Research Article

# Synthesis, Antibacterial Activity and DFT Study of New Derivatives Derived from Oxidation of 7-Hydroxy-4-Methyl Coumarin.

**Dana M. Hussein[1], Ammar A. Razzak Mahmood[2*], Sahar B. Al-Juboory[3]**
[1]Faculty of Medical Sciences-School of Pharmacy-Dept. of Pharmaceutical Chemistry-University of Sulaimani-Sulaimani, Iraq.
[2]College of Pharmacy-Dept. of Pharmaceutical Chemistry-University of Baghdad-Baghdad-Bab-Almudam-Iraq.
[3]College of Al-Rafiden University-Dept. of Pharmacy-Baghdad-Iraq.
***Corresponding author's E-mail:** kubbaammar1963@gmail.com

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**ABSTRACT**

A series of seven new derivatives were prepared from 7-hydroxy-4-methyl coumarin, following its oxidation via selenium oxide in hot xylene to form 7-hydroxy-4-formyl coumarin 1. The chalcones 2-4 were prepared from the condensation of 1 with different aromatic ketones at room temperature using 10% NaOH solution. Refluxing equimolar quantities of 1 and thiosemicarbazide using absolute ethanol, yielded hydrazine carbothioamide derivative 5. Refluxing 1 with 2,4-dinitrophenyl hydrazine in absolute ethanol and glacial acetic acid, afforded hydrazone derivative 6. Treatment of 1 with thiourea using glacial acetic acid and few drops of HCl under reflux condition afforded 7. The reaction of 5 with chloroacetic acid in a glacial acetic acid containing anhydrous sodium sulfate leads to ring closure and produced 8.The characterization of synthesized compounds has been done on the basis of FTIR,$^{13}$CNMR and mass spectral data. All the newly synthesized coumarins have been evaluated for their antibacterial activity against two Gram-positive bacteria: *Staphylococcus aureus* and *Micrococcus luteus*; and two Gram-negative bacteria: *E*.coli and *Pseudomonas aeruginosa*, using macro broth dilution method. Molecular modelling studies using DFT (Density Functional Theory) calculations showed that there is a high correlation between Dipole moment, Ionization potential (IP), Electron affinity (EA), Hardness (η), Softness (S), Electro negativity (μ), log P, energy gap, HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) energies and antioxidant activity. Initially, we were using 7-hydroxy-4-methyl coumarin as a starting material and all the synthesized coumarins are depicted in Scheme 1.

**Keywords:** Antibacterial activity, broth dilution method, coumarin derivatives, density functional theory (DFT), synthesis.

## INTRODUCTION

Coumarins consisting of fused benzene and -pyrone rings are present in significant amounts in plants, and more than 1300 coumarins have been identified from natural sources [1, 2]. Coumarins possess remarkable and broad medicinal applications, like antimicrobials, antitumors, anticoagulants, antithrombotic, anti-human immunodeficiency virus and scavenger use [3–7].

The effect of diverse substituents on coumarins as antioxidants has been extremely studied by scientists, who discovered that number and nature of the hydroxyl; alkoxy or alkyl substituents as electron-giving gatherings are the most crucial elements responsible for modifying the cancer prevention agent activities of coumarins. In other words, coumarins that have a different number of hydroxyl groups possess great cancer prevention properties [8].

There is an increasing concern in antioxidants, predominantly in those intended to prevent the presumed harmful effects of free radicals in the human body and to prevent the deterioration of fats and other constituents of foodstuffs, there is a favorite for using antioxidants from natural rather than from synthetic sources [9]. As better antioxidant status helps to diminish the oxidative injury and thus, delay or prevent pathological changes, potential antioxidant therapy should be integrated either as natural free-radical-scavenging antioxidant enzymes or as an agent which is competent of augmenting the activity of antioxidant enzymes [10]. In this work, our approach is to increase the antioxidant activity founded on a conjugated system and applied theoretical studies to relate the antioxidant activities with electronic structures, with a good relationship between the abstraction of H-atom and unpaired electron delocalization. In order to identify the correlation between an electron delocalization and the reactivity of the radicals, one can report the electron distribution in the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital). Our earlier work on the same coumarin nucleus was to derivatize new Schiff bases as antibacterial agents[11] is quite forceful, affording many promising research challenges. The aim of this work was to optimize structures of all the synthesized compounds to make clear the structure-antioxidant relationship, therefore, new series of chalcones, hydrazine carbothioamide, hydrazone and thiourea, derivatives have been synthesized and derived from 7-hydroxy-4-methyl coumarin, then screening of their preliminary antibacterial activities against both Gram-positive and Gram-negative bacteria, as well, we are concerned to calculate some antioxidant descriptors and also the favored mechanism of antioxidants, a computational work was planned to calculate some thermodynamic parameters.

## MATERIALS AND METHODS

All reagents were purchased from Sigma-Aldrich and used as received. Solvents were dried and distilled before use. Precoated TLC silica gel 60 $F_{254}$ Aluminum sheets from (Merck) (Germany), were used for thin-layer chromatography (0.25mm layer thickness for the analytical purpose) and visualized under short (254nm) and long (366nm) wavelength UV light.

Melting points were measured using Stuart/SMP3 melting point apparatus, version 5.0 in open capillary tubes and are uncorrected. The IR spectra (KBr) (υ, $cm^{-1}$) were recorded using Thermo Scientific™ Nicolet ™ iS™ 10FT-IR Spectrometer in Pioneer company for pharmaceutical industry-Sulaimani-Kurdistan-Iraq.[13] CNMR spectra were recorded at 100MHz on Bruker FT-NMR spectrophotometer 400, in the College of Pharmacy-Hamedan University of Medical Sciences-Hamedan-Iran, using DMSO-$_{d6}$ as a solvent, and TMS as an internal standard. Chemical shifts were expressed in δ ppm. Mass spectra were recorded using Agilent Technology (HP), GC/MS model 5973 network mass selective detector at the College of Pharmacy- Hamedan University of Medical Sciences. The values were expressed as m/z. All compounds showed satisfactory analytical results.

### Synthesis of 7-hydroxy-4-formyl coumarin (1) [12-15]

7-Hydroxy-4-methyl coumarin (0.005 mol, 1 g) was dissolved in hot xylene (50 ml), the solution was cooled and selenium dioxide (0.009 mol, 1 g) was added. The solution was then refluxed for a period of 12 h and then filtered while hot to remove the insoluble selenium. The solvent was removed by rotary evaporator to get the desired product and recrystallized from ethanol.

Yellow powder, yield 35%; m.p 222-224 ºC;IR (KBr) υ,$cm^{-1}$: 3233(OH) str, 3050 Ar(CH) str, 2840 (H-C=O) aldehydic hydrogen str, 1723(C=O) str of lactone, 1698(C=O) str of aldehyde, 1599,1516 (ArC=C) str, 1410(OH phenol) bend, 1068(C-O) str of lactone; $^{13}$CNMR(100MHz),DMSO-$d_6$, δ ppm): 194.31 (C=O aldehyde),161.54(C=O lactone),160.78, 155.26,127.08,112.49 and 102.57(C aromatic and alkene); mass spectroscopy Calcd. for $C_{10}H_6O_4$(m/z%):190[M]$^{+\cdot}$ (27.6%), 162[M-CO](10%),161[M-COH](14.9%), 148[M-ketene)(100%),104(17%).

### General procedure for synthesis of chalcones (2-4) [16-19]

Compound (**1**) (0.01 mol, 1.9 g) was mixed with appropriate aromatic ketones (0.02 mol) of (acetophenone 2.4 g, 2-hydroxy acetophenone 2.7 g, and (0.01 mol, 1.35 g) of 4-amino acetophenone,) and dissolved in absolute ethanol (30 ml) in a 100 ml round-bottom flask equipped with a magnetic stirrer. To the reaction mixture sodium hydroxide (10 ml, 10%) was added with vigorous stirring for about 30 minutes until the solution became turbid. By the use of cold water bath on the magnetic stirrer temperature of the reaction was maintained at 20-25 $^0$C. After vigorous stirring for 8-9 h, the reaction mixture was left to stand 24 h in the refrigerator. The precipitate was obtained, collected by filtration, washed with cold ice water and recrystallized from ethyl acetate.

### Synthesis of 7-hydroxy-4-(3-oxo-3-phenylprop-1-en-1-yl)-2*H*-chromen-2-one (2)

Chartreuse powder, yield 34%,m.p 178-181 ºC; IR (KBr) υ,$cm^{-1}$: 1755(C=O lactone) str, 1682(C=O chalcone) str,1640(C=C) str, 1582(Ar C=C) str,1408(OH phenol)bend, 1068 (C-O lactone) str; mass spectroscopy Calcd. for $C_{18}H_{12}O_4$(m/z%): 292[M]$^{+\cdot}$(3.8%), 291[M-1](10.2%),275[M-OH](5.1%), 187(12.8%),161(15.3%).

### Synthesis of 7-hydroxy-4-(3-(2-hydroxyphenyl)-3-oxoprop-1-en-1-yl)-2*H*-chromen-2-one (3).

Chartreuse powder, yield 41%, m.p 163-167 ºC; IR (KBr) υ,$cm^{-1}$: 3586(OH *br.*)str,1755 (C=O lactone) str, 1685(C=O chalcone) str, 1652(C=C) str, 1575,1396(Ar C=C) str, 1407 (OH) bend, 1214(C-O lactone) str; mass spectroscopy Calcd. for $C_{18}H_{12}O_5$ (m/z%): 308[M]$^{+\cdot}$(3%), 187(2.4%),161(6.1%).

### Synthesis of 4-(3-(4-aminophenyl)-3-oxoprop-1-en-1-yl)-7-hydroxy-2*H*-chromen-2-one (4).

Red powder, yield 29%, m.p 192-195 ºC; IR (KBr) υ,$cm^{-1}$: 3526(OH) str, 3420,3330 ($NH_2$) str, 3002(ArCH) str, 1733(C=O lactone)str, 1683(C=O chalcone) str, 1646 (C=C) str, 1595,1395(ArC=C) str,1410(OH)bend, 1215(C-O lactone) str; mass spectroscopy Calcd. for $C_{18}H_{13}NO_4$(m/z%): 307[M]$^{+\cdot}$(5.1%),306(5.7%),290[M-OH] (4.6%),187(8%),161(13.8%)

### Synthesis of -((7-hydroxy-2-oxo-2*H*-chromen-4-yl)methylene)hydrazine carbothioamide (5) [20]

Equimolar amounts (0.005 mol, 0.95 g) of compound(**1**) and (0.005 mol,0.45 g) thiosemicarbazide were refluxed in absolute ethanol (100 ml) in a round-bottom flask for 2 h, then the reaction mixture was cooled down. The obtained faint yellow-colored powder was collected by filtration and recrystallized from methanol.

Faint yellow powder, yield 67%,m.p 203-207 ºC; IR (KBr) υ,$cm^{-1}$: 3500(OH) str, 3360 and3260 ($NH_2$) str, 3177 (Ar-CH) str, 1755 (C=O lactone) str, 1610 (C=N) str, 1593 and 1490(ArC=C) str, 1525 (NH) bend, 1408(OH) bend, 1273 and 1069 (C=S) str ; $^{13}$CNMR(100MHz), DMSO-$_{d6}$,δ ppm): 179.08 (C=O lactone), 161.79 (C=S),160.79(C=N), 156.06, 155.29,154.04,127.08,113.34,112.48 and 102.64 (C aromatic and alkene); mass spectroscopy Calcd. for $C_{11}H_9N_3O_3S$(m/z%): 263[M]$^{+\cdot}$(11.5%), 188(10.3%), 161 (18.4%).

### Synthesis of4-((2-(2,4-dinitrophenyl)hydrazono)methyl)-7-hydroxy-2*H*-chromen-2-one (6) [21]

Compound (**1**),(0.005 mol, 0.95 g) and 2,4-dinitrophenylhydrazine (0.005 mol, 1 g) were mixed in a round bottom flask using absolute ethanol (30 ml) as a solvent, (3-4) drops of glacial acetic acid was added and the mixture was refluxed for 7 h. The reaction monitored

by TLC, an intense orange-colored precipitate was formed, collected by filtration and recrystallized from ethanol.

Intense orange powder, yield 72%,m.p 237-241 ºC; ; IR (KBr) υ,$cm^{-1}$:3460 (OH) str, 3321(NH)str, 3103(Ar-CH) str, 1681(C=C) str, 1645(C=N) str, 1599(ArC=C) str, 1573(NH) bend, 1504 and 1310 ($NO_2$) str, 1107 (C-O lactone) str; $^{13}$CNMR(100MHz), DMSO-$_{d6}$,δ ppm):161.64(C=O lactone),160.76(CH=N),155.28, 153.99, 149.63, 134.72, 130.00, 127.99, 123.93, 116.02, 113.31, 112.41, and 102.62 (C aromatic and alkene); mass spectroscopy Calcd. for $C_{16}$ $H_{10}N_4O_7$ (m/z%): 370[M]$^+$ (7.1%), 324[M-$NO_2$] (1.4%), 174(7.1%), 161(4.2%).

**Synthesis of 1-((7-hydroxy-2-oxo-2*H*-chromen-4-yl) methylene) thiourea (7)[20]**

A solution of equimolar amounts of compound **(1)** (0.005 mol, 0.95 g) and thio urea (0.005 mol, 0.38 g) is prepared in glacial acetic acid(35 ml), (2-3) drops of conc. HCl acid was added to the solution. The reaction mixture was refluxed for 2 h. The yellow colored powder was formed, collected by filtration and recrystallized from glacial acetic acid.

Yellow powder, yield 49%,m.p 247-250 ºC ; IR (KBr) υ,$cm^{-1}$:3327($NH_2$) str,1710(C=O lactone ) str, 1670(C=C) str, 1652 (C=N)str, 1593 and 1507(Ar-C=C) str, 1388 (OH) bend, 1067(C=S ) str; $^{13}$CNMR(100MHz), DMSO-$_{d6}$,δ ppm): 184.29(C=O lactone),161.76(C=S), 160.34 (CH=N), 155.27, 154.07, 127.03, 113.40, 112.41, 102.66 (C aromatic and alkene); mass spectroscopy Calcd. for $C_{11}H_8N_2O_3S$ (m/z%):248[M]$^{+\cdot}$(3.9%),247(3.2%),232[M-$NH_2$](2.6%), 188(13%),174(26%),161(13%)

**Synthesis of 2-(2-((7-hydroxy-2-oxo-2*H*-chromen-4-yl) methylene)hydrazinyl)thiazol-4(5H)-one (8) [20,22,23]**

A mixture of chloroacetic acid (0.01 mol,0.94 g) and compound **(5)** (0.01 mol, 2.63 g) in glacial acetic acid (40 ml) containing anhydrous sodium acetate (0.04 mol, 3.28 g) was refluxed for 12h, and monitored by TLC. The reaction mixture was cooled; a pale yellow colored precipitate was formed, collected by filtration and recrystallized from ethanol.

Pale yellow powder, yield 63%, m.p 310-314 ºC; IR (KBr) υ,$cm^{-1}$: 3150(NH)str, 3129 (Ar-CH) str, 2918($CH_2$)str, 1760(C=O lactone)str, 1674(C=O amide)str, 1651(C=C) str, 1615(C=N) str, 1590 and 1515(Ar-C=C) str, 1066(C-O lactone) str, 708(C-S) str; $^{13}$CNMR(100MHz), DMSO-$_{d6}$,δ ppm): 175.68 (C=O amide) ,162.35 (C=O lactone), 160.89 (CH=N), 155.33, 154.08, 126.88, 113.59, 112.11, 102.72 (C aromatic and alkene), 44.82 ($CH_2$); mass spectroscopy Calcd. for $C_{13}H_9N_3O_4S$ (m/z%):303[M]$^{+\cdot}$(4%),203 (13.1%),188(26.3%),161(32.9)%

**Antibacterial Activity**

The synthesized compounds **2-8** were tested for their antibacterial activity using macro broth dilution method against two Gram-positive (G$^{+ve}$) bacteria, *Staphylococcus aureus* and *Micrococcus luteus,* and two Gram-negative (G-$^{ve}$) bacteria, *Escherichia coli* and *Pseudomonas aeruginosa* to determine the MIC *in vitro*. A series of tested tubes containing 1ml of Muller-Hinton media autoclaved with a 50µl bacterial inoculum of bacterial suspension at McFarland turbidity of 0.5. Then specified concentrations of coumarin derivatives are added to each tube except the negative control in which the solvent(DMSO) was added and a positive control with bacterial inoculums without adding any synthesized coumarin derivative, all tubes were incubated aerobically at 37 ºC for 24 h. Then MIC is determined by visual observation as the minimum concentration, (most potent) that inhibits bacterial growth appears clear solution[24].

## RESULTS AND DISCUSSION

**Chemistry**

The new coumarin derivatives,(scheme1), have been synthesized from the oxidation of methyl group at C4 of 7-hydroxy-4-methyl coumarin, using $SeO_2$ as an oxidizing agent and hot xylene as a solvent, to give 7-hydroxy -4-formyl coumarin 1, this compound characterized by IR spectrum through the appearance of a band attributed to aldehydic (C=O) displayed at 1698 $cm^{-1}$, and aldehyde hydrogen stretching (H-C=O) recorded at 2840 $cm^{-1}$.

The $^{13}$CNMR showed distinct peak due to aldehydic (C=O) at δ= 194.54ppm, besides that, MS gives the molecular ion peak $(M)^{+\cdot}$ at m/z 190 , while the base peak (100%) of 1 displayed at m/z 148, due to losing of ketene.

The chalcones 2-4 were synthesized by condensation of 1 with appropriate aromatic ketones using 10% NaOH to produce the corresponding chalcones. The IR spectra exhibited a new band of the carbonyl of chalcone (C=O) at (1685-1682) $cm^{-1}$, in addition to the carbonyl peak of lactone ring displayed at (1755-1733) $cm^{-1}$. The mass spectra confirmed the molecular weight of these compounds from their molecular ions and their fragmentation. The molecular ions $[M]^{+\cdot}$ of 2, 3 and 4 recorded at m/z 292,308, and 307, respectively.

Compound 5, hydrazine carbothioamide derivative. The IR spectrum showed the appearance of ($NH_2$) stretching at 3360 and 3260 $cm^{-1}$, imine group (C=N) stretching at 1610 $cm^{-1}$,(C= S) stretching band at 1273 and 1069 $cm^{-1}$.

The $^{13}$CNMR displayed the (C=O) group at δ = 179.08 ppm, (C=S) at δ =161.79 ppm and (C=N) at δ =160.79 ppm, while MS showed the molecular ion peak $[M]^{+\cdot}$ at m/z 263.

Compound 6, a new hydrazone derivative of coumarin. The IR spectrum exhibited new signal of (NH) group displayed at 3321 $cm^{-1}$, the imine group(C=N) at 1645$cm^{-1}$ and the ($NO_2$) groups recorded at 1310 and 1504 $cm^{-1}$.

The $^{13}$CNMR exhibited the (C=O) and (C=N) groups at δ= 161.64 and 160.76 ppm, respectively, While MS showed the molecular ion peak $[M]^{+\cdot}$ at m/z 370, in addition to the

other fragments, that confirm the structural compound of 6 (experimental part).

Compound 7 is a thio urea derivative , The IR spectrum showed the ($NH_2$) peak at 3327 $cm^{-1}$, (C=N) group at 1652 $cm^{-1}$ and (C=S) stretching at 1067 $cm^{-1}$. The $^{13}$CNMR spectrum displayed two new characteristic peaks δ =161.76 and 150.34 ppm, belonging to (C=S) and (C=N) groups, respectively, while MS recorded the molecular ion peak $[M]^{+\cdot}$ at m/z 248.

Finally, The IR spectrum for 8 showed distinctly a band at 2918 $cm^{-1}$ due to the aliphatic ($CH_2$) group, (C=O) of an amide at 1674$cm^{-1}$, (C=N) stretching at 1615 $cm^{-1}$ and (C-S) band at 708 $cm^{-1}$, which indicates the success of cyclization method.

The $^{13}$CNMR displayed two distinct peaks, one at δ=175.68 ppm attributed to (C=O) of an amide, and the other at δ =44.82 ppm due to the aliphatic ($CH_2$) of the cyclized ring.

All the aromatic carbons of coumarin nucleus appeared at their expected region, while MS exhibited the molecular ion peak $[M]^{+\cdot}$ at m/z 303, for 8, in addition to the other fragment peaks (experimental part).

**Antibacterial Activity**

The antibacterial activity of the tested compounds 2-8, (table 1) illustrated that the title coumarin derivatives display antibacterial, in *vitro*, against Gram-positive and Gram-negative bacteria with MICs range between 63-300 µg/ml, in which they vary according to the synthesized derivative and bacteria.

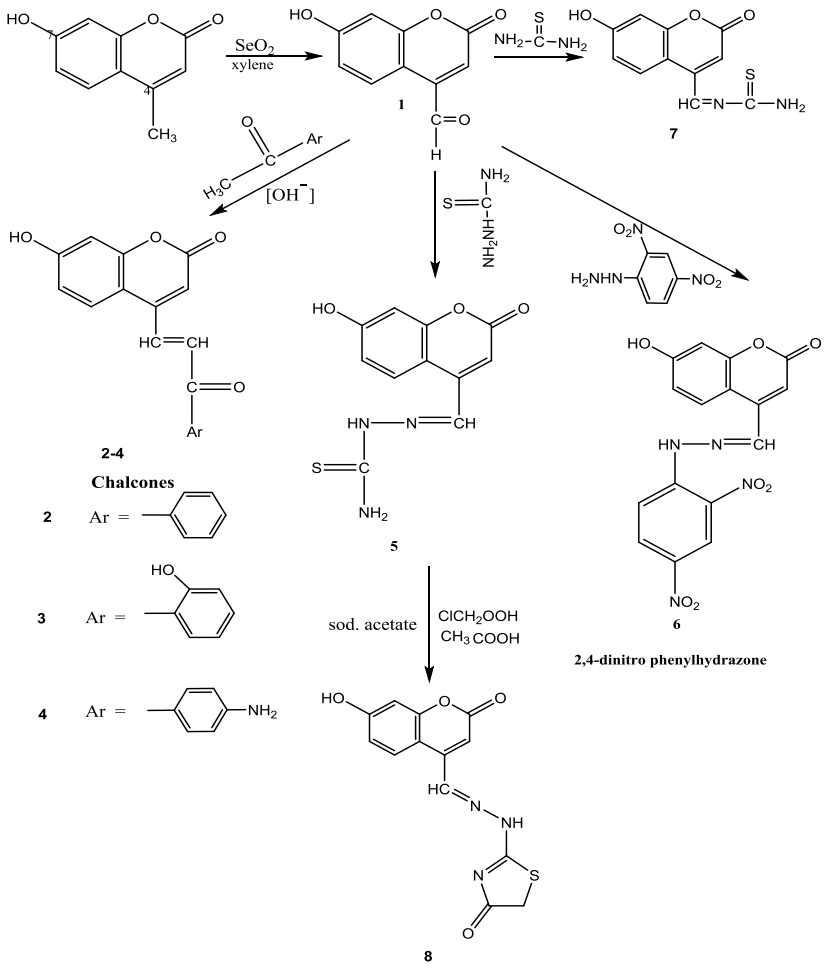
The lowest MIC is 63 µg/ml for compound 5 against both *Micrococcus luteus* and *Pseudomonas aeruginosa*, while the MIC for each 4 and 7 was 79 µg/ml against *Micrococcus luteus*, while 8 exhibited the most antibacterial activity against *E.coli* with MIC 79 µg/ml.

**Computational Studies**

The quantum chemical parameters were calculated on newly synthesized coumarins using DFT theory, a widely used computational method with 3-21* basis. The molecular demonstration sketch of the new coumarin compounds was plotted using Chem. Bio-Office 2010 software. The DFT global chemical reactivity descriptors (total energy (**ε**), dipole moment (**Debye**), ionization potential (**IP**), electron affinity (**EA**), chemical hardness (**η**), electro negativity **(µ)**, **log P**, and softness (**S**) ) were calculated for five synthesized compounds and used to predict their relative stability and reactivity.

**Structural and electronic properties**

Compounds **1, 3, 4, 6** and **8** with optimized geometries and 3D geometrical structures are shown in figure 1.




**Scheme 1:** Synthesis of title coumarin derivatives 2-8

**Table 1:** Antibacterial activity of title coumarin derivatives 2-8

| Comp No. | *Staphylococcus aureus* ($G^{+ve}$) Conc.µg/ml | *Micrococcus luteus* ($G^{+ve}$) Conc.µg/ml | *Escherichia coli* ($G^{-ve}$) Conc.µg/ml | *Pseudomonas aeruginosa* ($G^{-ve}$) Conc.µg/ml |
|---|---|---|---|---|
| 2 | 192 | 79 | 240 | 123 |
| 3 | 123 | 98 | 192 | 154 |
| 4 | 154 | 79 | 240 | 300 |
| 5 | 98 | 63 | 123 | 63 |
| 6 | 123 | 154 | 192 | 98 |
| 7 | 123 | 79 | 154 | 98 |
| 8 | 123 | 192 | 79 | 98 |

Note: C- =negative control (solvent, DMSO), C+ = positive control indicates abroth without adding title coumarin derivatives.

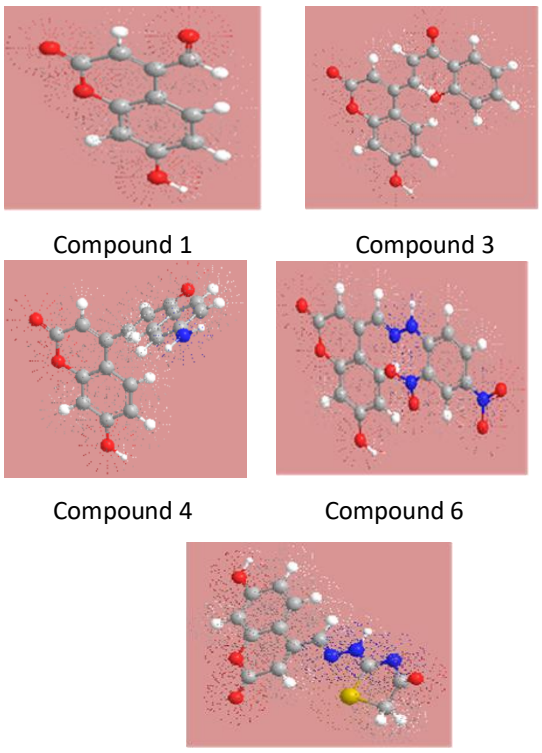


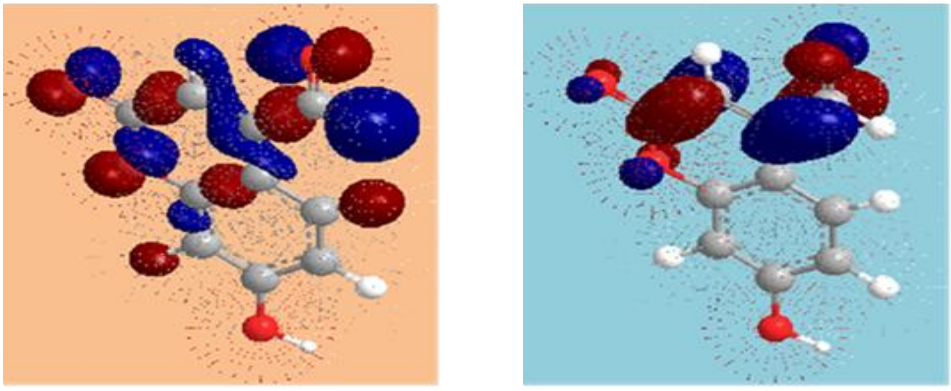

**Figure 1:** Optimized 3D geometrical structures for compounds **1, 3, 4, 6** and **8.**

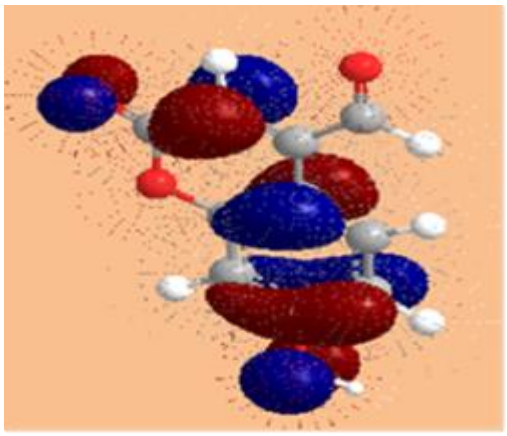
Molecular orbital calculations offer a detailed explanation of orbitals including spatial characteristics, nodal patterns, and individual atom contributions. The contour plots of the frontier orbitals for the ground state are shown in (fig. 2 to fig.6), including the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) [25-27].

In a pursuit of electronic level understanding of the antioxidant activities of compounds 1, 3, 4, 6 and 8, the HOMO and the LUMO studies have been carried out using density functional theory (DFT) based quantum chemical descriptors. The calculated HOMO and LUMO energies as displayed in (Figure 2 to 6) demonstrate that charge transfer occurs within the molecules.

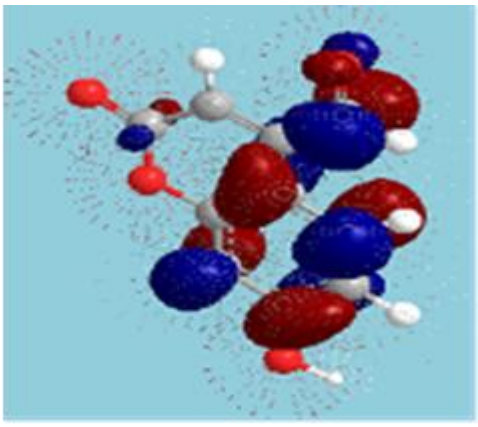
For compounds 1, 3, 4, 6 and 8, HOMO are delocalized over the entire molecules, which corresponds to the orbital containing the unpaired electron. The spin densities of the radicals formed from compounds 1, 3, 4, 6 and 8 were compared. The more delocalized the spin density in the radical is, the easier the formation of the radical and the lower the formation of compound 1. The spin population appears to be slightly more delocalized for the radicals issued from compounds 1, 3,4, than from compound 6 and 8.

It can be seen that the energy gaps between HOMO and LUMO of compound 1 are-3.932 eV, compound 3 is -6.951 eV, Compounds 4 and 6 are -3.853 eV, -2.246 eV respectively, and compound 8 is -4.35 eV. The lower value in the HOMO and LUMO energy gap explains the final charge transfer interaction arranged within the molecules. The larger the HOMO–LUMO energy gap, the harder and more stable/less reactive the molecule.



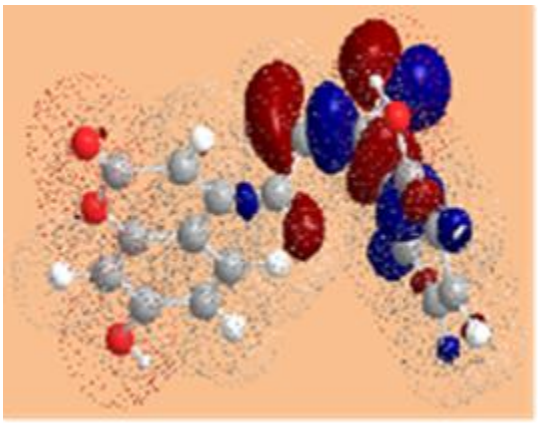


HOMO-1

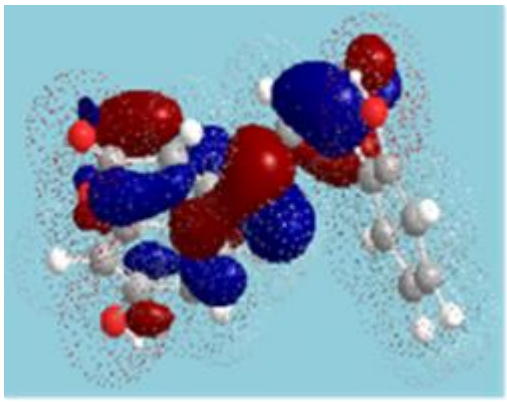


LUMO+1

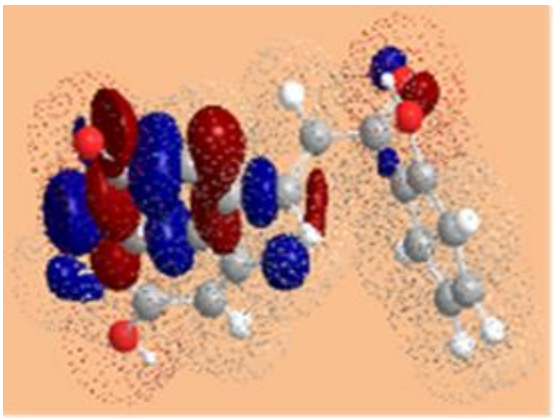
**Figure 2:** Highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of compound **1**.



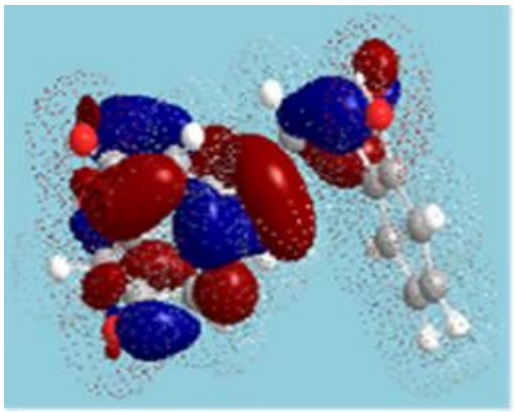
HOMO



LUMO

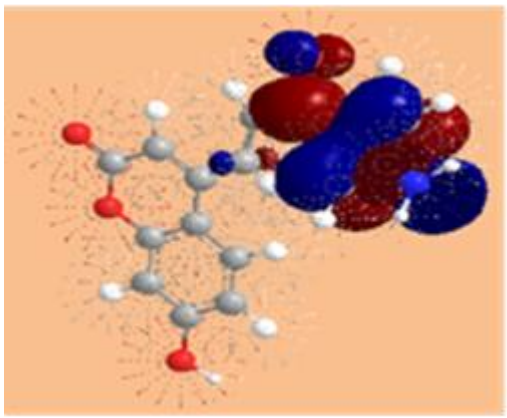


HOMO-1

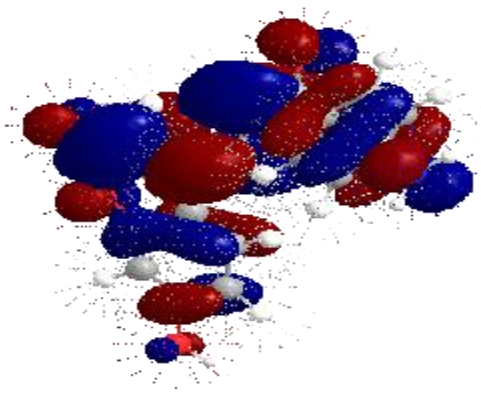


LUMO+1

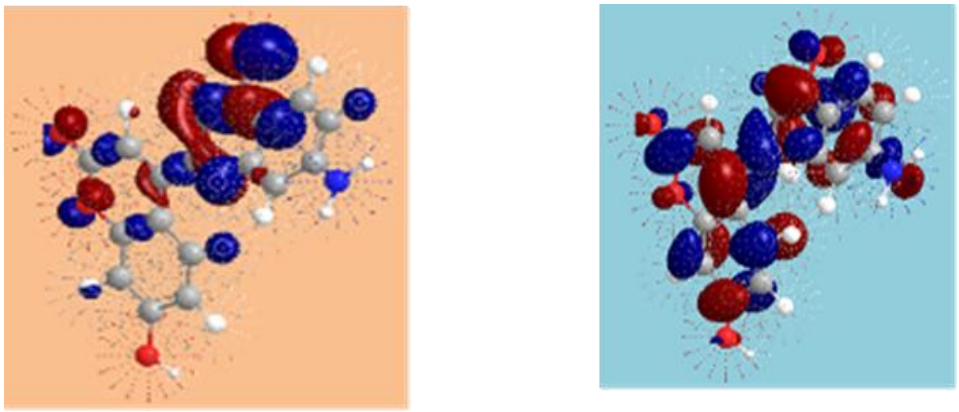
**Figure 3:** Highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of compound **3**



HOMO

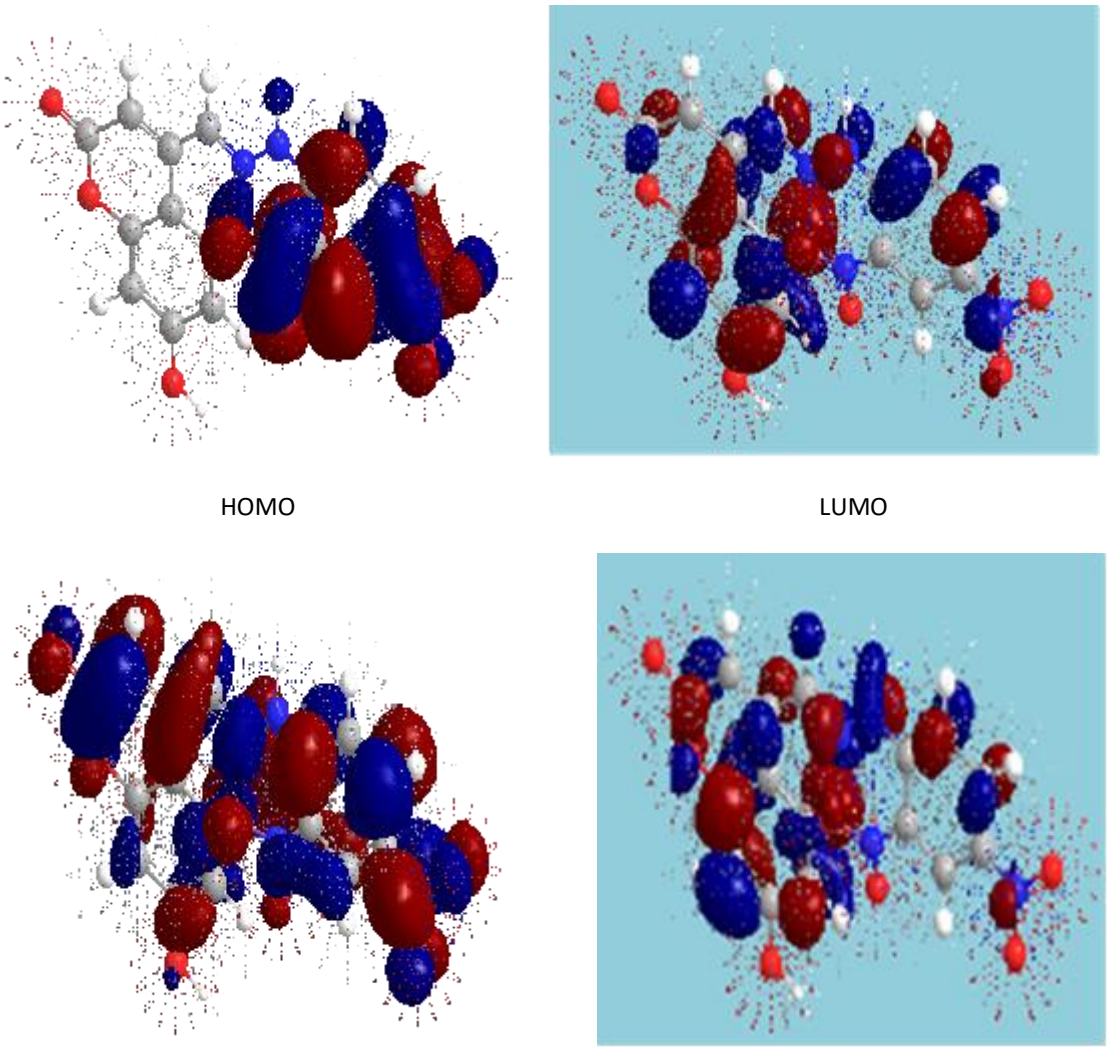


LUMO



HOMO-1 LUMO+1

**Figure 4:** Highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of compound **4**



HOMO LUMO

HOMO-1 LUMO+1

**Figure 5:** Highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of compound **6**

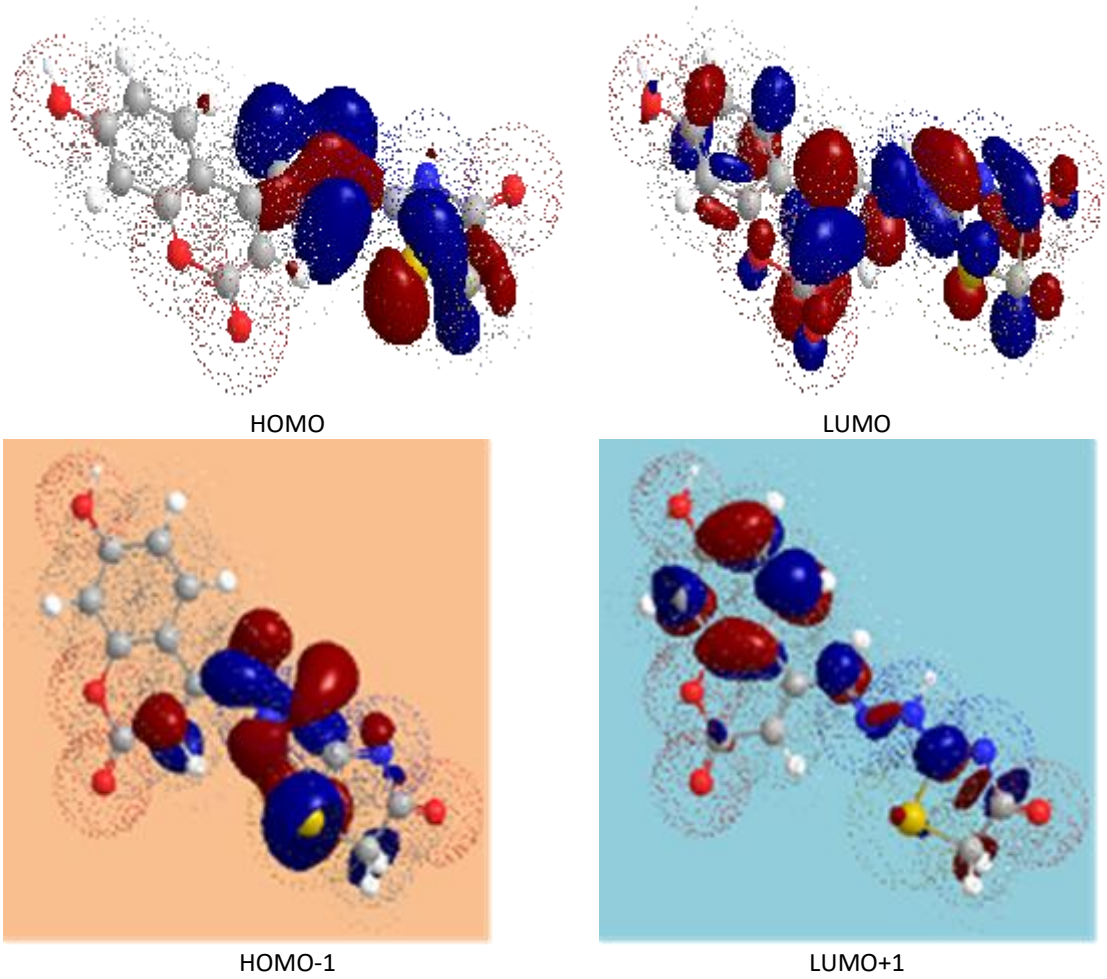



**Figure 6:** Highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of compound **8**

Compound **3** has the highest HOMO–LUMO energy gap, which indicates that, it is the most stable and less reactive than the compounds **8, 1, 4**, and **6**, as shown in table 2.

**Table 2:** HOMO and LUMO energies (eV) of the title compounds**.**

| Comp. | HOMO | LUMO | ΔE | HOMO-1 | LUMO+1 | ΔE |
|---|---|---|---|---|---|---|
| 1 | -10.859 | -6.927 | -3.932 | -12.294 | 0.029 | -12.323 |
| 3 | -10.781 | -3.830 | -6.951 | -12.031 | -3.360 | -8.671 |
| 4 | -10.897 | -7.044 | -3.853 | -11.017 | -1.907 | 9.11- |
| 6 | -4.941 | -2.695 | -2.246 | -5.319 | -0.60 | -4.719 |
| 8 | -8.454 | -4.104 | -4.35 | -9.684 | -0.790 | 8.894- |

**Table 3:** Electron density for synthesized coumarins**.**

| Comp. | Electron density | | | |
|---|---|---|---|---|
| | HOMO | LUMO | HOMO-1 | LUMO+1 |
| **1** | carbonyl group**(C=O)** substituted on coumarin | coumarin and carbonyl group**(C=O)** substituted on coumarin | coumarin ring | phenol ring of coumarin, and also carbonyl group substituted on coumarin |
| **3** | **C=C-C=O** is a bridge bond between hydroxyl phenyl ring and coumarin ring | **C=C-C=O** is a bridge bond between hydroxyl phenyl ring and coumarin ring | **C=C-C=O** is a bridge bond between hydroxyl phenyl ring and coumarin ring, and lactone ring in the coumarin ring | **C=C-C=O** is a bridge bond between hydroxyl phenyl ring and coumarin ring |

| | | | | |
|---|---|---|---|---|
| **4** | **C=C-C=O** is a bridge bond between the amino phenyl ring and coumarin ring. | whole molecule | **C=C-C=O** is a bridge bond between the aminophenyl ring and coumarin ring and lactone ring in the coumarin ring | whole molecule. |
| **6** | on the **C=Nexo-N**-bond, a bridge bond between the 2,4-dinitrophenyl ring and coumarin ring. | on the **$NO_2$** group substituted on the 2,4-dinitrophenyl ring, coumarin ring, and the **C=Nexo-N**-bond, a bridge bond between 2,4-dinitrophenyl ring and coumarin ring | whole molecule | on the **$NO_2$** group substituted on the 2,4-dinitrophenyl ring, coumarin ring, and the C=Nexo-N-bond , a bridge bond between 2,4-dinitrophenyl ring and coumarin ring |
| **8** | **C=Nexo-N** group a bridge between coumarin and thiazole ring. | whole molecule. | **C=Nexo-N** group a bridge between coumarin and thiazole ring and on $C=N_{endo}$ group in five-membered of thiazole ring. | **C=Nexo-N** group a bridge between coumarin and thiazole ring, lactone ring of coumarin and on C=O group in five-membered of thiazole ring**.** |

Figures 2, 3, 4, 5, and 6 showed the twelve main orbitals that have contributed in the vertical electronic transitions for compounds **1, 3, 4, 6** and **8**. These orbitals, namely, HOMO−1, HOMO, LUMO, and LUMO+1, signify the six highest occupied orbitals and six lowest unoccupied orbitals in the compounds **1, 3,4, 6** and **8**. Similar spatial distribution of orbitals between HOMO/HOMO−1and LUMO/LUMO+1 pairs and the population analysis for compounds **1, 3,4, 6** and **8** are listed in table 3.

**Electrostatic potential charges and related quantum chemical properties**

The distribution of the electronic density (electrostatic potential charges), related quantum chemical parameters , dipole moment (table 4, row 1), and the partition coefficients of the compounds (log P, table 4, row 5) were planned for observed coumarins. These values and properties are very helpful and can be used in order to estimate chemical properties and potential interaction of coumarins with biological macromolecules (receptors, enzymes). All these structural, electronic parameters and log P can be also used for a building of quantitative structure-activity relationship (QSAR) model because all of them are closely related to pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics.

Charge density (R), reactivity index and bond properties of synthetic compound **1, 3, 4, 6** and **8** were calculated and depend on dipole moment , can be calculated with the help of dipole moment of bonds. The values of dipole moment for synthetic **1, 3,4, 6** and **8** indicated that synthetic compounds **1, 3, 4, 6**, and **8** are polar molecules and soluble in polar solvents. Ionization potential gives the perception about energy launch of the electron, an electron from the molecules, and higher values mean that the molecules do not lose the electrons easily and in another word the inverse relationship between antioxidant and ionization potential. The electron affinity can be expressed as the total of energy released when an electron absorbed by a neutral molecule. The greater electronic affinity of molecules means to absorb the electrons easily, in another word, the positive relationship between antioxidant and electron affinity. The chemical hardness [28] is coupled with the stability and reactivity of a chemical system. In a molecule, it measures the resistance of chemical species to changes in its electronic configuration. Based on frontier molecular orbitals, chemical hardness corresponds to the gap between the highest occupied molecular orbital(HOMO) and lowest unoccupied molecular orbital (LUMO). The larger the HOMO–LUMO energy gap, the harder and more stable/less active. Table 4, row 6 displays the computed chemical hardness values for compounds **1** to **8**. The results indicate that compound **8** is harder and less reactive than **3**, which is harder and less reactive than **6**, which is harder and less reactive than **1 and 4**.

The electronic chemical potential[29] (table 4, row 8) is defined as the negative of electronegativity of a molecule. Physically, (**μ**) describes the escaping tendency of electrons from an equilibrium system. The values of (**μ**) for compounds **1** to **8** are presented in table 4. The trend in the electronic chemical potential for the compounds is **8**> **6**> **1** & **4**> **3**. The greater the electronic chemical potential, the less stable or more reactive is the compound. Therefore, **8** is the most reactive, and **3** is the least reactive of these compounds. Table 4 clearly describes the chemical potential values. These can also advocate their good antioxidant potential.

## CONCLUSION

In the present work new chalcones, hydrazine thiocarbamide, hydrazone, and thiourea derivatives were prepared by a simple and efficient protocol from the oxidation of 4-methyl group of the parent 7-hydroxy-4-

methyl coumarin, using selenium oxide as an oxidizing agent, their structures were proven by spectral analysis, and they were screened for their antibacterial activities. Some of the tested compounds**, (5)** showed promising antibacterial activity against both Gram-positive and Gram-negative bacteria. Compounds **(4)** and **(7)** displayed good antibacterial activity against *Micrococcus luteus*, while compound **(8)** exhibited good antibacterial activity against *E.coli*.

The synthesized coumarins were studied theoretically, and some chemical parameters were calculated using DFT theory. The comparative study of molecular modeling corroborated pharmacological trials, showing a high correspondence between calculated HOMO and LUMO energies and antioxidant activity. The availability of these coumarins would also make easy further investigations of their pharmacological properties.

**Table 4**: Electronic properties of synthesized title coumarins were obtained by using HF with 3-21G* basis set

| Parameters | Comp. 1 | Comp. 3 | Comp.4 | Comp.6 | Comp.8 |
|---|---|---|---|---|---|
| Dipole moment ( Debye) | 7.0936 | 7.5962 | 35.1321 | 12.1173 | 18.5388 |
| Total energy Kcal/mol | 19.370 | 40.1381 | 6.3399 | 19.7142 | 33.8850 |
| Ionization potential (IP ) eV | 10.859 | 10.781 | 10.859 | 4.941 | 8.454 |
| Electron affinity (EA) eV | 6.927 | 3.830 | 6.927 | 2.695 | 4.104 |
| Log P | 0.42 | 2.29 | 1.87 | 2.83 | 1 |
| Hardness( η) | 1.966 | 3.4755 | 1.966 | 2.246 | 4.35 |
| Softness( S) | -0.509 | -0.2877 | -0.509 | -0.890 | -0.459 |
| Electro negativity (μ) | -8.893 | -14.611 | -8.893 | -7.636 | -6.279 |

HF= Hartree-Fock method

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## REFERENCES

1. Hoult, J.R.; Payá, M. Pharmacological, and biochemical actions of simple coumarins: Natural products with therapeutic potential. Gen. Pharmacol., 27, 1996, 713–722.
2. Al-Amiery, A.A.; Al-Majedy, Y.K.; Kadhum, A.A.H.; Mohamad, A.B. Hydrogen. peroxide scavenging activity of novel coumarins synthesized using different approaches. PLoS ONE10 (7), 2015, e0132175.
3. I. Kostova, I. Manolov, and G.Momekov, "Cytotoxic activity of new neodymium (III) complexes of bis-coumarins." Eur J Med Chem., 39(9), 2004, 765–775.
4. I.Manolov, C.Maichle-Moessmer, and N. Danchev, "Synthesis, structure, toxicological and pharmacological investigations of 4-hydroxycoumarin derivatives,"Eur J Med Chem., 41(7), 2006, 882–890.
5. N. Hamdi, M. C. Puerta, and P. Valerga, "Synthesis, structure, antimicrobial and antioxidant investigations of dicoumarol and related compounds," Eur J Med Chem., 43(11), 2008, 2541–2548.
6. C.-C. Chiang, J.-F. Mouscadet, H.-J. Tsai, C.-T. Liu, and L.-Y. Hsu, "Synthesis and HIV-1 integrase inhibition of novel bisor tetra-coumarin analogues," Chem Pharm Bull., 55(12), 2007, 1740–1743.
7. D. Zavrsnik, S.Muratovi´c, S. Spirtovi´c, D. Softi´c, and M.Medi´c-Sari´c, "The synthesis and antimicrobial activity of some 4-hydroxycoumarin derivatives". Bosn J Basic Med Sci., 8(3), 2008, 277–281.
8. M. J. Matos, F. Perez-Cruz, S. Vazquez-Rodriguez et al., Remarkable antioxidant properties of a series of hydroxy-3-aryl coumarins. Bioorg Med Chem., 21(13), 2013, 3900-3906.
9. Abdalla, A.E.; Roozen, J.P.; Effect of plant extracts on the oxidative stability of sunflower oil and emulsion. Food Chem., 64, 1999, 323–329.
10. Bast, A.; Haenen, G.R. Doelman, C.J.; Oxidants, and antioxidants: State of the art. Am J Med., 30, 1999, 2–13.
11. Hussein D.; Al-Juboory S.; Kubba A., Synthesis, characterization and antibacterial evaluation with computational study of new Schiff bases derived from 7-Hydroxy-4-methyl coumarin. OJC, 33(2), 2017, 768-782.
12. Mashelkar UC, Audi AA. Synthesis of some novel 4-substituted coumarins having potential biological activity (Part III). Indian J Chem., 45B(06), 2006, 1463-1469.
13. Hamid SJ, Kubba A. Synthesis, and characterization of new coumarin derivatives containing various moieties with antibacterial activities. Int J Pharm Pharm Sci., 7(8),2015,70-74.
14. Kini SG, Choudhary S, Mubeen M. Synthesis, docking study and anticancer activity of coumarin substituted derivatives of benzothiazole. J Comput Methods Mol Des., 2(1), 2012, 51-60.
15. Lin W, Long L, Feng J, Wang B, Guo C. Synthesis of meso-Coumarin-conjugated porphyrins and investigation of their luminescence properties. Eur J Org Chem., 26, 2007, 4301-4304.
16. Mielcke TR, Mascarello A, Filippi-Chiela E, Zanin RF, Lenz G, Leal PC, et al. Activity of novel quinoxaline-derived chalcones on in vitro glioma cell proliferation. Eur J Med Chem., 48, 2012, 255-264.

17. Sashidhara KV, Kumara A, Kumara M, Sarkar J, Sinha S. Synthesis and in vitro evaluation of novel Coumarin–chalcone hybrids as potential anticancer agents. Bioorg Med Chem Lett., 20(24), 2010, 7205–7211.

18. Smit FJ, N'Da DD. Synthesis, in vitro antimalarial activity and cytotoxicity of novel 4-aminoquinolinyl-chalcone amides. Bioorg Med Chem Lett., 22, 2014, 1128–1138.

19. Zuo Y, Yu Y, Wang S, Shao W, Zhou B, Lin L, et al. Synthesis and cytotoxicity evaluation of biaryl-based chalcones and their potential in TNFa-induced nuclear factor-kB activation inhibition. Eur J Med Chem., 50, 2012, 393-404.

20. Trkovnik M, ekić MK, uleš MK, Gorenc A.; 3-Formyl-4-hydroxycoumarin derivatives syntheses of semicarbazone, phenylsemicarbazone, hydrazino(oxazolin-4-one-2-yl) hydrazone, urea derivatives, and their sulfur analogues. Z Naturforsch. 30 b(3-4), 1975, 237-238.

21. Nagamallu R, Kariyappa AK.; Synthesis and biological evaluation of novel formyl-pyrazoles bearing coumarin moiety as potent antimicrobial and antioxidant agents. Bioorg Med Chem Lett., 23,2013, 234-241.

22. Mohamed HM, El-Wahab AHFA, Ahmed KA, El-Agrody AM, Bedair AH, Eid FA, et al. Synthesis, reactions and antimicrobial activities of 8-ethoxycoumarin derivatives. Molecules. 17(1), 2012, 971-988.

23. Gomha SM, Khalil KD. A convenient ultrasound-promoted synthesis of some new thiazole derivatives bearing a coumarin nucleus and their cytotoxic activity. Molecules. 17(8),2012, 9335-9347.

24. Souza SMd, Monache FD, Jr AS.; Antibacterial activity of Coumarins. Z Naturforsch. 60(c), 2005, 693-700.

25. A. Beyramabadi, A. Morsali, Intramolecular proton transfer of 2-[(2,4-dimethyl phenyl)iminomethyl]-3,5-dimethoxyphenol Schiff-base ligand: A density functional theory (DFT) study. Int J Phys Sci., 6(7), 2011, 1780-1788.

26. C. A. Mebi, DFT study on structure, electronic properties, and reactivity of cis-isomers of [(NC5H4-S)2Fe(CO)2]. J Chem Sci., 2011, 727-731.

27. Monajjemi, M., Sayadian, M., Zare, K., Ilkhani, A. R., Mollaamin, F. Computational study of hydrogen bonding on calix[8]arene as nanostructure compound. Int J Phys. Sci., 6(16), 2011, 4063-4066.

28. R. G. Parr, R. G. Pearson, Absolute hardness: companion parameter to absolute electro negativity. J Am Chem Soc., 105(26), 1983, 7512-7516.

29. A. Vektariene, G. Vektaris, J. Svoboda, A theoretical approach to the nucleophilic behavior of benzo-fused thieno[3,2-b]furans using DFT and HF based reactivity descriptors. ARKIVOC. (vii), 2009, 311-329.

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