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## SYNTHESIS, PHYSICAL PROPERTIES OF NEW 4- METHYL COUMARIN DERIVATIVES

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**ABSTRACT:** The aim of the present study, synthesis of new compounds of 4-methyl coumarin derivatives, from starting material (7-dihydroxy-4-methyl coumarin). A variety of chalcones derivative have been synthesized, and the proposed structures were confirmed by physical properties like UV –Visible, FT-IR and <sup>1</sup>H NMR, Chem Bio Draw was used to evaluated the geometry optimization and total energies as well as dipole moment for all prepared compounds.

**INTRODUCTION:** Coumarin and its derivatives represent one of the most active curriculum of a compound possessing a broad spectrum of biological activity <sup>1, 2, 3</sup>. Several synthetic strategies for the synthesis of coumarins have already been developed. Classical routes to coumarins include Pechmann, Knoevenagel, Perkin, Reformatsky, and Wittig condensation reactions <sup>4, 5, 6</sup>. To create these typical reactions efficacious, several variations in terms of catalyst and reaction environment have been introduced <sup>7, 8</sup>. Chalcones are extensive components in all parts of the plants and are important as flower pigments, growth regulators, phytoalexins, animal toxins <sup>9, 10</sup>.

In the present work, we promoted by these observations to synthesize a series of new derivatives of coumarin which probable to have possible biological activity.

### EXPERIMENTAL:

**Instrumentation:** Melting points were determined on Gallenkamp(MFB-600) melting point apparatus and are uncorrected. The IR spectra of the compounds were recorded on Shimadzu FT-IR-3800 spectrometer as KBr disk. The UV-Vis spectra were performed on Cintra-5-Gbes scientific equipment. The <sup>1</sup>H-NMR spectra (solvent DMSO) were recorded on Bruker 400 MHz spectrophotometer using TMS as internal.

### Synthesis of Compounds:

**Synthesis of 7-Hydroxy-4-Methyl Coumarin [1]:** A mixture of (17.6gm, 0.1mole) m-Hydroxy phenol and (13 gm, 0.1 moles) of Ethyl acetoacetate, was cooled down below 15°C, then (45ml) of conc. Sulfuric acid was added dropwise throughout (30min), allowed the mixture to cool to room temperature. After that, the reaction mixture was poured slowly into ice water with continuous stirring. The precipitate was filtered and recrystallized from Methanol; creamy colored needles were formed. Physical properties are shown in **Table 1**.

**Synthesis of 7-Chloro -4- Methyl coumarin [2]:** A mixture of (1.76 gm, 0.01 mole) compound [1]

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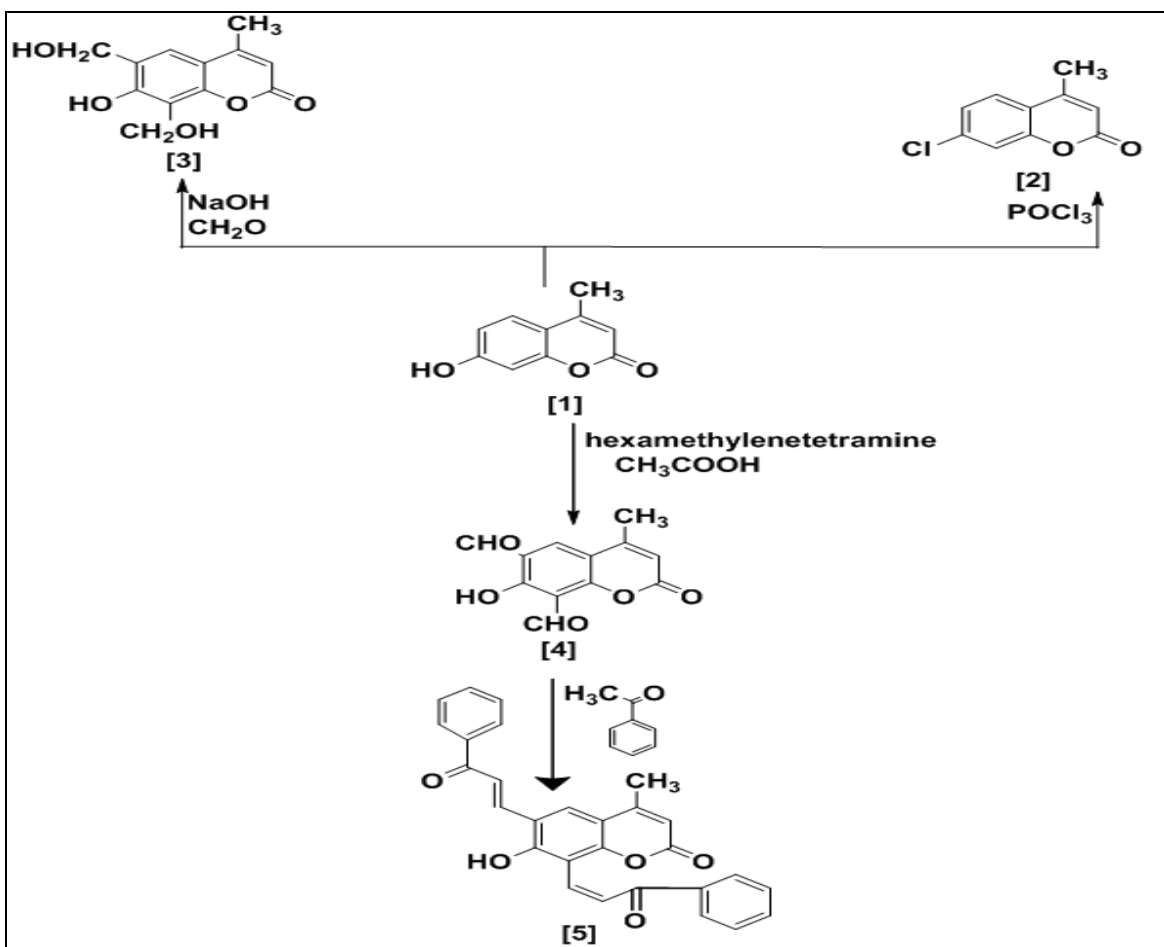
and (25 ml, 0.01 mole) of phosphorus oxychloride, was refluxed for (60 min.), then allowed to cool to room temperature. After that the reaction mixture was poured into crushed ice with vigorous stirring, the precipitate was filtered, washed with distilled water and recrystallized from methanol **Table 1** and **Scheme 1**.

**Synthesis of 7-Hydroxy-6,8-bis-hydroxymethyl-4-methyl Coumarin [3]:** (1.6 gm, 0.04 mole) of Sodium hydroxide was added to a mixture of (3.7 gm, 0.02mole) compound [1] and (4.1 ml, 0.02 mole) of Formaldehyde, the mixture was refluxed with continuous stirring for 3 hours at 60 °C. The mixture was cooled to room temperature and neutralized with 5% Phosphoric acid the precipitate was filtered off, dried, and recrystallized from ethanol **Table 1**.

**Synthesis of 4-methyl coumarin -6, 8 dicarbaldehyde derivative [4]:** To a solution of compound [1] (1.76 gm, 0.01mole) in (50 ml) of acetic acid was added (2.9 g, 0.02mole)

hexamethylene tetraamine were added. The mixture was stirred continuously at room temperature until a light brown viscous solution was obtained, and then heated to (70 -90) °C for two hours. The mixture was cooled to room temperature and (10 ml) concentrated H<sub>2</sub>SO<sub>4</sub> was added dropwise and faint yellow precipitate was formed, then collected by filtration and washed thoroughly with cold Methanol and recrystallized from ethanol 1:1. Physical properties can see in **Table 1**.

**Synthesis of (2E,2'Z)-3,3'-(7-hydroxy-4-methyl-coumarin -6,8-diyl)bis(1-phenylprop-2-en-1-one) [5]:** To a solution of compound [4] (2.32gm, 0.01 mole) in (30 ml) Ethanol, (2.4 gm, 0.02 mole) from Acetophenone was added in the presence of (4-5) drops of piperidine with continuous stirring for 1 hr. The mixture was refluxed for 8 h, then the reaction mixture was cooled. The product was filtered and recrystallized from ethanol **Table 1** and **Scheme 1**.



**SCHEME 1: SYNTHESIS OF COMPOUNDS [4-8] FROM 7-DIHYDROXY-4-METHYL COUMARIN**

**RESULTS AND DISCUSSION:** In this work, the first compound of coumarin derivatives was prepared as starting material for further synthesis **Scheme 1**. Compound (2) has been prepared by treatment of compound (1) with  $\text{POCl}_3$ . The FTIR spectrum of compound (2) table (2), shows C=C aromatic stretching frequency near ( $1641\text{cm}^{-1}$ ). Other significant bands were observed at ( $1718\text{cm}^{-1}$ ) being assigned to the C=O stretching frequency, and significant band was observed about ( $777\text{cm}^{-1}$ ) refer to the C-Cl stretching frequency [13]. The  $^1\text{H-NMR}$  spectrum of compound (2) showed the following data: (DMSO, 300MHZ) 2.7 ppm(s, 3H,  $\text{CH}_3$ ), 6.5-7.4 ppm (m, 4H, Ar-H).

Compound (3) was prepared by a condensation reaction between Compound [1] with formaldehyde in the presence of Sodium Hydroxide as a catalyst. The FTIR Spectrum of compound (3) showed absorption band in the region ( $3372, 3344\text{cm}^{-1}$ ) which was signal to OH group and absorption band at ( $2941, 2888\text{cm}^{-1}$ ) due to C-H aliphatic group [3]. The  $^1\text{H-NMR}$  spectrum of compound [6] shows the following data: 3.1 ppm(s, 3H,  $\text{CH}_3$ ), 6.9 ppm (m, 4H, Ar-H). 3.2 (t, 4H,  $\text{CH}_2$ ). 3.9 (s, 2H, OH) and 11.3 (s, 1H, OH).

Compound (4) has been prepared by treatment of compound (1) with hexamethylenetetramine. The FTIR spectrum of compound (4) shows the appearance ( $1708\text{cm}^{-1}$ ) of the C=O carbonyl band of Compound (4) C-H aldehyde appeared in the region ( $2865, 2783\text{cm}^{-1}$ ) band and O-H exhibited in the region ( $3327\text{cm}^{-1}$ ) [13]. The  $^1\text{H-NMR}$  spectrum of (4) in  $\text{DMSO-d}_6$  as a solvent was showed the following data. 3 (s, 3H,  $\text{CH}_3$ ), 6.3 (m, 1H, Ar-H), 7 (s, 1H, CH of lactam ring), 11.7 (s, 4H, CHO), 8.04(s, 2H, CHO) and 8.3 (s, 1H, OH).

Chalcone (5) synthesis by condensation of the compound (4) with acetophenone in the presence of piperidine. The FT-IR spectrum of compound (5) show the appearance ( $1682\text{cm}^{-1}$ ) of the C=O carbonyl band of Compound (12) C-H appeared in the region ( $2835-2932\text{cm}^{-1}$ ) band and O-H appeared in the region ( $3423\text{cm}^{-1}$ ) [14]. The  $^1\text{H-NMR}$  spectrum of (5) in  $\text{DMSO-d}_6$  as a solvent was showed the following data. 2.5ppm (S, 3H,  $\text{CH}_3$ ), 6.2-7.0 ppm (m, 8H, Ar-H), 8.6 ppm (s, 2H, CH of lactam ring). 3.6ppm (s, 3H,  $\text{O}=\text{C}-\text{CH}_3$ ), 8.9 ppm (d, 4H,  $\text{COCH}=\text{CH}$ ), 8.3ppm (s, 2H, CH ring). 12.3 ppm(s, 1H, OH).

**TABLE 1: PHYSICAL PROPERTIES OF THE SYNTHESIZED COMPOUNDS (1-8)**

Comp.	M.P °C	Yield %	Recryst. solvent
1	184-186	70	Methanol
2	102-104	62	Methanol
3	135-137	67	Ethanol
4	150-153	59	Ethanol
5	164-166	73	Ethanol

**TABLE 2: UV-VIS AND FTIR SPECTRAL DATA FOR NEW COMPOUNDS**

Comp.	UV Ethanol		Characteristic bands of FT-IR ( $\text{cm}^{-1}$ , KBr)			
	$\lambda_{\text{max}}$ nm	C=O	C=C	C-H ar.	C-H al.	Others
1	226 324	1678	1597	3013	2899-2965	$\nu(\text{OH})=3157$
2	-	1718	1614	3086	-	-
3	310 225	1708	1631	3001	2865, 2783	$\nu(\text{OH})=3400$ $\nu(\text{C}=\text{O})=1699$
4	244 340	1682	1487-1576	3070	2835-2932	$\nu\text{OH}=3423$ $\nu(\text{C}=\text{O})=1650$
5	282 205 317	1691	1607	3014	2941-2888	$\nu(\text{OH})=3372,$ 3344

**Computational Studies:** Compounds 2,3 and 5 with optimized geometries and 3D geometrical structures are given in Figure.

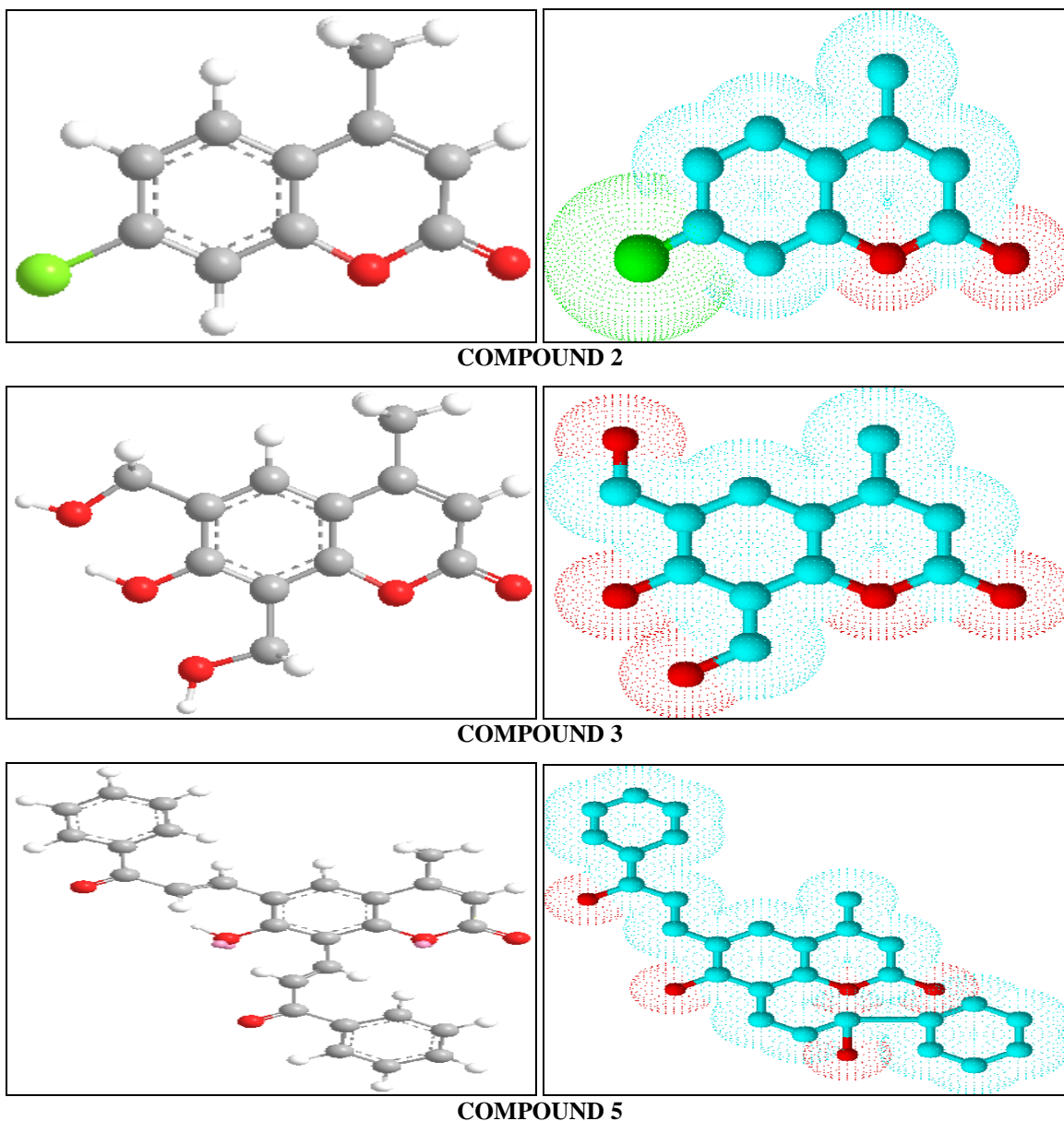
The data showed that the highest atomic charge in compound 2 is at [O(11) -0.723] followed by the next charge value at [C(8) 0.532]and C(2) 0.266].

These data clearly showed that these atoms are most reactive toward the addition substitution reactions. The determined bond angle and twist angle, stretch (0.6230), bend (2.0795), stretch-bend (-0.0445), torsion (-8.5569) and the 3D geometrical structure indicated that this molecule is a non-planar molecule with the stereochemistry at [C(9)-C(7): (Z)].

The data showed that the highest atomic charge in compound 3 is at [C(8) 0.529 ] followed by the next charge value at [O(11)-0.726] and C(6) 0.217]. These data clearly showed that these atoms are most reactive toward the addition substitution reactions. The determined bond angle and twist angle, stretch (1.4221), bend (7.4661), stretch-bend

(-0.0556), torsion (-13.0819) and the 3D geometrical structure indicated that this molecule is a non-planar molecule with the stereochemistry at [C(9)-C(7): (Z)].

The data showed that the highest atomic charge in compound 5 is at [C(26) 0.419] followed by the next charge value at [O(27)-0.558] and O(18) -0.552]. These data clearly showed that these atoms are most reactive toward the addition substitution reactions. The determined bond angle and twist angle, stretch (1.3260), bend (6.9459), stretch-bend (0.0180), torsion (-8.8272) and the 3D geometrical structure indicated that this molecule is a non-planar molecule with the stereochemistry at [C(9)-C(7):(Z) ,C(14)-C(15): (E), C(24)-C(25): (E)].



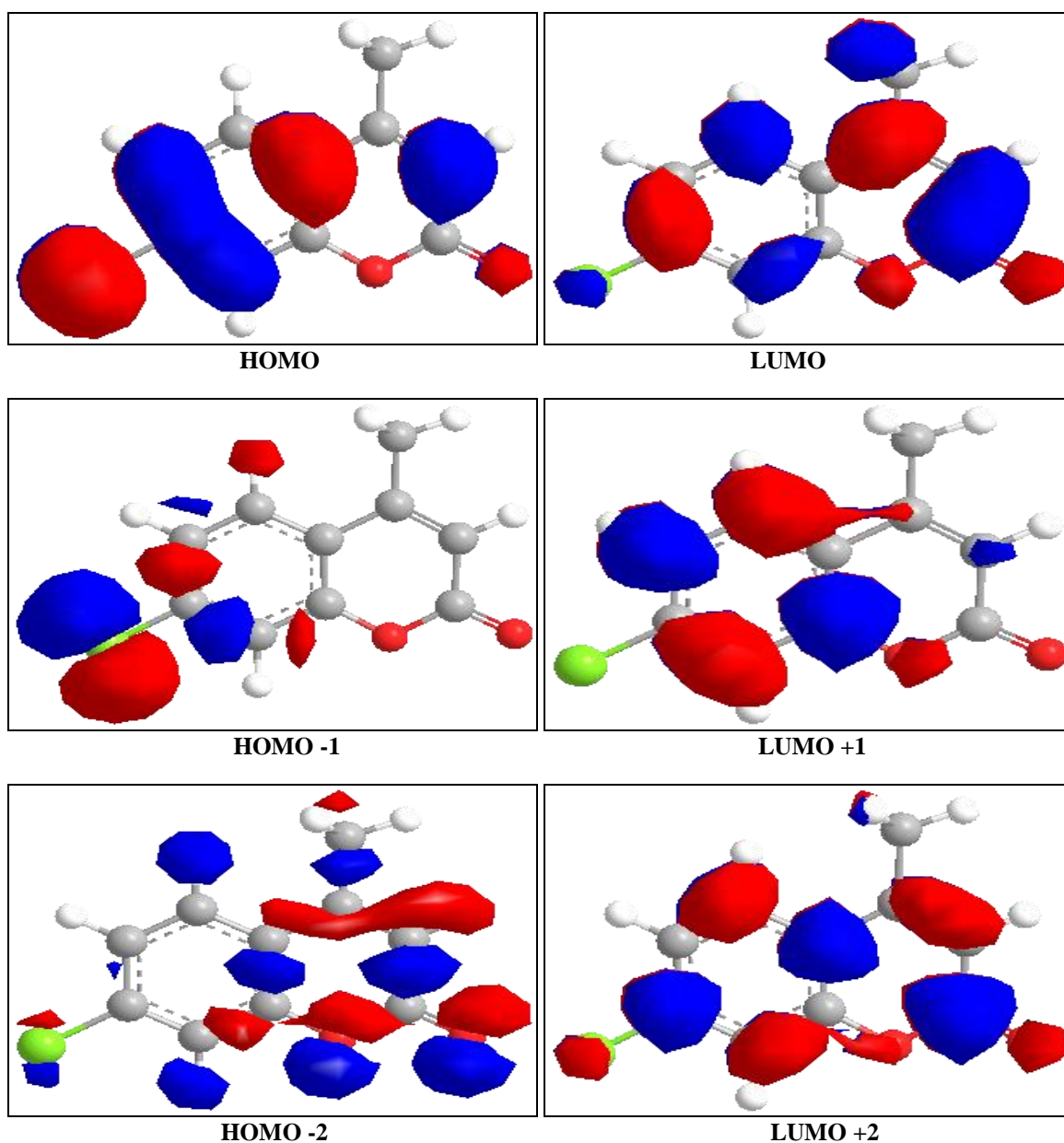
**FIG. 1: OPTIMIZED 3D GEOMETRICAL STRUCTURES FOR COMPOUNDS 2, 3 AND 5**

DFT calculations have been performed for compounds 2, 3 and 5. The optimized molecular structure of the most stable form is shown in **Fig. 1**. The calculated energies are presented in **Table 3**. Molecular orbital calculations could provide a detailed description of the orbitals including the spatial characteristics, nodal patterns, and individual atom contributions. The contour plots of

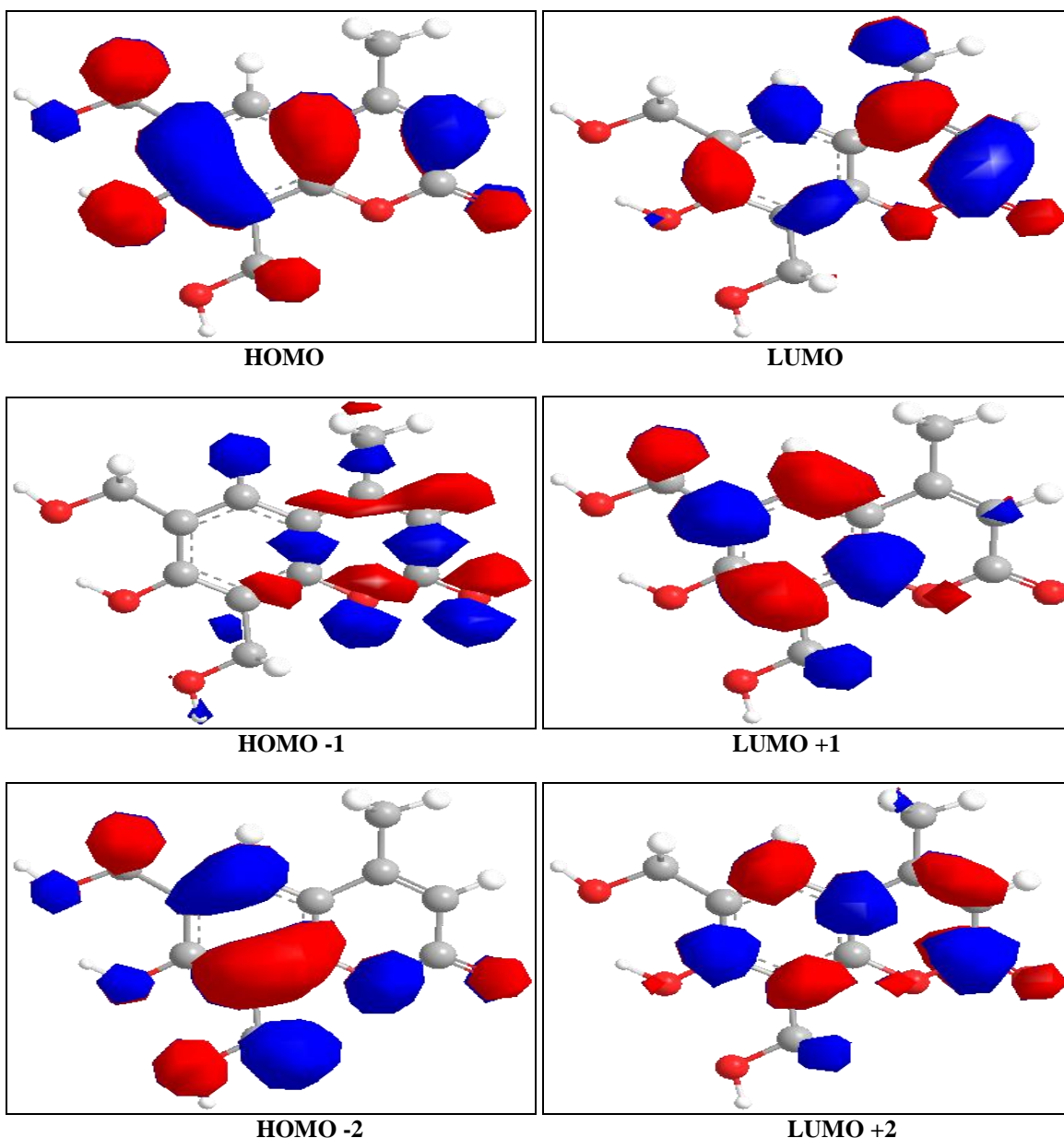
the frontier orbitals for the ground state of compounds 2, 3 and 5 are shown in **Fig. 2, 3** and **4** together with the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO). It is interesting to observe that both orbitals are substantially distributed over the conjugation plane.

**TABLE 3: TOTAL ENERGY AND DIPOLE MOMENTS (DEBYE) FOR COMPOUNDS 2, 3 AND 5**

Compound	Total Energy kcal/mol	Dipole Moments
2	5.9625	5.5958
3	4.8532	5.4259
5	17.3705	5.8576



**FIG. 2: HIGHEST OCCUPIED MOLECULAR ORBITAL (HOMO) AND THE LOWEST UNOCCUPIED MOLECULAR ORBITAL (LUMO) OF COMPOUND 2**

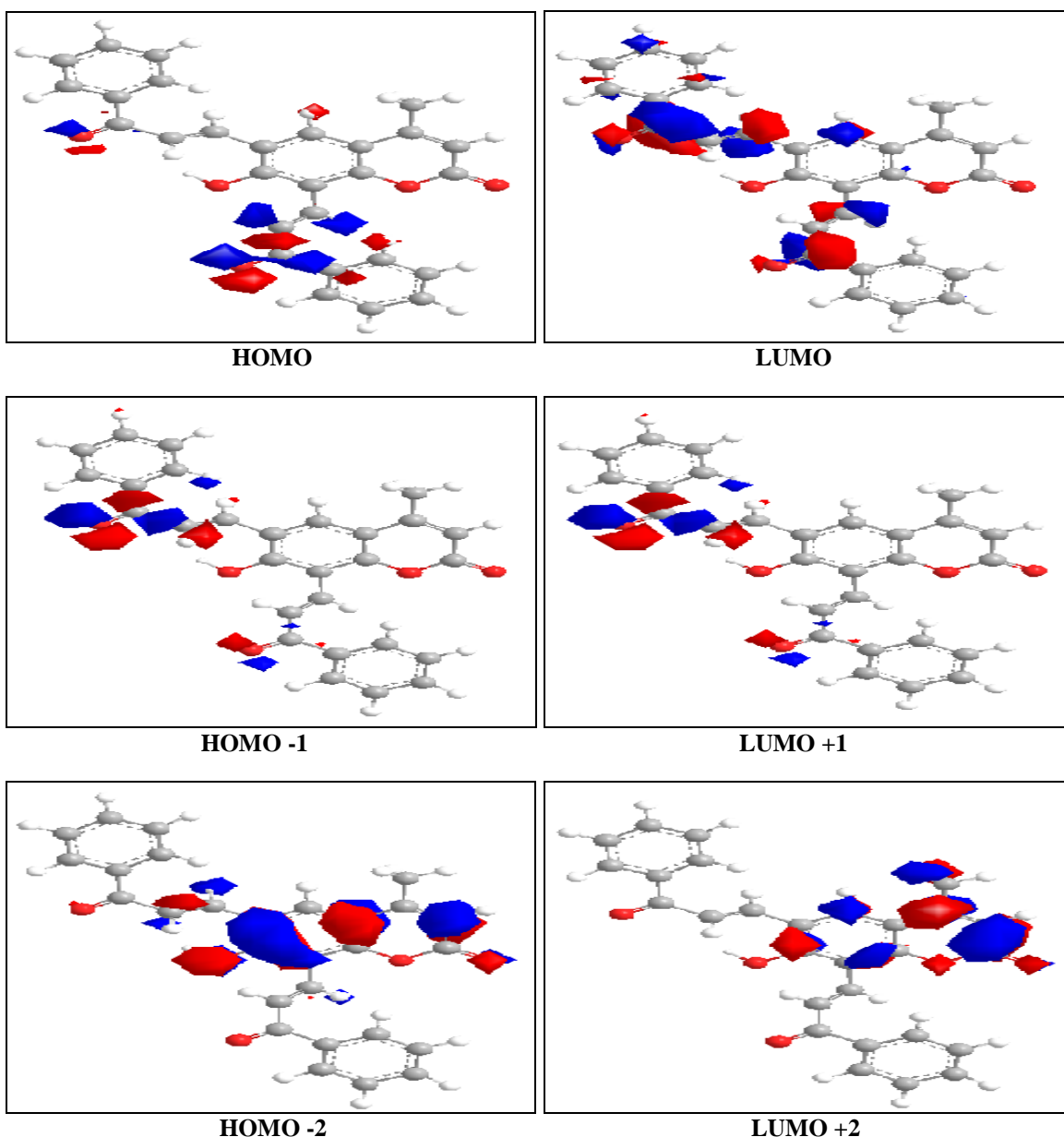


**FIG. 3: HIGHEST OCCUPIED MOLECULAR ORBITAL (HOMO) AND THE LOWEST UNOCCUPIED MOLECULAR ORBITAL (LUMO) OF COMPOUND 3**

In addition, it can also be seen from **Fig. 2, 3** and **4** that the HOMO orbitals are located on the substituted molecule while LUMO orbitals resemble those obtained for the unsubstituted molecule and therefore the substitution has contributed an influence on the electron donation ability while imposing only a small impact on electron acceptance ability. The orbital energy levels of HOMO and LUMO of compounds 2, 3 and 5 are listed in **Table 2**. An electronic system with a larger HOMO-LUMO gap should be less reactive compared to the one having a smaller gap. In the present study, the HOMO-LUMO gap values of compound 2 -7.793, -11.775 and -13.257eV

while for compound 3 and 5 are situated at: -7.986, -12.377 and -13.604 eV: -5.835, -6.121 and -8.125eV respectively.

The lower value in the HOMO and LUMO energy gap would explain the eventual charge transfer interaction taking place within the molecules. The low values of HOMO for compounds 2, 3 and 5 indicate that these molecules have low ionization energies inferring that they can lose the electrons easily thus indicating that compounds 2, 3 and 5 are potentially good corrosion inhibitors [15]. The dipole moments of compounds 2, 3 and 5 were also calculated and listed in **Table 3**.



**FIG. 4: HIGHEST OCCUPIED MOLECULAR ORBITAL (HOMO) AND THE LOWEST UNOCCUPIED MOLECULAR ORBITAL (LUMO) OF COMPOUND 5**

**TABLE 4: HOMO AND LUMO ENERGIES (eV) OF COMPOUNDS 2, 3 AND 5**

Comp.	HOMO	LUMO	$\Delta E$	HOMO-1	LUMO+1	$\Delta E$	HOMO-2	LUMO+2	$\Delta E$
2	-11.674	-8.81	-7.793	-11.769	0.006	-11.775	-12.082	1.175	-13.257
3	-11.825	-3.839	-7.986	-12.045	0.332	-12.377	-12.277	1.327	-13.604
5	-11.571	-5.736	-5.835	-11.626	-5.505	-6.121	-11.919	-3.794	-8.125

The UV-VIS absorption spectrum of compound 2 was recorded in the ethanol solution. The absorption peaks are observed at 310 and 225 nm and 317,282 and 205 nm for compound 5. It can be deduced that these peaks imply to the  $n \rightarrow \pi^*$  and  $\pi \rightarrow \pi^*$  transitions. The 3D plots of the HOMO-2, HOMO-1, HOMO, LUMO, LUMO+1, LUMO+2 and the corresponding energy levels for compounds 2, 3 and 5 are shown in **Fig. 2, 3 and 4** respectively.

The theoretical electronic transfers (ET) for compound 2 was at -7.793, -11.775, compound 3 was at -7.986, -12.377 and for compound 5 were at -5.835, -6.121 nm corresponding to the UV-VIS spectral absorption peaks and the electronic transfers of HOMO plus LUMO and HOMO-1 plus LUMO+1, respectively. The increased theoretical absorption wavelengths of the compounds have slight blue-shifts when compared to the

corresponding experimental absorption wavelengths. **Fig. 2, 3 and 4** shows the six main orbitals that have contributed in the vertical electronic transitions for compounds 2, 3 and 5. These orbitals, namely, HOMO-2, HOMO-1, HOMO, LUMO, LUMO+1, and LUMO+2, represent the three highest occupied orbitals and three lowest unoccupied orbitals in compounds 2, 3 and 5.

Similar spatial distribution of orbitals between HOMO/HOMO-1/HOMO-2 and LUMO/LUMO + 1/LUMO+2 pairs and the population analysis for compound 2 indicates that the electronic transitions and the electron clouds of the HOMO are delocalized on the C=C bond and the carbonyl of the  $\alpha$ - $\beta$ -unsaturated compound (chalcones). However, HOMO-1 is delocalized on C=C- bond, the carbonyl and the phenyl group of the chalcones, while the HOMO-2 is delocalized on the whole molecule. These orbitals are of the  $\pi$ -type bonding orbital.

LUMO is found mainly delocalized on the coumarin and the methyl group that substituted on coumarin and also the carbonyl group between the benzene ring and the five-member ring, while LUMO+1 is delocalized on the pyron ring of the coumarin and also the carbonyl group between the benzene ring and chalcones. For the LUMO+2 it is mainly delocalized on chalcone. For compound 3, the population analysis indicates that the electronic transitions and the electron clouds of the HOMO are delocalized on the C=O-bond and the carbonyl groups of the pyrene, while the HOMO-1 delocalized on the C=O bond, carbonyl bridge and the carbonyl groups of the pyrene but for the HOMO-2 is delocalized on the coumarin ring and carbonyl bridge.

LUMO is found mainly delocalized on pyrene and benzene ring while LUMO+1 coumarin ring and LUMO+2 are delocalized on the whole molecule. For compound 5, the population analysis indicates that the electronic transitions and the electron clouds of the HOMO and HOMO-1 are delocalized on the pyridazine-3,6-dionering, while the HOMO-2 delocalized on the whole molecule. LUMO, LUMO+1 and LUMO+2 are found delocalized on whole molecule.

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**CONFLICT OF INTEREST:** Nil

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