Electronic Supplementary Information (ESI)

A simple and efficient protocol for the Pechmann reaction to obtain 4-methylcoumarin derivatives using a high-speed mixer ball mill process

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Contents

1 General information

The reagents and solvents used in the synthesis of the intermediate and final compounds were of purity grade for synthesis. All reagents were purchased from Merck, J.T. Baker, Sigma, and Aldrich Chemical Co. and used without further purification. The composition and monitoring of the reactions, as well as the preliminary analysis of the purity of the synthesized compounds, was carried out by thin layer chromatography (TLC) on Silufol UV254 plates of 0.25 mm thickness, revealed in a UV light chamber of 254 nm or in an ethanolic solution of phosphomolybdic-sulfuric acids. Fisher-Johns melting point apparatus was used to measure the melting points (uncorrected).

Reactions were carried out in a mixer mill apparatus (amalgamator Zenith, Z-1A) at a frequency of 60 Hz using grinding jars of different materials (Nylon, Teflon, or stainless steel of volume 1.5-2 mL) and a single stainless steel ball with different sizes (d = 5 and 8 mm) (Table S1).

Table S1. Grinding tools used in Ball milling.

Grinding body	Different material jars		
	Nylon	Stainless steel	Teflon
 d = 8 mm, 2.1031 g  d = 5 mm, 0.6401 g	 3.4471 g, 1.5 mL	 26.3185 g, 1.5 mL	 8.1573 g, 2 mL

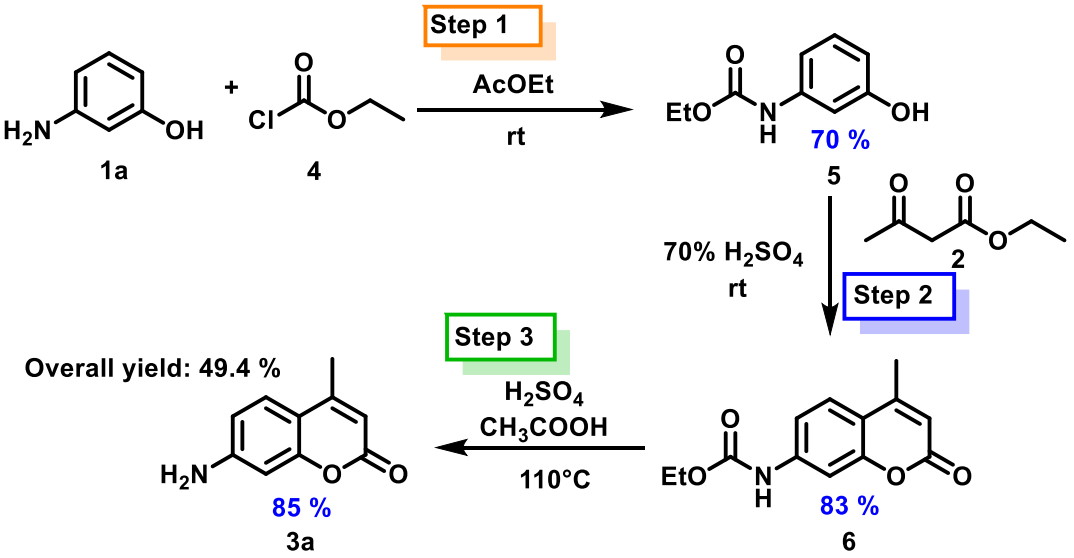
The acquisition of nuclear magnetic resonance spectra ^{1}H and ^{13}C was performed in a Bruker Avance–400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using deuterated chloroform ($CDCl_3$, 99.8% Merck®) as solvent. Chemical shift values (δ) are expressed in ppm. In ^{1}H NMR spectra, the scale was adjusted from the residual chloroform signal (7.26 ppm). Similarly, the ^{13}C NMR spectra were scaled from the signal characteristic of the solvent ($CDCl_3$). Coupling constants (*J*) are given in Hz; the multiplicity of signals is expressed by the following abbreviations: (s) singlet, (d) doublet, (dd) doublet of doublets, and (m) multiplet.

Infrared spectra were recorded on an FTIR Bruker Tensor 27 spectrophotometer coupled to a Bruker platinum with attenuated reflectance (ATR) cell at 31 scans and 2 cm^{-1} resolution. Elemental analyses were performed on a Thermo Scientific CHNS-O analyzer (Model. Flash 2000) and were within ± 0.4 of theoretical values.

2 Experimental procedures

2.1 Three-step synthesis of 7-amino-4-methylcoumarin (Scheme S1)

Obtaining 7-amino-4-methylcoumarin was carried out through the synthesis in three steps illustrated below:



Scheme S1. Synthesis of 7-amino-4-methylcoumarin by means of a three-stage procedure: **Step 1.** Protection of the NH_2 group, **Step 2.** Formation of the coumarin nucleus, **Step 3.** Deprotection of the NH_2 group.

The methodology used in each of the stages was carried out according to the experimental procedure reported by Reddy et al. [63].

Step 1. Synthesis of 3-carbethoxyaminophenol (**5**)

Ethyl chloroformate **4** (0.9 mL, 9.17 mmol) was added in one portion to a stirred suspension of *m*-aminophenol **1a** (1 g, 9.17 mmol) in ethyl acetate (15 mL). A white precipitate formed immediately. The reaction mixture was stirred for 2 h at room temperature. The amine hydrochloride precipitate was removed by filtration. Ethyl acetate was removed under reduced pressure to obtain colorless crystals of 3-carbethoxyaminophenol **5** (8.94 mmol, 1.16 g, 70%). Mp = 92-95 °C (lit. Mp = 94-96 °C), Rf = 0.37 (3:1, petroleum ether: ethyl acetate). IR (KBr, ν_{max}/cm^{-1}): 3297, 2987, 1684, 1622, 1554. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 1.23 (3H, t, *J* = 7.1 Hz, CH_3), 4.10 (2H, q, *J* = 7.1 Hz, CH_2), 6.38 (1H, dd, *J* = 8.0, 2.4 Hz, 2-H), 6.85 (1H, dd, *J* = 8.0, 1.8 Hz, 5-H), 7.02 (2H, m, 4,6-H), 9.31 (1H, s, N-H), 9.45 (1H, s, OH). ^{13}C NMR (101 MHz, DMSO-d6) δ (ppm): 14.6, 60.0, 105.4, 109.1, 109.5, 129.4, 140.3, 153.5, 157.7.

Step 2. Synthesis of 7-carbethoxyamino-4-methylcoumarin (**6**)

3-Carbethoxyaminophenol **5** (1.0 g, 5.52 mmol) and ethyl acetoacetate **2** (0.70 g, 5.38 mmol) were suspended in sulfuric acid 70 % wt (15 mL) and were stirred at room temperature for 4 h. The solution was poured into an ice-water mixture (3 x 15 mL) resulting in the formation of a precipitate which was collected and crystallized from ethanol to give 7-carbethoxyamino-4-methylcoumarin **6** as salmon-colored crystals (4.58 mmol, 1.13 g, 83 %). Mp = 187-190 °C (lit. Mp = 94-96 °C), Rf = 0.36 (3:1, petroleum ether: ethyl acetate). IR (KBr, ν_{max}/cm^{-1}): 3335, 2981, 1719,1684, 1618, 1571. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 1.24 (3H, t, *J* = 7.1 Hz, CH_3), 2.34 (3H, d, *J* = 1.2 Hz, 4-CH_3), 4.14 (2H, q, *J* = 7.1 Hz, CH_2), 6.16 (1H, d, *J* = 1.2 Hz, 3-H), 7.34 (1H, dd, *J* = 8.7, 2.1 Hz, 6-H), 7.48 (1H, d, *J* = 2.1 Hz, 8-H), 7.61 (1H, d, *J* = 8.7 Hz, 5-H), 10.07 (1H, s, NH). ^{13}C NMR (101 MHz, DMSO-d6) δ (ppm): 14.6, 18.2, 60.9, 104.5, 111.9, 114.4, 126.1, 143.0, 153.5, 153.6, 153.9, 160.40, 160.4. MS (EI, 70 eV) m/z (%): 247 (M^+, 100), 219 (63), 218 (75). Anal. calcd. for $C_{13}H_{13}NO_4$ (247.25): C, 63.15; H, 5.30; N, 5.67 %. Found: C, 63.38; H, 5.46; N, 5.52 %.

Step 3. Synthesis of 7-amino-4-methylcoumarin (**3a**)

7-Carbethoxy-4-methyl-coumarin **5** (1.0 g, 3.42 mmol) was heated to 110 °C in a solution of concentrated sulfuric acid (1.7 mL) and acetic acid (2.7 mL). After 4 hours of reaction, the mixture was allowed to cool to room temperature, and then 50 mL of water was added; letting it rest overnight. A 50 % NaOH solution was added to the resulting suspension until pH = 8 was obtained. The product obtained was filtered, washed with ice water, and subsequently recrystallized in ethanol; finally obtaining 0.60 g of **3a** (3.43 mmol, 85 %) as yellow crystals. Mp = 220-224 °C (lit. Mp = 220-224 °C), Rf = 0.50 (1:1, petroleum ether: ethyl acetate). IR (KBr, ν_{max}/cm^{-1}): 3337-3245, 3072, 2984, 1680, 1542. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 2.29 (3H, s, 4-CH_3), 5.90 (1H, s, 3-H), 6.09 (2H, s, NH_2), 6.40 (1H, d, *J* = 1.9 Hz, 8-H), 6.56 (1H, dd, *J* = 8.5, 2.0 Hz, 6-H), 7.40 (1H, d, *J* = 8.6 Hz, 5-H). ^{13}C NMR (101 MHz, DMSO-d6) δ (ppm): 18.4, 98.94, 107.9, 109.3, 111.6, 126.6, 153.5, 154.2, 155.9, 161.2. MS (EI, 70 eV) m/z (%): 175 (M^+, 100), 147 (80), 119 (26), 91 (6). Anal. calcd. for $C_{10}H_9NO_2$ (175.19): C, 68.56; H, 5.18; N, 8.00 %. Found: C, 68.35; H, 5.26; N, 8.15 %.

2.2 Synthesis of 4-methylcoumarins 3a-g via the Pechmann reaction using a high-speed mixer ball mill process

General methodology: In a cylindrical Teflon vessel (8.1573 g, 2.0 mL), the respective phenol **1a-g** (1.0 mmol), ethyl acetoacetate **2** (10 mmol), and $InCl_3$ (3 mol%) were added. Subsequently, a stainless steel ball of 0.8 mm in diameter with a weight of 2.1031 g was incorporated into the reaction mixture. Once the reactor was carefully sealed, it was subjected to a vibration of 60 Hz at a determined time in a Zenith amalgamator, Model Z-1A. The reaction was monitored by TLC and once completed, the crude was poured onto crushed ice,

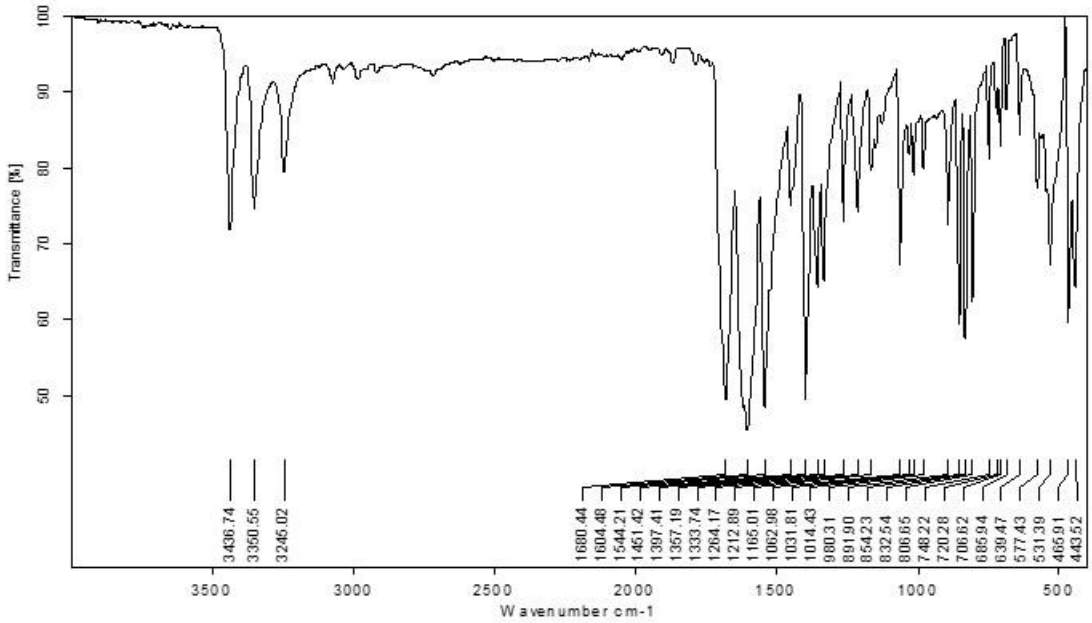
obtaining the solids corresponding to products **3a-g**, which were subsequently recrystallized in ethanol.

References

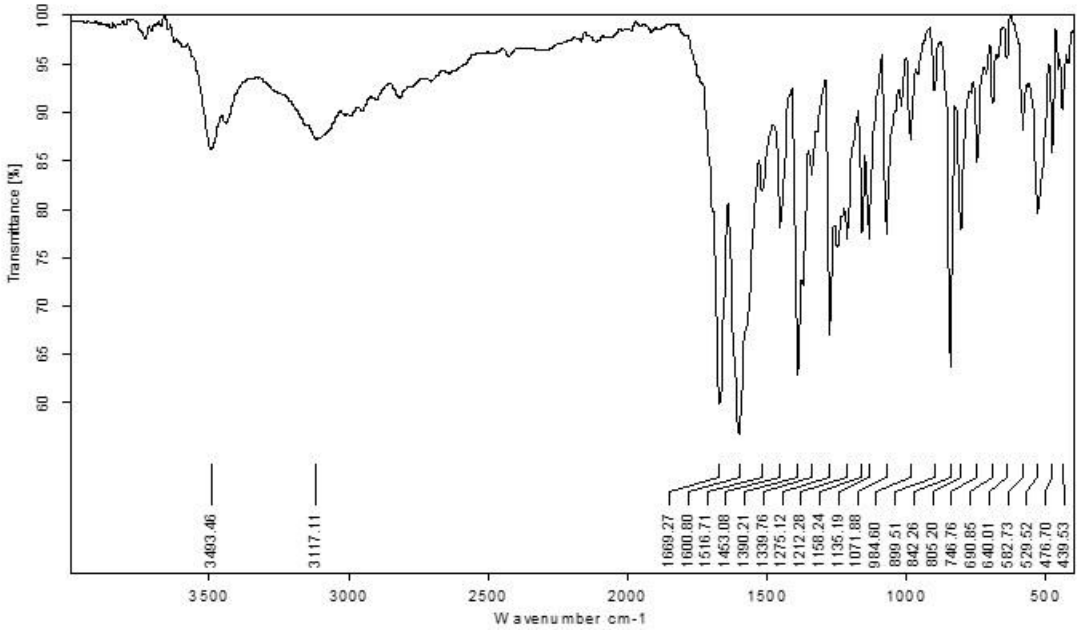
63. Reddy, T.S.; Reddy, A.R. Synthesis and fluorescence study of 6,7-diaminocoumarin and its imidazolo derivatives. *Dyes Pigm.* **2013**, *96*, 525–534.

3. IR spectra of products

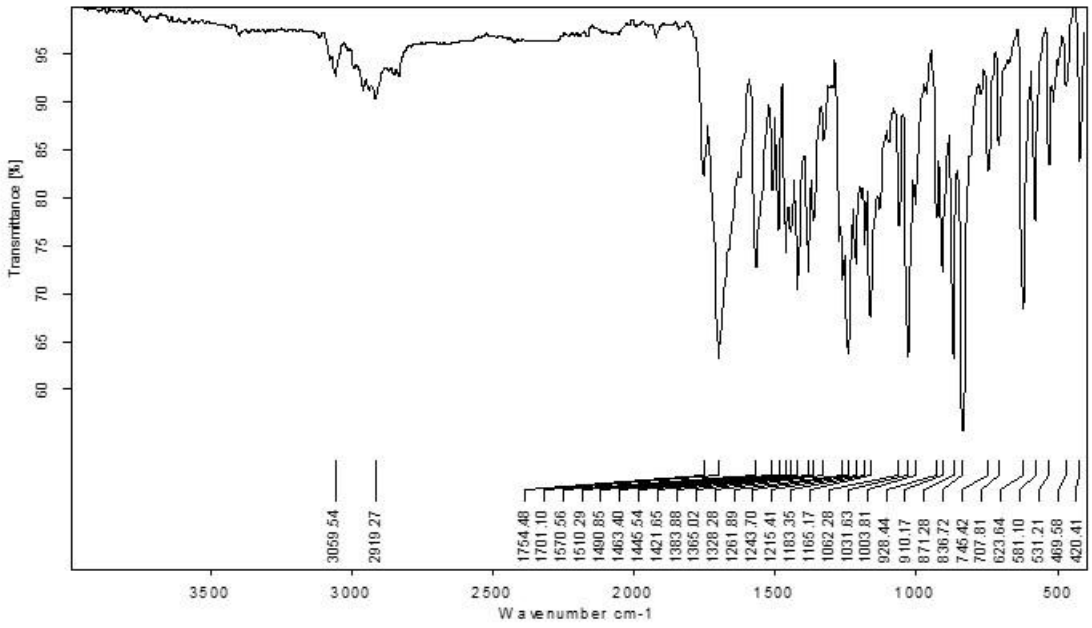
3.1 IR spectrum of 7-amino-4-methylcoumarin (3a)



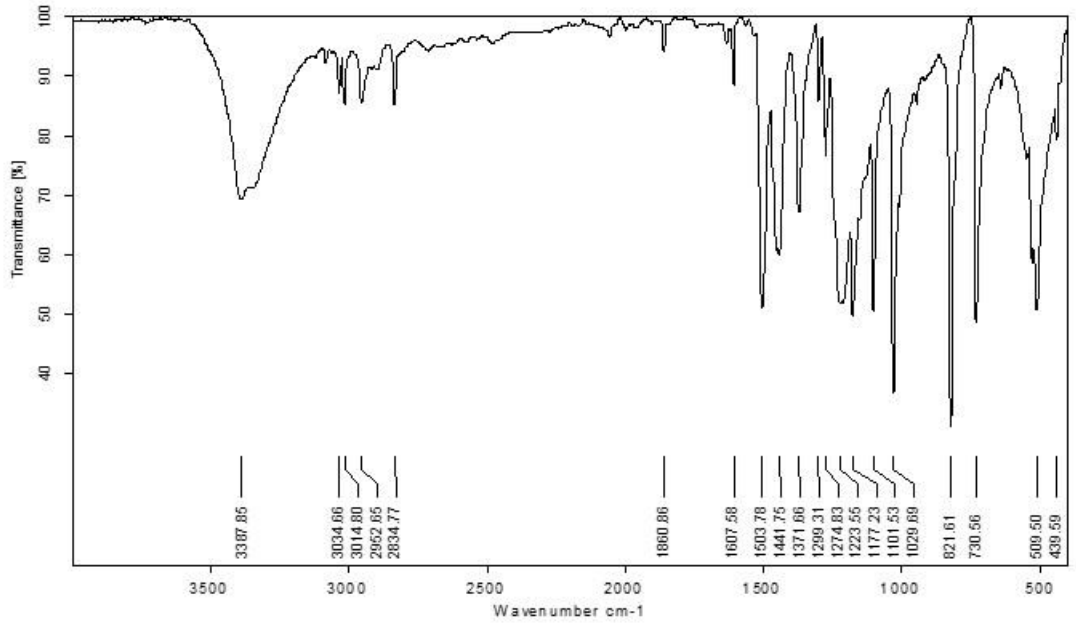
3.2 IR spectrum of 7-hydroxy-4-methylcoumarin (3b)



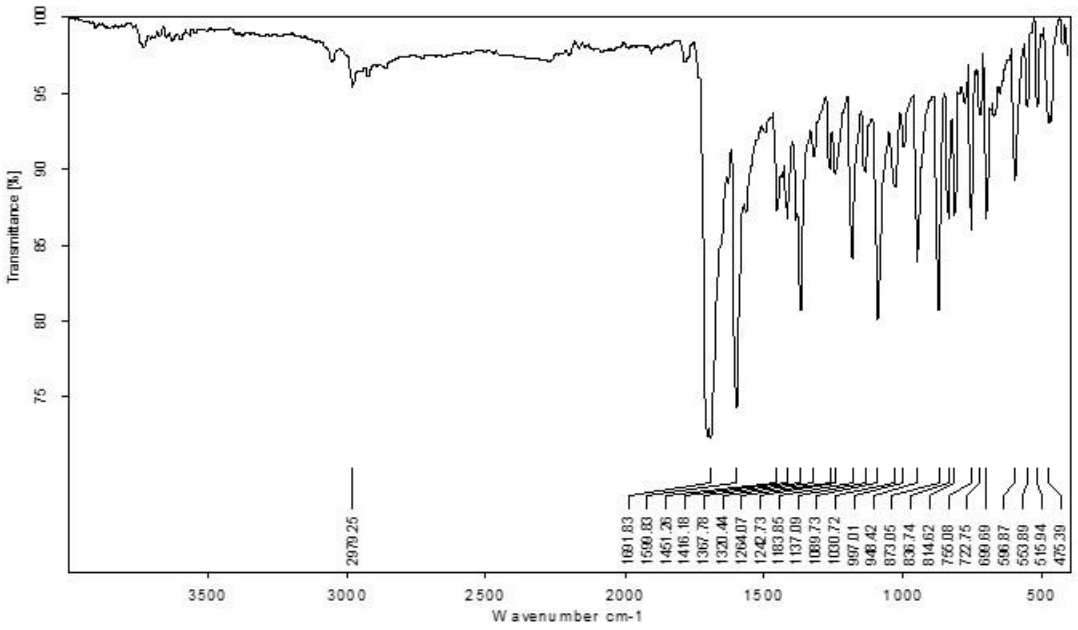
3.3 IR spectrum of 7-methoxy-4-methylcoumarin (3c)



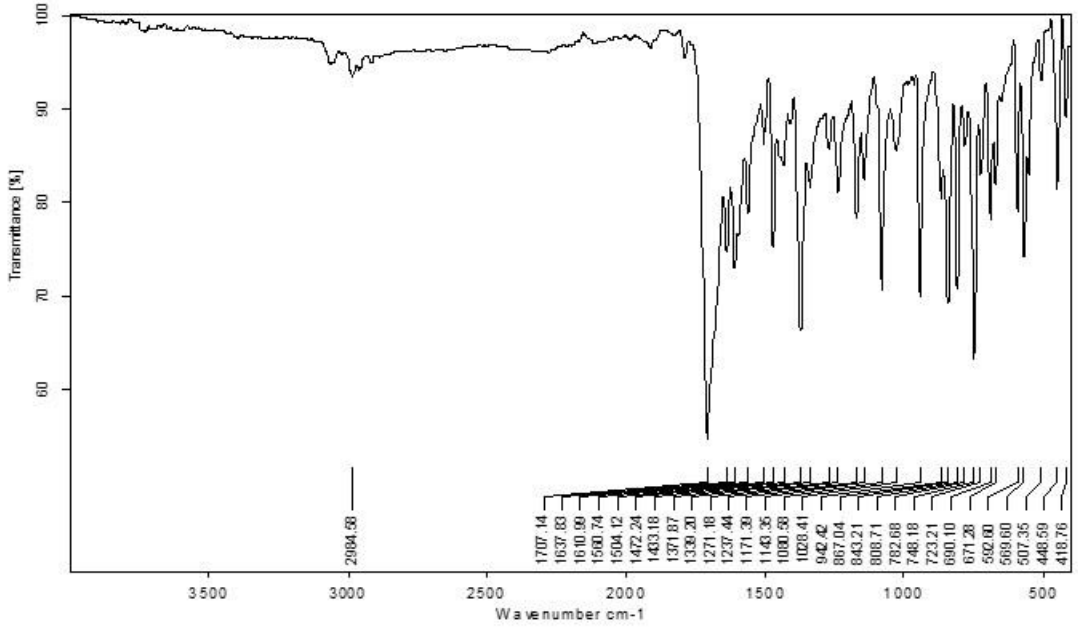
3.4 IR spectrum of 4-methylcoumarin (3d)



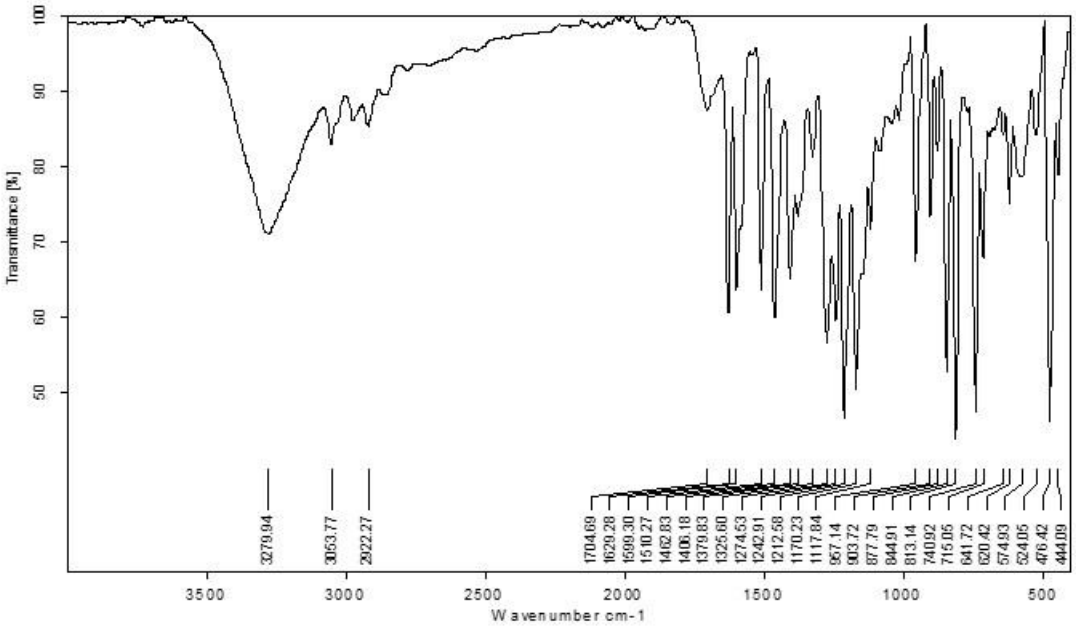
3.5 IR spectrum of 4,7,8-trimethylcoumarin (3e)



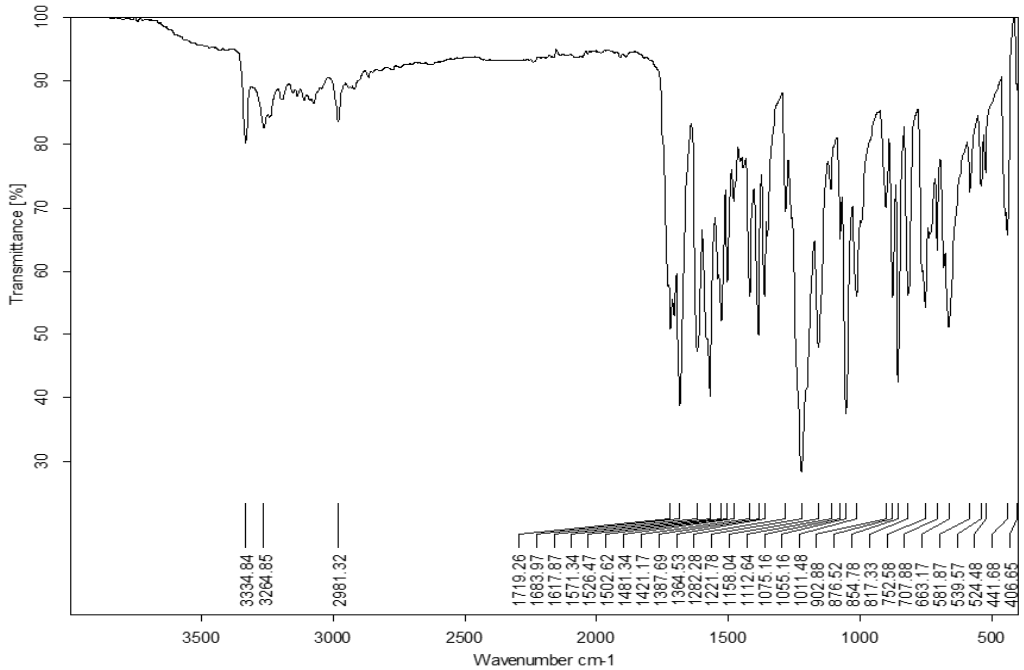
3.6 IR spectrum of 4-methyl-2*H*-benzo[*h*]chromon-2-one (3f)



3.7 IR spectrum of 1-methyl-3*H*-benzo[*f*]chromen-3-one (3g)

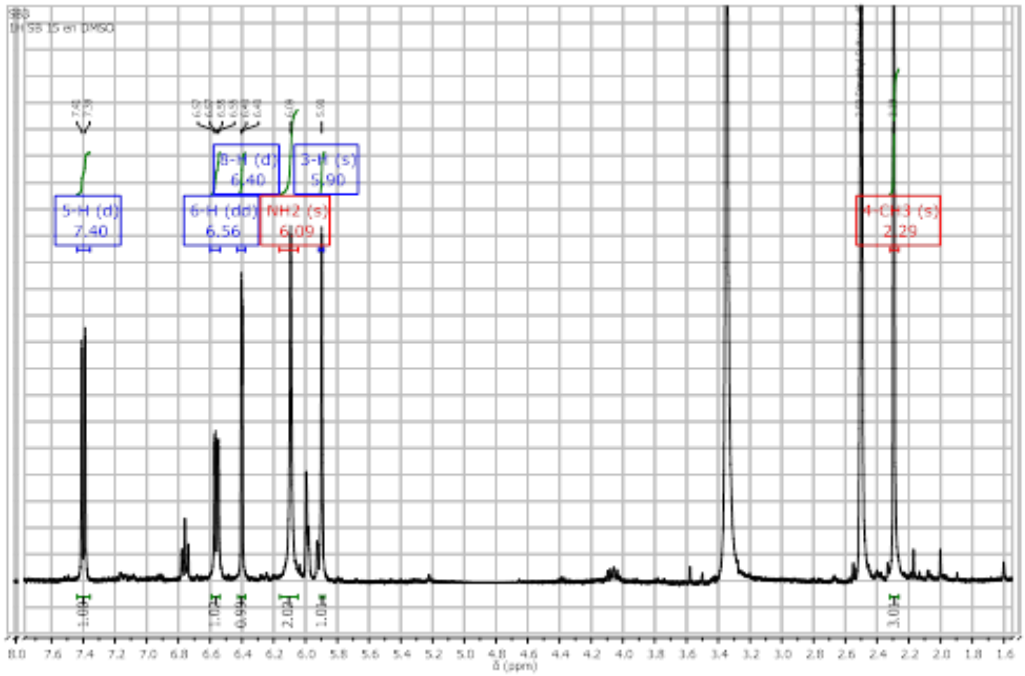


3.8 3.7 IR spectrum of 7-carbethoxyamino-4-methylcoumarin (5)

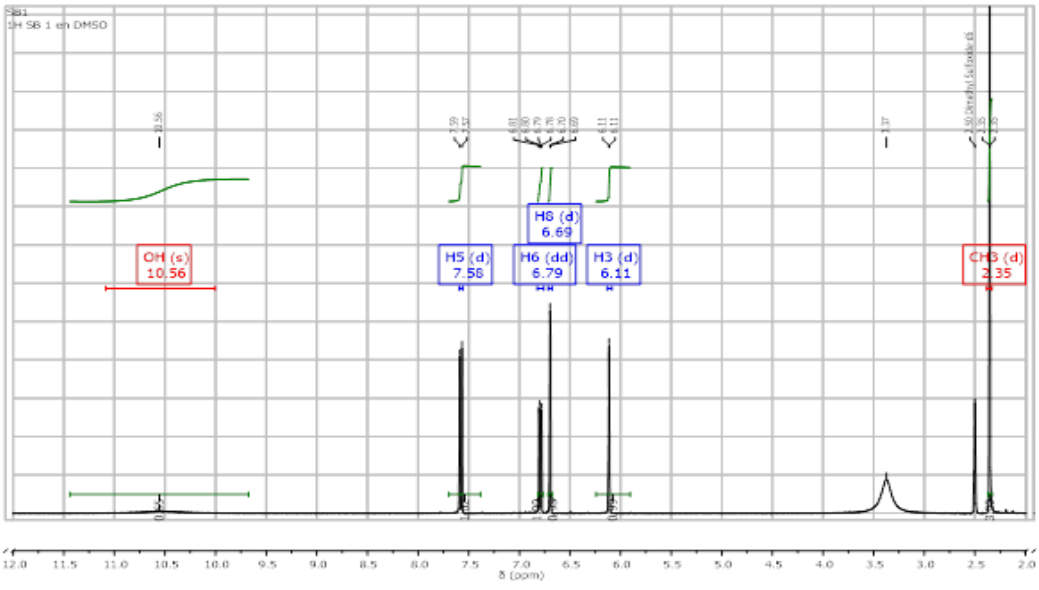


4. NMR spectra of products

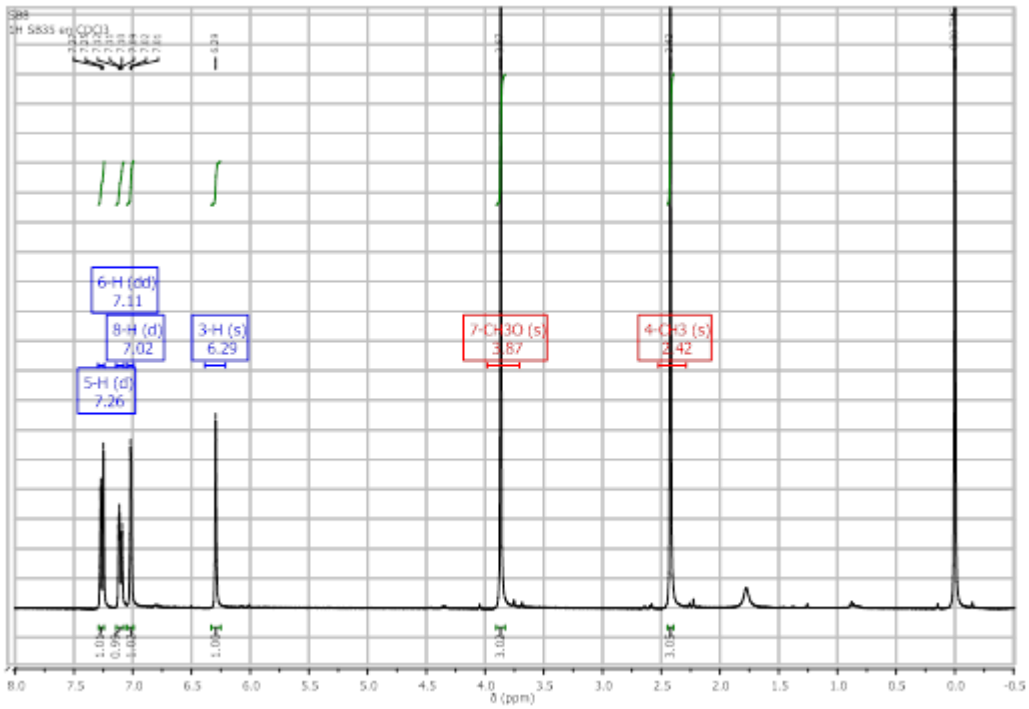
4.1 ^{1}H NMR spectrum of 7-amino-4-methylcoumarin (3a)



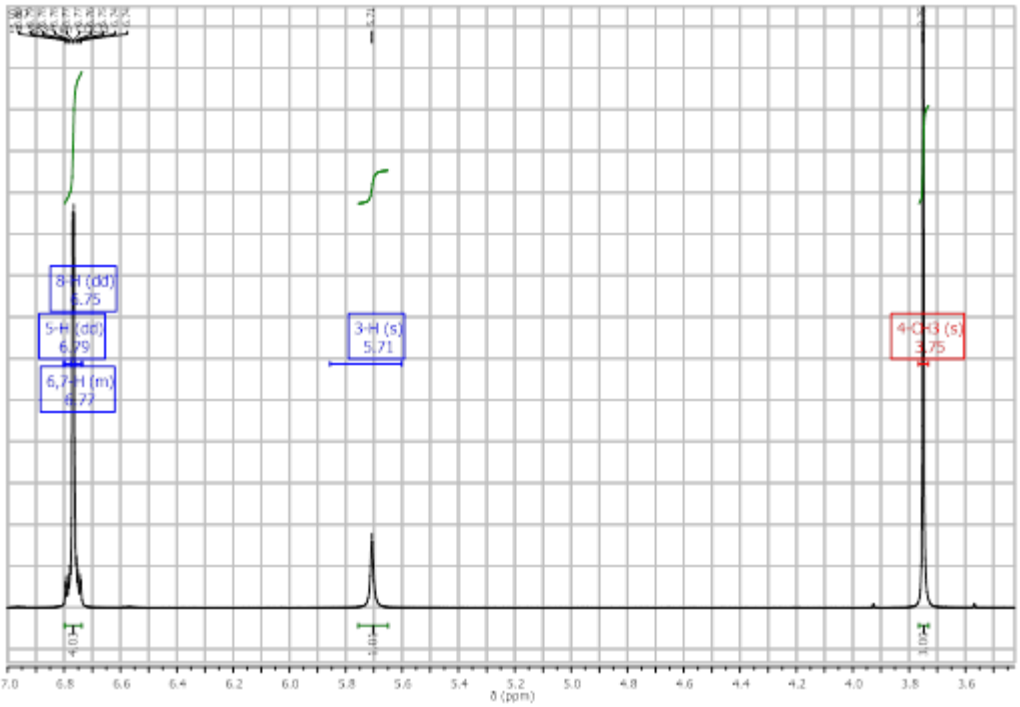
4.2 ^{1}H NMR spectrum of 7-hydroxy-4-methylcoumarin (3b)



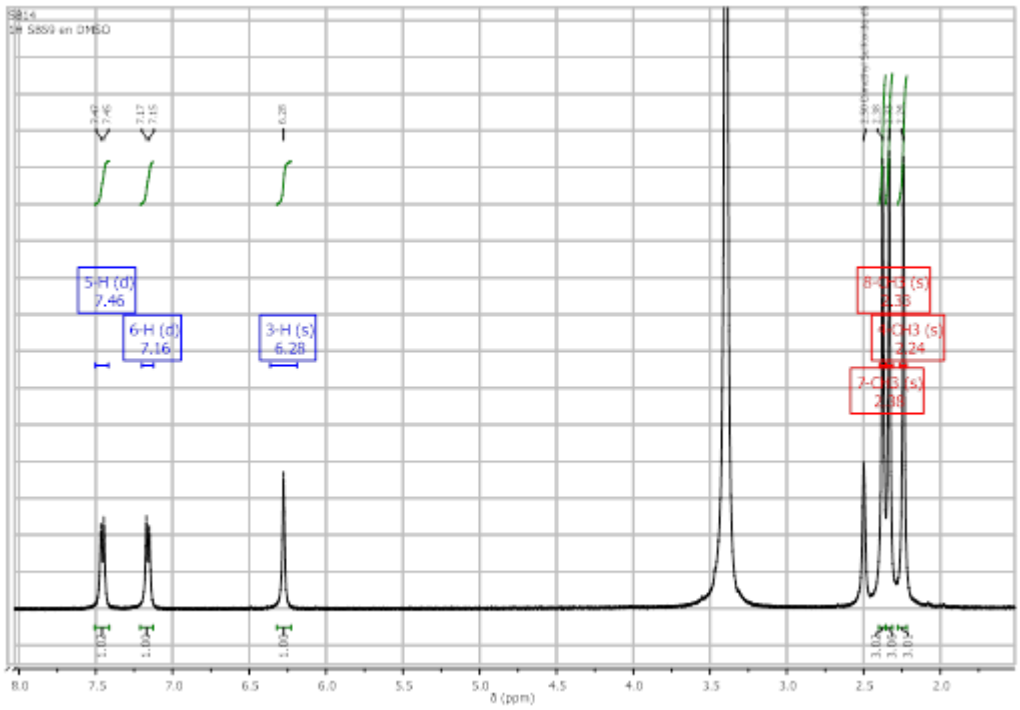
4.3 ^{1}H NMR spectrum of 7-methoxy-4-methylcoumarin (3c)



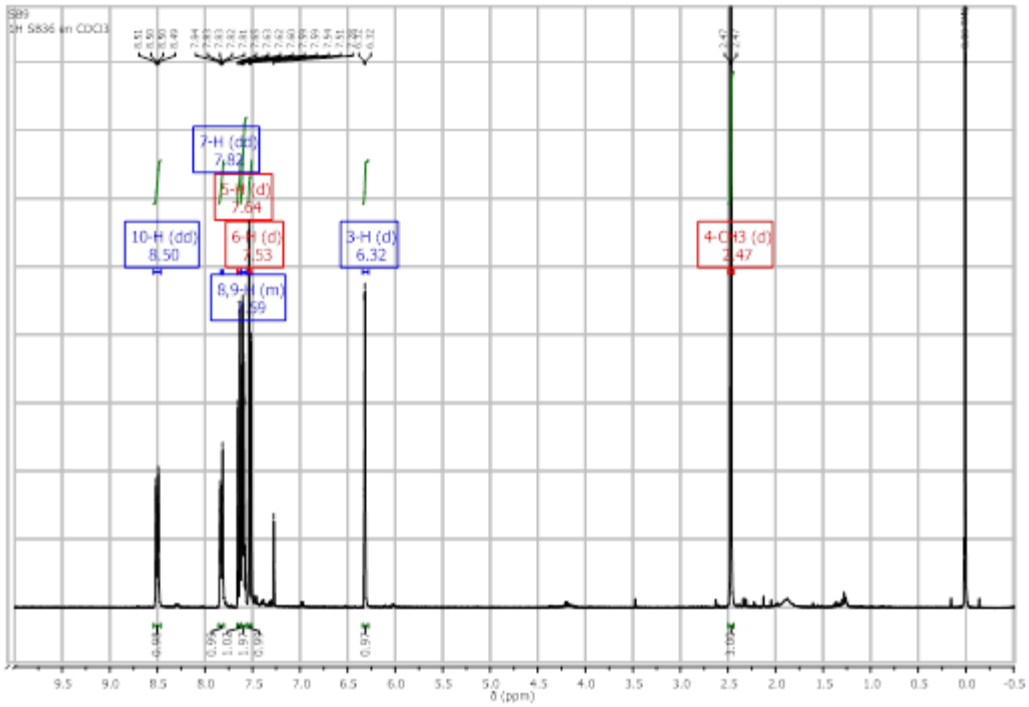
4.4 ^{1}H NMR spectrum of 4-methylcoumarin (3d)



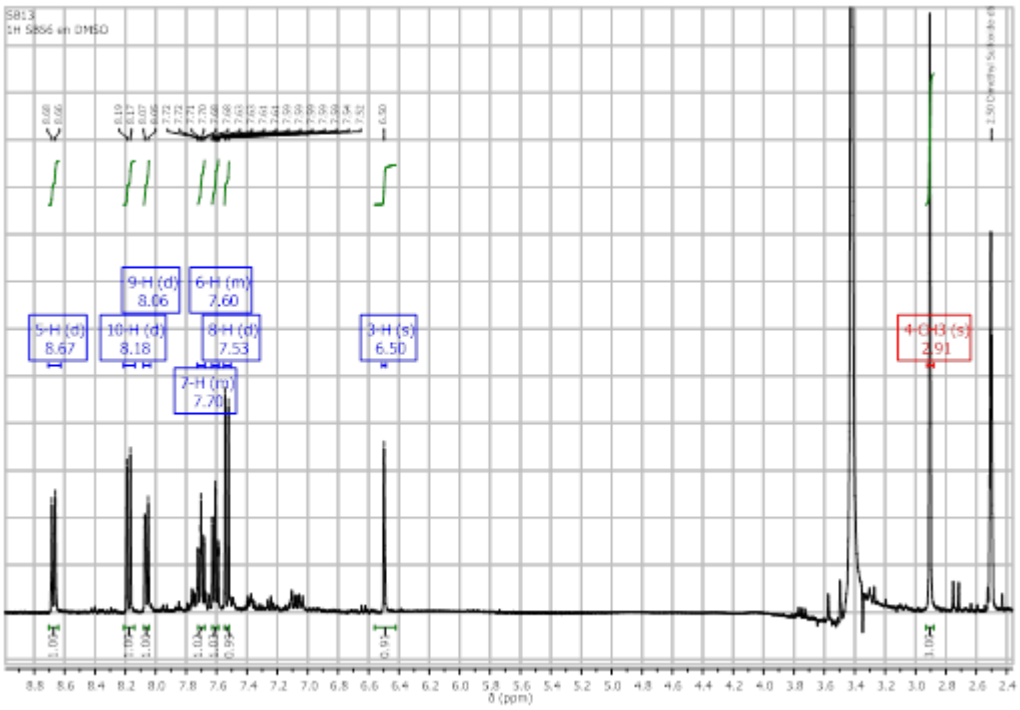
4.5 ^{1}H NMR spectrum of 4,7,8-trimethylcoumarin (3e)



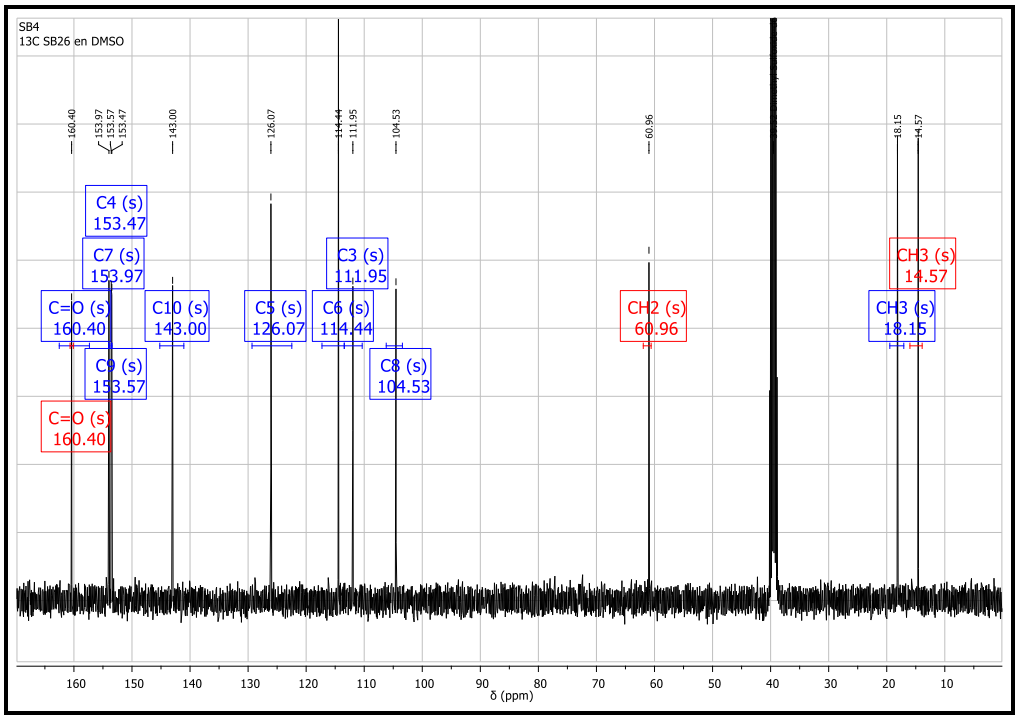
4.6 ^{1}H NMR spectrum of 4-methyl-2*H*-benzo[*h*]chromon-2-one (3f)



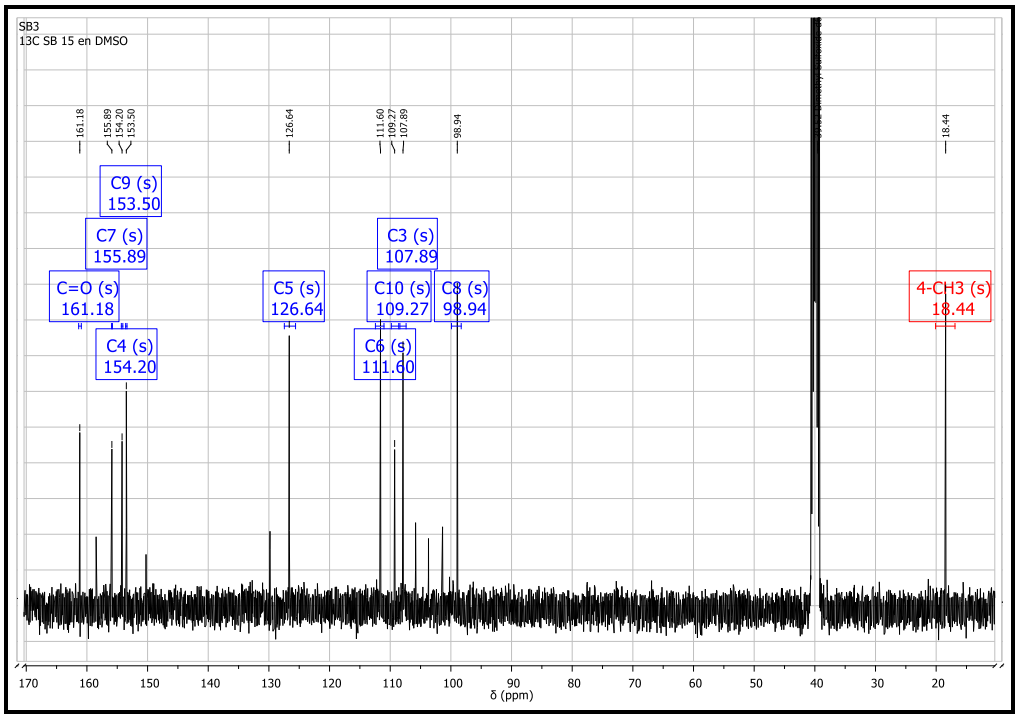
4.7 ^{1}H NMR spectrum of 1-methyl-3*H*-benzo[*f*]chromen-3-one (3g)



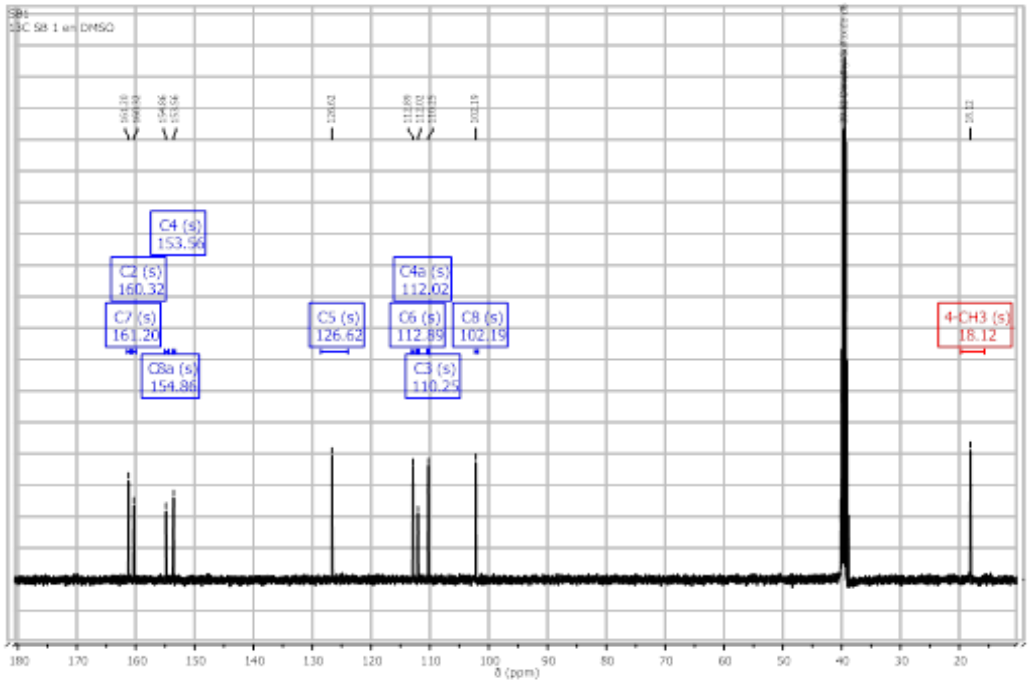
4.8 ^{1}H NMR spectrum of 7-carbethoxyamino-4-methylcoumarin (5)



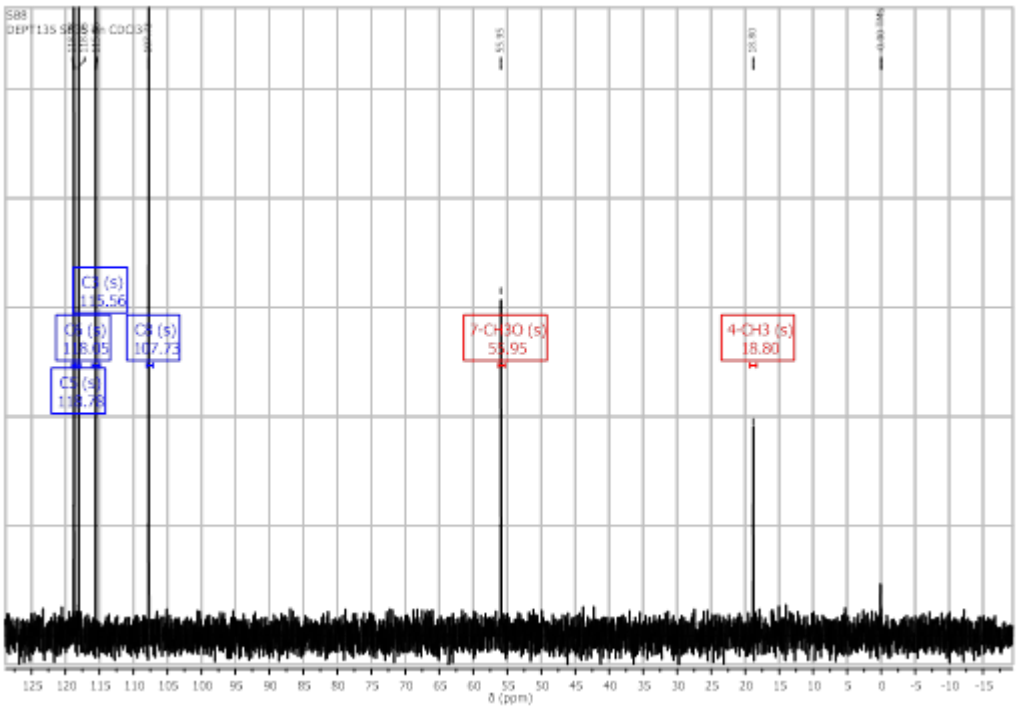
4.9 ^{13}C NMR spectrum of 7-amino-4-methylcoumarin (3a)



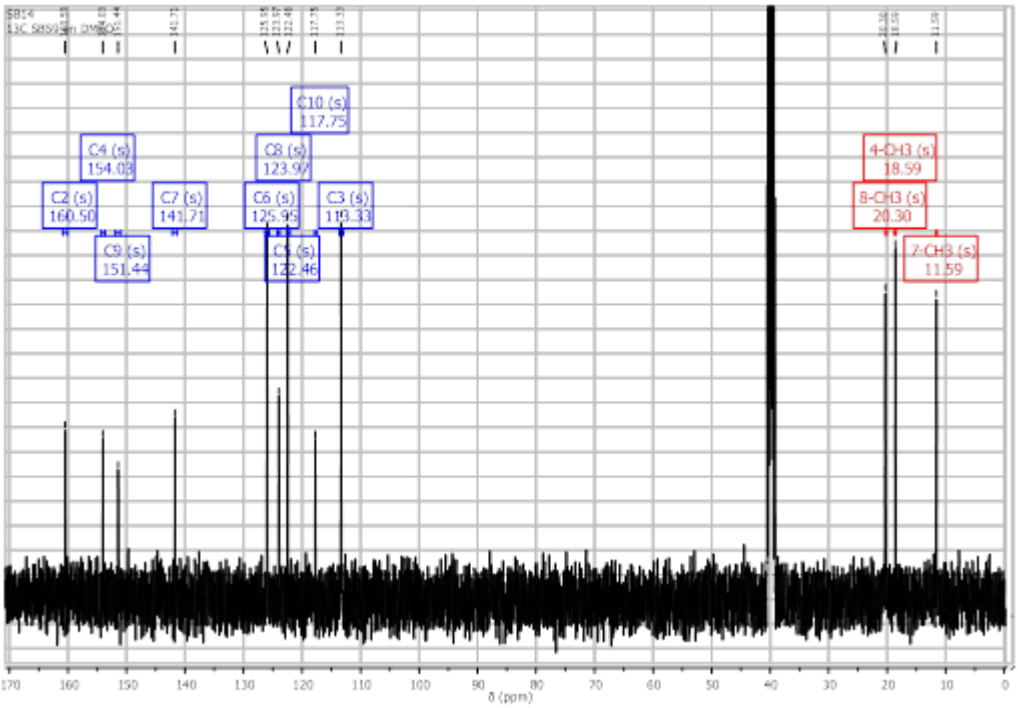
4.10 ^{13}C NMR spectrum of 7-hydroxy-4-methylcoumarin (3b)



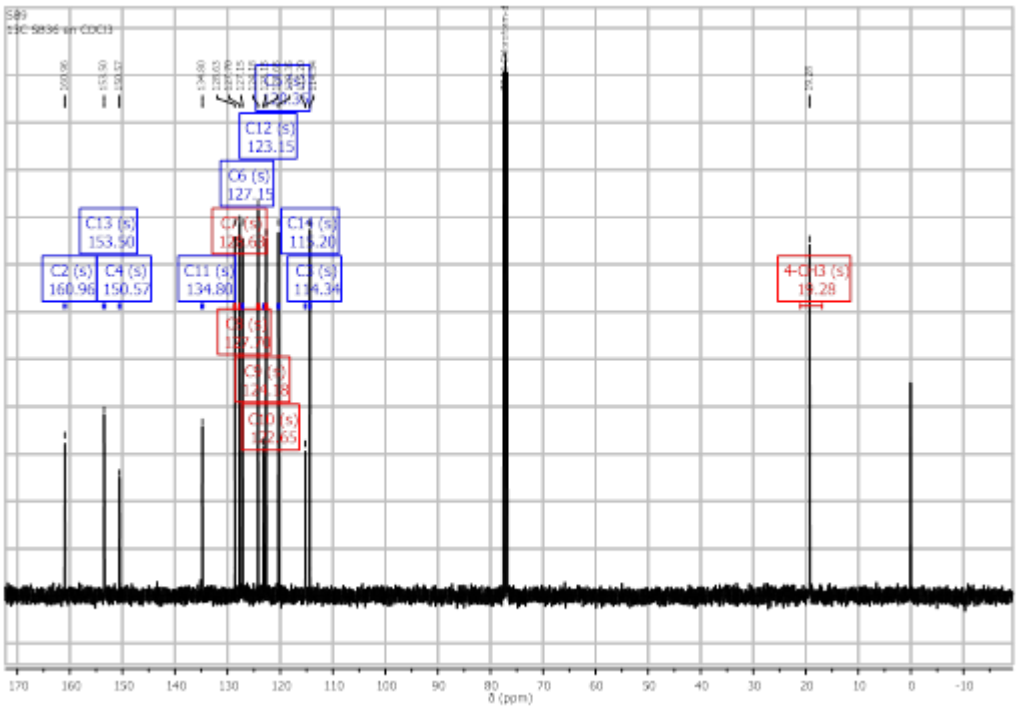
4.11 ^{13}C NMR spectrum of 7-methoxy-4-methylcoumarin (3c)



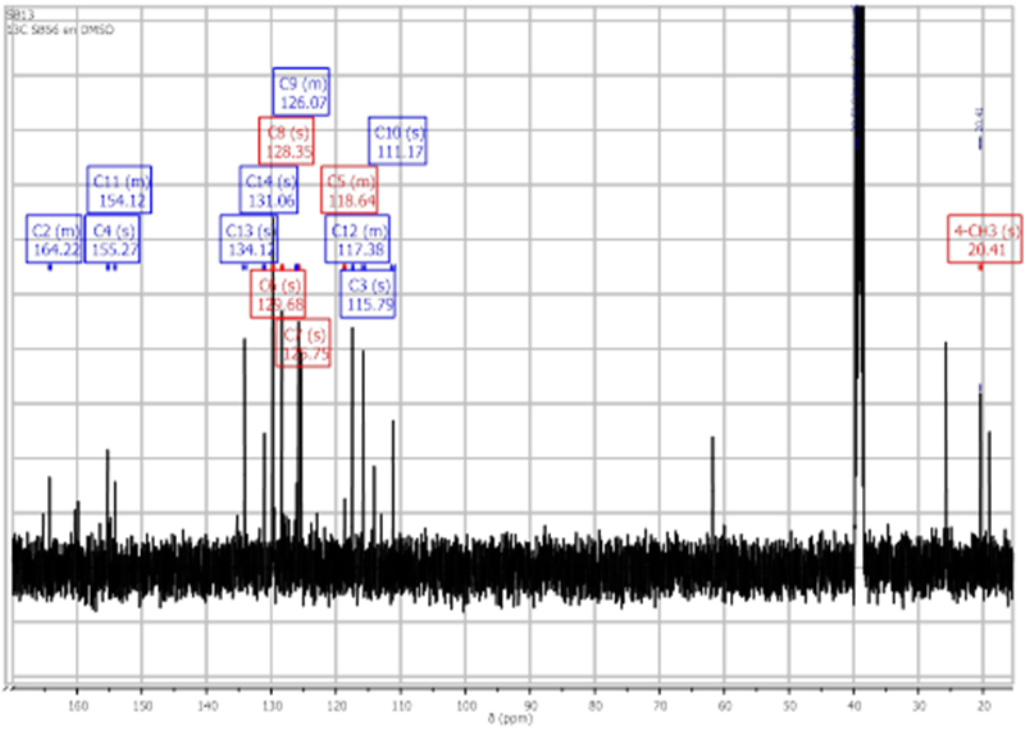
4.12 ^{13}C NMR spectrum of 4,7,8-trimethylcoumarin (3e)



4.13 ^{13}C NMR spectrum of 4-methyl-2*H*-benzo[*h*]chromon-2-one (3f)



4.14 ^{13}C NMR spectrum of 1-methyl-3*H*-benzo[*f*]chromen-3-one (3g)



4.15 ^{13}C NMR spectrum of 7-carbethoxyamino-4-methylcoumarin (5)