Synthesis, Characterization and Antibacterial Evaluation With Computational Study of New Schiff Bases Derived from 7-Hydroxy-4-Methyl Coumarin

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ABSTRACT

New derivatives of 7-hydroxy-4-methylcoumarin were synthesized via oxidation of methyl group at C4 of parent coumarin nucleus using SeO_2 as an oxidizing agent. Then the condensation with different aromatic amines and amino acids under conventional method. The structures of the title Schiff bases were elucidated by spectral analysis: FT-IR,^{13}CNMR, and MS.All the compounds were tested *in vitro* for their preliminary antibacterial activity against two Gram-positive and two Gram –negative bacteria, using serial dilution method, and determining their minimum inhibitory concentrations for the title compounds. Most of the derivatives showed moderate to high antibacterial activity.Compound **7** showed a good antibacterial activity against Gram- positive *Staphylococcus aureus* and *Micrococcus luteus* also very potent antibacterial activity against Gram-negative *E.coli*. Density functional theory (DFT)calculations for the synthesized coumarins were performed using a molecular structure with optimized geometry. Molecular orbital calculations supported a full description of the orbitals, including spatial characteristics, nodal patterns, and the contributions of individual atoms.Highest occupied molecular orbital/lowest unoccupied molecular orbital energies and structures are demonstrated.

Keywords: Antibacterial activity, broth dilution method, density functional theory(DFT), 7-hydroxy-4-methylcoumarin, Schiff base,

INTRODUCTION

Coumarins are important class of compounds, they demonstrate useful and different activities, often depending on the substituents they include, benzopyran moiety [1,2]. Coumarins are natural compounds produced by various plant sources. Their structures contain fused benzene and pyrone

rings. Recently, they have fascinated and attractive research work, due to their remarkable biological and pharmacological activities, which include antibacterial, antifungal, anticoagulant, antioxidant, anticancer, and anti-inflammatory properties [3,4]. Coumarins showed strong antibacterial activity against both Gram-positive and Gram-negative bacteria, especially against Gram-negative bacteria, by damaging cell membrane.

The advantages of coumarins as potential antibacterial compounds, due to their broad range of antibacterial activity; also they are secreted by plants as phytoalexins and have defensive mechanism against attacks from pathogens, and they are environmentally friendly and not vulnerable to develop bacteria resistance [4-6].

Azomethine group (-C=N-) containing compounds usually known as Schiff bases have been synthesized by the treatment of primary amines with active carbonyls. Schiff bases form a significant class of compounds in medicinal chemistry, with diverse biological applications that include antioxidant, antibacterial[7-10]. Coumarins containing a Schiff base moiety are predictable to have improved antitumor and other distinctive activities [11].

Some literatures show that the reaction of 4-methyl benzo coumarin with selenium dioxide reveals the corresponding 4-formyl derivative, which eventually has been reacted with some primary aromatic amines to get Schiff bases with significant antibacterial activities [12]

Due to the importance and established pharmacological activity of these compounds, the aim of the present work is to synthesize new Schiff bases at C4 of the parent coumarin nucleus, as promising antibacterial agents, against both
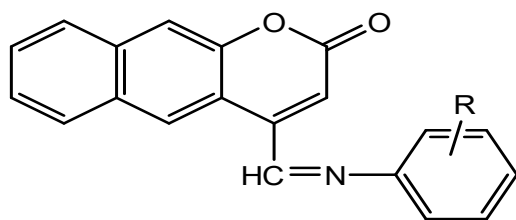
Gram positive and Gram negative bacteria. Also, a computational study was planned to calculate some thermodynamic parameters. Thus, the synthesis of new series of Schiff bases derived from 7- hydroxyl-4-methyl coumarin has been achieved.

MATERIALS AND METHODS

Chemicals used during the synthesis, supplied by Sigma-Aldrich. Solvents were dried and distilled before use. Completion of reactions and the purity of compounds were ascertained by thin-layer chromatography (TLC) , using Silica gel GF_{254} (type 60) pre-coated Aluminium sheets, Merck (Germany). Melting points were determined using Stuart/SMP3 melting point apparatus version 5.0 in open capillary tubes, and were uncorrected. IR(KBr) spectra υcm^{-1} were recorded using Thermo Scientific™ Nicolet™ iS™10 FT-IR Spectrometer in Pioneer company for pharmaceutical industry-Sulaimani-Kurdistan-Iraq. ^{13}C-NMR spectra were recorded on Bruker FT–NMR spectrophotometer 400, in the College of Pharmacy-Hamedan University of Medical Sciences- Hamedan-Iran, using deuterated dimethyl sulfoxide (DMSO-d_6) and deuterated chloroform (CDCl$_3$) as internal standards. Chemical shifts were expressed in δ ppm. MS was run at College of Pharmacy-Hamedan University of Medical Sciences- Hamedan-Iran, using Agilent Technology (HP), GC/MS model 5973 network mass selective detector. The values were expressed as m/z. The synthetic method is depicted in Scheme 1.

Synthesis of 7-hydroxy-4-formyl coumarin (1)[13, 14]

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

Yellow powder, yield 35%; m.p. 222-224 ºC; IR(KBr) υ, cm^{-1}:3233 (OH) str.,3050 Ar(CH) str., 2850 (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,

Benzocoumarin schiff bases

R= 3-NO$_2$, 4-OCH$_3$, 4-F, 4-Cl

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]$^{+.}$(27.6%), 162[M-CO](10%), 161[M-COH](14.9%),148[M-ketene](100%) ,104(17%).

General method for the synthesis of aromatic amine Schiff bases (2-6)[15-17]

Appropriate aromatic amine (0.005) mol of [4-Nitro aniline 0.69 g, 4-amino acetophenone 0.67 g, 4-amino antipyrine 1.01g,4-amino ethyl benzoate 0.82 g, and 2-amino-5-mercapto-1,3,4-thiadiazole 0.66 g] each was added with continuous stirring to a solution of compound **1**, (0.005 mol, 0.95g) and two drops of glacial acetic acid in absolute ethanol (30 ml). The mixture was refluxed for 7 h, and the reaction was monitored by TLC, the yellow colored precipitate was formed and collected by filtration, dried and recrystallized from ethanol.

Synthesis of 7-hydroxy-4-(4-nitrophenyl)imino) methyl)-2*H*-chromene-2-one(2)

Yellow powder,yield 65%;m.p. 201-204ºC; IR(KBr) υ,cm^{-1}:3481(OH)str., 1710(C=O)str. of lactone, 1682 (C=C) str., 1624(C=N) str., 1592 and 1500 (Ar-C=C) str., 1389 (NO$_2$) str., 1068 (C-O) str. of lactone; ^{13}CNMR(100MHz),CDCl$_3$,δ ppm):162.61(C=O lactone), 160.46 (C=N), 155.02, 154.02, 154.00, 152.78 ,138.92, 128.52, 126.41, 125.99, 113.26, 111.07, and 102.96(C-aromatic and alkene); mass spectroscopy Calcd. for$C_{16}H_{10}N_2O_5$, (m/z,%): 310 [M]$^{+.}$(31.2%), 293[M-OH](23.7%), 264[M-NO$_2$](6.2%),188[M-C$_6$H$_4$-$_p$NO$_2$](3.7%), 161(7.5%).

Synthesis of 4-(4-acetylphenyl)imino)methyl)-7-hydroxy-2*H*-chromene-2-one (3)

Yellow powder, yield 53%;m.p. 187-189 ºC; IR) (KBr)υ,cm^{-1}:3359(OH) str., 3080 Ar(CH) str.,2920 (CH$_3$)str., 1704(C=O) str., 1670(C=C) str., 1610(C=N) str., 1589Ar(C=C) str., 1388(CH$_3$) bend., and 1068(C-O) str. of lactone; ^{13}CNMR(100 MHz),CDCl$_3$, ,δ ppm):197.51(C=O ketone),162.52(C=O lactone), 160.90(C=N),155.09,153.86,151.66,131.5 131.05,129.93,125.90,113.52,112.53,103.31(C-aromatic and alkene) and 26.07 (CH$_3$-C=O);mass spectroscopy Calcd. for C$_{18}$H$_{13}$NO$_4$,(m/z,%):307 [M]$^{+.}$(8.9%), 292(3.8%), 264(12.8%),188(5.1%),161(3.8%).

Synthesis of 4-(7-hydroxy-2-oxo-2*H*-chromene-4-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1*H*-pyrazole-3(2*H*)-one(4)

Intense yellow powder ,yield 71%;m.p.192-195 ºC; IR(KBr)υ,cm^{-1}:3300(OH) str.,3065 Ar(CH) str.,1718(C=O) str.of lactone 1652(C=C) str.,1137(C-N) str. of diazole, 1607 (C=N) str., 1507 Ar(C=C) str., 1403(OH) bend.,1368(CH$_3$) bend.,1070(C-O) str. of lactone; ^{13}CNMR(100 MHz),CDCl$_3$, ,δ ppm):166.28(C=O lactone), 161.80(C=O cyclic amide),160.90(C=N), 158.10,151. 10,129.50,125.73,113.28,111.12, 103.25(C-aromatic and alkene),34.70(CH$_3$-N),18.73(CH$_3$); mass spectroscopy Calcd. forC$_{21}$H$_{17}$N$_3$O$_4$, (m/z,%):375 [M]$^{+.}$(7%), 374(3.3%),188(6.6%),161(13.3%).

Synthesis of ethyl 4-(7-hydroxy-2-oxo-2*H*-chromene-4-yl)methylene)amino)benzoate (5)

Pale yellow powder, yield 44%; m.p. 211-213ºC; IR(KBr)υ,cm^{-1}:3350(OH) str., 3080 Ar(CH) str.,2978(CH$_3$) str., 1760(C=O) str. of lactone, 1745(C=O) str., of ester,1682(C=C) str., 1640(C=N) str., 1597 and 1517 Ar(C=C) str.,1474(CH$_2$) bend.,1389(CH$_3$) bend., 1069(C-O) str. of lactone, 1044(C-O) str. of ester; ; ^{13}CNMR(100 MHz),CDCl$_3$, δ ppm): 166.97 (C=O ester), 162.58(C=O lactone), 160.74(C=N),158.63,155.03,150.76, 131.60, 130.77, 125.90, 112.48, 111.29, 103.26(C-aromatic and alkene), 60.56(CH$_2$-O), 14.42(CH$_3$); mass spectroscopy Calcd. forC$_{19}$H$_{15}$NO$_5$,(m/z,%):337[M]$^{+.}$(32.4%), 320[M-OH(9.5%)],308[M-CH$_3$-CH$_2$](16.2%), 292[M-CH$_3$CH$_2$O](20.2%), 264[M-CH$_3$CH$_2$CO$_2$](33.7%).

Synthesis of 7-hydroxy-4-(5-mercapto-1,3,4-thiadiazole-2-yl)imino)methyl)-2*H*-chromene-2-one (6)

Pale yellow powder, yield 61%;m.p.251-254 ºC; IR(KBr)υ,cm^{-1} 3380(OH)str.,3074Ar(CH) str.,2550(SH) *weak* str.,1760 (C=O lactone) str., 1676(C=C) str.,1639(C=N) str.,1598 and 1505 Ar(C=C) str.,1066(C-O) str. of lactone; ^{13}CNMR(100 MHz),CDCl$_3$, δ ppm):181.11(C-SH),162.17(C=O lactone), 158.88(C=N), 155.09, 153.46, 113.24, 111.48 and 103.40 (C-aromatic and alkene);mass spectroscopy Calcd. for C$_{12}$H$_7$N$_3$O$_3$S$_3$, (m/z,%):305[M]$^{+.}$ (4%), 304(4%), 272[M-SH] (6.5%),188(9.2%),161(30.2%).

Synthesis of amino acid Schiff bases (7-8)[17-20]

A solution of compound 1 (0.01 mol, 1.9 g) in absolute ethanol(20 ml) was added dropwise to a homogenous solution of each amino acid (0.01mol); glycine (0.75 g and alanine 0.89 g) and sodium hydroxide (0.01mole, 0.4 g) in absolute ethanol (20 ml) with continuous stirring. The solution's color changed immediately and after 2-3 minutes. (1 ml) acetic acid was added. Stirring continued for 24 h and 12 h for glycine and alanine respectively, the obtained precipitate was collected by filtration, washed with cold ethanol, dried and recrystallized from methanol.

Synthesis of 2-(7-hydroxy-2-oxo-2*H*-chromene-4-yl)methylene)amino)acetic acid (7)

Pale yellow powder, yield 61%, m.p. 198-200 ºC; IR(KBr)υ,cm^{-1}:3465 phenolic (OH) str., 3200-2500 (OH) *br*.str., of carboxylic acid,3031Ar(CH) str., 2987,2871 (CH$_2$) str., 1704 (C=O) str., reduced due to conjugation,1640 (C=C) str.,1600 (C=N) str., 1500 Ar(C=C) str.,1470 (CH$_2$) bend.

1410(OH) bend., 1071(C-O) str.; ^{13}CNMR (100 MHz),DMSO-*d$_6$*,δ ppm): 174.16 (C=O carboxylic acid), 163.25(C=O lactone), 161.01(C=N),1 56.91, 154.16, 126.85,113.89, 111.69 and 106.05(C-aromatic and alkene), 56.52 (CH$_2$-); mass spectroscopy Calcd. for

C$_{12}$H$_9$NO$_5$,(m/z,%): 247[M]$^+$·(13.7%), 246(7.5%), 202(12.5%), 188(15%),161(82.5%).

Synthesis of 2-(7-hydroxy-2-oxo-2*H*-chromene-4-yl)methylene)amino)propanoic acid(8)

Milky powder, yield 173-176 ºC; **I**R(KBr) υ,cm^{-1}:3364 phenolic(OH),3253-2503(OH) *br*.str of carboxylic acid, 3078Ar(CH) str.,2948 (CH$_3$) str.,1720 (C=O) reduced due to conjugation,1645(C=C) str.,1617 (C=N) str.,1585 and 1519 Ar(C=C) str.,1411(OH) bend., 1361(CH$_3$) bend.,1065(C-O) str.; ^{13}CNMR(100 MHz),DMSO-*d$_6$*,δ ppm):174.20(C=O carboxylic acid),165.1(C=O) lactone,161.18 (C=N),155.83,154.17,126.64,114.56,110.65,102.82 (C-aromatic and alkene),56.8(CH-),18.60 (CH$_3$); mass spectroscopy Calcd. for C$_{13}$H$_{11}$NO$_5$,(m/z,%): 261[M]$^+$(6%), 260(4.8%), 246[M-CH$_3$](5.4%), 229(42.1%), 216[M-COOH](12%),188(10.8%).

Antibacterial Activity

The new title compounds 2-8 were screened for their preliminary antibacterial activity by 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 13 tubes containing 1 ml of Muller-Hinton media autoclaved and cooled then inoculated with 50
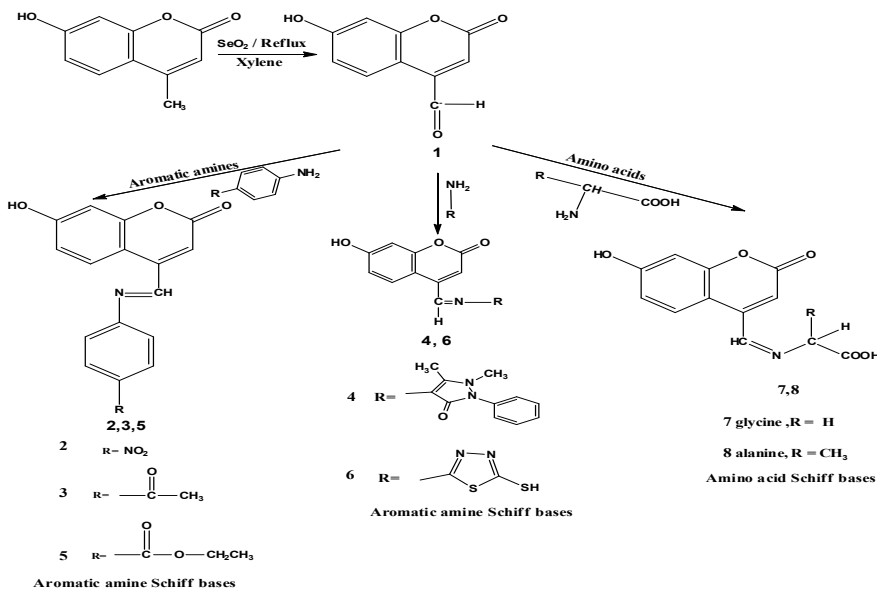
Scheme 1: Synthesis of title coumarin derivatives (2-8)

µl bacterial inoculum of bacterial suspension at McFarland turbidity of 0.5. Then defined 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 inoculum without adding any coumarin derivative, all are incubated aerobically at 37 ⁰C for 24 hour, then MIC is determined by visual observation as the lowest concentration that inhibits bacterial growth appears clear solution.

RESULTS AND DISCUSSION

Chemistry

The new title coumarin derivatives, (Scheme 1) have been synthesized from 7-hydroxy-4-methyl coumarin by oxidation of the methyl group (CH_3) at the carbon 4, using SeO_2 as an oxidizing agent and hot xylene, to afford 7-hydroxy-4-formy coumarin 1, which is characterized by an IR band of aldehyde (C=O) stretching displayed at 1698cm^{-1}, aldehydic hydrogen stretching (H-C=O) at 2850

Table1: Minimum inhibitory concentration(MIC) of coumarin derivatives 2-8 by using tube dilution method

Compound 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	79	40	123	192
3	63	50	98	154
4	40	63	192	240
5	98	123	154	192
6	40	40	98	79
7	40	40	31	50
8	300	240	192	123

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

Table 2:Calculated chemical parameters of synthesized coumarin derivatives, using DFT with 3-21G* basis.

Comp.	highest atomic charge	next charge value	bond angle (⁰)	twist angle (⁰)	stretch-bend	torsion (⁰)	stereochemistry
1	O(12) -0.440	O(14) -0.239	1.1036	4.7345	0.0187	-5.9089	C(10)-C(9): (E)
3	O(22)-0.719139	O(12)-0.616306 N(14)- 0.31403	1.8247	10.9945	0.1582	-0.7736	C(8)-C(9): (E) & C(13)-N(14): (Z)
4	O(22) -0.719	O(12) - 0.616 ; N(14) - 0.314 O(7) - 0.208	1.8247	10.9945	0.1582	-0.7736	C(5)-C(4): (E); C(12)-N(14): (Z) and C(16)-C(22): (E)
6	O(3)-0.889268	N(18)-0.457364; N(17) -0.330912	2.1491	24.6082	0.0802	-1.6192	C (5)-C (4): (E) and C (12)-N (14): (Z)
8	O (18)-0.669779	O(3) -0.638914; N(14)-0.237179; O(13)-0.195336	1.4799	6.6175	0.1416	-13.2039	C (15): (S); C(5)-C(4): (E) and C(12)-N(14): (E)

cm[-1] , in addition, the ^{13}CNMR-exhibited characteristic peak due to aldehydic (C=O) at 194.54ppm.

The aromatic amine Schiff bases 2-6 produced in a satisfactory yield, and by the condensation of compound 1 with different aromatic amines using absolute ethanol as a solvent. The(C=N) band showed in the IR spectra at the range 1640-1607 cm^{-1} and in the ^{13}CNMR-displayed characteristic peak at 160.90-159.88 ppm.

The amino acid Schiff bases 7-8 were prepared by the reaction of the compound 1 with each of glycine and alanine in a basic medium (NaOH), using absolute ethanol as a solvent. The

(C=N) stretching of the amino acid Schiff base, has been characterized in the IR at 1617 and 1600 cm^{-1} and in ^{13}CNMR-displayed peaks at161.18 and 161.01ppm for alanine and glycine, respectively.

It must be noted, for the mass spectral data of each title compound 2-8, showed a characteristic peak (m/z) assigned the molecular ion peak[M][+·], also, prominent peaks assigned for the fragment of each derivative,(experimental part).

Antibactrial Activity

From the results illustrated in table 2, showed that all title coumarin derivatives have

Compound 1

Compound 3

Compound 4

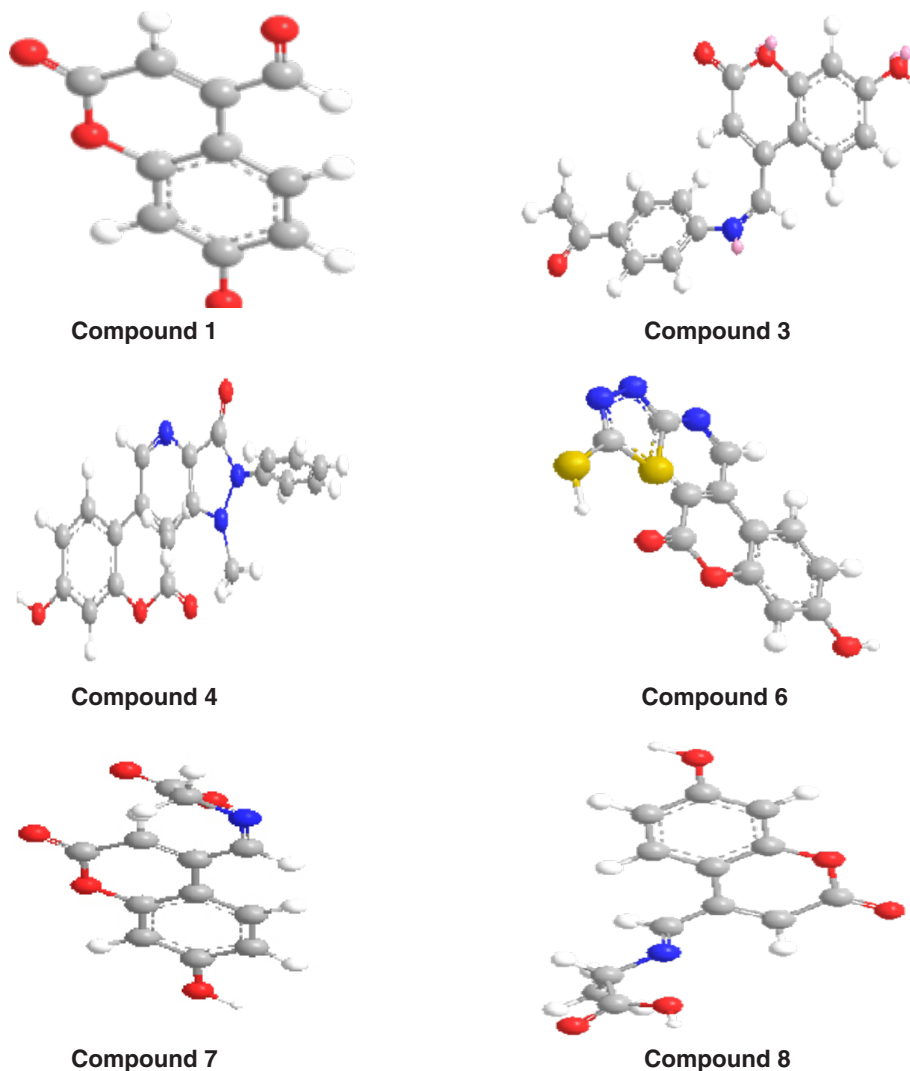**Compound 6**

Compound 7

Compound 8

Fig. 1: Optimized 3D geometrical structures for compounds: 1,3, 4, 6,7 and 8.

antibacterial activity *in vitro* against both Gram positive and Gram negative bacteria with MICs range between 31-300 µg/ml in which they vary according to the derivatives and bacteria.

The lowest MIC is 31µg/ml for compound 7, (most potent), against *Escherichia coli*, and also MIC is 40 µg/ml observed for the compounds 6 and 7 against Gram-positive *Staphylococcus aureus* and *Micrococcus luteus*, respectively.While the highest MIC is 300µg/ml for compound 8 against *Staphylococcus aureus*.
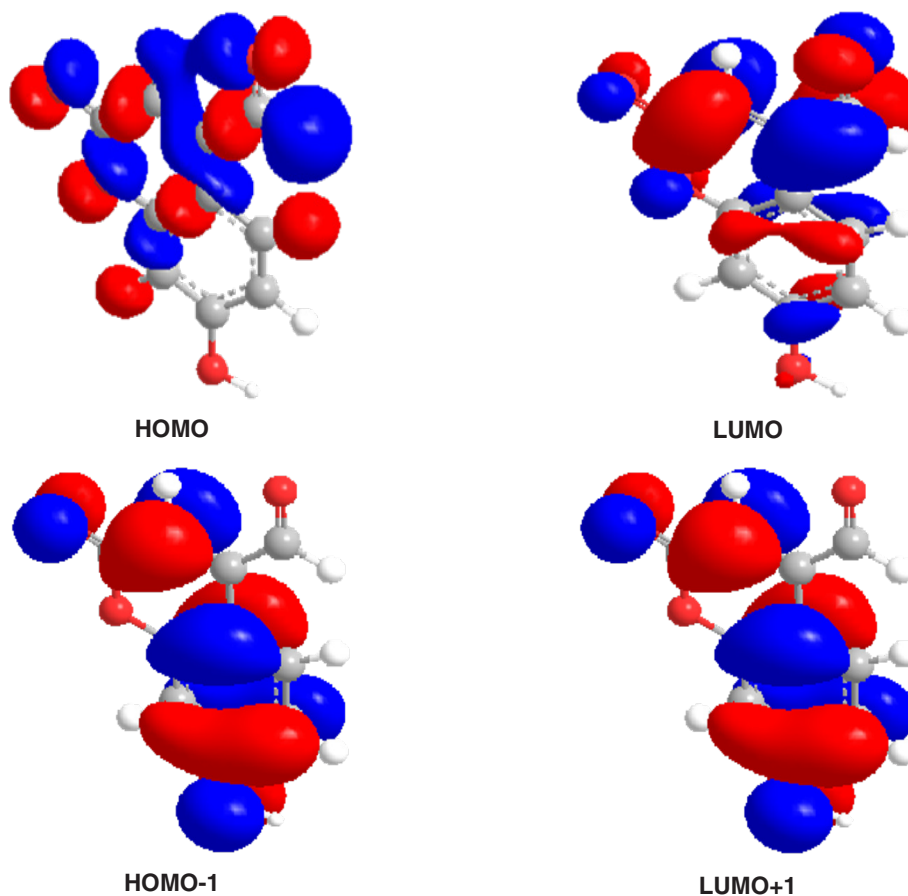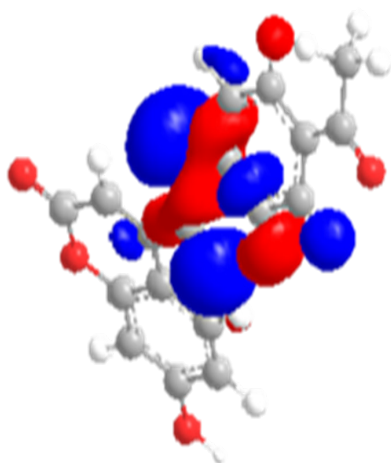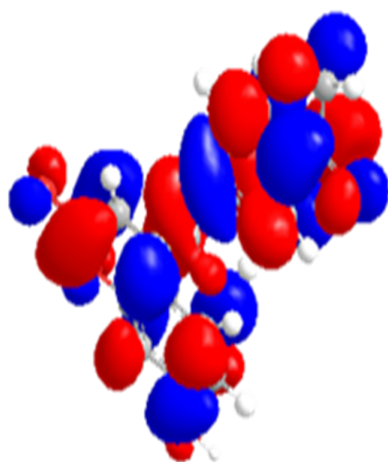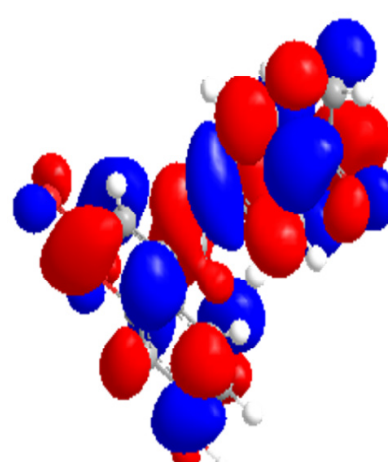

HOMO

LUMO

HOMO-1

LUMO+1

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

Table 3: Global chemical reactivity of compounds 1, 3, 4, 6, 7 and 8

Parameter	Comp.1	Comp.3	Comp.4	Comp.6	Comp.7	Comp.8
Total energy (Kcal / mol)	19.3707	43.2876	60.986	60.986	32.8275	19.4169
Dipole moment (debye)	7.0936	6.2501	7.7916	7.7916	13.5102	10.0628
Log P	0.42	1.85	0.99	3.18	0.14	0.63
electronic chemical potential (μ)	-8,893	-7.574	-0.053	-1.3075	-7.087	-4.375
chemical hardness (η)	1.966	0.914	0.051	1.0085	1.624	1.585
electrophilicity (ω)	20.174	31.38	0.0274	0.847	15.464	6.013

Table4: HOMO and LUMO energies (eV) of title coumarin derivatives

Comp.	HOMO	LUMO	ΔE (eV)	HOMO-1	LUMO+1	ΔE (eV)
1	-10.859	-6.927	-3.932	-12.294	0.029	-12.323
3	-8.488	-6.66	-1.828	-11.5	-3.293	-8.207
4	-0.104	-0.002	-0.102	-0.55	1.912	-2.462
6	-2.316	-0.299	-2.017	-4.128	0.303	-4.431
7	-8.711	-5.463	-3.248	-12.045	-0.315	-11.73
8	-5.945	-2.769	-3.176	-9.477	-0.293	-9.184

HOMO

LUMO

HOMO-1

LUMO+

Fig. 3: Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of compound 3

Computational Studies

The quantum chemical calculations were validated on the new coumarin derivatives using Density Functional Theory (DFT) methodology with 3-21G* basis,while the molecular atomic charges were approved using the Mulliken population analysis.

The molecular representation sketch of the new coumarin compounds was plotted using Chem. Bio-Office 2010 software.

The following chemical parameters calculated using DFT are: total energy (E), chemical hardness (η), electronic chemical potential (μ) and electrophilicity (ω)

Structural and electronic properties

Compounds 1, 3, 4, 6,7 and 8 with optimized geometries and 3D geometrical structures are demonstrated in figure 1, and the data listed in table 2 showed the highest atomic charge of all coumarin compounds 1-8 and confirmed the atoms are the most reactive toward the addition substitution reactions. The calculated bond angle and twist angle, stretch. , bend, stretch-bend, torsion and stereochemistry, indicated the title coumarin derivatives are non-planar molecules.

The quantum mechanical method have been approved for compounds 1, 3, 4, 6,7 and 8. The molecular structure (optimized form) of the most stable one is shown in figure 1. While the
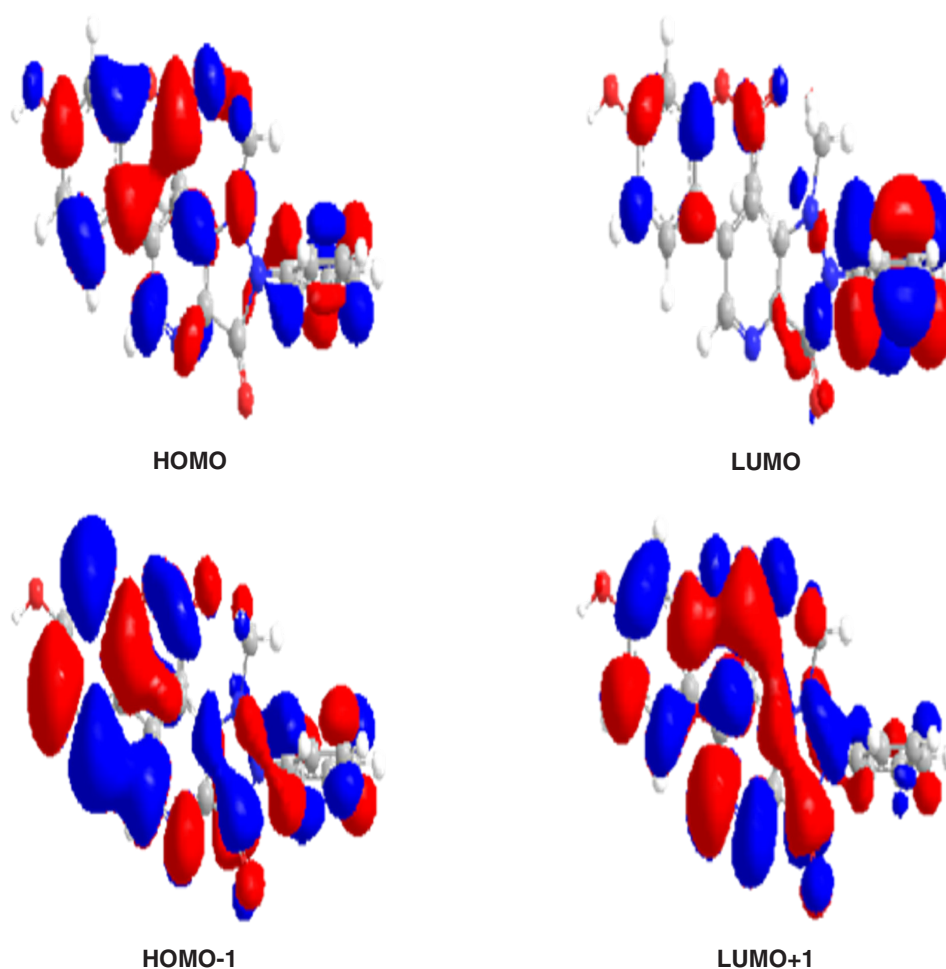

HOMO

LUMO

HOMO-1

LUMO+1

Fig. 4: Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of compound 4

calculated energies are presented in table 3. The contour plots of the frontier orbitals for the ground state of compounds 1, 3, 4, 6,7 and 8 are shown in the figures: 2, 3 4,5,6 and 7 together with the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO).

Table5: Electron density for title coumarin derivatives

Comp.			Electron density	
	HOMO	**LUMO**	**HOMO-1**	**LUMO+1**
1	carbonyl group substituted on coumarin	coumarin and carbonyl group substituted on coumarin	coumarin ring	phenol ring of coumarin, and also carbonyl group that substituted on coumarin
3	C=N- bond between benzene ring and coumarin ring	on C= N- bond between benzene ring and coumarin ring, and carbonyl of ketone and coumarin ring	C= N- bond between benzene ring and coumarin ring, and carbonyl of ketone and coumarin ring	on C= N- bond between benzene ring and coumarin ring, and carbonyl of ketone
4	N-N-bond of the five-member, on coumarin ring and methyl groups of diazo ring	whole molecule	whole molecule	N-N-bond of five-member, on coumarin ring, and the phenol group of coumarin ring
6	N-N-bond of five-member and on coumarin ring	lactone ring of coumarin, N-N-bond of five-member, and C=N group between coumarin and thiadiazole	N-N-bond of five-member and on coumarin ring	phenol ring of coumarin
7	C=N group between coumarin and carboxylic acid	C=N group between coumarin and carboxylic acid	whole molecule	C=N group between coumarin and carboxylic acid and phenol ring of coumarin
8	C=N group between coumarin and carboxylic acid	on C=N group between coumarin and carboxylic acid and coumarin	C=N group between coumarin and carboxylic acid	on C=N group between coumarin and carboxylic acid and phenol ring of coumarin

It is remarkable to view that both orbitals are considerably circulated over the conjugation plane. In addition, it can also be seen from the figures 2-7 that the HOMO orbitals are located on the substituted molecule, while LUMO orbitals look like those obtained for the unsubstituted molecule and therefore, the substitution has contributed a control on the electron donation ability while influencing only a small effect on electron acceptance ability. Table 4. Showed the HOMO and LUMO gap .The lower values in the HOMO and LUMO energy gap would give details the eventual electron- donor-acceptor-complex interaction occurring within the molecules. The values of HOMO for compounds 1, 3, 4, 6,7 and 8 are low. Indicate these molecules have low

ionization energies inferring that, they can lose the electrons easily[20]. Chemical hardness is related with the stability and reactivity of a chemical compounds , it measures the resistance to change in the electron distribution or charge transfer. The molecule with the higher HOMO–LUMO energy gap, is harder and more stable/less reactive molecule..

Electronic chemical potential (μ) is known as the negative of electronegativity of a molecule [21] and describes the escaping tendency of electrons from an equilibrium system. Global electrophilicity index (ω), is calculated using the electronic chemical potential and chemical hardness. This index measures capacity of a species, to accept

HOMO

LUMO

HOMO-1

LUMO+1
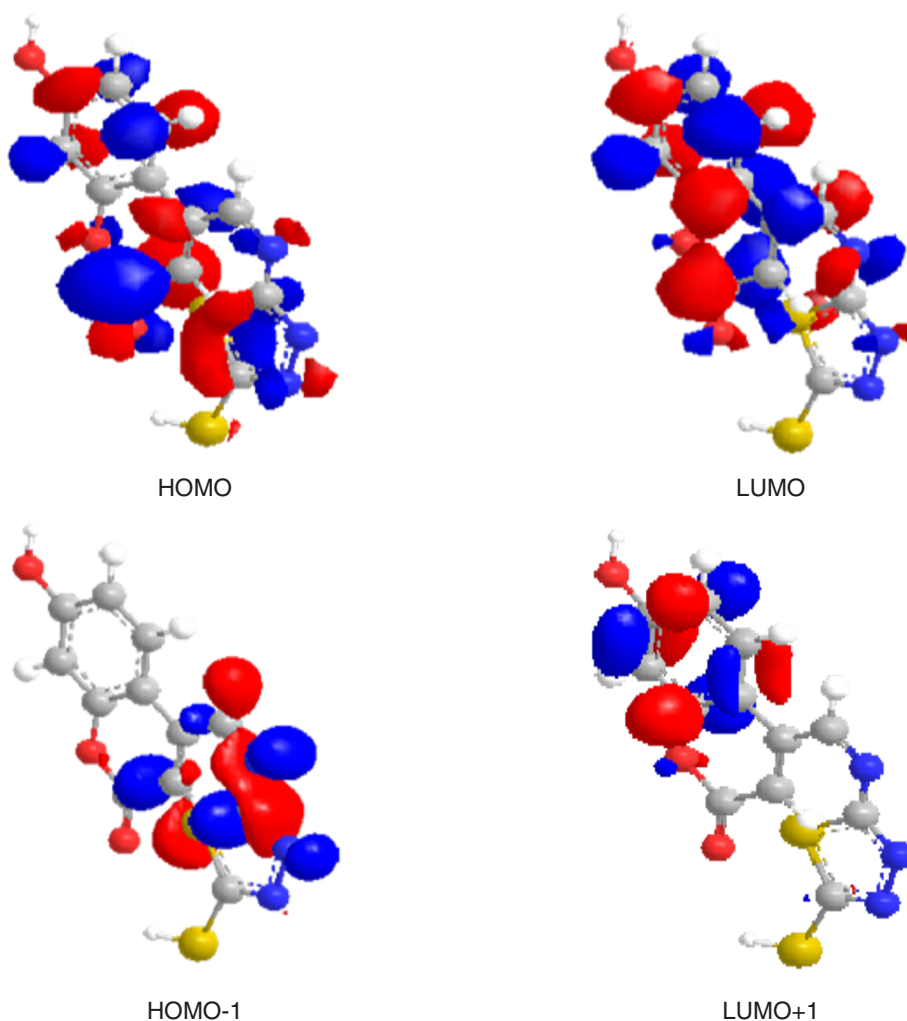
Fig. 5: Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of compound 6

electrons[22,23]. It is a total of the stabilization in energy after a system accepts an additional amount of electronic charge from the environment [24].

Table 3 (row 5)contains the computed chemical hardness values for compound 1,3,4,6,7 and 8. The consequences indicate that compound 1 is harder and less reactive than compound 3 which is harder and less reactive than compound 4. The values of (μ) for compound 1,3,4,6,7 and 8 are shown in Table 3 (row 4). The trend in electronic chemical potential for compound 4> compound 6 > compound 8> compound 7 > compound 3> compound 1 .

The dipole moments, total energy (E), the partition coefficient (logP), chemical hardness (η), electronic chemical potential (μ) and electrophilicity (ω) of compounds 1, 3, 4, 6,7 and 8. were also calculated and listed in Table 3.

The more reactive or less stable compound, is the higher chemical potential,. Therefore, compound 4 is the more reactive than other compounds. While compound 1 is the least reactive. The electrophilicity values (ω) (Table3, row 6) for the compound 1,3,4,6,7 and 8 are 20.174 eV, 31.38 eV , 0.0274 eV, 0.847 eV, 15.464eV and 6.013 eV, respectively. Among the compounds, compound 3 is considered the strongest
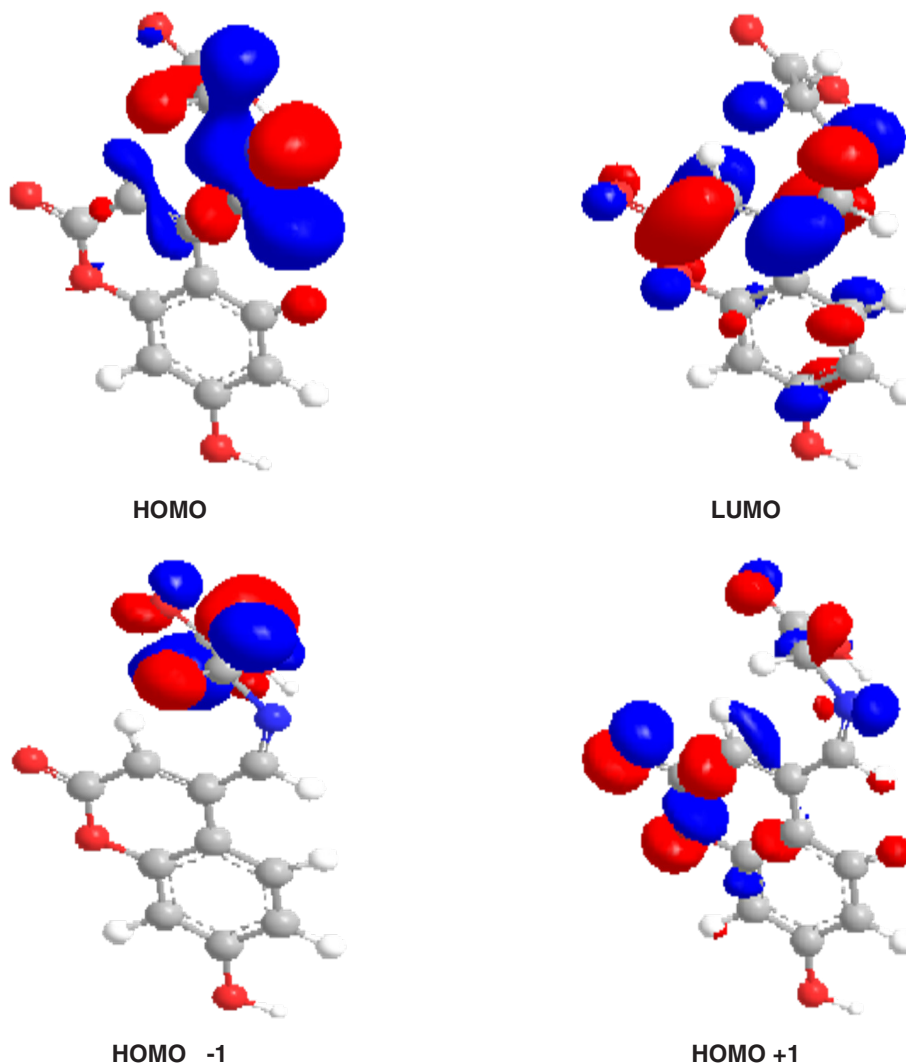

HOMO

LUMO

HOMO -1

HOMO +1

Fig. 6: Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of compound 7

nucleophile while compound 1 is considered as a strongest electrophile.

Electrostatic potential charges and related quantum chemical properties

The distribution of the electronic density (electrostatic potential charges), related quantum chemical parameters [dipole moment (Table 3, row 2), and the partition coefficients of the compounds (log P; Table 3, row 3) were calculated for observed compound 1,3,4,6,7 and 8. These values and properties are very helpful and can be used in order to estimate chemical properties and possibilities for the interaction of compounds 1,3,4,6,7 and 8 with target sites (receptors, enzymes) as well as their transporting system through the cell membranes and brain-blood barrier. All these structural, electronic parameters and log P can be used for a construction

of quantitative structure-activity relationship (QSAR) model because all of them are closely correlated to pharmacokinetics and pharmacodynamics properties [21].

Redox potential can be measured from HOMO/LUMO gap; it is significant for the oxidative-metabolism pathway involving cytochrome P450 enzymes. The observed HOMO/LUMO gap ,(ΔE) (Table 4), is used to calculate redox potential. The lower negative values of both HOMO and LUMO energies designate that these compounds have the general properties of the reductors. This information may be significant for drug metabolism, as the oxidation (and sometimes the reduction) is the main metabolic pathway for many drug molecules.
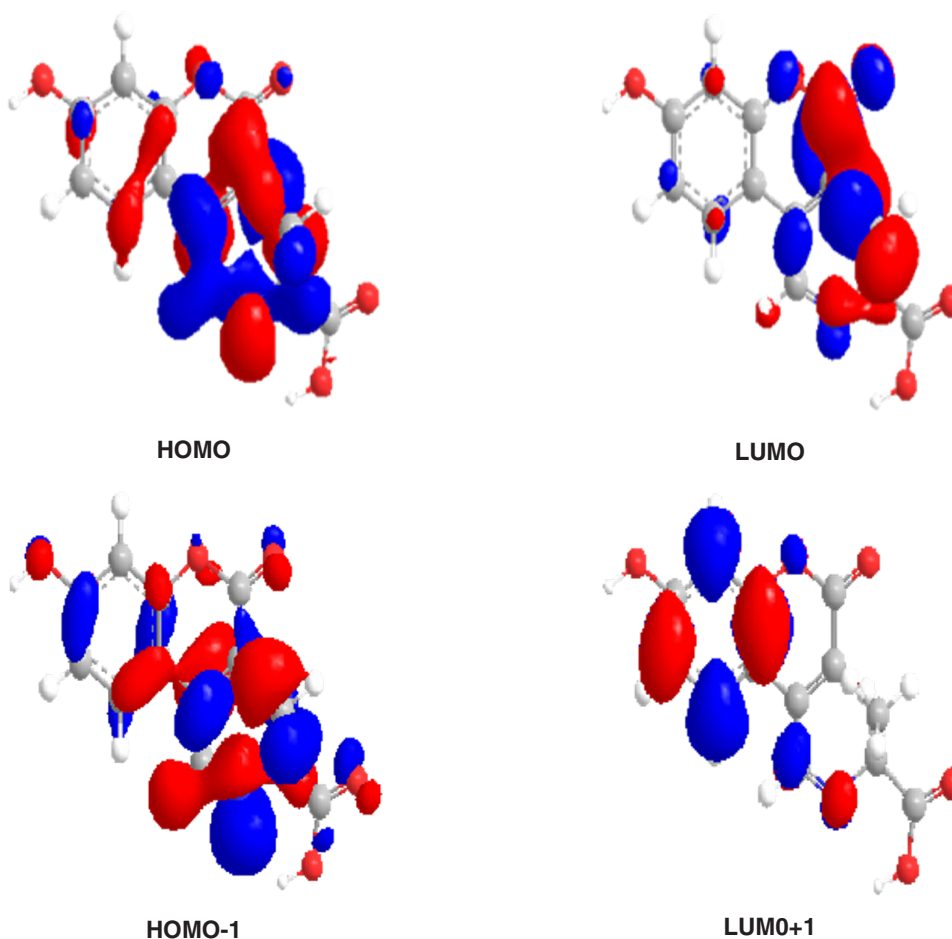
All title coumarin derivatives are polar

HOMO

LUMO

HOMO-1

LUM0+1

Fig. 7: Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of compound 8

molecules, depending on their electric dipole moments (Table 3), The most polar molecule is compound 7, while compound 6 is found to be the most lipophilic according to the log P values (Table 3row 3).

The UV-VIS absorption spectra of the compounds: 1, 3and 4 were recorded in (ethanol). The absorption peaks are observed at 248, 287 and 222 nm, and 267 and 295 nm for the compounds 6, 8. It can be conclude that these peaks imply to the n→p* and p→p* transitions. The 3D plots of the, HOMO-1, HOMO, LUMO, LUMO+1, and the corresponding energy levels of the compounds 1, 3, 4,6,7 and 8 are shown in the figures 2, 3,4,5 and 6, respectively. The theoretical electronic transfer (ET) for compound 1, 3,4,6 were corresponding to the UV-VIS spectral absorption peaks and the electronic transfer of HOMO plus LUMO and HOMO plus LUMO+1, respectively. The increased theoretical absorption wavelengths of the title compounds have slight blue-shifts.

Figures 2-7 showed the six 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, represent the three highest occupied orbitals and three lowest unoccupied orbitals in the compounds 1, 3, 4, 6,7 and 8. Similar spatial distribution of orbitals between HOMO/HOMO-1and LUMO/LUMO+1 pairs and the population analysis for compounds 1, 3, 4, 6,7 and 8, are listed in table 5.

CONCLUSION

In the present work a series of new coumarin derivatives have been synthesized from 7-hydroxy-4-methylcoumarin by the oxidation of methyl group at C4 of the parent coumarin nucleus, using SeO_2, to produce formyl group, then the formation of different derivatives under conventional method. The title coumarin derivatives were screened for their preliminary antibacterial activity using serial dilution method, by determining their minimum inhibitory concentrations (MIC), and showed moderate to highest antibacterial activity against Gram-positive and Gram-negative bacteria.

Compound 7 showed the highest antibacterial activity against Gram- positive *Staphylococcus aureus* and *Micrococcus luteus*, and potent antibacterial activity against Gram-negative *E.coli*. The synthesized derivatives were studied theoretically by using DFT calculations., and the stereochemistry was estimated and found that compounds 1, 3, 4, 6, 7 and 8. are not- planar molecules.

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