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DFT study and microbiology of some coumarin-based compounds containing a chalcone moiety

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Abstract: In the present investigation, a series of coumarin-based compounds containing a chalcone moiety were studied for their *in vitro* and *in silico* properties. The DFT global chemical reactivity descriptors (chemical hardness, total energy, electronic chemical potential and electrophilicity) were calculated for four synthesized compounds and used to predict their relative stability and reactivity. The antibacterial activities of all compounds were screened against *Bacillus subtilis* (ATCC 6633) and *Bacillus cereus* (ATCC 11778). The quantum-chemical calculations indicated that the antibacterial activity correlates well with chemical reactivity descriptors of the molecules.

Keywords: coumarins; chemical reactivity descriptors; antimicrobial activity; HOMO and LUMO studies.

INTRODUCTION

Problem of multi-drug resistant microorganisms has reached an alarming level around the world and the synthesis of new efficient anti-infective compounds has become an urgent need for the treatment of microbial infections.[1]

In previous works, by the nucleophilic addition reaction of the synthesized precursor 3-acetyl-4-hydroxycoumarin with different aromatic aldehydes, in the presence of basic catalysts pyridine and piperidine, a series of 3-substituted derivatives of 4-hydroxycoumarins containing a chalcone moiety were synthesized and their structures were confirmed. The results of previous studies sug-

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gested interesting biological and physicochemical properties of synthesized compounds.[2–5] The lipophilicity of synthesized compounds was determined in order to predict their chemical behavior toward living organisms. The results of *in silico* and *in vitro* investigations for the lipophilicity parameters of the synthesized derivatives showed that this group of compounds has an optimal range of values (log *D7.4* from 1 to 3) for good absorption *in vivo* and for *per os* application.[5] All of the above was the stimulus for this new research. The reactivity of a molecule is always governed by its electronic properties and kinetic and thermodynamic stability. In this computational study, the structural and electronic properties of four compounds of some coumarin-based molecules containing a chalcone moiety were investigated and used to predict their relative stability and reactivity. The density functional theory (DFT) has been accepted by the chemistry community as a reliable and effective approach for the computation of molecular structure, vibration frequencies and energies of chemical reactions.[6–9] The DFT provides an efficient method to include correlation energy in electronic calculations.[10] In addition, it constitutes a solid support to reactivity models.[11] Besides the total energy (ε), global chemical reactivity description, such as electronic chemical potentials (μ),[12] chemical hardness (η)[13] and electrophilicity (ω),[14] can be calculated. Reactivity parameters have been associated with the response of the electronic properties and the microbiology of compounds **1** to **4**. Then, the reactivity parameters are identified with response functions and they are represented by derivates of the electronic properties.

MATERIALS AND METHODS

Investigated compounds

Four 3-substituted derivatives of 4-hydroxycoumarins containing a chalcone moiety, *i.e.*, 3-(3-(2-chlorophenyl)prop-2-enoyl)-4-hydroxy-2*H*-1-benzopyran-2-one (**1**), 3-(3-(3-chlorophenyl)prop-2-enoyl)-4-hydroxy-2*H*-1-benzopyran-2-one (**2**), 3-(3-(4-chlorophenyl)prop-2--enoyl)-4-hydroxy-2*H*-1-benzopyran-2-one (**3**) and 3-(3-(4-bromophenyl)prop-2-enoyl)-4--hydroxy-2*H*-1-benzopyran-2-one (**4**), were studied for their *in vitro* and *in silico* properties.

The structures of the tested compounds are presented in Fig. 1.

Chemical reactivity

The computations were performed using Spartan 10. The geometries of **1** to **4** were optimized at the semi-empirical AM1 level. The structures are minima on the potential energy surface with positive harmonic vibrational frequencies.

The chemical reactivity descriptors calculated using DFT are: total energy (ε), chemical hardness (η), electronic chemical potential (μ) and electrophilicity (ω).

The antimicrobial activity of the 3-substituted derivatives of 4-hydroxycoumarin

The microbiological activity of the compounds was tested by the diffusion method on the *Bacillus subtilis* (ATCC 6633) and *Bacillus cereus* (ATCC 11778) species of bacteria. For the determination of the antimicrobial activity, Müller–Hinton and nutritious bases A, B, and F were used. The diffusion method is based on monitoring the growth inhibition of a specific microorganism caused by certain concentrations of a tested compound. The results of tests are

shown as inhibition zones (*I*) expressed in mm. When using the diffusion method, the test samples were dissolved in dimethyl sulfoxide (99.5 % DMSO) to obtain 1 mg mL^{-1} stock solutions. The inhibition zones for bacteria were measured in mm at the end of an 18-hour incubation period at 37 °C with 100 μL of the solution per well. Compounds **3** and **4**, which were previously investigated against *B. subtilis* (ATCC No. 6633), were also included in the antimicrobial activity evaluations.[2]

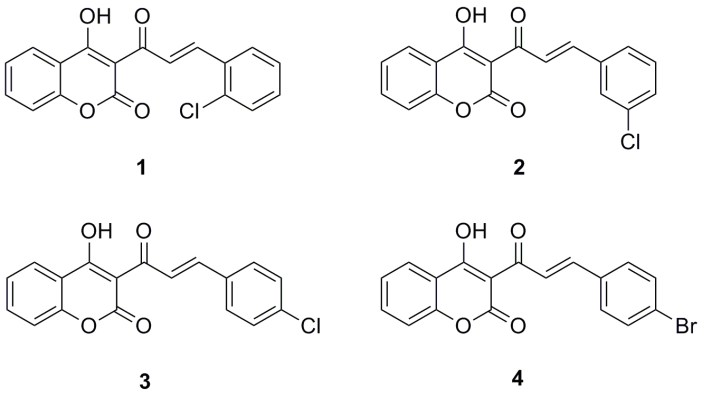

Fig. 1. Structures of the synthesized compounds **1**–**4**.

RESULTS AND DISCUSSION

Structural and electronic properties

The chemical hardness is associated with the stability and reactivity of a chemical system. In a molecule, it measures the resistance to change in the electron distribution or charge transfer. Based on frontier molecular orbitals, chemical hardness corresponds to the gap between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). Chemical hardness is approximated using the equation:[15]

$$\eta = \frac{(\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}})}{2} \quad (1)$$

where $\varepsilon_{\mathrm{LUMO}}$ and $\varepsilon_{\mathrm{HOMO}}$ are the LUMO and HOMO energies.

The larger the HOMO–LUMO energy gap, the harder and more stable/less reactive is the molecule.[16,17]

The electronic chemical potential is defined as the negative of electronegativity of a molecule[13] and is determined using the equation:

$$\mu = \frac{(\varepsilon_{\mathrm{HOMO}} + \varepsilon_{\mathrm{LUMO}})}{2} \quad (2)$$

Physically, μ describes the escaping tendency of electrons from an equilibrium system.

The global electrophilicity index (ω), introduced by Parr, is calculated using the electronic chemical potential and chemical hardness:[18]

$$\omega = \frac{\mu^2}{2\eta} \tag{3}$$

Electrophilicity index measures the propensity or capacity of a species to accept electrons. It is a measure of the stabilization in energy after a system accepts an additional amount of electronic charge from the environment.

Table I (row 5) contains the computed chemical hardness values for compounds **1** to **4**. The results indicate that compound **4** is harder and less reactive than **3**, which is harder and less reactive than **2**, which is harder and less reactive than **1**.

The values of μ for compounds **1** to **4** are presented in Table I. The trend in the electronic chemical potential for the compounds is **1** > **3** > **2** and **4**. The greater the electronic chemical potential, the less stable or more reactive is the compound. Therefore, **1** is the most reactive, and **2** and **4** are the least reactive of these compounds.

TABLE I. Global chemical reactivity indices for compounds **1**–**4**

Energy	Compound			
	1	**2**	**3**	**4**
Hartree	–4155.82	–4092.4	–4094.51	–4132.41
HOMO / eV*	–7.92	–8.09	–8.08	–8.12
LUMO / eV	–2.45	–2.44	–2.41	–2.41
μ / eV	–5.19	–5.27	–5.24	–5.27
η / eV	2.73	2.8	2.84	2.86
ω / eV	4.93	4.96	4.83	4.86

The electrophilicity values (Table I) for the compounds are 4.93 eV for **1**, 4.96 eV for **2**, 4.83 eV for **3** and 4.86 eV for **4**. Among these compounds, **3** is the strongest nucleophile while **2** is the strongest electrophile.

A molecule of compound **4** has the highest HOMO–LUMO energy gap, which indicates that it is the most stable and less reactive than the molecules of compounds **3**, **2** and **1**, as shown in Fig. 2.

*Atomic charges for compounds **1**–**4***

The synthesized compounds were studied theoretically and the atomic charges, heat of formation and stereochemistry were estimated. It was found that the compounds are planar (Table II).

The double bond bridge, the link between the planar benzopyrane heterocycle from the one side and the planar phenyl ring on the other side, gives rigi-

* 1 eV ≈ 1.60218×10^{-19} J

dity to all the investigated coumarins and is probably the reason for the planarity of these compounds.

Furthermore, the data show that the charge in the large atomic ligand compounds **1**–**4** are (O(11): –0.750 to –0.755). The following values are: O(22), –0.962 to –0.971. These data clearly show that these are the two most reactive atoms for substitution reactions.

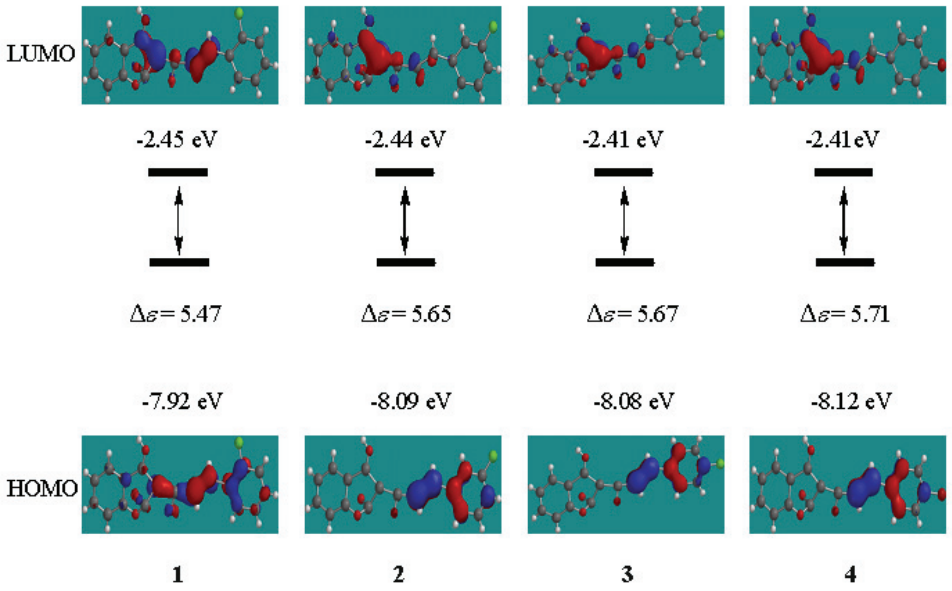

Fig. 2. Frontier molecular orbitals of compounds **1**–**4**.

TABLE II. Atomic charges for compounds **1**–**4**; All charges MM2 are 0

Atom	Atom type (MM2)	Charge Hückel	Atom	Atom type (MM2)	Charge Hückel	Atom	Atom type (MM2)	Charge Huckel
Compound **1**								
C(1)	C Alkene	–0.068	C(13)	C Carbonyl	0.120	H(25)	H	0.020
C(2)	C Alkene	–0.056	C(14)	C Alkene	0.106	H(26)	H	0.024
C(3)	C Alkene	–0.097	C(15)	C Alkene	–0.047	H(27)	H	0.026
C(4)	C Alkene	0.269	C(16)	C Alkene	0.221	H(28)	H	0.052
C(5)	C Alkene	–0.040	C(17)	C Alkene	–0.141	H(29)	H	0.343
C(6)	C Alkene	–0.055	C(18)	C Alkene	–0.186	H(30)	H	0.020
O(7)	O Enol	–0.033	C(19)	C Alkene	–0.081	H(31)	H	0.020
C(8)	C Carbonyl	0.538	C(20)	C Alkene	–0.181	H(32)	H	0.021
C(9)	C Alkene	–0.153	O(21)	O Enol	0.612	H(33)	H	0.029
C(10)	C Alkene	0.285	O(22)	O Carbonyl	–0.962	H(34)	H	0.244
O(11)	O Carbonyl	–0.753	Cl(23)	Cl	0.159			

TABLE II. Continued

Atom	Atom type (MM2)	Charge Hückel	Atom	Atom type (MM2)	Charge Hückel	Atom	Atom type (MM2)	Charge Huckel
				Compound **1**				
C(12)	C Alkene	–0.277	H(24)	H	0.020			
				Compound **2**				
C(1)	C Alkene	–0.068	C(13)	C Carbonyl	0.122	H(25)	H	0.020
C(2)	C Alkene	–0.051	C(14)	C Alkene	–0.234	H(26)	H	0.024
C(3)	C Alkene	0.097	C(15)	C Alkene	–0.008	H(27)	H	0.023
C(4)	C Alkene	0.272	C(16)	C Alkene	0.213	H(28)	H	0.052
C(5)	C Alkene	–0.037	C(17)	C Alkene	0.165	H(29)	H	0.017
C(6)	C Alkene	–0.042	C(18)	C Alkene	–0.250	H(30)	H	0.343
O(7)	O Enol	–0.033	C(19)	C Alkene	–0.028	H(31)	H	0.020
C(8)	C Carbonyl	0.537	C(20)	C Alkene	–0.194	H(32)	H	0.021
C(9)	C Alkene	–0.152	O(21)	O Enol	0.771	H(33)	H	0.030
C(10)	C Alkene	0.289	O(22)	O Carbonyl	–0.962	H(34)	H	0.216
O(11)	O Carbonyl	–0.755	Cl(23)	Cl	0.036			
C(12)	C Alkene	–0.279	H(24)	H	0.0210			
				Compound **3**				
C(1)	C Alkene	–0.068	C(13)	C Carbonyl	0.103	H(25)	H	0.020
C(2)	C Alkene	–0.074	C(14)	C Alkene	–0.117	H(26)	H	0.024
C(3)	C Alkene	–0.102	C(15)	C Alkene	–0.024	H(27)	H	0.023
C(4)	C Alkene	0.262	C(16)	C Alkene	0.225	H(28)	H	0.052
C(5)	C Alkene	–0.044	C(17)	C Alkene	–0.095	H(29)	H	0.017
C(6)	C Alkene	–0.063	C(18)	C Alkene	0.550	H(30)	H	0.343
O(7)	O Enol	–0.036	C(19)	C Alkene	–0.090	H(31)	H	0.020
C(8)	C Carbonyl	0.543	C(20)	C Alkene	–0.133	H(32)	H	0.021
C(9)	C Alkene	–0.152	O(21)	O Enol	0.749	H(33)	H	0.029
C(10)	C Alkene	0.246	O(22)	O Carbonyl	–0.971	H(34)	H	0.216
O(11)	O Carbonyl	–0.750	Cl(23)	Cl	0.009			
C(12)	C Alkene	–0.261	H(24)	H	0.021			
				Compound **4**				
C(1)	C Alkene	–0.068	C(13)	C Carbonyl	0.107	H(25)	H	0.020
C(2)	C Alkene	–0.068	C(14)	C Alkene	–0.120	H(26)	H	0.024
C(3)	C Alkene	–0.100	C(15)	C Alkene	–0.020	H(27)	H	0.023
C(4)	C Alkene	0.264	C(16)	C Alkene	0.221	H(28)	H	0.052
C(5)	C Alkene	–0.042	C(17)	C Alkene	–0.087	H(29)	H	0.017
C(6)	C Alkene	–0.057	C(18)	C Alkene	–0.004	H(30)	H	0.343
O(7)	O Enol	–0.035	C(19)	C Alkene	–0.077	H(31)	H	0.021
C(8)	C Carbonyl	0.542	C(20)	C Alkene	–0.138	H(32)	H	0.021
C(9)	C Alkene	–0.152	O(21)	O Enol	0.754	H(33)	H	0.030
C(10)	C Alkene	0.257	O(22)	O Carbonyl	–0.969	H(34)	H	0.216
O(11)	O Carbonyl	–0.751	Br(23)	Br	0.015			
C(12)	C Alkene	–0.265	H(24)	H	0.021			

Comparison of the DFT analysis with the antibacterial activity

The results of the antibacterial activities are summarized in Table III.

The diffusion method showed that almost all the synthesized compounds, to a greater or lesser extent, inhibit the growth of the Gram-positive aerobic bacteria *B. subtilis* ATCC 6633 and *B. cereus* ATCC 11778.

TABLE III. Antimicrobial activity of tested derivatives expressed as the inhibition zone, *I* (mm)

Compound	Microorganism	
	B. subtilis (ATCC 6633)	*B. cereus* (ATCC 11778)
$C_{18}H_{11}ClO_4$ (**1**)	16.0	19.5
$C_{18}H_{11}ClO_4$ (**2**)	21.0	22.5
$C_{18}H_{11}ClO_4$ (**3**)	21.5	22.75
$C_{18}H_{11}BrO_4$ (**4**)	22.5	23.75
DMSO (control)	–	–
Erythromycin	32.0	23.0
Gentamicin	32.2	27.8

Compound **4**, having the largest chemical potential (η), is the most stable and the least reactive by DFT analysis (Fig. 3). Compound **4** has the best antimicrobial activity. An examination of the mechanism of the antimicrobial action of these compounds remains for the future.

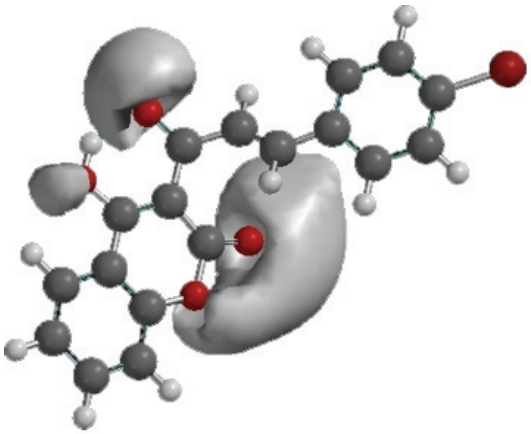

Fig. 3. Potential for compound **4**.

An increase in ε_{HOMO} and a decrease in ε_{LUMO} increase the reactivity of the synthesized compounds and decrease their activity against the tested microorganisms.

The most reactive derivative, compound **1**, showed the lowest activity against both the tested microorganisms, while the most stable compound **4** showed the best activity against both the tested microorganisms.

Bromine is less electronegative than chlorine, and as such increases the stability of the system (DFT confirmed), which contributes to a better activity (the derivative with bromine as a substituent exhibited the best antimicrobial activity).

CONCLUSION

The quantum-chemical and physicochemical calculations indicated that the calculated chemical reactivity descriptors of the molecules correlated well with antibacterial activity.

Reduction of ε_{HOMO} and increase of ε_{LUMO}, that is, a reduction in the reactivity and an increase in the stability of the synthesized compounds increased their activity against the tested microorganisms. The most reactive derivative, compound **1**, showed the lowest activity, indicating that the most chemically stable compound had the best antibacterial activity.

The promising antibacterial activity of the compounds could be helpful in the synthesis of a large number of analogues for extensive antimicrobial studies, which could be used to develop more appropriate drug candidates. It could be concluded that these classes of compounds certainly hold promise towards good active leads in medicinal chemistry.

ИЗВОД

СТУДИЈА ГУСТИНЕ И МИКРОБИОЛОГИЈЕ НЕКИХ КУМАРИНСКИХ ДЕРИВАТА КОЈИ САДРЖЕ ХАЛКОНСКИ ФРАГМЕНТ ПОМОЋУ ТЕОРИЈЕ ФУНКЦИОНАЛА

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Серија кумаринских деривата који садрже халконски фрагмент истраживана је с обзиром на њихова *in vitro* и *in silico* својства. За синтетизована једињења израчунати су DFT методом глобални хемијски реакциони дескриптори (хемијска тврдоћа, укупна енергија, електронски хемијски потенцијал и електрофилност) који су употребљени за предвиђање стаблиности и реактивности. Антибактеријска активност свих једињења одређена је у односу на *Bacillus subtilis* (ATCC 6633) и *Bacillus cereus* (ATCC 11778). Нађена антибактеријска активност се добро слаже са израчунатим дескрипторима хемијске реактивности.

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