

# Evaluation of the Antioxidant Properties of Coumarin Derivatives Using Spectroscopic Methods

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## Abstract

Coumarin derivatives are perceived as part of defense mechanisms in plants due to their commonly observed antimicrobial, antioxidant, antitumor, anti-inflammatory, and other biological activities. Investigating the molecular structure of coumarin derivatives using computational programs like Gaussian is an effective method for understanding the biological, chemical, and physical properties of these compounds. Therefore, in this study, the molecular structure parameters and spectroscopic (IR, NMR) properties of our coumarin derivative compound were theoretically examined using the DFT method with the B3LYP/LanL2MB basis set. This investigation is crucial for understanding the biological activities of coumarin derivative compounds, obtaining clues for new drug design, and elucidating reaction mechanisms.

**Keywords:** dft; lanl2mb; coumarin; ir; nmr

## Introduction

Coumarin is a naturally occurring compound in plants and is generally associated with vanilla, cinnamon, and sweet aromas [1]. Coumarin derivatives are chemical compounds used in various industrial and medicinal applications [2]. The first property of coumarin derivatives is Fragrance: Coumarin and its derivatives usually have a pleasant smell, making them useful in perfumes, cosmetics, and personal care products [3]. The second property is Anticoagulant Characteristics: Coumarin derivatives have anticoagulant properties that prevent blood clotting, and thus, can be used in the treatment of certain medical conditions [4]. However, due to these properties, they should be used carefully as incorrect dosages can cause serious bleeding. The third property is Antimicrobial [5] Characteristics: Some coumarin derivatives have antimicrobial properties and can be used in the treatment of bacterial or fungal infections. The last property is Antioxidant [6] Characteristics: Some studies show that coumarin derivatives have antioxidant properties, which can be beneficial in reducing oxidative stress caused by free radicals and preventing cellular damage [7].

The appropriate use of coumarin derivative molecules depends on specific applications and needs. For example, they can be used as a fragrance in the perfume industry, for their anticoagulant effects in medical applications, or as a food preservative. However, in some cases, coumarin derivatives can be toxic, and their use must be regulated. Especially due to their anticoagulant effects, they must be used carefully in medical applications.

Coumarin derivatives containing benzopyrone structures are secondary metabolites commonly found in plants. These natural compounds act as part of plants' defense mechanisms and are typically stored in plant

tissues. Coumarin derivatives can help strengthen plants' defense mechanisms against environmental stresses and protect against the harmful effects of insects or fungi. Natural coumarins have antitumor, anticoagulant, anti-inflammatory, antioxidant, antifungal, and antiviral effects. These properties are important in evaluating coumarin derivatives as potential therapeutic agents or natural product-based drugs. Additionally, investigating the biological activities of coumarin derivatives can be an important source for the discovery and development of new drugs.

Therefore, coumarin derivatives have various applications in the medical and agricultural fields and attract great interest in pharmacological research. However, it is known that some coumarin derivatives can have toxic effects, and their use and effects should be carefully examined.

To better understand the biological activities and effects of coumarin derivatives, calculations were performed in this study using the DFT method (Density Functional Theory) under the B3LYP/LanL2MB basis set with the Gaussian software. Thus, in this study, the molecular structures and spectroscopic properties of the fluorinated 7-hydroxycoumarin derivative molecule ((E)-6-chloro-3-fluoro-7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde O-ethyl oxime) were examined in detail using spectroscopic methods.

## Computational Details

### DFT Calculations

The geometric structure of the coumarin derivative compound was drawn using the Gaussian View 5 program [8]. In this study, theoretical

calculations of the coumarin derivative compound were performed. These calculations were conducted under the Density Functional Theory (DFT) method with the B3LYP [9,10] (Becke's Three-Parameter Hybrid Functional) and LanL2MB [11] basis set. This method [12] is used to predict the molecular structure, energy levels, and other chemical properties of the compound and is designed for systems containing heavy metals and transition metals. The theoretical calculations of the coumarin derivative compound were conducted to aid in understanding its molecular structure, determining its chemical properties, and confirming experimental results.

### IR and NMR Spectroscopy

The vibrational frequencies and IR spectra of the compound were calculated using the Density Functional Theory (DFT) method with the B3LYP functional and the LANL2MB basis set. Theoretical IR spectra were obtained by analyzing the vibrational frequencies derived from these calculations. The computed harmonic vibrational frequencies were subsequently scaled using appropriate scale factors to better match the experimental values. This scaling is crucial as it accounts for the anharmonicity effects and the limitations of the basis set used.

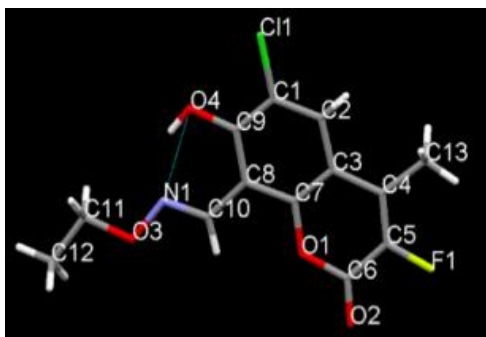
In addition to vibrational analysis, the study included calculations of NMR [13] chemical shifts employing the Gauge-Including Atomic Orbital (GIAO) [14] method. The GIAO method is a robust technique for predicting NMR chemical shifts as it calculates the chemical shielding tensors of atoms within a molecule. This method provides a detailed and accurate prediction of the chemical environments in the molecule, which is essential for elucidating the structure and dynamics of complex molecules [15].

The NMR spectra were computed using the DFT/B3LYP method in conjunction with the LANL2MB basis set. This approach allows for the accurate simulation of both <sup>1</sup>H and <sup>13</sup>C NMR spectra, offering insights into the electronic environment of hydrogen and carbon atoms within the compound. The calculated chemical shifts were then compared with experimental NMR data to validate the theoretical models. The close agreement between theoretical and experimental values highlights the reliability of the DFT/B3LYP/LANL2MB combination for such studies. This comprehensive approach, combining vibrational frequency analysis and NMR chemical shift calculations, provides a detailed understanding of the molecular structure and dynamics of the compound. By integrating theoretical and experimental data, the study offers a robust framework for analyzing and predicting the properties of complex organic molecules. This expanded version includes more context about the methods and their importance, the scaling process for vibrational frequencies, and additional details on how the GIAO method works and its significance in NMR chemical shift calculations.

## Results And Discussion

### Geometric Structure

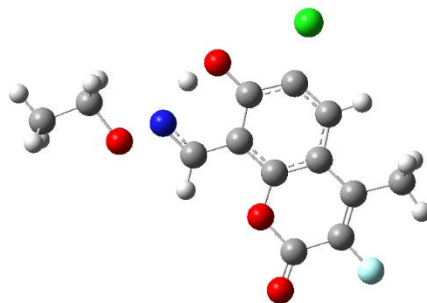
The synthesis and spectral properties of the coumarin derivative ((E)-6-chloro-3-fluoro-7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde O-ethyl oxime) were reported by Qing-Qing Wang et al. [16], and the experimental structure of the atoms is depicted in Figure 1. The X-ray single crystal structure of the synthesized coumarin derivative is available in the Cambridge Crystallographic Data Centre (CCDC) with the code CCDC 2043279.



**Figure 1:** The experimental structure and atom numbering of the coumarin derivative compound.

The crystal structure data retrieved from the CSD served as the foundation for calculating the theoretical geometric arrangement of the coumarin derivative molecule, facilitating a meticulous comparison with experimental findings. Employing Density Functional Theory (DFT), intricate calculations were executed utilizing the GAUSSIAN 09 software, integrating the LANL2MB basis set coupled with the B3LYP methodology. The refinement of the stable form was meticulously achieved through the DFT/B3LYP/LanL2MB(d,p) approach, culminating

in the depiction illustrated in **Figure 2**. These calculations stand as pivotal endeavors, unraveling the intricate geometric configuration and chemical bonds inherent within the molecule. DFT, renowned for its prowess in elucidating electron behavior and molecular properties, emerges as an indispensable tool in comprehending the structural intricacies of the coumarin derivative. The findings encapsulated herein not only enrich our understanding of molecular structures but also serve as a linchpin for ensuring coherence with experimental observations and theoretical projections within pertinent scientific domains.



**Figure 2:** The optimized geometry of the coumarin derivative compound calculated using the B3LYP/LANL2MB method.

The geometric parameters such as bond lengths and bond angles of the molecule optimized in the gas phase, at the stable state, and under vacuum using the Gaussian 09 package program were performed with the

DFT/B3LYP method. The optimized theoretical bond lengths and bond angles were compared with experimental data obtained from single crystal X-ray diffraction from the literature, and listed in **Table 1**.

<b>Bond Lengths</b>		
	<b>X-ray [16]</b>	<b>B3LYP</b>
C11-C1	1.73428	1.90688
C1-C9	1.38048	1.43791
C9-O4	1.35325	1.36650
C9-C8	1.40439	1.44871
C8-C10	1.44715	1.47166
C10-N1	1.27965	1.34229
N1-O3	1.37977	1.45272
O3-C11	1.44206	1.49758
C12-C11	1.47806	1.55289
C8-C7	1.41069	1.43623
C7-C3	1.37712	1.43153
C3-C2	1.39784	1.43057
C2-C1	1.37250	1.38920
O1-C7	1.37517	1.40868
O1-C6	1.38182	1.47043
O2-C6	1.17965	1.25094
C6-C5	1.44970	1.51898
F1-C5	1.35341	1.37092
C5-C4	1.32181	1.37739
C4-C13	1.49816	1.53417
C4-C3	1.45848	1.47034
<b>Bond Angles</b>		
	<b>X-ray [16]</b>	<b>B3LYP</b>
C11-C1-C9	119.22497	117.20348
C11-C1-C2	119.16397	118.46970
C1-C9-O4	118.91282	121.06824
C1-C9-C8	120.09841	115.82230
C9-C8-C10	123.35376	118.83505
C8-C10-N1	120.18847	117.36230
C10-N1-O3	112.27486	111.82726
N1-O3-C11	109.82190	105.57458
O3-C11-C12	107.69750	106.42466
C9-C1-C2	121.57929	124.32682
C9-C8-C7	116.62734	120.18121
C8-C7-O1	114.66972	114.42623
C8-C7-C3	123.61715	121.68334
O1-C6-O2	118.57616	116.47289
O1-C6-C5	114.05075	116.56809
O2-C6-C5	127.37239	126.95901
C6-C5-F1	112.41816	114.35684
F1-C5-C4	121.23147	122.12585
F1-C5-C6	112.41816	114.35684
C5-C4-C13	122.21860	120.29514
C5-C4-C3	116.69088	118.12315

Within **Table 1**, a meticulous examination of the experimental and theoretical values pertaining to various molecular geometric parameters of the coumarin derivative compound reveals intriguing insights. Evidently, the bond length between atoms C11 and C1, as empirically determined, stands at 1.73428 Å, contrasting with the theoretically computed value of 1.90688 Å via the B3LYP method. Similarly, the experimental bond angle involving atoms C11, C1, and C9 registers at 119.22497°, whereas the B3LYP-calculated angle subtly deviates to 117.20348°. The meticulous scrutiny across all entries of Table 1 unveils

a compelling congruence between experimental observations and theoretical projections derived from DFT methodology.

This congruence serves as a testament to the robustness of the computational framework employed, affirming the fidelity with which the compound's molecular structure has been delineated and computed. Moreover, beyond mere numerical agreement, this alignment underscores a deeper narrative of scientific validation and advancement. It signifies not only the precision of the predictive model but also the profound

understanding garnered regarding the nuanced molecular architecture of the coumarin derivative compound.

Indeed, such harmonization between experimental and theoretical realms transcends mere numerical concordance, epitomizing the symbiotic relationship between empirical observation and computational modeling in contemporary scientific inquiry. It underscores the iterative nature of scientific exploration, wherein each experimental datum and theoretical conjecture inform and refine one another, ultimately propelling our collective comprehension of molecular phenomena to new heights. Thus, within this paradigm, the convergence observed within Table 1 not only validates the predictive prowess of theoretical frameworks but also heralds a new frontier of interdisciplinary collaboration and knowledge synthesis within the realm of molecular chemistry.

### Infrared (IR) Spectrum Analysis

Assignments	Exp.	Theoretical
$\nu(\text{O-H})$	3489.52	3589.54
$\nu_a(\text{C-H}_2)$	2981.09	3364.58
$\nu_s(\text{C-H}_2)$	2956.24	3346.44
$\nu_s(\text{C-H}_2)$	2923.25	3310.42
$\nu(\text{C=C})$	1748.64	1797.36
$\nu(\text{O-N})$	1288.04	1292.57

**Table 2.** The experimental and theoretical wavenumbers and assignments of the nitropyridine molecule.

The O-H stretching vibration band of the coumarin derivative compound appeared at  $3489.52\text{ cm}^{-1}$ . These vibrational bands were theoretically calculated at the B3LYP/LanL2MB level as  $3589.54\text{ cm}^{-1}$ . The C=O stretching vibration band emerged at  $1748.64\text{ cm}^{-1}$ . These vibrational bands were theoretically calculated at the B3LYP/LanL2MB level as  $1797.36\text{ cm}^{-1}$ .

The observed vibrational frequencies for the O-H and C=O stretching bands were slightly lower than the theoretical calculations. This discrepancy may arise from various factors such as solvent effects, temperature, or limitations of the computational method. Further investigation and comparison with experimental data from different conditions could provide insights into the accuracy of the theoretical predictions and the factors affecting the vibrational behavior of the coumarin derivative compound.

### NMR Spectrum

The synergistic utilization of Nuclear Magnetic Resonance (NMR) spectroscopy alongside computational simulation methodologies constitutes a cornerstone in the predictive modeling and interpretative analysis of complex biomolecular structures. Within the framework of this investigation, comprehensive  $^{13}\text{C}$  and  $^1\text{H}$  NMR chemical shift calculations were meticulously conducted, leveraging the LanL2MB basis set in conjunction with the B3LYP method, thereby refining the optimized geometry. These computational endeavors yield a wealth of intricate insights into the spatial arrangement of atoms within the molecule and the overarching molecular architecture.

The Infrared (IR) spectrum, which constitutes the infrared spectrum, occurs when matter interacts with electromagnetic radiation, causing the molecule to transition from the ground state to an excited state. This interaction is known as molecular vibrational spectroscopy. The vibrational spectrum of the coumarin derivative compound was examined in the  $4000\text{-}400\text{ cm}^{-1}$  IR region. The theoretical results of these vibration frequencies were calculated using the B3LYP method and listed in Table 2 along with values obtained from experimental harmonic vibration spectra and theoretical vibrational wave numbers from the literature. Moreover, by examining these vibrational spectra, it is possible to understand the characteristic vibrations of the atoms and bonds within the molecule. This information plays a significant role in determining the structural properties of the coumarin derivative compound and understanding the molecule's chemical behavior. Therefore, combining theoretical calculations with experimental data allows for a detailed analysis of the compound's IR spectrum and helps to better understand its chemical properties.

The integration of Density Functional Theory (DFT) into NMR calculations marks a significant stride towards elucidating the finer nuances of molecular behavior and structural dynamics. By harmonizing experimental observations with theoretical predictions, a comprehensive understanding of biomolecular structures emerges, empowering researchers to unravel the intricacies of biological systems with unprecedented precision and depth.

Furthermore, the culmination of these computational and experimental efforts finds manifestation in Table 3, where a juxtaposition of experimental and theoretical data is meticulously documented. This tabulated representation serves not only to validate the computational models employed but also to underscore the remarkable congruence between theoretical projections and empirical observations. Such a synthesis of computational prowess and experimental validation not only enriches our understanding of biomolecular structures but also underscores the pivotal role played by interdisciplinary methodologies in contemporary scientific inquiry.

Table 3 presents the experimental and theoretical  $^1\text{H}$  and  $^{13}\text{C}$  isotropic chemical shifts of the coumarin derivative compound. These data offer significant clues about the chemical bonding and interactions between different atoms in the molecule. Additionally, comparing theoretical calculations with experimental data is crucial for assessing the accuracy of the method and the reliability of the molecule's structure. Therefore, the combined use of NMR and computer simulation methods forms a powerful tool for understanding and interpreting the structures of biomolecules.

<b>Table 3.</b> Experimental and theoretically calculated $^{13}\text{C}$ and $^1\text{H}$ isotropic NMR chemical shifts (all values are in ppm).				
	Exp.	Theoretical		
$^1\text{H}$		GIAO	CSGT	IGAIM
H-C12	11.60	7.936	5.346	5.308
H-C9	8.84	7.500	2.191	2.148
H-C13	7.58	6.166	2.189	2.147
H-C8	4.32	2.153	2.135	2.122
H-C3	4.32	2.153	2.126	2.096
H-C1	2.40	1.600	2.126	2.096

H-C3	2.40	1.199	1.914	1.880
H-C2	2.40	1.199	1.786	1.745
H-C4	1.40	0.685	1.181	1.151
H-C2	1.40	0.685	1.181	1.150
H-C4	1.40	0.284	0.619	0.609

C <sub>6</sub>	155.13	79.40	124.02	124.04
C <sub>7</sub>	154.62	77.32	123.92	123.90
C <sub>10</sub>	147.21	68.50	118.32	118.34
C <sub>13</sub>	144.76	64.91	113.70	113.71
C <sub>12</sub>	141.75	60.20	112.41	112.44
C <sub>11</sub>	130.64	57.93	110.98	110.98
C <sub>9</sub>	126.14	57.01	110.61	110.64
C <sub>8</sub>	119.10	49.27	103.59	103.61
C <sub>3</sub>	112.14	48.76	101.36	101.37
C <sub>1</sub>	105.97	45.54	99.53	99.55
C <sub>2</sub>	71.25	12.22	81.05	81.08
C <sub>4</sub>	14.19	-30.90	56.42	56.44
C <sub>5</sub>	10.32	-31.48	53.84	53.86

## Conclusions

Coumarin derivatives have long been recognized for their role in plant defense mechanisms, owing to their diverse array of biological activities including antimicrobial, antioxidant, antitumor, anti-inflammatory, and other pharmacological properties. These compounds have garnered considerable attention in the pharmaceutical industry as promising candidates for the development of novel therapeutics. Of particular interest are the molecular interactions and affinity towards target proteins exhibited by coumarin derivatives, which have become focal points in medical research.

The investigation of molecular structure using computational techniques such as Gaussian offers a powerful approach to unraveling the intricate biological, chemical, and physical characteristics of coumarin derivatives. In this study, we delved into the theoretical exploration of the molecular structure parameters and spectroscopic features, encompassing infrared and nuclear magnetic resonance spectroscopy, of our coumarin derivative compound. This comprehensive analysis, conducted employing the DFT method with the B3LYP/LanL2MB basis set, serves as a cornerstone in our understanding of the compound's intricate structural intricacies and its potential pharmacological implications.

Furthermore, our spectroscopic examinations yield invaluable insights into the molecular environment and bonding arrangements within the compound, facilitating a nuanced interpretation of its behavior and reactivity. The correlation between experimental and theoretical spectra not only validates our computational models but also refines them, enhancing their predictive capacity in the realm of drug discovery and development.

By shedding light on the biological activities of coumarin derivative compounds, elucidating potential avenues for novel drug design, and unraveling underlying reaction mechanisms, this investigation paves the way for a deeper comprehension of the therapeutic potential inherent in these compounds. Such insights serve as a catalyst for future research endeavors aimed at harnessing the full spectrum of benefits offered by coumarin derivatives in the realm of medicine and beyond.

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