_2O.

The photocleaved product **23** was isolated and fully characterized by IR, ^{1}H NMR, and MS (cf. Experimental section). The appearance of two new stretching bands at

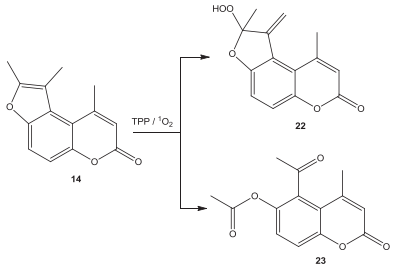
Scheme 2. Photooxygenation mechanisms of **13**.



Scheme 3. Fries rearrangement of **19**.



Scheme 4. Photooxygenation of **14**.



1770.33 and 1708.62 cm^{-1} that were assigned to two new carbonyl groups in IR and the presence of three singlet signal of three methyl moieties at δ 2.62, 2.31, and 2.30 ppm in ^1H NMR confirmed the structure of **23**.

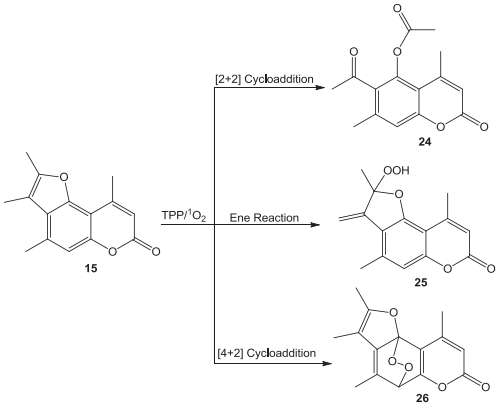
In the same way, the photooxygenation reaction of **15** afforded the photocleaved product 6-acetyl-4,7-dimethyl-2-oxo-2*H*-chromen-5-yl acetate (**24**) ([2 + 2] cycloaddition) and the photooxygenated products 2-hydroperoxy-2,4,9-trimethyl-3-methylene-2*H*-furo[2,3-*f*]chromen-7(3*H*)-one (**25**) [*ene* reaction] and endoperoxide of 2,3,4,9-tetramethyl-7*H*-furo[2,3-*f*]chromen-7-one (**26**) ([4 + 2] cycloaddition) in 44, 7, and 37% yields, respectively (Scheme 5).

All photoproducts were isolated and fully characterized by IR, ^1H NMR, and MS (cf. Experimental section). The mass spectra of compounds **24–26** showed a molecular ion M^+ *m/z*, 274 indicating that the singlet oxygen is inserting in the molecule without losing any fragments. The hydroperoxide **25** gave a broad band at 3600–3250 cm^{-1} in IR spectrum assigned to OOH that resonates at δ 13.07 ppm, exchangeable with D_2O, in ^1H NMR spectrum.

^1H NMR spectrum of the endoperoxide **26** showed a singlet signal at δ 3.32 ppm for one proton assigned to H-8.

On the other hand, compound **24** showed a broad band for two new carbonyl groups at 1758.76 cm^{-1} in the IR spectrum. Moreover, ^1H NMR spectrum of **24** showed four singlet signals of four methyl moieties protons at δ 2.48, 2.45, 2.38, and 2.31 ppm.

Scheme 5. Photooxygenation of **15**.



Acid hydrolysis of the photocleaved product **24** gave the corresponding hydroxyacetyl derivative **28**. Compound **28** was further confirmed through Fries rearrangement of **27**, which was obtained by acetylation of **9** (Scheme 6).

CONCLUSION

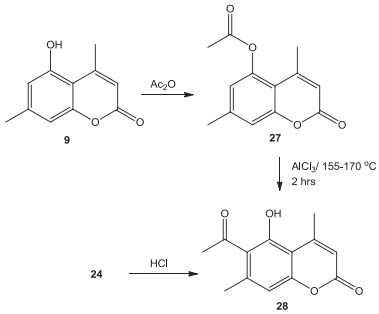
Linear and angular furocoumarin derivatives were synthesized through Williamson reaction of hydroxycoumarins with 3-chloro-2-butanone followed by cyclization with PPA or by heating in a strongly alkaline solution. The photooxygenation reactions of synthesized furocoumarins were performed in the presence of TPP as singlet oxygen sensitizer ($^1O_2$). The photooxygenation reactions afforded the photocleaved product through [2 + 2] cycloaddition and the photooxygenated products through *ene* reaction and [4 + 2] cycloaddition.

EXPERIMENTAL

Melting points were obtained on a Gallenkamp melting point apparatus (open capillary tubes) and were uncorrected. Silica gel (ADWIC 60 GF_{254}) was used for thin layer chromatography (TLC). Silica gel (ADWIC 60–120 mesh, size 0.13–0.25 nm) was used for column chromatography. ^1H NMR spectra were performed on a Varian Mercury-VX-300 (300 MHz) at the Micro Analytical Unit, Cairo University and a BRUKER (600 MHz) ultra shield Avance III spectrometer at the Faculty of Science, King Abd-Elaziz University, Jeddah, KSA, using TMS as an internal stander and DMSO or $CDCl_3$ as solvents. Chemical shifts were expressed as δ ppm. IR spectra were performed on a Jasco 4100 FTIR spectrophotometer (KBr pellet) at the Department of Chemistry, Faculty of Science at New Damietta, Mansoura University, Damietta branch. The electron impact mass spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV at the Micro Analytical Unit, Cairo University. The elemental analyses were performed on a PERKIN-ELMER 2400 C, H Elemental Analyzer at the Micro Analytical Unit, Cairo University, within ±0.4 deviation from the calculated value.

Synthesis of 7-hydroxy-4-methyl-2H-chromen-2-one (7). A mixture of resorcinol (11 g, 100 mmol) and ethyl acetoacetate (12.8 g, 100 mmol) was stirring in ice bath, and 70% sulfuric acid (100 mL) was added dropwise and refluxed for 1 h. The reaction mixture was poured onto ice/water, and the separated solid was

Scheme 6. Fries rearrangement of **27**.



filtered off. The product was purified by recrystallization from aqueous methanol 80% to give white crystals of **7** (16.73 g, 95%), MP 184–186°C (lit [22], 184–186°C, 89%).

Synthesis of 6-hydroxy-4-methyl-2H-chromen-2-one (8). A mixture of quinol (15 g, 136.36 mmol) and ethylacetoacetate (17.73 g, 136.36 mmol) was stirring in ice bath, and 80% sulfuric acid (150 mL) was added dropwise within half an hour. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured onto ice/water, and the separated solid was filtered off. The crude product was purified by recrystallization from ethanol to give white crystals of **8** (8.4 g, 35%), MP 239–241°C (lit [23], 243–245°C, 40%).

Synthesis of 5-hydroxy-4,7-dimethyl-2H-chromen-2-one (9). Compound **9** was prepared from orcinol (10 g, 80.6 mmol) and ethyl acetoacetate (10.5 g, 80.77 mmol) according to the method given for **8** to afford a crude product that was purified by crystallization from methanol to give white crystals of **9** (11.95 g, 78%), MP 246–250°C (lit [15], 245–247°C, 71%).

Synthesis of 4-methyl-7-(3-oxobutan-2-yloxy)-2H-chromen-2-one (10). To a solution of **7** (4 g, 22.73 mmol) in dry acetone (70 mL), anhydrous potassium carbonate (10 g) and 3-chloro-2-butanone (2.44 g, 22.9 mmol) were added. The mixture was refluxed at 80°C for 24 h. The reaction was monitored by TLC for the disappearance of reactants. The inorganic salt was filtered off, and the solvent was concentrated under reduced pressure and poured onto ice/water. The separated solid was filtered off and washed with excess of water. The crude product was purified by recrystallization from ethanol to afford white crystals of **10** (2.85 g, 51%), MP 95–97°C. IR (KBr, cm^{-1}): 3066.26 (CH arom.), 2931.27 (CH aliph.), 1712.48 (br, 2CO), and 1608.34 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, 1H, J = 9 Hz), 6.81 (d, 1H, J = 9 Hz), 6.73 (s, 1H), 6.14 (s, 1H), 4.69 (q, 1H, J = 6.9 Hz), 2.39 (s, 3H), 2.19 (s, 3H), and 1.54 (d, 3H, J = 6.9 Hz). MS (*m/z*, %): 246 (M^+, 54), 204 (M^+-C_2H_2O, 12), 203 [M^+-(CH_3+CO), 90], 189 (M^+-C_3H_5O, 6), 176 (M^+-$C_3H_2O_2$, 5), 175 (M^+-C_4H_7O, 19), 161 (M^+-$C_4H_5O_2$, 2), 160 (M^+-$C_5H_{10}O$, 7), 147 (M^+-$C_5H_7O_2$, 54), and 132 (M^+-$C_6H_{10}O_2$, 4). Anal. calcd for $C_{14}H_{14}O_4$ (246.26): C, 68.82; H, 5.73. Found: C, 69.20; H, 5.40.

Synthesis of 4-methyl-6-(3-oxobutan-2-yloxy)-2H-chromen-2-one (11). Compound **11** was prepared from **8** (4 g, 22.73 mmol) and 3-chloro-2-butanone (2.44 g, 22.9 mmol) according to the method given for **10**. The crude product was recrystallized from ethanol to give white crystals of **11** (3.63 g, 65%), MP 76°C. IR (KBr, cm^{-1}): 3089.4 (CH arom.), 2923.56 (CH aliph.), 1735.62 (CO), 1712.48 (CO), and 1616.06 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, 1H, J = 9 Hz), 7.04 (d, 1H, J = 9 Hz), 6.99 (s, 1H), 6.30 (s, 1H), 4.64 (q, 1H, J = 6.9 Hz), 2.39 (s, 3H), 2.19 (s, 3H), and 1.53 (d, 3H, J = 6.9 Hz). MS (*m/z*, %): 246 (M^+, 40), 204 (M^+-C_2H_2O, 14), 203 [M^+-(CH_3 + CO), 100], 189 (M^+-C_3H_5O, 4), 176 (M^+-$C_3H_2O_2$, 8), 175 (M^+-C_4H_7O, 30), 161 (M^+-$C_4H_5O_2$, 3), 160 (M^+-$C_5H_{10}O$, 7), 147 (M^+-$C_5H_7O_2$, 47), and 132 (M^+-$C_6H_{10}O_2$, 6). Anal. calcd for $C_{14}H_{14}O_4$ (246.26): C, 68.28; H, 5.73. Found: C, 67.77; H, 5.70.

Synthesis of 4,7-dimethyl-5-(3-oxobutan-2-yloxy)-2H-chromen-2-one (12). Compound **12** was synthesized from **9** (3 g, 15.79 mmol) and 3-chloro-2-butanone (1.67 g, 15.67 mmol) according to the method given for **10**. The crude product was crystallized from ethanol to give white crystals of **12** (3.2 g, 83%), MP 152–154°C. IR (KBr, cm^{-1}): 3062.41 (CH arom.), 2931.27 (CH aliph.), 1720.19 (br, 2CO), and 1616.06 (C=C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.78 (s, 1H), 6.26 (s, 1H), 6.10 (s, 1H), 4.74 (q, 1H, J = 7.2 Hz), 2.65 (s, 3H), 2.34 (s, 3H), 2.18 (s, 3H), and 1.6 (d, 3H, J = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 208.8, 160.7, 155.5, 153.5, 143.2, 114.0, 111.2, 108.3, 107.9, 107.7, 79.7, 24.7, 24.6, 22.0, and 17.6. MS (*m/z*, %): 260 (M^+, 61), 218 (M^+-C_2H_2O, 18), 217 [M^+-(CH_3 + CO), 100], 190 (M^+-$C_3H_2O_2$, 11), 175 (M^+-$C_4H_5O_2$, 6), 174 (M^+-$C_5H_{10}O$, 8), 161 (M^+-$C_5H_7O_2$, 40.74), 146 (M^+-$C_6H_{10}O_2$, 15.29), 133 (M^+-$C_7H_{11}O_2$, 13.57), 132 (M^+-$C_7H_{12}O_2$, 6), and 131 (M^+-$C_7H_{13}O_2$, 10). Anal. calcd for $C_{15}H_{16}O_4$ (260.29): C, 69.22; H, 6.20. Found: C, 69.32; H, 5.80.

Synthesis of 2,3,5-trimethyl-7H-furo[3,2-g]chromen-7-one (13). A solution of **10** (1 g, 4.06 mmol) in 10-mL absolute ethanol was added to 30 mL of alcoholic 3% potassium hydroxide (KOH), and the mixture was refluxed for 2 h. The reaction mixture was poured onto ice/diluted hydrochloric acid (HCl). The separated solid was filtered off and crystallized from methanol, giving pale yellow crystals of **13** (0.74 g, 80%), MP 200–204°C. IR (KBr, cm^{-1}): 3068.26 (CH arom.), 2921.32 (CH aliph.), 1702.53 (CO), and 1627.74 (C=C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.28 (s, 1H), 6.21 (s, 1H), 2.49 (s, 3H), 2.39 (s, 3H), and 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 161.4, 155.3, 153.0, 152.7, 151.0, 127.9, 114.9, 113.2, 112.5, 109.6, 98.9, 19.2, 11.9, and 7.9. MS (*m/z*, %): 228 (M^+, 72), 171 (M^+-C_3H_5O, 72), 147 (M^+-C_5H_5O, 86), and 146 (M^+-C_5H_6O, 100). Anal. calcd for $C_{14}H_{12}O_3$ (228.24): C, 73.67; H, 5.30. Found: C, 73.90; H, 4.90.

Synthesis of 1,2,9-trimethyl-7H-furo[3,2-f]chromen-7-one (14) and 2,3,8-trimethyl-6H-furo[2,3-g]chromen-6-one (16). Compound **11** (1 g, 4.06 mmol) was added to PPA (5 g), and the mixture was heated for 2 h at 80°C. The reaction mixture was cold and poured onto ice/water. The separated solid was filtered off with suction and recrystallized from methanol to afford **14**. The filtrate was evaporated and purified through column chromatography by eluting with 70% of a mixture of petroleum ether 40–60 and ethyl acetate to give **16**. Compound **14** (0.4 g, 43%), pale yellow crystals, MP 204–208°C. IR (KBr, cm^{-1}): 3066.26 (CH arom.), 2977.55 (CH aliph.), 1708.62 (CO), and 1592.91 (C=C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 (d, 1H, J = 9 Hz), 7.19 (d, 1H, J = 9 Hz), 6.28 (s, 1H), 2.70 (s, 3H), 2.46 (s, 3H), and 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 160.9, 154.6, 152.8, 151.6, 151.1, 125.4, 115.0, 114.7, 114.1, 113.0, 109.8, 25.5, 15.1, and 12.7. MS (*m/z*, %): 228 (M^+, 61), 200 (M^+-CO or M^+-C_2H_4, 43), 199 (M^+-C_2H_5, 33), 186 (M^+-C_3H_6, 22), 185 [M^+-(CH_3 + CO) or M^+-C_3H_7, 100], 184 (M^+-C_3H_8, 19), and 171 (M^+-C_3H_5O, 20). Anal. calcd for $C_{14}H_{12}O_3$ (228.08): C, 73.67; H, 5.30. Found: C, 73.35; H, 4.89. Compound **16** (0.094 g, 10%), white powder, MP 140–144°C. IR (KBr, cm^{-1}): 3081.69 (CH arom.), 2962.13 (CH aliph.), and 1639.2 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.31 (s, 1H), 6.26 (s, 1H), 2.48 (s, 3H), 2.36 (s, 3H), and 2.17 (s, 3H). Anal. calcd for $C_{14}H_{12}O_3$ (228.08): C, 73.67; H, 5.30. Found: C, 73.41; H, 5.44

Synthesis of 2,3,4,9-tetramethyl-7H-furo[2,3-f]chromen-7-one (15). Compound **15** was synthesized from **12** (3.3 g, 13.52 mmol) according to the method given for **14**. The crude product was purified by crystallization from ethanol to give buff crystals of **15** (1.77 g, 54%), MP 208–210°C. IR (KBr, cm^{-1}): 3066.26 (CH arom.), 2927.41 (CH aliph.), 1712.48 (CO), and 1616.06 (C=C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.89 (s, 1H), 6.15 (s, 1H), 2.68 (s, 3H), 2.64 (s, 3H), 2.39 (s, 3H), and 2.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 161.4, 152.1, 150.9, 150.8, 149.3, 135.2, 125.0, 113.2, 112.9, 110.4, 104.8, 22.0, 19.6, 11.7, and 10.5. MS (*m/z*, %): 242 (M^+, 100), 214 (M^+-CO or M^+-C_2H_4, 91), 213 (M^+-HCO or M^+-C_2H_5, 91), 186 (M^+-C_3H_4O, 11), and 185 (M^+-C_3H_5O, 11). Anal. calcd for $C_{15}H_{14}O_3$ (242.27): C, 74.36; H, 5.82. Found: C, 73.82; H, 5.99.

General procedure of the photooxygenation of furocoumarins. A solution of the furocoumarin (1 g) and (2 mg) of TPP in chloroform (30 mL) was irradiated externally by means of a sodium lamp at room temperature. During the irradiation, a continuous stream of dry oxygen gas was allowed to pass through the reaction mixture at a slow rate to avoid solvent evaporation. The irradiated solution was monitored by TLC for the disappearance of reactants, and the solvent was evaporated at 20° C/15 torr. The photoproducts were isolated and purified by column chromatography on silica gel by eluting with a 70% mixture of petroleum ether 40–60 and ethyl acetate.

Photooxygenation of 13. According to the general procedure of the photooxygenation, the irradiation of **13** (1 g, 4.39 mmol) yielded 2-hydroperoxy-2,5-dimethyl-3-methylene-2*H*-furo[3,2-*g*] chromen-7(3*H*)-one (**17**) and 6-acetyl-4-methyl-2-oxo-2*H*-chromen-7-yl acetate (**18**). Compound **17**, white powder (0.114 g, 10%), MP 144–148°C. IR (KBr, cm^{-1}): 3500–3250 (br, OOH), 3085.55 (CH arom.), 2931.27 (CH aliph.), 1685.48 (CO), and 1621.58 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.62 (s, 1H, exchangeable with D_2O, OOH), 8.08 (s, 1H), 7.97 (s, 1H), 6.87 (s, 1H), 6.33 (d, 1H, J = 1.2 Hz), 6.19 (d, 1H, J = 1.2 Hz), 2.61 (s, 3H), and 1.56 (s, 3H). Compound **18**, white powder (0.684 g, 60%), M.P. 160–162°C. IR (KBr, cm^{-1}): 3043.12 (CH arom.), 2927.41 (CH aliph.), 1754.9 (CO), 1685.48 (CO), 1631.48 (CO), and 1623.77 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.12 (s, 1H), 6.33 (s, 1H), 2.61 (s, 3H), 2.49 (s, 3H), and 2.40 (s, 3H). Anal. calcd for $C_{14}H_{12}O_5$ (260.24): C, 64.61; H, 4.65. Found: C, 65.10; H, 4.96.

Synthesis of 4-methyl-2-oxo-2H-chromen-7-yl acetate (19). A solution of **7** (1.7 g, 9.66 mmol) in 20-mL acetic anhydride was refluxed for 1 h. The reaction mixture was poured onto water, and the separated solid was filtered off. The solid was purified by recrystallization from ethanol to give white crystals of **19** (2 g, 95%), MP 152°C. IR (KBr, cm^{-1}): 3050.83 (CH arom.), 2931.27 (CH aliph.), 1762.62 (CO), 1720.19 (CO), and 1623.77 (C=C).

Synthesis of 6-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one (20) and 8-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one (21). Compound **19** (1 g, 4.59 mmol) was mixed with $AlCl_3$ powder (2 g, 15.2 mmol), and the mixture was heated at 155–170°C for 2 h. After cooling to 50°C, the melt was treated with diluted HCl. The deposited product was filtered off, washed with water, and purified by column chromatography by eluting with 70% of a mixture of petroleum ether 40–60 and ethyl acetate to give **20**, **21**, and **7**. Compound **20**, white powder (0.33 g, 33%), MP 203–204°C. IR (KBr, cm^{-1}): 3430 (OH), 3054.69 (CH arom.), 2927.41 (CH aliph.), 1739.48 (br, 2CO), and 1619.91 (C=C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 12.65 (s, 1H, exchangeable with D_2O, OH), 7.97 (s, 1H), 6.86 (s, 1H), 6.19 (s, 1H), 2.71 (s, 3H), and 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 203.3, 165.3, 159.9, 158.7, 151.6, 128.1, 117.0, 113.0, 112.8, 105.4, 26.7, and 18.6. MS (*m*/*z*, %): 218 (M^+, 45), 204 (M^+-CH_2, 14), 203 (M^+-CH_3, 100), 190 (M^+-CO, 11), 189 (M^+-C_2H_5, 3), 176 (M^+-C_2H_2O, 11), 175 [M^+-(CH_3 + CO), 96], 161 (M^+-C_3H_5O, 4.7), and 147 (M^+-$C_3H_3O_2$, 37). Anal. calcd for $C_{12}H_{10}O_4$ (218.21): C, 66.05; H, 4.62. Found: C, 66.16; H, 4.67. Compound **21**, white powder (0.57 g, 57%), MP 164°C. IR (KBr, cm^{-1}): 3440.39 (OH), 3090 (CH arom.), 2920 (CH aliph.), 1739.48 (br, 2CO), and 1608.34 (C=C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.57 (s, 1H, exchangeable with D_2O, OH), 7.68 (d, IH, J = 9 Hz), 6.91 (d, 1H, J = 9 Hz), 6.17 (s, 1H), 2.96 (s, 3H), and 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 204.5, 166.7, 159.5, 155.2, 153.1, 131.3, 115.2, 111.9, 111.3, 109.3, 33.9, and 19.4. MS (*m*/*z*, %): 218 (M^+, 100), 204 (M^+-CH_2, 65), 203 (M^+-CH_3, 100), 190 (M^+-CO, 97), 189 (M^+-C_2H_5, 11), 176 [M^+-(CH_2 + CO), 22], 175 [M^+-(CH_3 + CO), 100], 161 (M^+-C_3H_5O, 7), and 147 (M^+-$C_3H_3O_2$, 20). Compound **7**, white powder (0.017 g, 2%), MP 184–186°C.

Acid hydrolysis of 6-acetyl-4-methyl-2-oxo-2H-chromen-7-yl acetate (18). A solution of **18** (0.8 g, 3.08 mmol) in 20-mL HCl was refluxed for half an hour and then cool in air to obtain a precipitate that was separated with suction, washed with water, dried, and recrystalized from ethanol to give white crystals of 6-acetyl-7-hydroxy-4-methyl-2*H*-chromen-2-one (**20**) (0.6 g, 90%), MP 203–204°C.

Photooxygenation of 14. According to the general procedure of the photooxygenation, the irradiation of **14** (1 g, 4.39 mmol) for 5 h yielded 2-hydroperoxy-2,9-dimethyl-1-methylene-1*H*-furo [3,2-*f*]chromen-7(2*H*)-one (**22**) and 5-acetyl-4-methyl-2-oxo-2*H*-chromen-6-yl acetate (**23**). Compound **22**, white powder (0.07 g, 6%), MP 76–80°C. IR (KBr cm^{-1}): 3600–3200 (br, OOH), 3087 (CH arom.), 2928 (CH aliph.), 1700.48 (CO), and 1620 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 1H, J = 9.6 Hz), 7.30 (s, 1H, exchangeable with D_2O, OOH), 7.11 (d, 1H, J = 9.6 Hz), 6.33 (d, 1H, J = 0.9 Hz), 6.32 (s, 1H), 5.16 (d, 1H, J = 0.9 Hz), 2.62 (s, 3H), and 1.27 (s, 3H). MS (*m*/*z*, %): 227 (M^+-OOH, 19), 199 [M^+-(OOH + CO) or M^+-(OOH + C_2H_4), 8], and 185 [M^+-(OOH + CO + CH_2), 25]. Compound **23**, pale yellow powder (0.63 g, 55%), MP 126°C. IR (KBr, cm^{-1}): 3081.69 (CH arom.), 2927.41 (CH aliph.), 1770.33 (CO), 1708.62 (CO), 1648 (CO), and 1596.77 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, 1H, J = 9 Hz), 7.31 (d, 1H, J = 9 Hz), 6.33 (s, 1H), 2.62 (s, 3H), 2.31 (s, 3H), and 2.30 (s, 3H). MS (*m*/*z*, %): 218 (M^+-C_2H_2O, 63), 204 (M^+-C_3H_4O, 2), 203 (M^+-C_3H_5O, 12), 190 (M^+-$C_3H_2O_2$, 6), 189 (M^+-C_4H_7O, 5), 176 (M^+-$C_4H_4O_2$, 100), 175 (M^+-$C_4H_5O_2$, 7), 161 (M^+-$C_5H_7O_2$, 6), and 147 (M^+-$C_5H_5O_3$, 10). Anal. calcd for $C_{14}H_{12}O_5$ (260.24): C, 64.61; H, 4.65. Found: C, 64.92; H, 4.88.

Photooxygenation of 15. According to the general procedure of the photooxygenation, the irradiation of **15** (1 g, 4.13 mmol) for 4 h yielded 6-acetyl-4,7-dimethyl-2-oxo-2*H*-chromen-5-yl acetate (**24**), 2-hydroperoxy-2,4,9-trimethyl-3-methylene-2*H*-furo[2,3-*f*]chromen-7(3*H*)-one (**25**), and endoperoxide of 2,3,4,9-tetramethyl-7*H*-furo[2,3-*f*]chromen-7-one (**26**). Compound **24**, yellow crystals (0.5 g, 44%), MP 120–122°C. IR (KBr cm^{-1}): 3058.55 (CH arom.), 2935.13 (CH aliph.), 1758.76 (br, 2CO), 1693.19 (CO), and 1608.34 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (s, 1H), 6.21 (s, 1H), 2.48 (s, 3H), 2.45 (s, 3H), 2.38 (s, 3H), and 2.31 (s, 3H). MS (*m*/*z*, %): 274 (M^+, 10), 232 (M^+-C_2H_2O, 69), 231 [M^+-(CO + CH_3), 9], 218 (M^+-C_3H_4O, 15), 217 (M^+-C_3H_5O, 100), 204 (M^+-$C_3H_2O_2$ or M^+-C_4H_6O, 18), 203 (M^+-C_4H_7O, 6), 190 (M^+-$C_4H_4O_2$, 6), 189 (M^+-$C_4H_5O_2$, 30) , and 161 (M^+-$C_5H_5O_3$, 15). Anal. calcd for $C_{15}H_{14}O_5$ (274.27): C, 65.69; H, 5.15. Found: C, 65.91; H, 4.97. Compound **25**, semi oil (0.08 g, 7%). IR (KBr, cm^{-1}): 3600–3250 (br, OOH), 3072 (CH arom.), 2928.27 (CH aliph.), 1680.12 (CO), and 1620 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.07 (s, 1H, exchangeable with D_2O, OOH), 6.67 (s, 1H), 6.11 (s, 1H), 6.67 (d, 1H, J = 1.2 Hz), 6.05 (d, 1H, J = 1.2 Hz), 2.51 (s, 3H), 2.30 (s, 3H), and 1.46 (s, 3H). MS (*m*/*z*, %): 276 (M^+ + 2, 69), 275 (M^+ + 1, 7), 241 (M^+-OOH, 4), 232 (M^+-C_2H_2O, 9), 231 [M^+-(CO + CH_3], 40), 216 (M^+-C_3H_6O or M^+-$C_2H_2O_2$, 19), and 215 (M^+-$C_2H_3O_2$, 5). Compound **26**, yellow powder (0.416 g, 37%), MP 120–126°C. IR (KBr, cm^{-1}): 3062.41 (CH arom.), 2927.41 (CH aliph.), 1727.91 (CO), and

1619.91 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (s, 1H), 3.32 (s, 1H), 2.49 (s, 3H), 2.30 (s, 3H), 1.81 (s, 3H), and 1.64 (s, 3H). MS (*m/z*, %): 274 (M^+, 2), 231 [M^+-(CH_3 + CO), 100], 203 (M^+-C_4H_7O or M^+-(CH_3 + 2CO), 3), 189 (M^+-C_5H_9O, 3), 175 (M^+-$C_5H_7O_2$, 2), 161 (M^+-$C_6H_9O_2$, 11), 160 (M^+-$C_6H_{10}O_2$, 5), 105 (M^+-$C_9H_{13}O_3$, 4), and 104 (M^+-$C_9H_{14}O_3$, 3). Anal. calcd for $C_{15}H_{14}O_5$ (274.27): C, 65.69; H, 5.15. Found: C, 65.78; H, 5.28.

Synthesis of 4,7-dimethyl-2-oxo-2H-chromen-5-yl acetate (27). Compound **27** was prepared from **9** (0.4 g, 2.1 mmol) and 5-mL acetic anhydride according to the method given for **19**. The crude product was purified by recrystallization from ethanol to give **27** (0.44 g, 90%) as white crystals, MP 194–196°C. IR (KBr, cm^{-1}): 3062.41 (CH arom.), 2927.41 (CH aliph.), 1743.33 (br, 2CO), and 1677.77 (C=C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.06 (s, 1H), 6.79 (s, 1H), 6.17 (s, 1H), 2.47 (s, 3H), 2.42 (s, 3H), and 2.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 169.2, 160.1, 154.6, 150.8, 147.3, 142.7, 120.4, 115.9, 115.6, 111.3, 22.7, 21.5, and 21.4. MS (*m/z*, %): 232 (M^+, 19), 190 (M^+-C_2H_2O, 97), , 189 [M^+-(CH_3 + CO), 8], 162 (M^+-$C_3H_2O_2$, 100), 161 (M^+-$C_3H_3O_2$, 36), 148 (M^+-$C_4H_4O_2$, 1), 147 (M^+-$C_4H_5O_2$, 6), 146 (M^+-$C_4H_6O_2$, 2), 133 (M^+-$C_5H_7O_2$, 7), and 132 (M^+-$C_5H_8O_2$, 2). Anal. calcd for $C_{13}H_{12}O_4$ (232.23): C, 67.23; H, 5.21. Found: C, 67.20; H, 4.65.

Synthesis of 6-acetyl-5-hydroxy-4,7-dimethyl-2H-chromen-2-one (28). Compound **28** was prepared from **27** (0.4 g, 2.1 mmol) according to the method given for **21**. The crude product was purified by column chromatography by eluting with 70% of a mixture of petroleum ether 40–60 and ethyl acetate to give **28** and **9**. Compound **28**, white powder (0.42 g, 42%), MP 168–170°C. IR (KBr, cm^{-1}): 3432.67(OH), 3066.26 (CH arom.), 2931.27 (CH aliph.), 1727.91 (br, 2CO), and 1608.34 (C=C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 14.61 (s, 1H, exchangeable with D_2O, OH), 6.67 (s, 1H), 6.08 (s, 1H), 2.71 (s, 3H), 2.66 (s, 3H), and 2.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 205.5, 165.2, 160.0, 158.0, 155.0, 144.0, 116.9, 113.6, 112.0, 108.5, 33.4, 25.3, and 24.3. MS (*m/z*, %): 232 (M^+, 9), 218 (M^+-CH_2, 4), 217 (M^+-CH_3, 13), 204 (M^+-CO or M^+-C_2H_4, 11), 203 (M^+-C_2H_5, 6), 190 (M^+-C_2H_2O, 4), 189 [M^+-(CH_3 + CO), 23], 161 [M^+-(CO + CH_3 + CO), 52], and 131 (M^+-$C_5H_9O_2$, 49). Compound **9**, white powder (0.156 g, 19%), MP 246–250°C.

Acid hydrolysis of 6-acetyl-4,7-dimethyl-2-oxo-2H-chromen-5-yl acetate (24). A solution of **24** (0.6 g, 2.19 mmol) in 20-mL HCl was hydrolyzed according to the method given for **18**; the product was purified by column chromatography on silica gel by eluting with 70% of a mixture of petroleum ether 40–60 and ethyl acetate to give white powder of 6-acetyl-5-hydroxy-4,7-dimethyl-2*H*-chromen-2-one (**28**) (0.3 g, 59%), MP 168–170°C.

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