Journal of Applied Sciences and Nanotechnology, Vol. 2, No. 1 (2022)

Journal of Applied Sciences and Nanotechnology

Journal homepage: https://jasn.uotechnology.edu.iq/

Synthesis, Bio-evaluation and Quantum Chemical Studies of Some Coumarin Derivatives

Samar M. Shakir, Yasameen K. Al-Majedy*
Branch of Chemistry, Department of Applied Sciences, University of Technology – Iraq

Article information

Article history:
Received: August, 17, 2021
Accepted: November, 14, 2021
Available online: March, 05, 2022

Keywords:
Three coumarin,
Hydrazinhydrate,
DFT

Corresponding Author:
Yasameen K. Al-Majedy
yasameen.k.hasan@uotechnology.edu.iq

Abstract

Coumarins are oxygen heterocyclic compounds that exist naturally and have a wide range of pharmacological properties, making them ideal as lead compounds for developing more powerful analogs. The modification of 4-methyl, 7-hydroxycoumarin by different reaction steps was done in this study to yield target compounds. They were characterized by different spectroscopic techniques (FT-IR and NMR), melting point and a thin layer chromatography. The microbiological activity of these compounds was investigated in a variety of bacterial and fungal species. Since the newly synthesized derivatives contain a variety of functional groups and may be microbiologically active, so the microbiological function of these derivatives in a variety of bacteria and fungi species was examined. In terms of the microorganism growth inhibition, the prepared compounds showed various levels of the activity. Antimicrobial properties have been discovered in newly synthesized derivatives. Density functional theory calculations of the synthesized coumarins were performed using molecular structures with optimized geometries.

DOI: 10.53293/jasn.2021.4164.1076, Department of Applied Sciences, University of Technology

1. Introduction

Derivatives of Coumarin both natural and synthetic are beneficial in a variety of domains and are extensively used in medicine, often as glycosides. Plants from the Rutaceae, Rubiceae, and Hippocastanaceae families, as well as microorganisms from the Aspergillus and Streptomyces strains, are the most inspiring and richest sources of leading coumarin system structures. Several efforts have been made to explore and develop coumarins as potential pharmaceuticals, including laboratory synthesis of coumarin derivatives with unique structures and properties, as well as isolation and purification of naturally occurring coumarins from vsarious plants [1–4]. A bacterial infection treatment is still a difficult therapeutic problem. Despite an availability of the wide spectrum of antibiotics and chemotherapeutics, the growth of old and new antibiotic-resistant bacterial strains has fuelled demand for new antibacterial medications in recent decades [5]. The condensation of active carbonyls with primary amines has resulted compounds as known as Schiff bases. Schiff bases are a prominent class of chemicals in pharmaceutical chemistry and medical with antibacterial [6–10], antifungal [11], and anticancer activities [12, 13] among their biological applications. They are known to interact with metal ions through the azomethine nitrogen atom and have been widely researched as a class of ligands [14–16]. Schiff base complexes are important in the development of metal complexes for synthetic and natural oxygen carriers [17]. These chemicals work well as stereo specific catalysts for reduction, oxidation, biological activity, hydrolysis and other

organic and inorganic chemical transformations after complexation with metals [18]. When >C=N- and additional functional groups are present in organic molecules, they form more stable complexes than those with simply the (>C=N-) coordinating moiety. As a result, coumarins with a Schiff base should have better anticancer and other biological properties. It is responsible for the biological action of hydrazone molecules. As a result, several hydrazone compounds with this active moiety have anticancer bioactivities [19]. Quantum chemical computational methods have proven to be an essential tool for interpretations and prediction of vibrational spectra [20, 21]. To obtain highly accurate geometries and physical properties of molecules, density functional theory (DFT) could handle relatively large molecules [22]. The purpose of this study is to review new synthetics of 4- Methyl, 7-hydroxycoumarin derivatives, as well as DFT studies on their biological effects.

2. Method/ Experimental Work

2.1. General Procedure with Spectral Data

A. Preparation of methyl 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetate (**2**): a mixture of 4-Methyl,7-hydroxycoumarin (1.086 g, 6.17 mmol) in acetone (30ml) was refluxed with potassium carbonate K_2CO_3 (4.69 g, 33.91 mmol) and methyl bromoacetate (1.528 g, 9.15 mmol) for 12 hours. After cooling, to eliminate the moisture, the mixture was evaporated. The crude product was refined by crystallization from ethanol after being separated into water (50 ml) and chloroform (50 ml).

B. Preparation of 2-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetyl)hydrazinecarbothioamide (**3**): Compound (2) (2.48 g, 10 mmol) in 25 ml of ethanol was refluxed with thiosemicarbazide (7.5 g, 15 mmol) for 4 hours. to yield compound (**3**). The residue were dried to afford a crystalline powder. [24].

C. Preparation of 2-(2-(4-methyl-2-oxo-2H-chromen-6-yloxy)acetyl)-N-(4-(2-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetyl)hydrazinecarbonothioylimino)methyl)benzylidene)hydrazinecarbothioamide (**4**): a mixture of compound(3) (0.01 mol) in chloroform methanol (1:1v/v) mixture (30 ml), terephthalaldehyde (0.005mol) 1 ml glacial acetic acid was refluxed for 3 hours in a water bath. After allowing the mixture to cool, the separated material was filtered and washed with excess methanol [23].

2.2. Antimicrobial Activities

The antimicrobial properties of synthesized coumarins were examined on G+ bacterium species (*Staphylococcus aurous* and *Streptococcus pyogenes*) and G- bacteria species utilizing the diffusion technique [26]. (*Pseudomonas aeruginosa* and *E. coli*) as well as antifungal activities on *Candida albicans*. Antimicrobial activity was determined using nutrient agar. Inhibition zones were used to display the results, which were measured in millimeters. Stock solutions for manufactured target compounds at 1 mg/ml were created the inhibitory zone was measured in millimeters after an 18-hour incubation period at 37˚C by dissolving the target drugs in DMSO. The prepared solutions had the following concentrations: 0.5, 0.25, 0.125, 0.0625, and 0.03125 mg/ml. A typical antibiotic medication, gentamycin, was employed as a standard for antibacterial activity as a comparison.

2.3. DFT

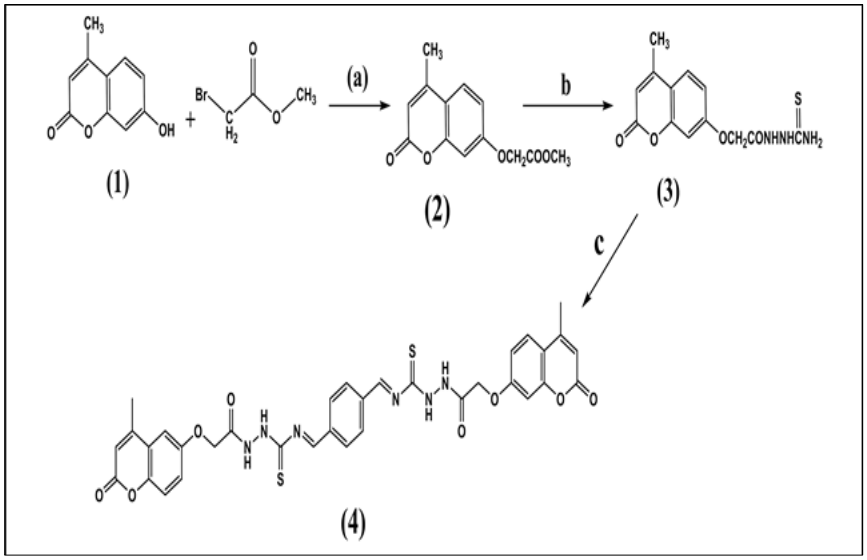
DFT is implemented in the Materials Studio 5.5. All quantum chemical computations were performed using employment to plot the molecular drawings of the compounds generated. To collect and optimize quantum chemical parameters in the molecular structure, the DMol3 model was employed. General gradient approximation (GGA) applying Perdew-Burke-Ernzerhof (PBE) as correlation functional and dual number d-functions was used to solve these equations (DND). This approach is well-known for providing acceptable geometries for a wide range of structures. The energy of the highest occupied orbital molecules (HOMO), the energy of the lowest unoccupied orbital molecules (LUMO), and the dipole moment were determined as quantum chemical indices[24, 25].

3. Results and Discussion

3.1. Chemistry

The reactions for the new compounds synthesis, namely, methyl 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetate(**2**),2-(2-(4-methyl-2-oxo-2H-chromen-7 yloxy)acetyl)hydrazinecarbothioamide(**3**),2-(2-(4-methyl-2-oxo-2H-chromen-6-yloxy)acetyl)-N-(4-(2-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetyl)hydrazinecarbonothioylimino)methyl)benzylidene)hydrazinecarbothioamide (**4**), so under the conventional methods, the compounds were successfully synthesized and completed. Scheme 1 depicts the

reaction pathway for the production of the compounds, commencing with 4-Methyl, 7-hydroxycoumarin. Coumarin derivatives have been produced by a number of researchers[20, 26–29].



Reagents and Conditions: a= Methyl bromoacetate*; b= Thiosiemacarbazide c= Terephthalaldehyde*

Figure 1: The reaction sequences of the produced chemicals.

Table 1: Physical properties and spectral data of the prepared compounds.

NO. COMP.	M.P (°C)	Yield (%)	Molecular formula (M.wt)	Spectral data	
				IR (cm^{-1})	^{1}H- NMR (δ, ppm)
2	93-95	80	$C_{13}H_{12}O_5$ 248.23	1763.00 cm^{-1} (C=O, ester), 1718.63 (C=O,lacton) , (Ar-CH) at 3086.21 cm^{-1} , 2960.83m^{-1} (C-H aliphatic) ,1618.33cm^{-1} C=C.	6.97 (H, s, 8-H), 7.71 (2H, d- d, 5, 6-H), 4.93 (2H, s, OCH_2), 6.23 (1H, s, 3-H), 3.68 (3H, s, CH_3), 2.41 (3H, s, CH_3).
3	175-178	70	$C_{13}H_{13}N_3O_4S$ 307.06	3369.75 , 3261.74 cm^{-1} (NH_2) ,3171.08cm^{-1} (NH) , 3103.57cm^{-1} C-H Aryl, 2955.04 cm-^{1} C-H aliphatic, 1641.48cm^{-1} (C=O lacton) , 1618.33cm^{-1} (C=O amide).	7.91(1H,s,NH), 8.4 (2H, s, NH_2), 8.1 (1H, s, NH) , 7.71 (1H, dd, 5,6-H), 6.90 (1H, s, 8-H), 6.21 (1H, s, 3-H), 6.22 (1H, s, 3-H), 4.45(2H,s,CH_3).
4	268-270	40	$C_{34}H_{28}N_6O_8S_2$ 712.75	3225.1cm^{-1} (NH) , 3153.72cm^{-1} (C-H Aryl), 2999.41 cm-^{1} (C-H aliphatic), 1699.34 cm^{-1} f(C=O lacton), 1658.84 cm^{-1} (C=O amide).	8.0 (1H, s, NH), 6.95-7.73 (2H, d-d, 5,6H),8.12 (1H, d-d, aromatic), 8.17 (1H, s, CH=N), 6.97 (1H, S,8-H), 6.23 (1H, s, 3-H), 4.61 (2H, s, OCH_2), 2.41(3H, s, CH_3) 2.0 (1H, s, NH).

3.2. Antimicrobial Activity

The newly synthesized compounds (1–4) have an antibacterial action, according to the findings have antimicrobial activity and that they have additional restraining effects in addition to the parent 4-hydroxycoumarin. Delocalization of pi-electrons over the entire produced molecule area electrons from specific molecules are not connected to a specific atom or bond in that molecule. Because they do not have a definite

position, these electrons are considered to be "delocalized" (not localized). In order to stabilize a structure, electrons become delocalized. This improves the lipophilic ability of the produced chemicals (1–4), allowing them to penetrate the bacteria's lipoid-layer membrane. A lipophilic nature of the produced compounds (1–4) was increased, which appears to be a cause of the increased antibacterial potency. A mechanism of the action of the produced chemicals (1–4) for killing bacteria may involve the deactivation of certain cellular enzymes that are important in various metabolic pathways of specific bacterium kinds. The toxicant's final impact is to disrupt the cell's proteins, resulting in the denaturation of natural cellular processes. Conductivity, solubility, and bond lengths are among other characteristics that might increase activity. According to the findings of the antibacterial screening research (1–4), Table 2 shows the results. To begin, all compounds had antibacterial activity against all of the species examined. Second, chemicals 3, 4 exhibit higher activity for the bacteria examined when compared to compounds 1 and 2. Third, compounds 3 and 4 include the ($NH\text{-}NH_2$) and (C=S) groups, which work together via the inductive effect.

Table 2: Antimicrobial activity of the prepared compounds (1 mg/ml), expressed as the inhibition zone (mm).

Microorganism	*S. aureus*	*Staphylococcus epidermidits*	*Streptococcus.sp*	*Klebsiella sp.*	*E. coli*	*C. albicans*
Compound	INHIBITION ZONES (mm)					
1	-	25	-	-	-	-
2	-	26	-	-	-	-
3	18	21	-	-	11	13
4	23	21	-	10	-	16
Tetracycline	19	11	12	12	21	---

3.3. Computational Studies

3.3.1. Atomic Stabilities and Charges

The existence of a substitute ring in compound 3 impacted the nuclear charges, according to the experimental results. (Additional file) and the 3D-geometric structure suggests that this molecule is not planar. Figure 2 shows that the largest atomic charge is [O (16) 0.915] and that the next charge is [O (3) 0.626]. These data indicate that these two atoms are the most reactive to reactions and metal bonds. This molecule is not plenary, as evidenced by the bond and twist angles determined (additional file) and the 3d-geometric structure.

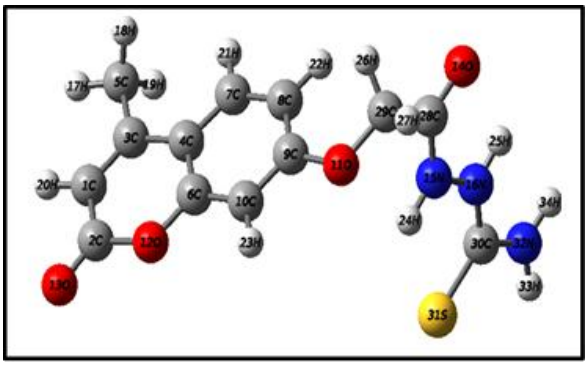


Figure 2: Compound form in three dimensions (3).

The compound minimum geometry is depicted in Figure 3, the atomic charges calculated for the material are also shown in the diagram. According to the findings, the greatest atomic charge is [O (3) 0.514], and the next highest is [O (17) 0.445]. These findings showed that those two atoms are the most reactive reaction sites and metal-binding sites in the system. This molecule is not planar, as evidenced by the governing bond's angles, twist angles, and 3d-geometric structure, as well as C (2)-C (3) stereochemistry (Z).

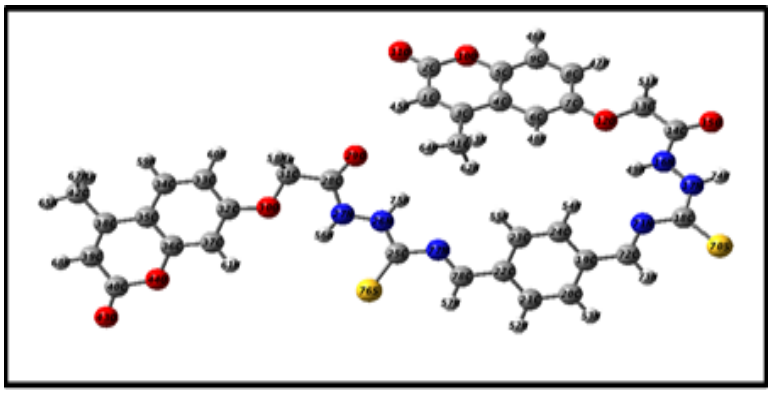


Figure 3: Compound form in three dimensions (4).

3.4. Density Functional Theory (DFT)

Compounds 1, 2, 3, and 4 were subjected to DFT calculations. Figure 2 shows optimized molecular structures of the most stable forms (2-4), Table 3 shows the calculated and relative energy of the participants. Theoretical results using the calculating approach given in this study revealed that compound 4 is more stable than other compounds based on the following factors total energy, which occupied higher-energy orbital molecular orbitals, and energy gap (EHOMO), The spatial properties, nodal patterns, and individual atom contributions are all described in detail via molecular orbital computations. Figure 3-5 shows the contour plots of the frontier orbitals for the ground states of 1, 2, 3, and 4, as well as the (HOMO) and (LUMO). It's noteworthy to note how evenly both orbitals are scattered around the conjugation plane. The HOMO orbitals are placed on the substituted molecule, however the LUMO orbitals mimic those obtained for the unsubstituted molecule, as shown in figures 4and 5 and so the substitution has an impact on electron donation ability but only a little impact on the electron acceptance ability. Table 1 lists the HOMO and LUMO orbital energy levels of compounds 1, 2, 3, and 4. The energy gaps between HOMO and LUMO for molecules 1, 2, 3, and 4 are roughly 0.16411, 0.16346, 0.15397, and 0.09082 Ha., respectively. The lower value of the HOMO and LUMO energy gaps, a reaction of the ultimate shipping movement within the molecules, is explained by the compound 4.

Table 3: Total Energy (a.u), HOMO and LUMO energies (Ha).

Molecular	Total energy	HOMO	LUMO	ΔE_{gap}	HOMO-1	LUMO+1	ΔE_{gap}
Comp. 1	-611.384212	-0.23158	-0.06747	0.16411	-0.25677	-0.01773	0.23904
Comp. 2	878.465808-	-0.23182	-0.06836	0.16346	-0.25464	-0.03286	0.22178
Comp. 3	1366.23818-	-0.22486	-0.07089	0.15397	-0.22576	-0.03198	0.19378
Comp.4	-3038.42972	-0.22431	-0.13349	0.09082	-0.22739	-0.08991	0.13745

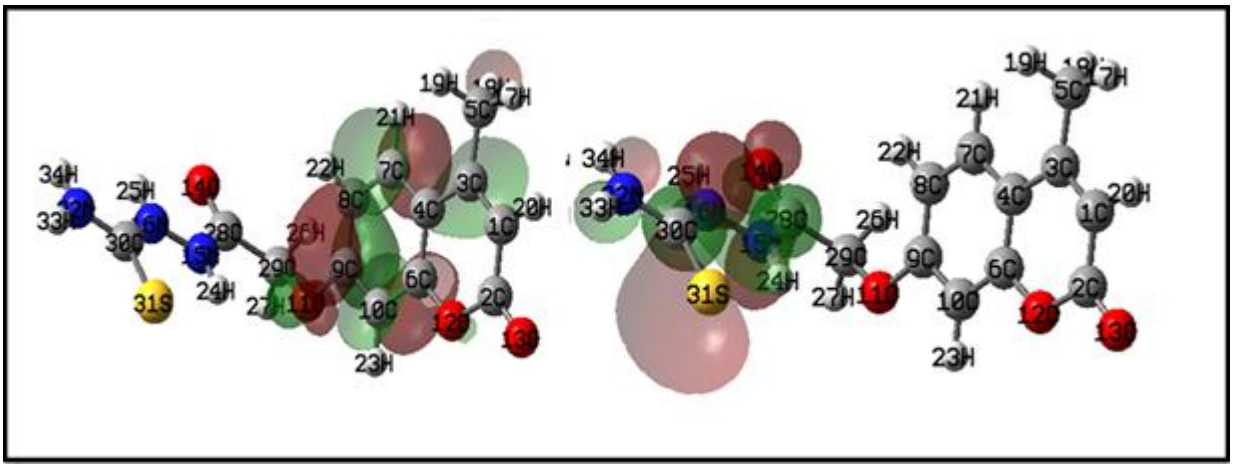


Figure 4: HOMO orbitals on the right and LUMO orbitals on the left of the compound 3.

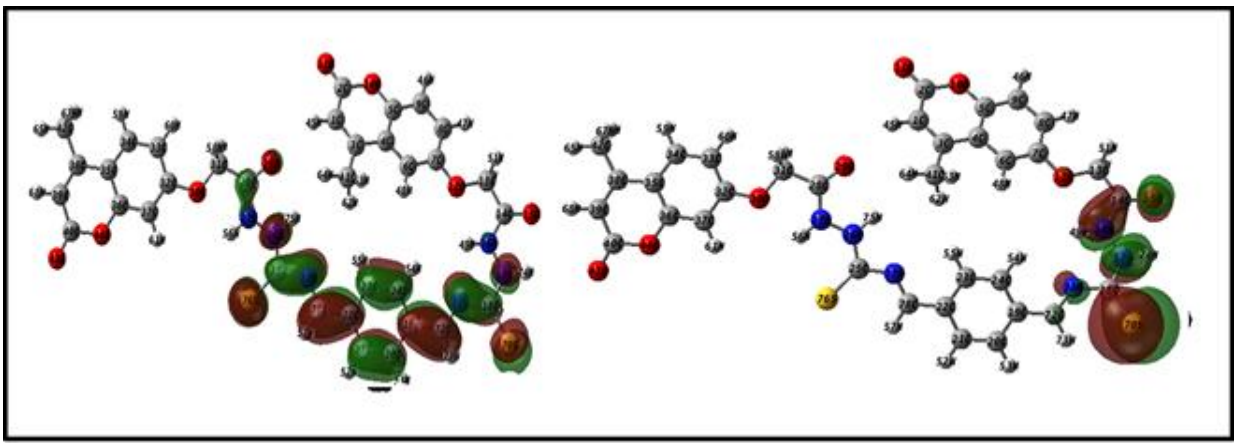


Figure 5: HOMO orbitals on the right and LUMO orbitals on the left of the compound 4.

4. Conclusions

Antimicrobial activity was produced of a variety of coumarin derivatives, developed and tested. The antibacterial activity of compounds 3, 4 was comparable to that of conventional medications, according to the biological test results. As a result, these compounds could be used as a lead compound for the creation of new antimicrobials. The synthesized compounds 3and 4 were studied theoretically using Density Functional Theory, in addition to their atomic charges and stereochemistry, they were estimated, and it was found that they are not planar. Molecular orbital calculations also were studied and have provided detailed description of the orbitals, including spatial characteristics, nodal patterns, and the contributions of individual atoms.

Acknowledgement

This study was supported by the University of Technology-Iraq, Department of Applied Science, and Chemical Division.

Conflict of Interest

The authors have no conflict of interest.

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