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NMR Spectra Investigation of Some New Prepared Tetrasubstituted Coumarin Derivatives

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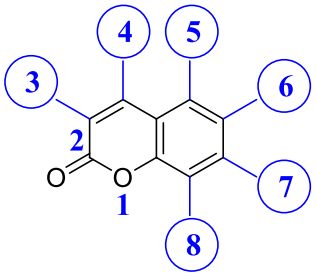
Abstract

Background: Coumarins possess a variety of biological properties, including antimicrobial, antiviral, antiinflammatory, antidiabetic, antioxidant, and enzyme inhibitory activity.
Objective: In these work a novel organic compounds tetrasubstituted coumarin derivatives were synthesized and their NMR spectra were investigated.
Methods: A new ethyl 6,8-dibromo-7-hydroxy coumarin-3-carboxylate (2) was prepared via the bromination of ethyl 7-hydroxy coumarine-3-carboxylate (1).
Results: Treatment of compound (2) with acetic anhydride and p-chlorobenzoic acid hydrazide yielded the corresponding acetyl derivatives (3) and substituted coumarin-3-carboxohydrazide (4). Alkylation of (4) with methyl iodide gave N-(p-chlorobenzoyl)-6,8-dibromo-7-methoxy coumarin-3-carboboxohydrazide (5).
Conclusion: The structure of the synthesized tetrasubstituted coumarin derivatives (2-5) were confirmed by IR, NMR, MS and elemental analysis.

Keywords: tetrasubstituted coumarin; IR; NMR; MS; elemental analysis.

1. INTRODUCTION

Various substituted coumarine based natural and synthetic derivatives are also found to have antimicrobial[1,2], antitumor[3], antioxidant[4], anti-inflammatory[5], anti-influenza[6], antituberculosis[7], antiviral[8], anti-Alzheimer[9, 10] and antihyperlipidimic activities[11, 12].
Structural features of coumarine derivatives containing six positions (**chart 1**) where any substituents can be added, and that can lead to increase and/or decrease in the biological activities (such as anticancer, anti-inflammatory, antimicrobial and antiviral activities)



As an extension of our previous work[13-19]. This paper reported the preparation of some new tetrasubstituted coumarin derivatives using ethyl-7-hydroxy coumarin-3-carboxylate (**1**) as a key starting material which was obtained in the reaction of 2, 4-dihydroxy benzaldehyde with diethyl malonate in the presence of piperidine according to literature procedure[20]. The NMR spectra of some synthesized

coumarine derivatives have also been recorded and discussed.

2. EXPERIMENTAL/MATERIALS AND METHODS

^{1}H-NMR (400 MHz) and ^{13}C-NMR spectra were run with a Broker 400 DRX-Avance NMR spectrometer. The compounds were diluted in deuterated DMSO as solvent. The IR data were obtained with a Shimadzu 470 spectrometer. Melting points were measured with an electrothermal melting point apparatus and have not been corrected. Mass spectra were recorded on a Probe Agilent MSD 5975 Ms-Engine thermospray and ionization by electron impact at 70 eV. All chemicals were purchased from Aldrich chemical company, *Merk* and *Fluka*.

Ethyl 6,8-dibromo-7-hydroxy coumarin-3-carboxylate (2)

A solution of ethyl 7-hydroxy coumarin-3-carboxylate (1, 0.01 mol) in glacial acetic acid (30 mL) was added a solution of bromine in acetic acid (0.02 mol/15 mL) *dropwise* with stirring at room temperature for 1.5-2 hr, the reaction mixture was poured ice-water, then left for 24 h, and the resulting solid was filtered and dried. Finally, the product was recrystallized from ethanol to give (**2**) as pale yellow crystals, yield 87%, m.p. 205 ºC, IR (KBr): broad 3420-3250 (br. OH), 1763, 1728 (C=O of ester and pyran ring), 1612, 1585 (C=C), 1205, 1053, 1117 (C-O) cm^{-1}. MS (m/z, %)= 394 (M^++4, 42.30), 392 (M^++2, 86.30), 390 (M^+, 44.36). Anal. Calcd for $C_{12}H_8Br_2O_5$: C, 36.92; H, 2.05; Br, 40.51. Found: C, 36.72; H, 1.98; Br, 40.32.

Ethyl 6,8-dibromo-7-acetoxy coumarin-3-carboxylate (3)

A solution of 7-hydroxy coumarin ester (2, 0.01 mol) in acetic anhydride (25 ml) was heated under reflux for 2 h, the cooled and poured into ice-water. The reaction mixture was left for 24 h, and the solid formed was filtered washed with water and dried. Finally, the product was recrystallized from ethanol to give (3) as colorless, , yield 68%, m.p. 170 ºC, IR (KBr): 1776, 1761. 1723 (C=O of ester and pyran ring), 1621, 1583 (C=C), 1205, 1176, 1093 (C-O) cm^{-1}. MS (m/z, %)= 436 (M^++4, 36.70), 434 (M^++2, 78.30), 432 (M^+, 37.30). Anal. Calcd for $C_{14}H_{10}Br_2O_6$: C, 38.84; H, 2.31; Br, 36.57. Found: C, 38.63; H, 2.12; Br, 36.33.

N- (p-chlorobenzoyl) 6,8-dibromo-7-hydroxy coumarin-3-carboxohydrazide (4)

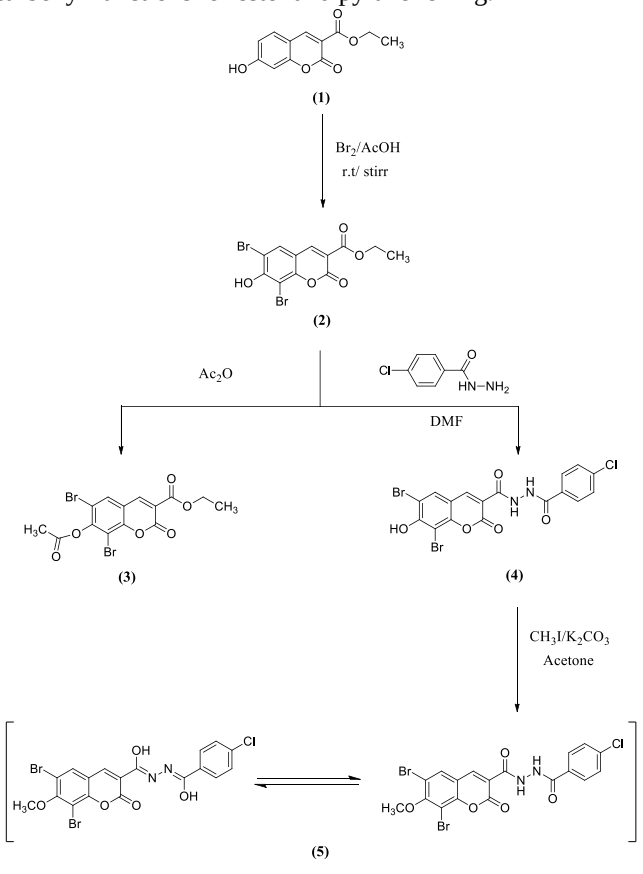
A mixture of Ethyl 6,8-dibromo-7-hydroxy coumarin-3-carboxylate (**2**, 0.01 mol) in dimethyl formamide (30 mL) was heated under reflux for 8 h, then cooled and poured into ice-water. The reaction mixture was neutralized with dilute hydrochloric acid (1N). the solid obtained was filtered off, washed with water, dried and purified by recrystallization from acetic acid to give (**4**) as yellow crystals. yield 71%, m.p. 235 ºC, IR (KBr): br. 3380-3150 (OH), 1723, 1693. 1723 (C=O of pyran ring and amide), 3210 (NH), 1613, 1593 (C=C), 1123, 1078 (C-O) cm^{-1}. MS (m/z, %)= 518 (M^++4, 33.20), 516 (M^++2, 78.60), 514 (M^+, 34.20). Anal. Calcd for $C_{17}H_9N_2Br_2ClO_5$: C, 39.69; H, 1.75; N, 5.45; Br, 30.74. Found: C, 39.39; H, 1.61; N, 5.25; Br, 30.55.

N- (p-chlorobenzoyl) 6,8-dibromo-7-methoxy coumarin-3-carboxohydrazide (5)

A mixture of **(4)** (0.01 mol), methyl iodide (0.01 mol) and anhydrous potassium carbonate (0.03 mol) in acetone was heated under reflux for 15 h, cooled and poured into beaker. The solvent was evaporated, and added water (50 mL) with stirring. The solid produced was filtered off, washed with water, dried and purified by recrystallization from ethanol to give (**5**) as pale yellow crystals. . yield 63%, m.p. 190 ºC, IR (KBr): 3221 (NH), 1723, 1697. 1723 (C=O of pyran ring and amide), 1617, 1583 (C=C), 1125, 1078 (C-O) cm^{-1}. MS (m/z, %)= 532 (M^++4, 31.20), 530 (M^++2, 67.30), 528 (M^+, 33.20). Anal. Calcd for $C_{18}H_{11}N_2Br_2ClO_5$: C, 40.91; H, 2.08; N, 5.30; Br, 29.92. Found: C, 40.73; H, 1.99; N, 5.11; Br, 29.69

3. RESULTS AND DISCUSSION

The synthetic pathway leading to the tetrasubstituted coumarin derivatives is outlined in **scheme 1**. Reaction of ethyl 7-hydroxy coumarin-3-carboxylate (**1**) with bromine in glacial acetic acid at room temperature afforded ethyl 6,8-dibromo-7-hydroxy coumarin-3-carboxylate (**2**). The IR spectrum of compound (**2**) revealed two bands at 3325, 1728 cm^{-1} assignable to two OH and carbonyl functions for ester and pyranone ring.



Scheme 1

The ethyl 6, 8-dibromo-7-hydroxy coumarin-3-carboxylate (**2**) was acetylated with acetic anhydride to give ethyl 6,8-dibromo-7-acetoxy coumarin-3-carboxylate (**3**). The IR spectrum of compound (**3**) showed absence the absorption band of hydroxyl group and the appearance of three absorption bands for carbonyl group at 1778, 1761 and 1723 cm^{-1}

Subsequently, ethyl 6,8-dibromo-7-hydroxy coumarin-3-carboxylate (**2**) was allowed to react with p-chloro benzoic acid hydrazide in dimethyl formamide under reflux led to the formation of *N*- (p-chlorobenzoyl) 6,8-dibromo-7-hydroxy coumarin-3-carboxohydrazide (**4**). The IR spectra of compound (4) indicated vibration absorption band at 3224 and 1695 cm^{-1} characteristic for carboxohydrazide function with disappearance absorption band of ester group.

Alkylation of *N*- (p-chlorobenzoyl) 6,8-dibromo-7-hydroxy coumarin-3-carboxohydrazide (**4**) with methyl iodide in the presenece of anhydrous potassium carbonate in acetone under reflux yielded the corresponding *N*- (p-chlorobenzoyl) 6,8-dibromo-7-methoxy coumarin-3-carboxohydrazide (**5**). The IR spectrum of compound (**5**) showed the disappearance band for hydroxyl group.

NMR spectra of tetrasubstituted coumarin derivatives.

In order to elucidate the structural features of the compounds, ^{1}H-NMR and ^{13}C-NMR spectra of the tetrasubstituted coumarin derivatives (**2-5**), recorded in DMSO-d_6, were examined. **Table 1** listed the data of ^{1}H-NMR and ^{13}C-NMR spectra of coumarin derivatives (**2-5**).

^{1}H-NMR spectra of coumarine derivatives (2-5):

Chemical structure of coumarin compound and the numbering of coumarin ring as shown in **chart 1**.

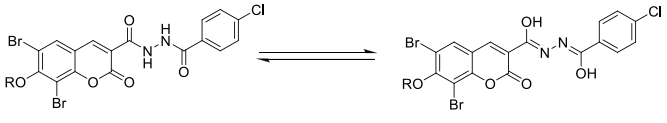
The synthesized coumarin derivatives containing different substituents in the positions 3, 6, 7 and 8, while the positions 4 and 5 in the compounds were attached to hydrogen atoms.

^{1}H-NMR spectra of these compounds (**2-5**) exhibited two singlet signals in region at δ 8.72 and δ 8.45-7.91 ppm assigned to H-4 and H-5 for the coumarin ring.

The coumarin derivatives **2** and **3** containing the same substituents in the position 3, 6 and 8, except the position 7, which is different. From the data of ^{1}H-NMR spectra for the compounds (**2**) and (**3**) gave clear cut evidence singlet signal at δ 11.21 ppm of proton for the hydroxyl group (OH) in the position 7 for the compound (**2**) (**Figure 1**), which in case of compound (3) (**Figure 2**) gave singlet signals at δ 2.37 ppm of methyl protons for the acetoxy group in position 7.

Also, compound (**2**) and (**3**) containing the same ester group in the position-3, which appeared in the ^{1}H-NMR spectra as quartet signal at δ 4.31, 4.35 ppm of methylene proton and triplet signal at δ 1.30, 1.31 ppm of methyl protons for the ethoxy group ($COOC_2H_5$).

From study, the ^{1}H-NMR spectra of compounds (**4**) and (**5**) showed the structure of these compounds in Keto-Enol tautomers as shown in **chart 2**.



Where **a, R = H** (compound **4**), **b, R = CH_3** (compound **5**)

Chart 2: keto-Enol tautomers for compounds **4** and **5**.

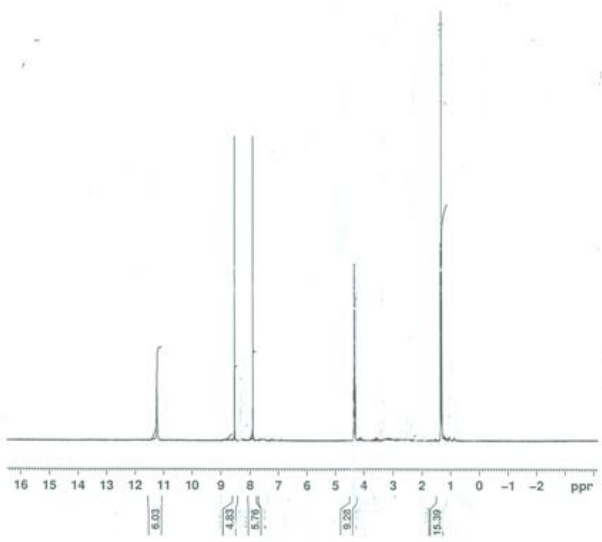


Figure 1: ^{1}H-NMR spectra of compound **2**

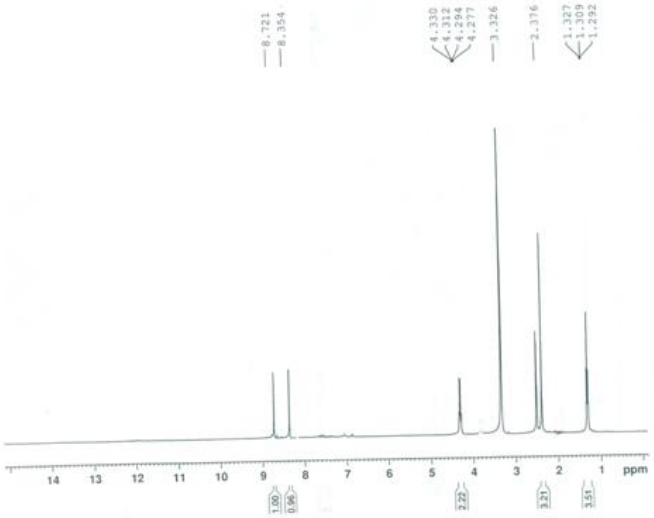


Figure 2: ^{1}H-NMR spectra of compound **3**

^{1}H-NMR spectra of these compounds (**4**) and (**5**) showed that the presented two characteristic singlet signals at δ 10.62, 10.63 ppm refer to the proton of hydroxyl groups (OH proton) for the enol form (50%) and at δ 6.88, 7.22 ppm attributed to the proton of NH groups for the keto form (50%). This occurred when both structures are in equilibrium (50% : 50%) state.

In addition, ^{1}H-NMR spectrum of compound (**4**) exhibited broad singlet signal at δ 11.95 ppm assigned to the proton of hydroxyl group in position-7, while compound (**5**) gave singlet signal at δ 3.97 ppm of methyl protons of the methoxy group in position-7.

Finally, the ^{1}H-NMR spectra of compound (**4**) (Figure 3) and compound (**5**) (Figure 4) displayed two doublet signals at δ 7.93 ppm (2H) and δ 7.61 ppm (2H) due to aromatic protons of p-chlorobenzoyl group.

^{13}C-NMR spectra of coumarin derivatives (2-5):

The ^{13}C-NMR spectral data of the newly synthesized tetra substituted coumarin derivatives (**2-5**) were given in table 1 and **(Figures 8**, **9**) illustrated, as examples, the ^{13}C-NMR spectra of compounds (**3**) and (**5**).

The ^{13}C-NMR spectrum of compound (**2**) displayed three carbon signals at δ 163.32 (C=O), δ 61.35 (OCH_2) and δ 14.12 (CH_3) assigned to ester group ($COOCH_2CH_3$). In addition, a characteristic carbon signals in region at δ 111.25-155.31 ppm for coumarin ring, among total 12 carbon signals.

The ^{13}C-NMR spectrum of compound (**3**) (**Figure 5**) showed the presence of two new signals at δ 167 (C=O) and δ 20.53 ppm (CH_3) refer to the acetyl group ($COCH_3$), and supported the formation of compound (**3**)

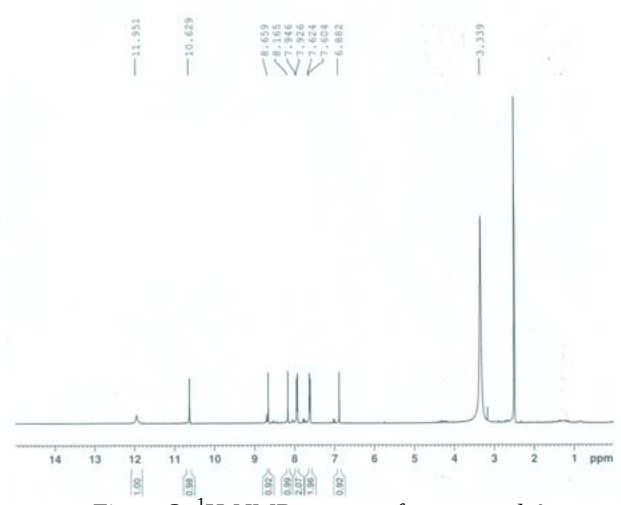


Figure 3: ^{1}H-NMR spectra of compound **4**

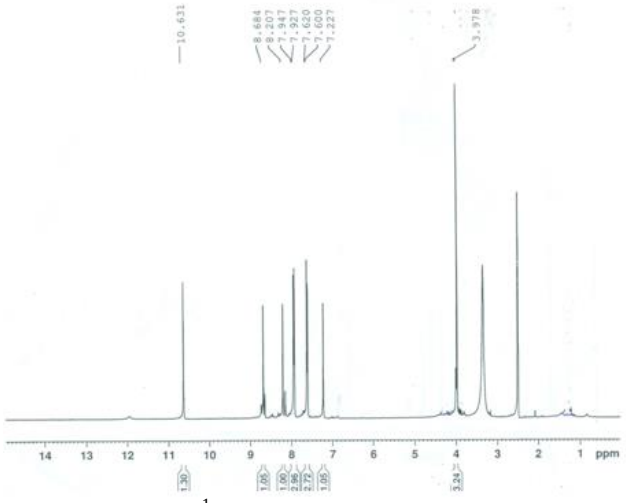


Figure 4: ^{1}H-NMR spectra of compound **5**

from the acetylation of compound (**2**) with acetic anhydride. The ^{13}C-NMR spectrum of compound (**3**) has 14 carbon signals.

The ^{13}C-NMR spectrum of compound (**4**) confirmed the absence of carbon signals of ester group ($COOC_2H_5$) which may appear at δ 163.32 ppm (C=O), δ 61.35 ppm (OCH_2) and δ 14.12 (CH_3). Whilst, a new carbon signals in the aromatic region and two carbon signals at δ 164.31 and δ 162.49 ppm (C=O) refer to (CONHNHCO-Ar) group in the position-3 were observed.

Also, ^{13}C-NMR revealed a characteristic carbon signals in the region δ 100.00-156.16 ppm due to the carbons of coumarin ring and the exited aromatic carbons.

The ^{13}C-NMR spectra of compound (**5**) (**Figure 6**) displayed new signal at δ 57.45 due to the methyl protons of methoxy group (OCH_3), these signal further supported the formation of compound (**5**). In addition, the spectra of compound (**5**) showed the same carbon signals in compound (**4**) which give total 18 carbon signals.

4. CONCLUSION

In this work, the synthesis of tetra substituted coumarin derivatives (**2-5**), via the halogenation of ethyl 7-hydroxy coumarin-3-carboxylate (**1**), with bromine to give dibromo derivative (**2**), followed by acetylation and condensation with p-chloro benzoic acid hydrazide yielded the corresponding acetyl and acid hydrazide derivatives (**3** and **4**). Alkylation of the latter compound with methyl iodide gave the methoxy derivative (**5**). The structure of these compounds (**2-5**) were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analysis. The ^{1}H-NMR spectra supported the structure of compound 4 and 5 in keto-enol tautomers, and also, the ^{1}H-NMR spectra showed that the enol form and keto form present in equal amount (50% : 50%). Supported the structure of compounds (**4**) and (**5**) in keto-enol tautomers, and also, the 1H-NMR spectra showed that the enol form and keto form present in equal amount (50% : 50%).

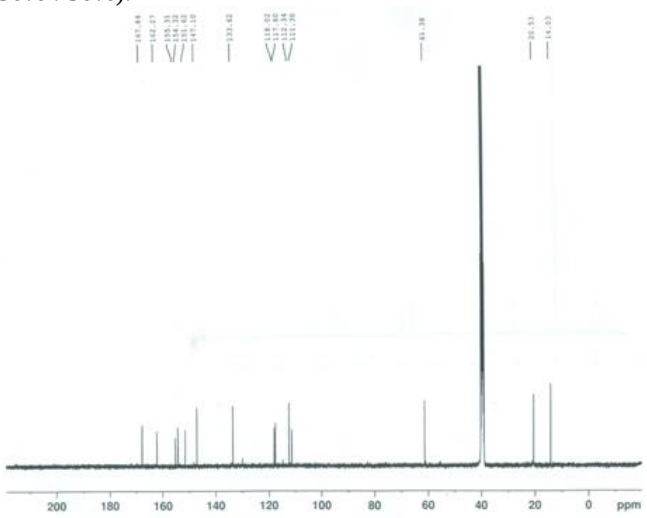


Figure 5: ^{13}C-NMR spectra of compound **3**

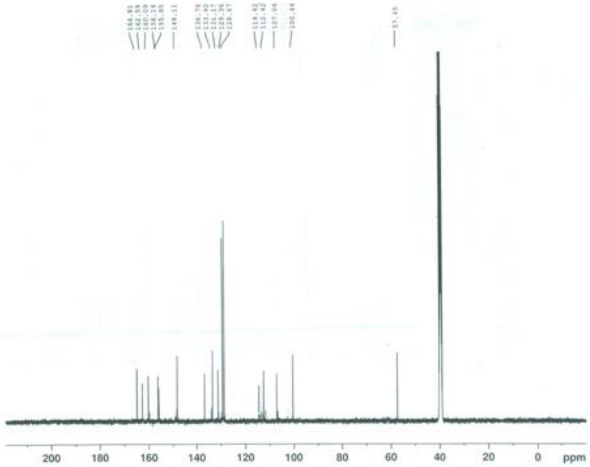


Figure 6: ^{13}C-NMR spectra of compound **5**

Table 1: ^{1}H-NMR, ^{13}C-NMR spectra of tetrasubstituted coumarin derivatives (2-5):

Comp. No.	δ, ppm
(2)	11.21 (s, 1H, OH), 8.65 (s, 1H, H-4 of coumarin ring), 7.91 (s, 1H, H-5 of coumarin ring), 4.35 (q, 2H, OCH_2) and 1.31 (t, 3H, CH_3). 163.32, 153.31 (C=O of ester and pyranonone ring), 154.37, 151.63, 147.10, 133.63, 118.06, 117.63, 112.33, 111.25 (C-coumarin ring), 61.35 (OCH_2). 14.12 (CH_3).
(3)	8.72 (s, 1H, H-4 of coumarin ring), 8.35 (s, 1H, H-5 of coumarin ring), 4.31 (q, 2H, OCH_2) 2.37 (s, 3H, $COCH_3$). and 1.30 (t, 3H, CH_3). 167.84, 162.27 (C=O of ester), 155.31 (C=O of pyranone ring), 154.32, 151.62, 147.10, 133. 26, 118.02, 117.60, 112.34, 111.30 (C-coumarin ring), 61.38 (OCH_2). 20.53 ($COCH_3$), 14.02 (CH_3).
(4)	11.95 (br. s, 1H, OH), 10 .62 (s, 1H, OH), 8.65 (s, 1H, H-4 of coumarin ring), 8.16 (s, 1H, H-5 of coumarin ring), 7.93 (d, 2H, Ar-H), 7.61 (d, 2H, Ar-H), 6.88 (s, 1H, NH). 164.31, 162.49, 160.03 (C=O of carboxamide and pyranone ring), 156.16, 155.68 (C-O), 147.98, 136.56, 133.23, 131.01, 129.33, 128. 52, 114.32, 112.32, 107.10, 100.34 (C-coumarin ring and aromatic ring).
(5)	10.63 (s, 1H, OH), 8.68 (s, 1H, H-4 of coumarin ring), 8.20 (s, 1H, H-5 of coumarin ring), 7.93 (d, 2H, Ar-H), 7.61 (d, 2H, Ar-H), 7.22 (s, 1H, NH), 3.97 (s, 3H, OCH_3). 164.81, 162.59, 160.09 (C=O of carboxamide and pyranone ring), 156.14, 155.85 (C-O), 148.11, 136.46, 133.40, 131.17, 129.36, 128. 67, 114.42, 112.42, 107.06, 100.44 (C-coumarin ring and aromatic ring), 57.45 (OCH_3).

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