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Comparative study of the 3-phenylcoumarin scaffold: Synthesis, X-ray structural analysis and semiempirical calculations of a selected series of compounds

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HIGHLIGHTS

- Compound **1** 6-methyl-3-phenylcoumarin was synthetized.
- Compound **2** (3-(o-methoxyphenyl)-6-methylcoumarin) was synthetized.
- Compound **3** (3-(m-methoxyphenyl)-6-methylcoumarin) was synthetized.
- ^{1}H and ^{13}C NMR and X-ray diffractometry determined the molecular structures.
- AM1 and PM3 yielded results reproducing the whole 3D structure of the three molecules.

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ABSTRACT

Compounds **1** (6-methyl-3-phenylcoumarin), **2** (3-(o-methoxyphenyl)-6-methylcoumarin) and **3** (3-(m-methoxyphenyl)-6-methylcoumarin) were synthesized by a Perkin reaction between the 2-hydroxy-5-methylbenzaldehyde and the corresponding phenyl acetic acid. ^{1}H and ^{13}C NMR and X-ray diffractometry determined the molecular structures of the derivatives. A comparative study between compounds **1**, **2** and **3**, based on the structural results, was carried out. In addition, the X-ray structures were compared to those obtained combining conformational analysis with semiempirical methodologies (AM1 and PM3). The results provided by the semiempirical calculations in gas phase are in strong agreement with the X-ray method for the three molecules under study, meaning that the determination of the 3D structure for this type of compounds could be extrapolated from semiempirical studies.

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1. Introduction

Coumarins are natural compounds that can be found in several sources [1–3]. Naturally occurring or synthetic produced derivatives of the benzopyrone moiety are of pharmaceutical interest due to the important biological activities that they display [1–3]. Coumarins have been previously described as anti-inflammatory, antimicrobial, anticancer, vasorelaxant, cardioprotective, and antioxidant agents [1–10]. Furthermore, in previous work we have reported inhibitory effects of several coumarins on monoamine oxidase B (MAO-B) activity, and in some cases this is accompanied by acetylcholinesterase (AChE) inhibitory activity [13]. Some of these compounds may be potential drug leads to treat neurodegenerative diseases [11–17]. The prevalence of these diseases combined with their complex etiology has led to an intensive search for compounds that interact with some specific receptors. Due to the biological importance of the coumarins, the synthesis and characterization of these derivatives is a topic of interest. The interaction between a specific molecule – a drug candidate – and a receptor is mediated through recognition between the small molecule compound and the protein structure. An important step in the study of molecular interactions is the correct determination of the structure of the potential drugs. This requires an analysis of the spatial arrangement of the different atomic groups and their chemical properties. The first step, in this analysis, is to obtain information about the intramolecular features responsible for the 3D structure of the molecule under study. The X-ray structure is an important tool for examining the chemical structure of the molecules and to better understands the interaction of the compound

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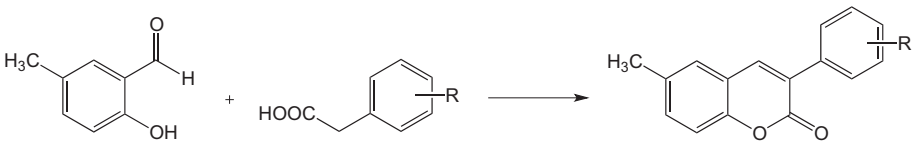

1: R = H
2: R = *o*-OCH_3
3: R = *m*-OCH_3

Scheme 1. Synthesis of the compounds **1**–**3**. Reagents and conditions: N,N′-dicyclohexylcarbodiimide (DCC), 110 °C, 24 h.

with the enzyme's active site. However, semiempirical methods offer an efficient alternative to investigate the molecular structure of novel 3-arylcoumarins, especially when no X-ray data are available. Molecular mechanics methods [18] are appropriate in the study of complex systems, such as proteins. Higher-level approaches, such as ab initio methods [19] are only applicable in small molecules due to the complexity of the quantum mechanical calculations. Nevertheless, an intermediary level of complexity is provided through semiempirical calculations [20], such as AM1 or PM3. These methods combine quantum chemical calculations with the use of some parameters from empirical data and accurately reproduce experimental molecular geometries [21–23]. Therefore, structural characteristics of coumarins make unnecessary to complement the semiempirical conformational analysis at higher computational levels [24].

In this work, we described experimental and semiempirical structural analysis of three synthesized 3-arylcoumarins without substituents in the aromatic ring (compound **1**), an ortho-methoxy group substitution (compound **2**), and a meta-methoxy substitution (compound **3**). Their structures were characterized by experimental methods such as NMR spectrometry (validated by X-ray diffractometry) and semiempirical calculations combining conformational analysis with the AM1 and PM3 methods. The comparison between the semiempirical and the crystal structure for all the compounds showed a high level of similarity. This demonstrates the capability of the semiempirical methods to reproduce experimental molecular geometry and establishes these methods as an alternative to obtain three-dimensional information when the crystal structure is not available.

2. Experimental section

2.1. Synthesis of compounds *1*–*3*

Compounds **1**–**3** (Scheme 1) were prepared according to the protocol described by us [11,12].

A solution of 2-hydroxy-5-methylbenzaldehyde (7.34 mmol) and the corresponding phenylacetic acid (9.18 mmol) in dimethyl sulfoxide (15 mL) was prepared. *N,N′*-Dicyclohexylcarbodiimide (11.46 mmol) was added, and the mixture was heated in an oil bath at 110 °C for 24 h. Ice (100 mL) and acetic acid (10 mL) were added to the reaction mixture. After keeping it at room temperature for 2 h, the mixture was extracted with ether (3 × 25 mL). The organic layer was extracted with sodium bicarbonate solution (50 mL, 5%) and then water (20 mL). The solvent was evaporated under vacuum, and the dry residue was purified by flash chromatography (hexane/ethyl acetate 9:1). Colorless solids were obtained in a yield of 68%, 59% and 53%, respectively. Suitable crystals for X-ray studies were grown from slow evaporation from acetone/ethanol.

2.1.1. Material and measurements

Melting points were determined using a Reichert Kofler thermopan or in capillary tubes on a Büchi 510 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts in δ values, J in Hz) and $CDCl_3$ as solvent. Mass spectra were obtained using a Hewlett Packard 5972-MSD spectrometer. Elemental analyses were performed using a Perkin-Elmer 240B microanalyser and were within ±0.4% of calculated values in all cases. Silica gel (Merck 60, 230–00 mesh) was used for flash chromatography (FC). Analytical thin layer chromatography (TLC) was performed on plates precoated

Table 1
Crystal data and structure refinement parameters for compound **1**–**3**.

	Compound **1**	Compound **2**	Compound **3**
Empirical formula	$C_{16}H_{12}O_2$	$C_{17}H_{14}O_3$	$C_{17}H_{14}O_3$
Formula weight	236.26	266.28	266.28
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1$	$P2_1/n$	P-1
Unit cell dimensions (Å)	a = 6.2360(4) b = 7.3111(3) c = 12.4092(7)	13.7688(15) 6.7855(10) 14.6983(18)	6.5861(3) 9.3113(5) 11.0593(5)
Volume (Å^3)	561.26(5)	1276.4(3)	658.63(6)
Z	2	4	2
Density (calculated) (Mg/m^3)	1.398	1.386	1.343
Absorption coefficient (mm^{-1})	0.091	0.095	0.092
F(000)	248	560	280
Crystal size (mm^3)	0.95 × 0.17 × 0.13	0.37 × 0.33 × 0.13	0.35 × 0.19 × 0.10
Theta range for data collection (°)	1.65–26.02	1.73–25.68	1.89–28.28
Index ranges	$-7 \leqslant h \leqslant 7$, $0 \leqslant k \leqslant 9$, $0 \leqslant l \leqslant 15$	$-16 \leqslant h \leqslant 15$, $0 \leqslant k \leqslant 8$, $0 \leqslant l \leqslant 17$	$-8 \leqslant h \leqslant 8$, $-12 \leqslant k \leqslant 12$, $0 \leqslant l \leqslant 14$
Reflections collected	8634	10,480	20,409
Independent reflections	1196 [R(int) = 0.0880]	2424 [0.0420]	3240 [0.0277]
Completeness to theta = 26.02°, 25.68° or 28.28° (%)	100.0	99.8	98.9
Max. and min. transmission	1.0000 and 0.9124	1.0000 and 0.9361	0.9806 and 0.9241
Data/restraints/parameters	1196/1/164	2424/0/183	3240/0/183
Goodness-of-fit on F^2	0.968	1.057	1.104
Final R índices [I > 2sigma(I)]	R1 = 0.0366, wR2 = 0.0764	0.0431, 0.1015	0.0456, 0.1197
R indices (all data)	R1 = 0.0449, wR2 = 0.0792	0.0571, 0.1093	0.0612, 0.1290
Largest diff. peak and hole (e Å^{-3})	0.164 and −0.243	0.213 and −0.232	0.337 and −0.372

Common parameters for all the molecules: temperature – 100(2) K; wavelength – 0.71073 Å; absorption correction – semi-empirical from equivalents; refinement method – full-matrix least-squares on F^2.

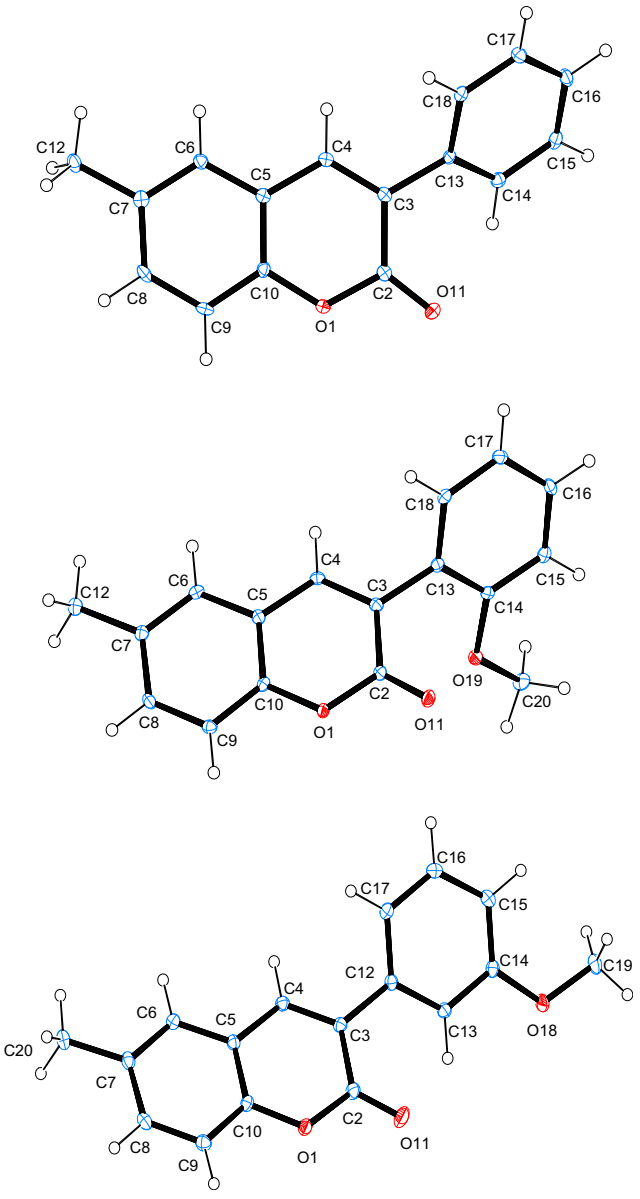

Fig. 1. Molecular structures of compounds **1**, **2** and **3**, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

with silica gel (Merck 60 F254, 0.25 mm). The purity of compounds was assessed by HPLC and was found to be higher than 95%.

6-Methyl-3-phenylcoumarin (**1**). It was obtained a colorless solid with a yield of 68%. Mp 148–149 °C. ^{1}H NMR: 2.42 (s, 3H, CH_3), 7.27 (m, 1H, H-7), 7.34 (m, 2H, H-4′ and H-8), 7.43 (m, 3H, H-2′, H-4′ and H-5), 7.70 (dd, 2H, H-1′ and H-5′, J = 7.7 and 1.8), 7.77 (s, 1H, H-4). ^{13}C NMR: 21.29 (CH_3), 116.67 (C-8), 119.57 (C-4a), 128.17 (C-5), 128.70 (C-3), 128.95 (C-4′), 129.02 (C-2′, C-3′), 129.26 (C-5′, C-6′), 132.95 (C-7), 134.65 (C-6), 135.35 (C-1′), 140.39 (C-4), 152.16 (C-8a), 161.31 (C-2). DEPT: 21.29 (CH_3), 116.67 (C-8), 128.17 (C-5), 128.95 (C-4′), 129.02 (C-2′, C-3′), 129.26 (C-5′, C-6′), 132.95 (C-7), 140.39 (C-4). EI MS m/z (%): 236 (M^+, 100), 208 (50), 178 (8), 165 (8) 76 (6), 51 (69). Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12; O, 13.54. Found: C, 81.44; H, 4.84. [11].

6-Methyl-3-(*o*-methoxyphenyl)coumarin (**2**). It was obtained a colorless solid with a yield of 59%. Mp 177–178 °C. ^{1}H NMR: 2.41 (s, 3H, CH_3), 3.82 (s, 1H, OCH_3), 7.02 (m, 2H, H-3′, H-4′), 7.24–7.41 (m, 5H, H-5, H-7, H-8, H-5′ and H-6′) 7.69 (s, 1H, H-4). ^{13}C NMR: 20.80 (CH_3), 55.81 (OCH_3), 111.31 (C-3′), 116.21 (C-8), 119.24 (C-1′), 120.57 (C-5′), 124.20 (C-4a), 126.36 (C-3), 127.58 (C-5), 130.14 (C-4′), 130.80 (C-6′), 132.21 (C-7), 133.89 (C-6), 141.84 (C-4), 151.82 (C-8a), 157.22 (C-2′), 160.55 (C-2). DEPT: 20.80 (CH_3), 55.81 (OCH_3), 111.31 (C-3′), 116.21 (C-8), 120.57 (C-5′), 127.58 (C-5), 130.14 (C-4′), 130.81 (C-6′), 132.21 (C-7), 141.84 (C-4). EI MS m/z (%): 267 (22), 266 (M^+, 100), 265 (10), 249 (29), 237 (22), 235 (14), 223 (22), 220 (12), 195 (29), 173 (26), 165 (25), 152 (17), 145 (19), 118 (19). Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.76; H, 5.22. [12].

6-Methyl-3-(*m*-methoxyphenyl)coumarin (**3**). It was obtained a colorless solid with a yield of 53%. Mp 84–85 °C. ^{1}H NMR: 2.44 (s, 3H, CH_3), 3.88 (s, 1H, OCH_3), 6.97 (m, 1H, H-4′), 7.26–7.42 (m, 6H, H-5, H-7, H-8, H-2′, H-5′ and H-6′), 7.78 (s, 1H, H-4). ^{13}C NMR: 20.77 (CH_3), 55.37 (OCH_3), 114.15 (C-2′), 114.38 (C-4′), 116.10 (C-8), 119.28 (C-4a), 120.86 (C-6′), 127.70 (C-5), 129.43 (C-5′), 132.48 (C-7), 134.12 (C-3), 136.12 (C-1′), 139.91 (C-4), 140.10 (C-6), 151.60 (C-8a), 159.45 (C-3′), 160.66 (C-2). DEPT: 20.77 (CH_3), 55.37 (OCH_3), 114.15 (C-2′), 114.38 (C-4′), 116.10 (C-8), 120.86 (C-6′), 127.70 (C-35), 129.44 (C-5′), 132.48 (C-7), 139.91 (C-4). EI MS m/z (%): 267 (48), 266 (M^+, 100), 239 (16), 238 (70), 237 (20), 195 (48), 194 (16), 166 (10), 165 (29), 152 (23). Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.76; H, 5.21. [12].

2.2. X-ray data collection and reduction

Colorless prismatic crystals of compounds **1** ($C_{16}H_{12}O_2$), **2** ($C_{17}H_{14}O_3$) and **3** ($C_{17}H_{14}O_3$) were mounted on a glass fiber for data collection. Cell constants and orientation matrix were obtained by least-squares refinement of the diffraction data for 1196, 2424 and 3240 reflections in the range of 1.7–26.0°, 1.7–25.7° and 1.9–28.3°, respectively, measured on a Bruker APEX2 [25]. Data were collected by the ω scan technique at 100 K using radiation (λ = 0.71073 Å), and were corrected for Lorentz and polarization effects. The crystal data and structure refinement were detailed in Table 1. A semiempirical absorption correction was also performed.

2.3. Structure solution and refinement

The structures were solved by direct methods [26], 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 refine the structures was SHELXL97 [27]. All hydrogen atoms were located from difference Fourier maps and were refined isotropically. Atomic scattering factors were taken from International Tables for X-ray Crystallography [28]. Molecular graphics were generated with Platon [29]. Finally, the software used to prepare material for publication was WinGX publication routines [30]. A summary of the crystals data, experimental details, and refinements results is given in Table 1.

2.4. Theoretical calculations: conformational analysis and semiempirical methods

A stochastic conformational search was performed using MOE software [31]. MMFF94x force field was used to implement the partial charges. Calculation parameters were established with a RMS gradient of 0.005 and an interaction limit of 500. Although different conformations were retained using a RMSD limit of 0.25 and energy window of 7 kcal/mol regarding the global minimum energy, the conformations with the lowest energy were representative of the calculation and were optimized using AM1 and PM3 semiempirical methods implemented in the Schrödinger package [32,33]. All the calculations were performed in gas phase.

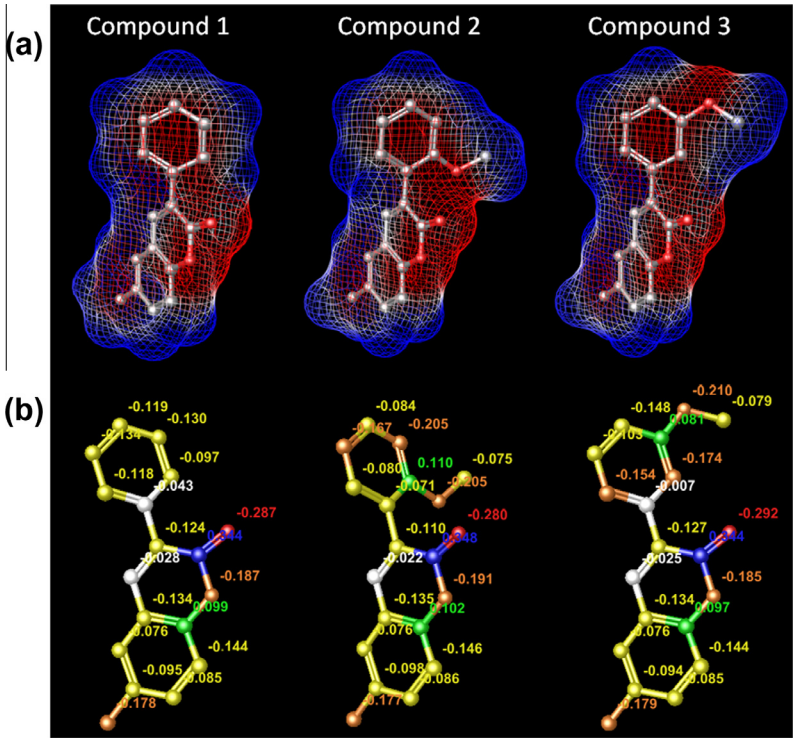

Fig. 2. (a) Electrostatic potential surfaces for compounds **1**–**3**. Color-coded: blue (positive), white (neutral) and red (negative). (b) Partial charge distribution for compounds **1**–**3**. Atoms are coloured according to the charge range.

3. Results and discussion

Compound **1** was prepared in 68% yield, by Perkin reaction between the 2-hydroxy-5-methylbenzaldahyde and the phenyl acetic acid (Scheme 1) [11]. Compound **2** was prepared in 59% yield, by Perkin reaction between the 2-hydroxy-5-methylbenzaldahyde and the o-methoxyphenyl acetic acid (Scheme 1) [12]. Finally, compound **3** was prepared in 53% yield, by Perkin reaction between the 2-hydroxy-5-methylbenzaldahyde and the m-methoxyphenyl acetic acid (Scheme 1) [12]. Through examination of the NMR spectra we identified the chemical shifts of the different protons and carbons for all the compounds. Also, the molecular structures of the three compounds were resolved by X-ray diffractometry and are shown in Fig. 1, together with the atomic numbering scheme used.

As it can be observed in Fig. 1, the molecules adopted some similar aspects in the conformation of the crystal. In all cases the coumarin nucleuses and the aromatic rings attached to them are planar, as expected. The main difference between the molecular structures of the compounds is the dihedral angle formed between those planes. These relative positions depend on the substituent presented in aromatic ring attached to the coumarin. The greatest conformational freedom of the molecules resides, therefore, in the link between the coumarin scaffold and the 3-aryl ring. The dihedral angle between the main planes is higher in compound **2** (56.48°), compound that presents an ortho-methoxy group. This compound proved to be the less active of these series against MAO-B isoenzyme (inactive at 100 μM, highest concentration tested; at higher concentrations the compounds precipitate) [11], proving that the accommodation of this derivative in the active site of this enzyme is the less efficient. In the case of compound **1**, the non-substituted derivative, the dihedral angle between the main planes is 38.69°. This compound is more active (IC_{50} MAO-B = 283 nM) than compound **2** [12]. The relative position between planes is better tolerated to the active site than the first one. Finally, compound **3** has a dihedral angle (33°) between planes similar to compound **1**. This compound proved to be the best one of the series (IC_{50} MAO-B = 0.802 nM) [12]. Therefore, the relative position between the main planes of the molecule could be important to modulate the accommodation of the derivatives in the active site of the receptor, regardless of the same nature of the substituent group.

The described compounds are structurally similar to the compound previously described by us [34]. The previously described compound is the 3-phenylcoumarin. In that crystal, the dihedral angle between the coumarin core and the 3-phenyl ring is 47.6°. The activity against MAO-B of this compound is higher than compound **2** (IC_{50} MAO-B = 11.81 μM) [14], but is less than compound **1** and **3**. In all cases the activity is related to the angle formed between the main planes of the 3-arylcoumarin scaffold.

The compounds have also shown different charge distribution patterns due to the diverse substituents that can further explain the described changes in the activity. The structures for the compounds **1**–**3** extracted from the AM1 calculation showed differences in the electrostatic potential surfaces (see Fig. 2a). An area of negative charge is placed in *ortho* position of the 3-aryl ring for the compound **2**, whereas a similar area is placed in *meta* position for compound **3**. Moreover, substitution in *ortho* or *meta* position causes a redistribution of the charges in the different carbon atoms in the aryl ring (see different colors in the aryl carbon atoms in Fig. 2b) that can also influence the complementarity with the receptor. Nevertheless, the fact that the methoxy group in *meta* position rather than *ortho* could fit better in the hydrophobic entrance cavity of the MAO-B receptor could also be important for the MAO-B activity.

Tables 2–4 (Supplementary information) list the bond lengths, bond angles and dihedral angles obtained for the three described compounds (**1**, **2** and **3** respectively), according to the X-ray analysis. The results for the semiempirical calculations (conformational analysis combined with AM1 and PM3 methods) are also shown in the tables.

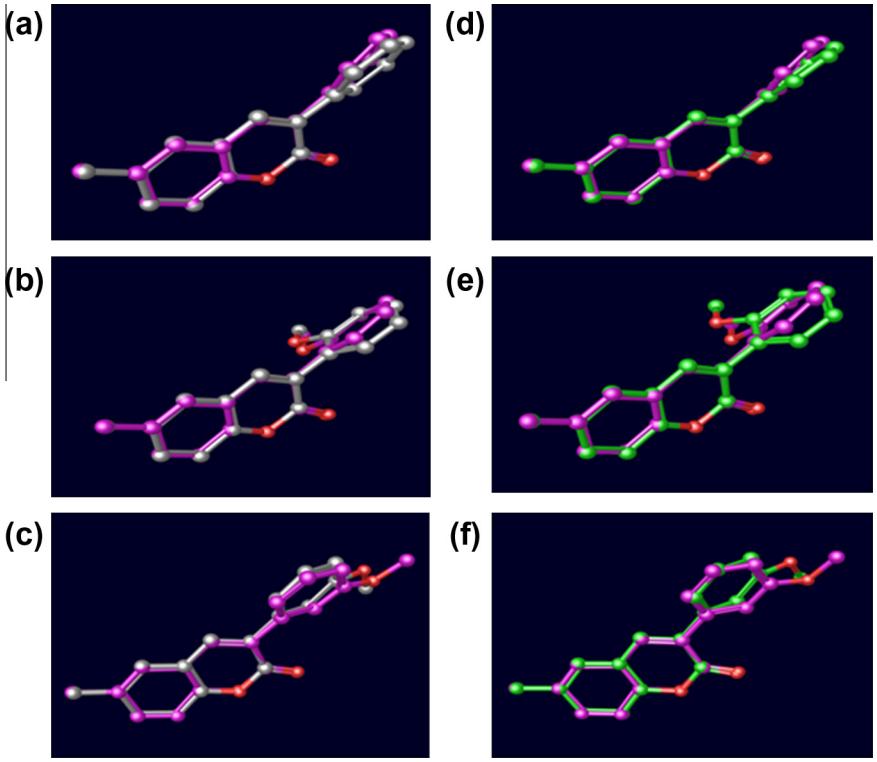

Fig. 3. Superposition of the crystal structure (pink carbons) and the semiempirical conformations calculated through AM1 (grey carbons) and PM3 (green carbons) for compounds **1** (panels a and d), **2** (panels b and e) and **3** (panels c and f).

The 3D structures determined through semiempirical methods are highly coincident with the information provided by X-ray. The calculations yielded for all the compounds two possible conformational states that differentiate in the orientation of the aryl fragment regarding the plane of the coumarin nucleus. As an example, the dihedral angles C(2)–C(3)–C(13)–C(14) calculated with AM1 method for compounds **1**, **2** and the equivalent dihedral C(2)–C(3)–C(12)–C(13) for compound **3** could present values of 36.7, 73.2 and 36.5 or −35.8, −73.2 and −36.4 degrees respectively. In Fig. 3 we superimposed the coumarin ring of the crystal structure and the conformations extracted from AM1 and PM3 for the three compounds (semiempirical conformations with values for the dihedral angle connecting the coumarin ring and the aryl fragment of 36.7°, 73.2° and 36.5° for compounds **1**, **2** and **3**, using AM1 method). The comparison between experimental and semiempirical 3D structures showed a high level of coincidence. The RMSD (root mean square deviation) values for distances (Å), bond angles (°), dihedral angles (°) and the heavy atoms coordinates are shown in Table 5. PM3 performed slightly better to reproduce the bond lengths. However, AM1 method yielded better results in the reproduction of angles and dihedral angles (see Table 5). It is worth noting that the RMSD value for the dihedral angles is higher in compound **3** using both semiempirical methods. This is due to the different methoxy orientation found between the crystal and the calculated conformers. However, a similar methoxy conformation can be found through these methods with a slightly higher semiempirical energy and showing a possible conformational state equilibrium for the methoxy orientation. Nevertheless, the RMSD dihedral angle value drastically decreases if we exclude the methoxy group of the aryl fragment in the calculation (see Table 5). The RMSD of the heavy atoms coordinates also showed that AM1 is more coincident with the crystal structures. However, our intention is not to justify the selection of one method since both AM1 and PM3 performed with high degree of accuracy. The results are in agreement with previous publications [23–25].

Table 5
RMSD between the 3D structures determined through X-ray and semiempirical methods for compounds **1**, **2** and **3**. The values are shown for distances (Å), bond angles (°), dihedral angles (°) and the heavy atoms coordinates (no hydrogens were considered).

	Compound **1**		Compound **2**		Compound **3**	
RMSD	AM1	PM3	AM1	PM3	AM1	PM3
Distance	0.013	0.009	0.014	0.012	0.013	0.010
Angles	1.848	2.431	1.717	2.223	3.009	3.505
Dihedral angles	2.971	5.057	7.039	9.809	37.749[a]	37.812[a]
Heavy atoms coordinates	0.115	0.137	0.168	0.302	0.502	0.569

[a] The RMSD values excluding the methoxy group in the aryl fragment are 2.523 and 6.128 respectively.

Packing diagram of the three structures allows the interpretation of the spatial orientation of the molecules and are shown in Fig. 4.

4. Conclusion

In summary, we have determined and analyzed the entire structural parameters in the crystalline state of three coumarin derivatives, and demonstrated that the results are well reproduced using conformational analysis in combination with semiempirical AM1 and PM3 methods. Therefore, when X-ray data is not available, semiempirical approaches could be an alternative method to determine the 3D structure for this type of compounds. We can also conclude that it is possible to modulate the relative position of the coumarin scaffold and the aromatic ring at position 3 by modifying the position of the chemical substituent in the aromatic ring. These modifications are correlated with the affinity for the

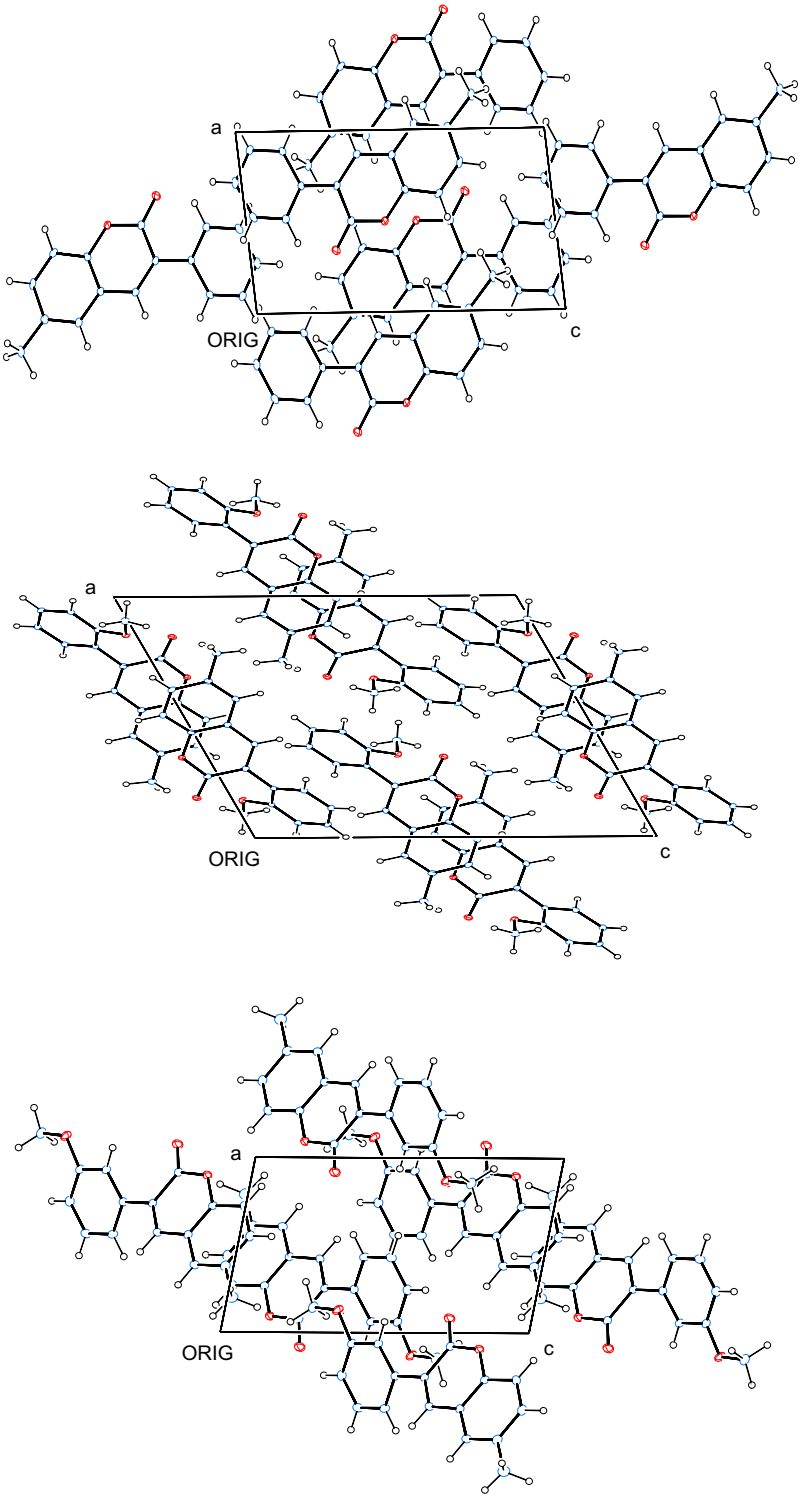

Fig. 4. Packing diagram of both structures viewed along the b axis.

active site of the target and with the compounds activity. With simple semiempirical calculations it can be easily reproduced the 3D structure of the studied compounds, which allows establish important structure–activity relationship studies.

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Appendix A. Supplementary material

CCDC 929059, CCDC 929168 and CCDC 929169 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data

Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2013.07.037.

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