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SYNTHESIS AND FLUORESCENCE STUDY OF A SERIES OF 4-HYDROXYCOUMARIN *O*-ACYLATION DERIVATIVES

Abdoulaye Djandé[1]*, Lamine Cissé[2], Jules Yoda[1], Léopold Kaboré[1] and Fabrice Duvernay[3]

[1]Laboratoire de Chimie Moléculaire et de Matériaux, Equipe de Chimie Organique et de Phytochimie, Université Ouaga I Pr Joseph KI-ZERBO, Burkina Faso.

[2]Laboratoire de Photochimie et d'Analyse, Faculté des Sciences et Techniques, Université Cheikh Anta DIOP, Dakar, Sénégal.

[3]Laboratoire de Physique des Interactions Ioniques et Moléculaires (PIIM), Equipe SDM, Campus Scientifique de Saint Jérôme, Aix-Marseille Université, France.

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***Corresponding Author**
Abdoulaye Djandé
Laboratoire de Chimie Moléculaire et de Matériaux, Equipe de Chimie Organique et de Phytochimie, Université Ouaga I Pr Joseph KI-ZERBO, Burkina Faso.

ABSTRACT

*Some coumarin derivatives were synthesized starting from 4-hydroxycoumarin and benzoyl chlorides. The structures of the obtained compounds were confirmed by mass and NMR spectra. Additionally, their crystal structures were determined by X-ray diffractometry, excepting the compound **C1**. Absorption and fluorescence spectra of these derivatives have been investigated in acetonitrile medium. The effects of various electron donating substituents R on fluorescence emission were examined. As a result, compound **C5** with an electron-donating substituent dimethyl amino (R = Me_2N) exhibited the strongest fluorescence.*

KEYWORDS: 4-hydroxycoumarin, O-acylation, (coumarin-4-yl)-benzoates, fluorescence, substituent R.

INTRODUCTION

Coumarins or benzo-2-pyrone derivatives are one of the most significant families of natural product compounds and are also important in synthetic organic chemistry. They have been widely used as starting materials or precursor molecules in the pharmaceutical, perfumery and agrochemical industries. Coumarin derivatives are also used as fluorescent brighteners, efficient laser dyes and additives in food and cosmetics.[1] Specifically, 4-hydroxycoumarin

derivatives represent a large class of compounds that have been reported to possess a wide range of biological activities.[2–4] They can be among others, antibacterial[5,6], anti-HIV active and anti-tumoral.[7-10] Many 4-hydroxycoumarin derivatives show significant anticoagulant action by antagonizing the action of vitamin K.[11,12]

Recently, coumarins have attracted considerable attention for electronic and photonic applications due to their inherent photochemical characteristics[13,14], reasonable stability and solubility in various organic solvents. Many coumarin derivatives have been commercialized as blue-green lasers for fluorescent labels and fluorescent probes.[15–18] They exhibit intense fluorescence upon substitution with various functional groups at different positions.[19–20]

Herein, we report a facile synthesis and structural analysis of five 4-substituted coumarin derivatives, presenting at that position an ester function (compounds **C**). The fluorescence properties of this series of (coumarin-4-yl)-benzoates were then investigated.

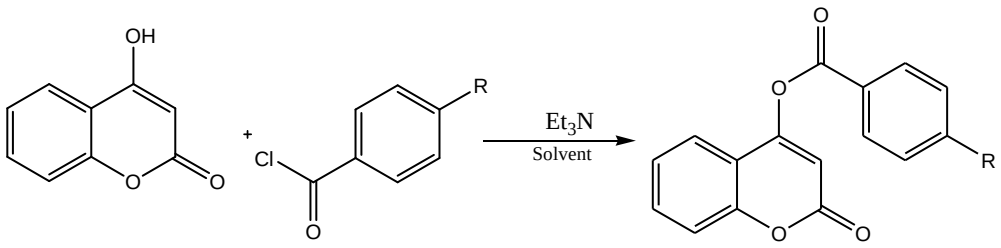
Thus, the title compounds were synthesized according to a described convenient method, in satisfactory yields, from 4-hydroxycoumarin and benzoyl chlorides in the presence of triethylamine (TEA).[21-24] Their molecular structures were characterized by FT-IR, ^{1}H and ^{13}C NMR and ESI-MS spectrometries and were finally determined by X-ray diffractometry, with the exception of compound **C1** which is in the shape of powder. The fluorescence spectra were recorded in acetonitrile. We evidenced the effects of different substitutions on fluorescence emission.

MATERIALS AND METHODS

Synthesis and Characterization of compounds C

Synthesis

Compound **C** were prepared in high yields (74%–89%), by an esterification reaction of 4-hydroxycoumarin with various benzoyl chlorides. The hydroxyl at position 4 of **A** was acylated to benzoyl, methyl-benzoyl, *t*-butyl-benzoyl, methoxy-benzoyl and dimethlaminobenzoyl. We used exploited HSAB theory of Pearson in the choice of the base.[25,26] According to this principle, acylation with benzoyl chlorides, which were known to be hard acids, leads to best yields by using a hard base like TEA. Further, the preferable solvents were ethers: diethyl ether or tetrahydrofuran (THF), but it was necessary to raise the temperature of reaction to solvent reflux. On the whole, the global process of this O-acylation is given below (**Scheme 1**).



A B C

R = H: Solvent = Diethyl ether;

Other cases: Solvent = THF.

C1: R = H; **C2**: R = CH_3; **C3**: R = *t*-Bu; **C4**: R = MeO; **C5:** R = Me_2N.

Scheme 1: Synthetic route of (Coumarin-4-yl)benzoates.

Synthesis and crystallization (compound C1)

To a solution of benzoyl chloride (6.17 mmol) in dried diethyl ether (25 mL) was added dried TEA (3.2 mL; 3.6 molar equivalents) and 4-hydroxycoumarin (1 g; 6.17 mmol) by small portions over 30 min., under strong stirring. The reaction mixture was left under agitation for 2 h at room temperature and then refluxed for 2 h. The obtained solution was poured in a separating funnel containing 40 ml of chloroform and washed with diluted hydrochloric acid solution until the pH was 2-3. The organic phase was extracted, washed with water to neutrality, dried using MgSO4 and the solvent removed. The crude product was filtered off with suction, washed with petroleum ether and recrystallized from a solvent mixture of chloroform–hexane (1/3, V/V) to offer white powder of the compound **C1**.

Synthesis and crystallization (compounds C2, C3, C4, C5)

To a solution of the corresponding 4-substitutedbenzoyl chloride (6.17 mmol) in dried THF (40 mL) was added dried TEA (2.6 mL ; 3 molar equivalents) and 4-hydroxycoumarin (1g; 6.17 mmol) by small portions over 30 min, under high speed stirring. The mixture was then refluxed for 4 h and poured into 40 mL of chloroform. The resulting solution was acidified with diluted hydrochloric acid until the pH was 2–3. The organic layer was extracted, washed with water to neutrality, dried over MgSO4. The resulting precipitate was filtered off with suction, washed with petroleum ether and recrystallized from chloroform to afford desired crystals C2–C5**.** To sum up, the results of synthesis are given in the following table (table 1).

Table 1: Preparation of (coumarin-4-yl)benzoates.

Compound	R	Yield %	MP °C	Aspect
C1	H	89	**183-184**	White powder
C2	CH_3	76	**120**	Colourless crystals
C3	*t*-Bu	74	**108-110**	Colourless crystals
C4	MeO	84	**148-149**	Colourless crystals
C5	Me_2N	83	**172**	Colourless crystals

Material and measurements

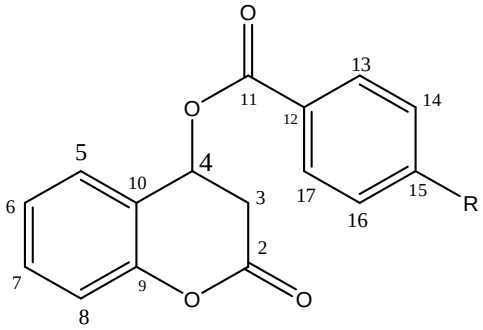
Melting points were determined in capillary tubes on a Stuart SMP 11 apparatus and are uncorrected. **^{1}H** and **^{13}C (+ DEPT 135) NMR spectra** were recorded on a BRUKER AMX-400 spectrometer at 400 MHz and 100 MHz respectively, using TMS as internal standard (chemical shifts δ in ppm, J in Hz).

Mass spectra were obtained on a 3200 QTRAP (Applied Biosystems SCIEX) spectrometer equipped with a pneumatically assisted air pressure ionization (API) source.

All the compounds were analyzed by **X-ray diffractometry**. In this part, we highlight the crystallographic data that justify their 3D structures. Data were collected by the X scan technique at 298 K on a Nonius Kappa CCD diffractometer, using radiation MoKα (λ = 0.71073 Å), and were corrected for Lorentz and polarization effects. The structures were solved by direct methods which revealed the positions of all non-hydrogen atoms, and were refined on F^2 by a full-matrix least-squares procedure using anisotropic displacement parameters. The program used to solve structure was SIR92 for compound C5[27] and SIR2004 for the others.[28] The program used to refine the structures was CRYSTALS for compound C5[29] and SHELXL97 for **C2-C4**.[30] All hydrogen atoms were located from difference Fourier maps and were refined isotropically. Molecular graphics were generated with Platon.[31] Finally, the software used to prepare material for publications was CRYSTALS for compound **C5** and SHELXL97, publCIF and WinGX for C2-C4.[32,33]

A summary of the crystals data, experimental details, and refinements results is given below in the crystal structure Determination. It's the occasion for us to signalize that the crystal structures of compounds **C2**, **C3**, **C4** and **C5** have previously been published by our research team.[21-24]

Characterization



Scheme 2: Numbered structure of compounds C.

(Coumarin-4-yl)benzoate (C1)

C1: **ESI-MS**: $[M+H]^+$, m/z 267; **^{1}H NMR** (Bruker TOPSPIN, Acétone-d6, 300 MHz, ppm) *δ*: 8.3 (d, 2H, H13 et H17); 7.9 (t, 1H, H15); 7.75 (dd , 2H, H14 and H16); 7.64 (d,1H, H5); 7.45 (dd, 1H, H7); 7.33 (m, 2H, H6 and H8); 5.7 (s, 1H, H3). **^{13}C NMR** (Bruker TOPSPIN, Acétone-d6, 100 MHz, p.p.m.) *δ*: 165.95 (C-4); 161.30 (C-2); 155.02 (C-11); 154.61 (C-9); 135.61 (C-15); 131.26 (C-13 and C-17); 130.01 (C-14 and C-16); 129.10 (C-12); 125.41 (C-7); 124.58 (C-5); 124.09 (C-6); 117.64 (C-8); 116.76 (C-10); 92.58 (C-3). **DEPT 135°**: 135.61 (C-15); 131.26 (C-13 et C-17); 130.01 (C-14 and C-16); 125.41 (C-7); 124.58 (C-5); 124.09 (C-6); 117.64 (C-8); 92.58 (C-3).

(Coumarin-4-yl)-4-mehylbenzoate (C2)

C2: **ESI-MS**: $[M+H]^+$, m/z 281; **^{1}H NMR** (Bruker TOPSPIN, Acétone-d6, 400 MHz, ppm) *δ*: 8.2 (d, 2H, H-13 and H-17); 7.9 (d,1H, H-5); 7.75 (t, 1H, H-7); 7.5 (m, 2H, H-6 et H-8); 7.4 (m, 2H, H-14 and H-16); 6.69 (s, 1H, H-3); 2.5 (s, 3H, CH_3). **^{13}C NMR** (Bruker TOPSPIN, Acétone-d6, 100 MHz, p.p.m.) *δ*: 163.55 (C-4); 161.28 (C-2); 159.84 (C-11); 154.67 (C-9); 146.80 (C-15); 133.88 (C-13 and C-17); 131.34 (C-14 and C-16); 130.65 (C-7); 126.32 (C-12); 125.39 (C-5); 124.05 (C-6); 117.64 (C-8); 116.68 (C-10); 106.44 (C-3); 21.74 (CH_3). **DEPT 135°**: 133.88 (C-13 et C-17); 131.34 (C-14 and C-16); 130.65 (C-7); 125.39 (C-5); 124.05 (C-6); 117.64 (C-8); 106.44 (C-3); 21.74 (CH_3).

***Crystal structure Determination* (C2)**

Chemical formula: $C_{17}H_{12}O_4$; Formula weight: 280.27; Crystal description: prism, colourless; Melting point (K): 393 ; Crystal system: Triclinic; space group: P -1; Temperature (K): 298; Wavelength (Å): 0.71073; Unit cell dimensions: a = 9.2790 (5) Å, b = 10.7696 (5) Å, c = 14.5758 (9) Å, α = 95.274 (2)°, β = 97.875 (2)°, β = 97.875 (2)°; Volume (Å^3): 1382.75 (13);

Z = 4; Radiation type: MoKα; Absorption coefficient (mm^{-1}): 0.10; Density (Mg m^{-3}): 1.346; F(000): 584; Crystal size (mm): 0.35 × 0.20 × 0.20 mm; 16045 measured reflections; 6907 independent reflections; *R*int = 0.055; $R[F^2 > 2\sigma(F^2)]$ = 0.071; *wR* (F^2) = 0.193; *S* = 1.02; 3981 reflections; 381 parameters.

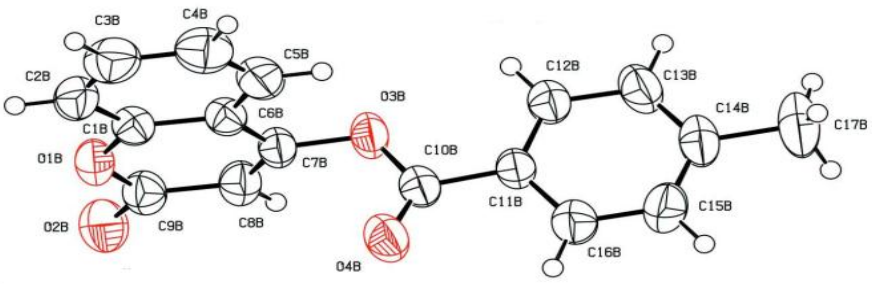


Figure 1: Molecular structure of compound C2 showing the atomic labeling scheme with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

(Coumarin-4-yl)-4-tertiobutylbenzoate (C3)

C3: **ESI-MS**: $[M+H]^+$, m/z 323; **^{1}H NMR** (Bruker TOPSPIN, Acétone-d6, 400 MHz, ppm) *δ*: 8.23 (d, 2H, H-13 and H-17); 7.9 (d,1H, H-5); 7.74 (m, 3H, H-6, H-7 et H-8); 7.45 (m, 2H, H-14 and H-16); 6.68 (s, 1H, H-3); 1.4 (s, 9H, $3CH_3$).

^{13}C NMR (Bruker TOPSPIN, Acétone-d6, 100 MHz, ppm) *δ*: 163.48 (C-4); 161.27 (C-2); 159.88 (C-15); 159.48 (C-11); 154.67 (C-9); 133.89 (C-13 and C-17); 131.25 (C-7); 127.00 (C-5); 126.32 (C-12); 125.39 (C-6); 124.08 (C-14 and C-16); 117.64 (C-8); 116.69 (C-10); 106.47 (C-3); 35.93 (C-18); 21.74 (CH_3). **DEPT 135°**: 133.89 (C-13 and C-17); 131.25 (C-7); 127.00 (C-5); 125.39 (C-6); 124.08 (C-14 and C-16); 117.64 (C-8); 106.47 (C-3); 21.74 (CH_3).

***Crystal structure Determination* (C3)**

Chemical formula: $C_{20}H_{18}O_4$; Formula weight: 322.34; Crystal description: Parallelepiped, colourless; Melting point (K): 381–383 K; Crystal system: Triclinic; space group: P-1; Temperature (K): 298; Wavelength (Å): *λ* = 0.71073; Unit cell dimensions: a = 6.4319 (2) Å, b = 9.3498 (3) Å, c = 14.5505 (5) Å, α = 98.481 (1)°, β = 93.655 (1)°, γ = 102.359 (2)°; Volume ($Å^3$): 841.27 (5); Z = 2; Radiation type: Mo*Kα*; Absorption coefficient (mm^{-1}): 0.09; Density (Mg m^{-3}): 1.273; F(000): 340; Crystal size (mm): 0.50 × 0.30 × 0.14; 11164

measured reflections; 4198 independent reflections; *R*int = 0.031; $R[F^2 > 2\sigma(F^2)]$ = 0.057; $wR(F^2)$ = 0.157; *S* = 1.05; 4198 reflections; 247 parameters.

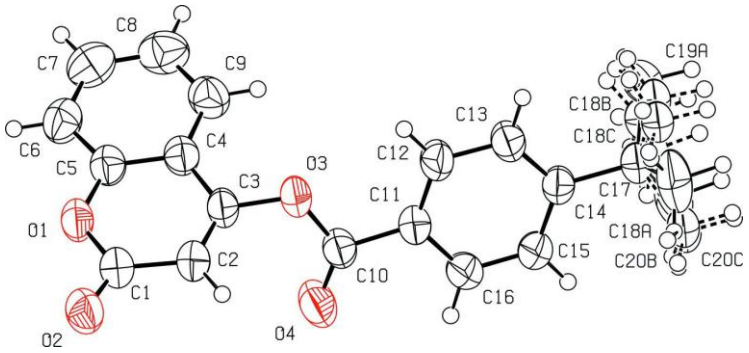


Figure 2: Molecular structure of compound C3, showing displacement ellipsoids at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

(Coumarin-4-yl)-4-methoxybenzoate (C4).

C4: **ESI-MS**: $[M+H]^+$, m/z 297; **^{1}H NMR** (Bruker TOPSPIN, CDCl3, 400 MHz, ppm) δ : 8.2 (d, 2H, H-13 and H-17); 7.73 (d, 1H, H-8); 7.61 (t.d,1H, H-7); 7.43 (d, 1H, H-5); 7.33 (t.d, 1H, H-6); 7.05 (d, 2H, H-14 and H-16); 6.63 (s, 1H, H-3); 3.93 (s, 3H, CH_3). **^{13}C NMR** (Bruker TOPSPIN, $CDCl_3$, 100 MHz, p.p.m.) δ: 164.85 (C-11); 162.23 (C-2); 161.54 (C-4); 158.95 (C-12); 153.73 (C-9); 132.77 (C-13 and C-17); 127 (C-5); 126 (C-8); 124.32 (C-6); 120.04 (C-15); 117.15 (C-7); 115.93 (C-10); 113 (C-14 and C-16); 108 (C-3); 55.68 (CH_3). **DEPT 135°**: 132.77 (C-13 et C-17); 127 (C-5); 126 (C-8); 124.32 (C-6); 117.15 (C-7); 113 (C-14 and C-16); 108 (C-3); 55.68 (CH_3).

Crystal structure Determination **(C4)**

Chemical formula: $C_{17}H_{12}O_5$; Formula weight: 296.27; Crystal description: Prism, colourless; Melting point (K): 421–422 K; Crystal system: Triclinic; space group: P-1; Temperature (K): 298; Wavelength (Å): λ = 0.71073; Unit cell dimensions: a = 4.371 (1) Å b = 10.535 (4) Å, c = 15.193 (2) Å, α = 85.218 (3)°, β = 83.688 (2)°, γ = 81.893 (1)°; Volume (Å^3): 686.8 (3); Z = 2; Radiation type: Mo*Kα*; Absorption coefficient (mm^{-1}) : 0.11; Density (Mg m^{-3}): 1.433; F(000): 308; Crystal size (mm): 0.25 × 0.15 × 0.04; 5683 measured reflections; 2731 independent reflections; *R*int = 0.055; $R[F^2 > 2\sigma(F^2)]$ = 0.066; $wR(F^2)$ = 0.163; *S* = 1.11; 2731 reflections; 200 parameters.

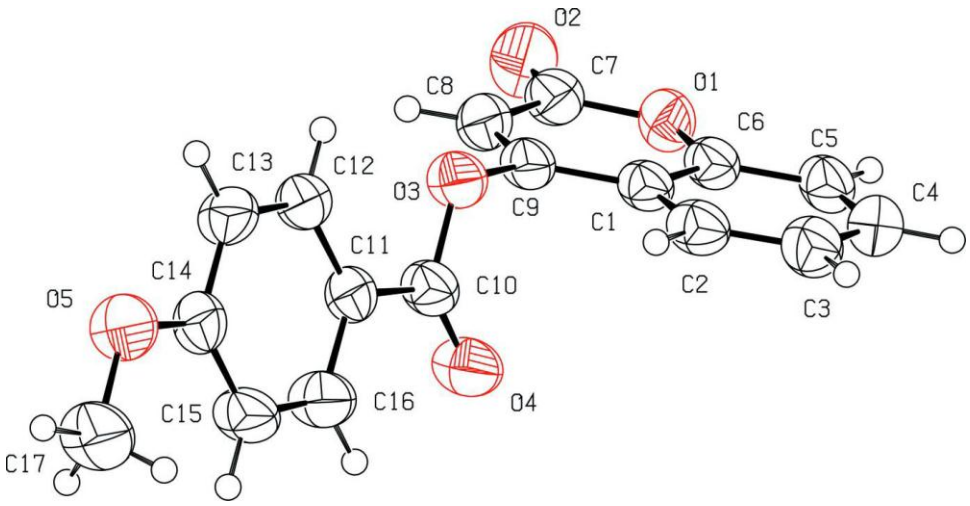


Figure 3: Molecular structure of compound C4, showing displacement ellipsoids at the 50% probability level. H atoms areshown as spheres of arbitrary radius.

(Coumarin-4-yl)-4-dimethylaminobenzoate (C5)

C5: **ESI-MS**: $[M+H]^+$, m/z 310; **^{1}H NMR** (Bruker TOPSPIN Acétone-d6, 400 MHz, ppm) δ: 8.10 (d, 2H, H-13 and H-17); 7.86 (d, 1H, H-8); 7.73 (t.d,1H, H-7); 7.45 (t.d, 1H, H-6); 7.42 (d, 1H, H-5); 6.89 (d, 2H, H-14 and H-16); 6.6 (s, 1H, H-3); 3.16 (s, 6H, $2CH_3$). **^{13}C NMR** (Bruker TOPSPIN, Acétone-d6, 100 MHz, p.p.m.) δ: 162.5 (C-4); 160.8 (C-2); 154.65 (C-15); 153.2 (C-11); 150.4 (C-9); 133.68 (C-13 and C-17); 133.15 (C-7); 125.27 (C-5); 124.06 (C-6); 119.8 (C-12); 118,01 (C-10); 117.59 (C-8); 111.99 (C-14 and C-16); 105.59 (C-3); 40.09 ($2CH_3$). **DEPT 135°**: 133.68 (C-13 et C-17); 133.15 (C-7); 125.27 (C-5); 124.06 (C-6); 117.59 (C-8); 111.99 (C-14 and C-16); 105.59 (C-3); 40.09 ($2CH_3$).

***Crystal structure Determination* (C5)**

Chemical formula: $C_{18}H_{15}NO_4$; Formula weight: 309.32; Crystal description: Parallelepiped, colourless; Melting point (K): 445 K; Crystal system: Triclinic; space group: P-1; Temperature (K): 298; Wavelength (Å): λ = 0.71073; Unit cell dimensions a = 7.4939 (2) Å b = 10.2361 (3) Å, c = 10.6620 (3) Å, α = 92.307 (3)°, β = 103.935 (1)°, γ = 109.852 (4)°; Volume (Å^3): 739.92 (4); Z = 2; Radiation type: Mo$K\alpha$; Absorption coefficient (mm^{-1}): 0.10; Density (Mg m^{-3}): 1.433; F(000): 324; Crystal size (mm): 0.5 × 0.4 × 0.3; 8424 measured reflections; 3590 independent reflections; *R*int = 0.024; $R[F^2 > 2\sigma(F^2)]$ = 0.048; $wR(F^2)$ = 0.120; *S* = 0.98; 3585 reflections; 209 parameters.

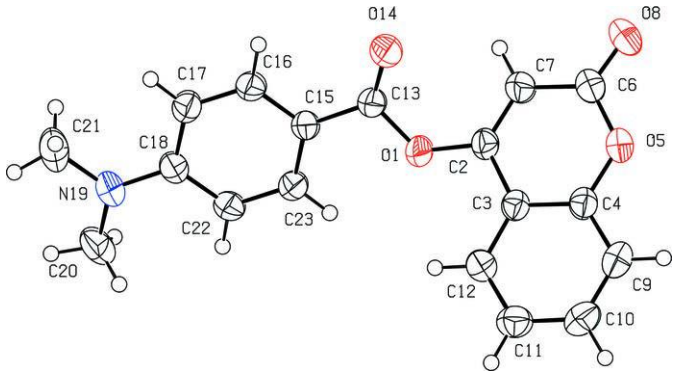


Figure 4: Molecular structure of compound C5 with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

Fluorescence spectra

Fluorescence spectra of compounds **C** were recorded on KONTRON SFM 25 fluorimeter (L.P.A / U.C.A.D). Spectra acquisition were performed in 2D (Excitation-Emission Matrices) at room temperature. The solvent used was acetonitrile (Fluka, analytic quality), the only solvent in which all the compounds were soluble, at a concentration of 10^{-4} M for all the samples. The fluorescence spectra were performed using excitation into the maximum of the longest wavelength absorption band program. All the compounds were excited at their respective maximum excitation wavelength.

RESULTS AND DISCUSSION

Characterization

The *O*-acylation derivatives (**C1**–**C5**) were synthesized by esterification of 4-hydroxycoumarin with the corresponding benzoyl chloride in the presence of trimethylamine. Examination of the information obtained from the NMR spectra enabled us to assign the chemical shifts of the different protons and carbons for all compounds. ESI-MS confirmed the molecular mass of proposed structures. The molecular structures of compounds **C2-C5** were resolved by X-ray diffractometry and are shown in the different ORTEP structures obtained, with the atomic numbering scheme used.

As it can be observed, all the molecules under study adopted some similar aspects in the conformation of the crystal. Coumarin nucleus and aromatic ring attached to the ester bridge in each molecule are planar, as expected. The main difference between the molecular structures of compounds **C** is the dihedral angle between coumarin ring system and the benzene ring: **C2**: 88.3(1)°; **C3**: 60.70(7)°; **C4**: 69.82(9)°; **C5**: : 43.43(6)°.

For all compounds, the C-O-C-C torsion angle and the dihedral angles between the coumarin cycle and the benzoate group also vary with steric hindrance. In the different structures, intramolecular bonds, valence bonds and stacking modes (C-H ... π; π ... π) have been observed, connecting the molecules in a three-dimensional supramolecular framework [30-33]. The analysis of the crystallographic data provides further evidence on the results of the structural characterization of the compounds **C2-C5**.

Fluorescence properties

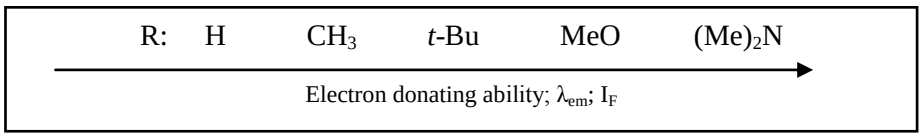
The different bands are characterized by the position of the maximum emission, analyzed through the wavelength (λ_{em}) and the fluorescence intensity (I_F). Figures 5 to 9, described in **table 2** report the results.

Table 2: Excitation wavelengths (λ_{ex}), emission wavelengths (λ_{em}) and fluorescence intensities (I_F)

Compound	R	λ_{ex} (nm)	λ_{em} (nm)	I_F
C1	H	317	372	45
C2	Me	291	378	95
C3	*t*-Bu	320	386	140
C4	MeO	305	392	225
C5	$(Me)_2N$	312	394	450

All the synthesized compounds **C**, including substituting groups R with varying electron donating ability, exhibited fluorescence emission with wavelength ranging from 372 to 394 nm. Nevertheless, we observed a clear relationship between the electron donating ability of the substituent R at the para position of carbonyl group and fluorescence emission:

- The fluorescence intensity increased with the electron donating ability of the substituent R. So, it was pronouncedly high in the cases of **C4** (R = CH_3O) or **C5** (R= Me_2N) and weaker in the cases of **C1**, **C2** and **C3** with respectively R = H, CH_3 and *t*-Bu.
- Moreover, emission wavelength (λ_{em}) was as high as the electron donating ability of R was great. In this manner, it was the highest in the case of compound **C5**. These behaviors of compounds C in fluorescence emission, which are dependent on substituent R, are recapitulated in Scheme 3 below.



Scheme 3

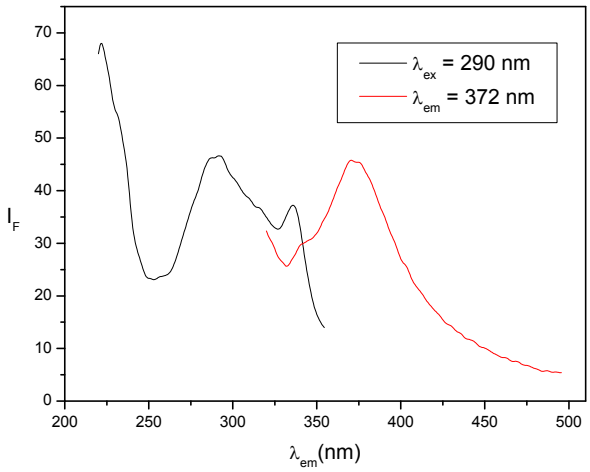


Figure 5: Fluorescence emission of compound C1.

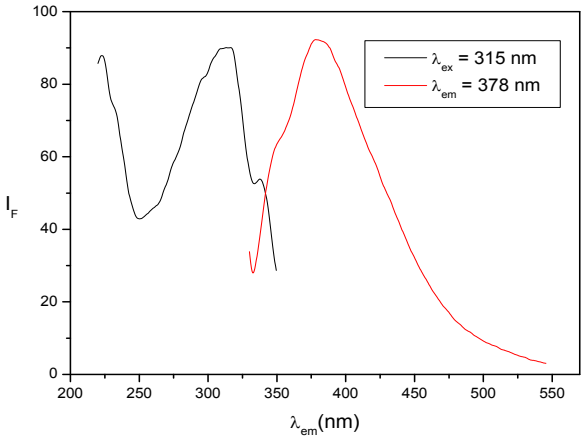


Figure 6: Fluorescence emission of compound C2.

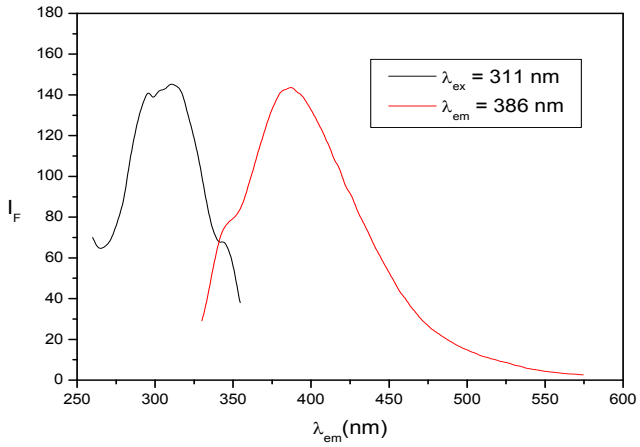


Figure 7: Fluorescence emission of compound C3.

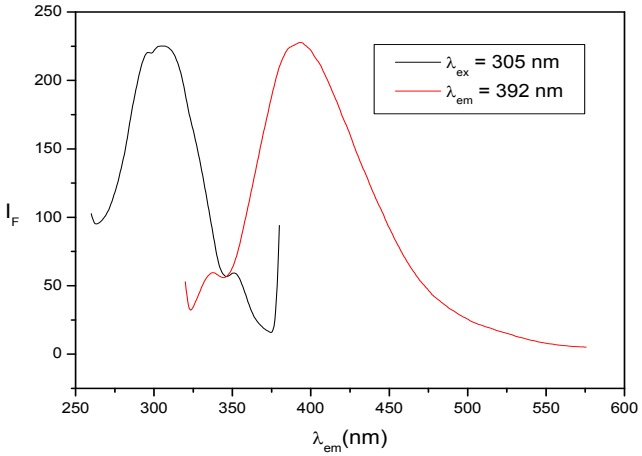


Figure 8: Fluorescence emission of compound C4.

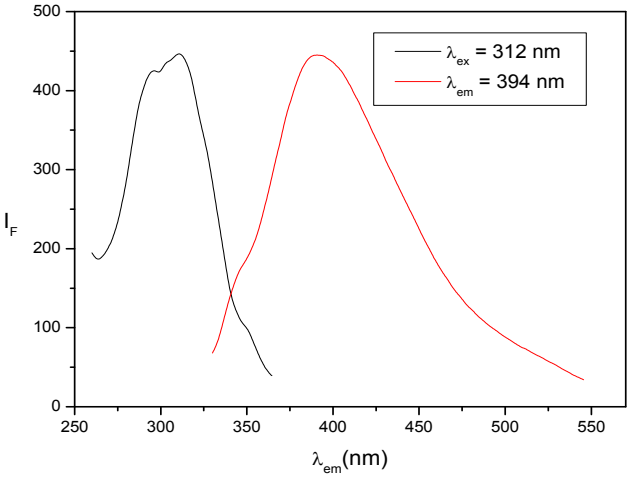


Figure 9: Fluorescence emission of compound C5.

CONCLUSION

A series of 4-substituted coumarin derivatives (compounds **C1-C5**) were successfully synthesized and the proposed structures were determined by spectral analysis performed by NMR and ESI-MS, and confirmed by X-ray diffractometry.

Fluorescence properties of these (coumarin-4-yl)benzoates were investigated in acetonitrile. As a result, both bathochromic and hyperchromic effects were observed with the increasing of the electron donating character of the substituting group R. (Coumarin-4-yl)-4-dimethylaminobenzoate (Compound **C5**) exhibited the most intense fluorescence.

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