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Synthesis, NMR characterization, X-ray structural analysis and theoretical calculations of amide and ester derivatives of the coumarin scaffold

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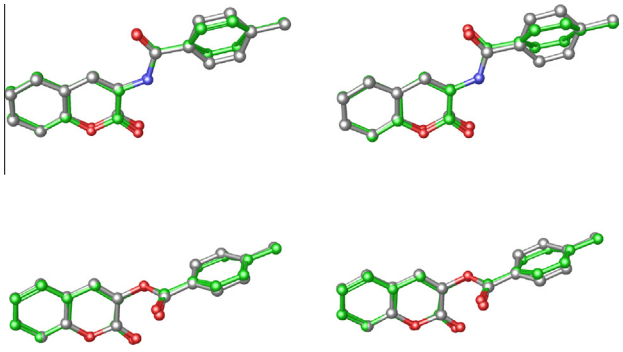
HIGHLIGHTS

- Compound 1 (4-Methyl-N-(coumarin-3-yl)benzamide) was synthesized.
- Compound 2 (coumarin-3-yl)-4-methylbenzoate was synthesized.
- ^{1}H and ^{13}C NMR and X-ray diffractometry determined the molecular structures.
- Semiempirical calculations presented an alternative to determine the 3D structures.
- AM1 and PM3 yielded results reproducing the whole 3D structure of both molecules.

GRAPHICAL ABSTRACT



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ABSTRACT

Compounds 1 (4-methyl-N-(coumarin-3-yl)benzamide) and 2 ((coumarin-3-yl)-4-methylbenzoate) were synthesized by linking the coumarin system (3-aminocoumarin or 3-hydroxycoumarin, respectively) to a p-toluoylchloride. ^{1}H and ^{13}C NMR and X-ray diffractometry determined the molecular structures of both derivatives. The X-ray results were compared to those obtained by conformational analysis followed by semiempirical methodologies (AM1 and PM3). The theoretical calculations yielded results reproducing the whole three-dimensional (3D) structure of both molecules in a good agreement with X-ray structural analysis. The global structures of the two compounds are very similar in the two studied environments, meaning that the structural determination in the gas phase can be extrapolated. A comparative study between compounds 1 and 2, based on the structural results, was carried out.

1. Introduction

The complex etiology and the actual prevalence of neurodegenerative diseases have led to an intensive search for compounds that interact with some specific receptors. In particular, in our research group we have paid special attention to compounds that can inhibit monoamine oxidase B (MAO-B isoform) and acetylcholinesterase (AChE) enzymes. In the last years we are synthesizing and studying an important family of compounds, the coumarin derivatives, focusing on those targets. Coumarin (2H-1-benzopyran-2-one) is a natural compound that can be found in several plants like tonka bean, vanilla grass and sweet woodruff [1–3]. Derivatives of this benzopyrone are of pharmaceutical interest because they have been showing different important biological activities [1–3]. Coumarins have been described as anticancer, anti-inflammatory, antimicrobial, cardioprotective, vasorelaxant and antioxidant agents [4–13]. Furthermore, several coumarins showing a significant MAO inhibitory activity, in some cases accompanied by AChE inhibitory activity, have been reported by our research group, and some of them are suggested as potential drugs with application on neurodegenerative diseases [14–20]. Due to the biological importance of these derivatives, the synthesis and characterization

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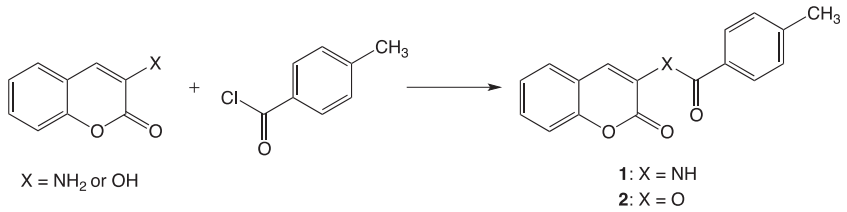

Scheme 1. Synthesis of compounds 1 and 2. Reagents and conditions: Pyridine, dicloromethane, 0 °C to r.t., 4 h.

Table 1
Crystal data and structure refinement parameters for compounds 1 and 2.

	Compound 1	Compound 2
Empirical formula	C17H13NO3	C17H12O4
Formula weight	279.28	280.27
Temperature	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Triclinic
Space group	P-1	P-1
Unit cell dimensions	a = 7.9932(4) Å, α = 113.893(3)° b = 9.2074(6) Å, β = 97.003(3)° c = 10.3711(7) Å, γ = 101.145(3)°	a = 6.7771(7) Å, α = 91.563(8)° b = 7.0925(9) Å, β = 91.436(7)° c = 13.9318(18) Å, γ = 101.984(7)°
Volume	667.43(7) Å3	654.49(14) Å3
Z	2	2
Density (calculated)	1.390 Mg/m3	1.422 Mg/m3
Absorption coefficient	0.096 mm−1	0.102 mm−1
F(0 0 0)	292	292
Crystal size	0.38 × 0.30 × 0.25 mm3	0.47 × 0.37 × 0.14 mm3
Theta range for data collection	2.20–26.37°	2.93–26.02°
Index ranges	−9 ⩽ h ⩽ 9, −11 ⩽ k ⩽ 10, 0 ⩽ l ⩽ 12	−8 ⩽ h ⩽ 8, −8 ⩽ k ⩽ 8, 0 ⩽ l ⩽ 17
Reflections collected	9965	14,492
Independent reflections	2715 [R(int) = 0.0326]	2573 [R(int) = 0.0479]
Completeness to theta = 26.37°	99.6%	99.8%
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.9773 and 0.8884	1.0000 and 0.9573
Refinement method	Full-matrix least-squares on F2	Full-matrix least-squares on F2
Data/restraints/parameters	2715/0/196	2573/0/191
Goodness-of-fit on F2	1.078	1.084
Final R indices [I > 2sigma(I)]	R1 = 0.0445, wR2 = 0.1049	R1 = 0.0438, wR2 = 0.1045
R indices (all data)	R1 = 0.0622, wR2 = 0.1132	R1 = 0.0610, wR2 = 0.1127
Largest diff. peak and hole	0.218 and −0.271 e Å−3	0.237 and −0.259 e Å−3

of coumarins is a topic of interest. The interaction between a specific molecule, a drug candidate, and a receptor occurs through recognition between the different compounds involved. An important step in the study of molecular interaction processes is the determination of the structure of the potential drugs. This means carrying out an analysis of the spatial arrangement of the different atomic groups and their chemical properties. In this way, the first step must be 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 to better understand the interaction of the compound with the active site of the enzyme.

According to the latest findings related to the conformational preferences of these molecules, it is interesting to investigate the 3-D structure of novel 3-substituted coumarins by using both experimental and theoretical approaches. Computational approaches can offer an alternative solution to determine the three-dimensional molecular structure of the compounds under study. Depending on the molecular complexity and the precision required for the study, different types of calculations can be carried out. Molecular mechanics methods [21] could be appropriate for the calculation of the 3-D structure of large molecules while more accurate quantum mechanical methods, such as ab initio calculations [22], would require long periods of time making the complexity of the calculations a limiting factor to be applicable in large systems. An intermediate level of accuracy is provided by the so-called semiempirical quantum chemical calculations that use some parameters from empirical data [23]. Among these methods, the rapid, inexpensive and user-friendly AM1 and PM3 are probably two of the most popular methodologies [24,25]. The analysis of semiempirical methods results is an interesting tool for reproducing the experimental geometry of specific molecules for further studies directed to the molecular modeling and design of active molecules.

In the current work described here, experimental and theoretical structural analysis of two synthesized 3-substituted coumarin derivatives, presenting at that position an amide (compound 1) or an ester (compound 2), were undertaken. Their structures were characterized by experimental methods such as NMR spectrometry and were finally determined by X-ray diffractometry and theoretical calculations combining conformational analysis with AM1 and PM3 methods. The comparison between the theoretical and the crystal structure for both compounds showed a high level of similarity. This fact manifested the capability of the theoretical methods to reproduce the experimental molecular geometry being an alternative methodology to obtain three-dimensional information when the crystal structure is not available.

2. Experimental section

2.1. Material and measurements

Melting points were determined using a Reichert Kofler thermopan or in capillary tubes on a Büchi 510 apparatus and are