Journal of Molecular Structure 1050 (2013) 185–191

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

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

Maria J. Matos [a,*], Santiago Vilar [a,b], Nicholas P. Tatonetti [b], Lourdes Santana [a], Eugenio Uriarte [a]

[a] Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain
[b] Department of Biomedical Informatics, Columbia University Medical Center, New York, NY 10032, USA

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.

ARTICLE INFO

Article history:
Received 7 May 2013
Received in revised form 23 July 2013
Accepted 23 July 2013
Available online 27 July 2013

Keywords:
Coumarin derivatives
Synthesis
X-ray structural analysis
Conformational analysis
Semiempirical calculations

ABSTRACT

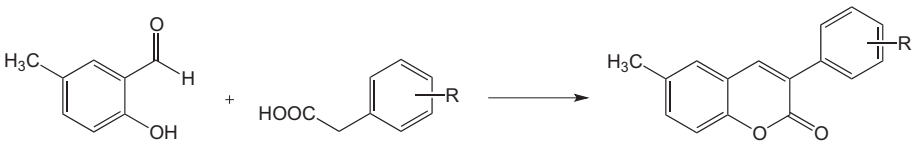
Compounds **1** (6-methyl-3-phenylcoumarin), **2** (3-(o-methoxyphenyl)-6-methylcoumarin) and **3** (3-(m-methoxyphenyl)-6-methylcoumarin) were synthesized by a Perkin reaction between the 2-hydroxy-5-methylbenzaldehyde and the corresponding phenyl acetic acid. ^{1}H and ^{13}C NMR and X-ray diffractometry 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.

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

* Corresponding author. Tel.: +34 881 814 936.
E-mail addresses: mariacmatos@gmail.com (M.J. Matos), qosanti@yahoo.es (S. Vilar), npt@dbmi.columbia.edu (N.P. Tatonetti), lourdes.santana@usc.es (L. Santana), eugenio.uriarte@usc.es (E. Uriarte).

0022-2860/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molstruc.2013.07.037



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.