Quantum computational and Molecular Docking Studies on 6,7-Dihydroxy-4-Methylcoumarin

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Abstract

In this work normal mode analysis of 6,7-Dihydroxy-4-Methylcoumarin [DHMC], a natural product, reported to possess anti-oxidant, anti-inflammatory activity and anticarcinogenic properties have been performed using DFT technique with GAUSSIAN 09W software. The vibrational analysis has been performed at their equilibrium geometries with the help of PED (Potential energy Distribution). The electronic descriptors like HOMO, LUMO, frontier energy gap and molecular electrostatic potential surface (MESP) analyses along with calculation of some electrical parameters like dipole moment, molecular polarizability and first static hyperpolarizability, are used to predict the NLO properties of the molecule The molecular docking analysis of title molecule DHMC has been performed with the 6IUA, in order to support its reported anti-inflammatory properties. To the best of our knowledge this work is not reported yet.

Keywords: 6,7-Dihydroxy-4-Methylcoumarin; Coumarin, Esculetin, Vibrational Analysis; DFT; Molecular Docking.

1. Introduction

Coumarin derivatives, such as esculetin, have various physiological functions, including antioxidant, anti-inflammatory, antibacterial, antiviral, and anti-cancer [1]. The present study on the title compound 6,7-Dihydroxy-4-Methylcoumarin ($C_{10}H_8O_4$) [DHMC] has been carried out to support the work of reported literature of the compound. In this work we have produced some theoretical quantum chemical calculations of DHMC by DFT/B3LYP method using 6-311++G (d, p) as the basis set. The electronic descriptors like HOMO, LUMO, frontier energy gap and molecular electrostatic potential surface (MESP) analyses along with calculation of some electrical parameters like dipole moment, molecular polarizability and first static hyperpolarizability, are used to predict the NLO properties of the molecule. HOMO-LUMO predicts how the compound interacts with other organisms which help to characterize the chemical reactivity of the molecule. Reactive sites of the title compound DHMC are predicted by MESP plot. Since the present compound possesses some biological activities which are of medicinal importance we have performed its molecular docking in order to get a deeper insight into its possible target molecules. The contenders for its targets are molecules from bacterial cell surface which may impart anti-inflammatory activity to the title compound. In this study, we have restricted our focus on molecules involved in

anti-inflammatory activities and found a tight docking of DHMC with the protein 6IUA which is obtained from protein database (PDB) bank [2].

2. Computational details

Entire calculations have been done using Gaussian 09 software, performing gradient geometry optimization and using the B3LYP/6-311++G (d, p) levels of theory for the molecular structure and vibrational wave numbers [3, 4].This basis set 6-311G (d, p), with 'p' polarization functions on hydrogen atoms and 'd' polarization functions on heavy atoms, is used for better description of polar bonds of molecule [5, 6]. Initial geometry is modelled with the help of Gaussview software 5.0.8.2 and the model molecular structure is shown in Figure 1 [7].The molecular geometry is fully optimized by Becke's three parameter exchange term combined with the gradient-corrected correlation functional of Lee, Yang and Parr [8-10].The potential energy distribution (PED) analysis has been performed by VEDA 4 software [11]. The target protein 6J7A for molecular docking study was obtained from the protein data bank.

3. Result and Discussion

3.1 Vibrational Assignments

The title molecule 6,7-Dihydroxy-4-Methylcoumarin (C10H8O4) [DHMC] contains 22 atoms so contains 60 normal modes of vibrations. These vibrations are analyzed with the help of Gaussview 5.0.8.2 and VEDA 4.0 programs. We have ignored electron-electron interaction and an-harmonicity [12]. Due to these approximations calculated frequencies are found in higher region than experimental values and that's why we have scaled the calculated frequencies by 0.958 up to 1700 cm-1 and below that by 0.9688. Some of the important modes of vibrations are discussed below.

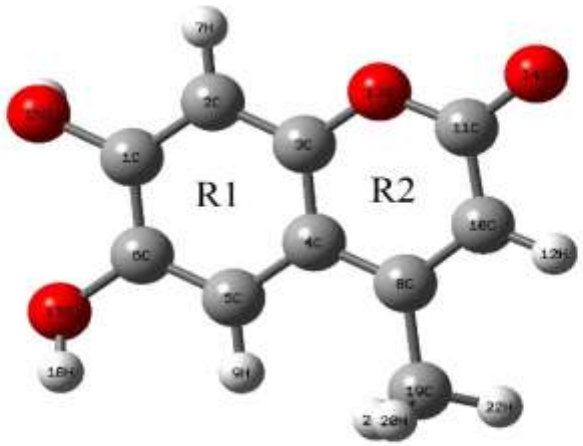


Fig 1: Model molecular structure of title compound DHMC plotted by Gaussview 5.0.8.2

3.1.1 OH- Stretch

The O-H stretching is calculated in the region 3922-3872 cm^{-1} is and is in good agreement with the literature [13] with 100% PEDs.

3.1.2 CH- Stretch

In the DFT calculations the CH stretching vibrations are found in the range 2800-3100 cm^{-1} which is well matched with the reported values. These modes also bear high PED values.

3.1.3 *C=O Stretch*

The C=O stretching is calculated at 1810-1692 cm^{-1} and is in good agreement with the literature [13].

3.1.4 *C-C-Stretch*

These are calculated in the frequency range 1489-1322 cm^{-1} and are mixed with the in plane bending modes.

Table I : Frequency assignments for DHMC at B3LYP/6-311G(d,p) level in cm^{-1}, with PED % in square brackets

S.No.	Calc Freq		Assignment Modes[PED]
	Unscaled	Scaled	
1	4094	3922	ν(C1-O15)s[100]
2	4039	3869	ν(C6-O17)s[43]+ν(C11-O14)s[26]
3	3452	3307	ν(C3-13)sR3[99]
4	3403	3260	ν(C2-7)sR5[99]

5	3441	3296	ν(C5-H9)aR3[55]+ν(C10-H12)aR3[44]	
6	3321	3182	ν(C19-H20,21,22)s[85]	*{CHAR}*
7	3281	3143	ν(C19-H20,21,22)s[85]	
8	3208	3073	ν(C2-H7)sR5[99]	
9	1890	1810	ν(C11=O14)s[92]	
10	1839	1762	ν(C11=O14)as[8	
11	1810	1734	ν(C11=O14)s[52]+φ(H20-C19-H21,22)[49]	
12	1766	1692	ν(C11=O14)[67]	
13	1692	1663	R1-def[38]+φ(C8-C10-H12)[35]	
14	1644	1616	R2-def[56]	
15	1640	1612	ν(C4-C8)R3[26]+φ(H9-C5-C6)R3[29]	
16	1591	1564	R2-def[48]	
17	1579	1552	ν(C6-C1)[26]+φ(H7-C2-C1)[29]	
18	1541	1515	ν(C2-C3)[13]+φ(H7-C2-C3)[19]	
19	1464	1440	ν(C10-C8)[23]+φ(H12-C10-C8)[59]	
20	1430	1406	ν(C5-C4)[28]+φ(H9-C5-C4)[41]	
21	1384	1361	ν(C19-C8)[12]+φ(H20,21,22-C19-C8)[21]	
22	1369	1346	ν(C3-O13)a[13]+φ(H8-O15-C1)[14]	
23	1364	1341	ν(C11-O13)a[16]+φ(H18-O17-C6)[14]	
24	1318	1296	ν(C6-O17)a[13]+φ(H18-O17-C6)a[19]	
25	1275	1253	ν(C11-O13)a[11]+φ(H18-O17-C6)[16]	
26	1257	1236	ν(C8-C4)[28]+φ(C4-C5-C8)[11]	
27	1213	1192	ν(C6-O17)a[13]+φ(H18-O17-C6)a[18]	
28	1195	1175	ν(C8-C19)[15]++φ(H22-C19-C20)a[18]	
29	1173	1153	ν(C8-C10)[14]++φ(H20-C19-C20)a[13]	
30	1105	1086	ν(C10-C11)a[16]++φ(H21-C19-C20)a[10]	
31	1026	1008	φ(C-C-C)R1[12] +τ(H-C-C-H)R1[10]	
32	1009	992	φ(C-C-C)R2[18] +τ(H-C-C-H)R1[15]	
33	998	981	ω(H-C-C-C)R1[10]+ φ(C-C-C)R2[18]	
34	984	967	R1,R2-def[17]	*{CHAR}*
35	893	877	ν(C1-C6)R1[25]+ν(C6-O17)R2[19]	
36	851	837	ϕ(C-C-H)R1[13] +τ(H-C-C-H)R1[26]	
37	839	825	ν(C6-O17)a[10]+φ(H18-O17-C6)a[17]	
38	804	791	ν(C6-O17)a[12]+φ(O13-C11-O14)a[14]	
39	770	757	ν(C-C)R1[19] + φ(H-C-C)R1[11]	
40	760	747	φ(C-C-H)R1[18] +τ(H-C-C-O)R1[22]	
41	710	698	ω(H-C-C-C)R2[15]+ φ(C-C-C)R2[18]	
42	613	603	ω(H-C-C-C)R1[10]+ φ(C-C-C)R1[15]	
43	612	602	ν(C1-C6)R1[10]+ φ(C-C-C)R1[11]+φ(C10-C11-O13)[11]	
44	592	582	ν(C1-O15)[10]+ φ(C-C-C)R2[11]+φ(O13-C11-O14)[15]	
45	534	524	φ(H-C-C)R1[11] + φ(H-C-C)R2[11]	
46	509	501	φ(H-C-C)R2a[32] + ω(H-C-C-C)R1[10]	
47	494	486	φ(C-C-H)R1[76] +τ(H-C-C-C)R1[22]	*{CHAR}*
48	452	444	ν(C6-O17)a[12]+φ(O13-C11-O14)a[14]	
49	435	428	ν(C-C)R2[19] + φ(H-C-C)R2[11]	
50	407	400	ω(H-C-C-C)R2[15]+ τ(H-C-C-O)R1[12]	
51	339	333	τ(H-C-C-)R1[22]	
52	321	316	φ(C-C-H)R1[16] +τ(H-C-C-C)R1[22]	
53	297	292	τ(H-C-C-)R1[20]	

54	232	228	R1,R2-breath[54]
55	232	228	R2-def[24]
56	215	211	τ(H-C-C-C)R2[22] +τ(H-C-C-C)R1[12]
57	190	187	ω(O15-C1-C2-C6)[10]+ φ(C-C-C)R1[15]
58	184	181	ω(O17-C6-C5-C1)[10]+ φ(C-C-C)R1[15]
59	117	115	τ(H-C-C-)R1[22]
60	81	80	ω(O17-C6-C5-C1)a[14]

3.1.5 C-O-Stretch

Due to mixing of vibrations in this region the C-O stretching vibrations are difficult to identify. These are obtained in DFT calculations in the frequency range 1346-1192 cm-1. These modes are in good agreement with the literature [13].

3.1.6 Some lower order modes

The lower order spectral modes are important for vibrational study of a molecule as they provide the information about weak intermolecular interactions, which happens in many biological reactions. Other lower order calculated frequency modes are found in the frequency range 438 to 29 cm-1. All the vibrational assignments modes along with respective PEDs are presented in supplementary table -I.

3.2 Electronic Properties

The HOMO represents to an outer electron with orbit whose tendency is to donate these electrons and hence characterizes the tendency of a compound towards electrophilic attack, while LUMO gives the tendency to accept the electrons and characterizes the susceptibility of a molecule for the nucleophilic attack, whereas the energy difference of HOMO and LUMO helps, to quantify the chemical reactivity of the molecule [14,15].Reactive sites of the title molecule 6,7-Dihydroxy-4-Methylcoumarin (C10H8O4) [DHMC] are identified from molecular electrostatic potential (MESP) plot shown in Fig 2, which displays the map of electrostatic potential over constant electron density and gives the molecular size, shape as well as positive, negative and neutral electrostatic potential regions in terms of color coding ranging from -4.003 e-4 to 4.003 e-4.The red region indicates the areas of extreme negative electrostatic energy whereas blue region indicates the extreme positive electrostatic energy or potential, rest of the color regions are intermediate of the two extreme regions. It is clear from figure 2 entire MESP potential is distributed to both rings R1 and R2. The HOMO and LUMO energies are computed by DFT/B3LYP method using 6-311++G (d, p) basis set. The calculated values of energy gap for the title molecule is *10.18 eV* which clearly indicates that the molecule possesses more polarizability, high chemical reactivity and therefore lies in the category of *soft molecule* [16,17].

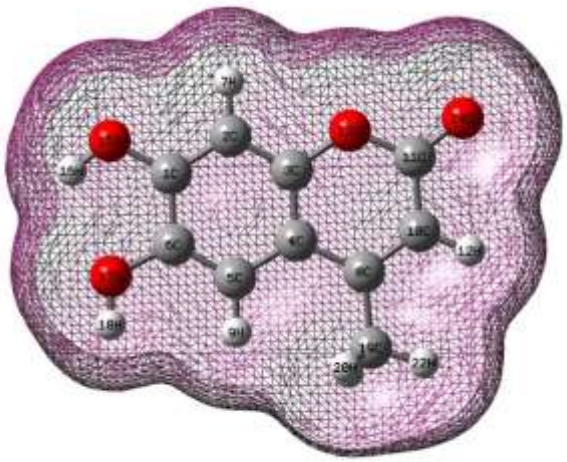
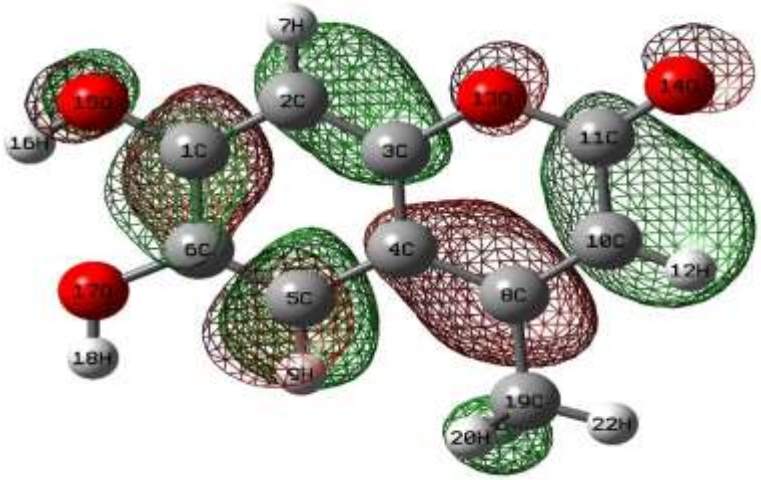


Fig 2 :MESP surface of the title compound DHMC



ΔE = 10.186 eV

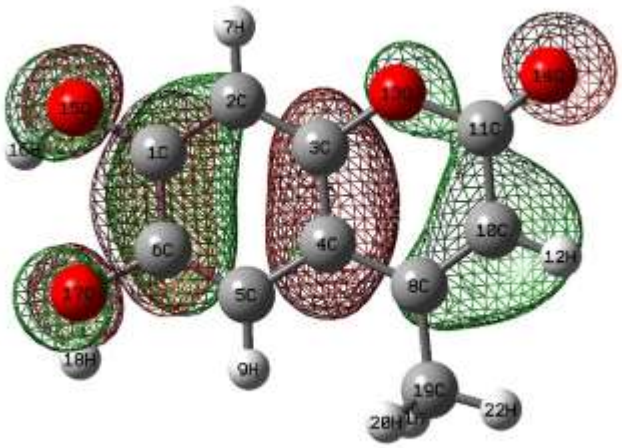


Figure 3: LUMO-HOMO- surfaces of DHMC

Table II : Global chemical reactivity parameters of DHMC by DFT/B3LYP- 6-311++G(d,p)

Parameters	**DFT-Values**
E_{HOMO} (eV)	-8.7200
E_{LUMO} (eV)	1.4660
ΔE (eV)	10.1860
Ionization potntial (I)	8.7200
Electron affinity(A)	-1.4660
Electronegativity(χ)	3.6270
Chemical potential(μ)	-3.6270
Chemical hardness(η)	5.0930
Global softness(S)	0.0982
Electrophilicity index (ω)	1.2915
Fukui function(f_k^{+-})(max vlaue)	0.8550
Local softness ($S*f_k^{+-}$)	0.0839
Electrophilitcity($\omega*f_k^{+-}$)	1.1042

The 2D plots of HOMO and LUMO are shown in Fig 3. It is clear from figure 3 that the LUMO is spread equally over rings R1, R2 and entire HOMO is. The high electronegativity value (3.6270 eV) shows the high tendency for electron attraction. The low electrophilicity index ω (1.2915 eV) and low value of chemical potential (-3.6270 eV) suggests that the title molecule have a greater tendency for nucleophilic attack. All the electronic parameters with their values for the title compound have been listed in Table II.

3.5 Electric moments & NLO behavior

The value of dipole moment for title compound 6,7-Dihydroxy-4-Methylcoumarin (C10H8O4) [DHMC] is calculated as 9.2302 Debye. The mean polarizability and total first static hyperpolarizability (β_{total}) of the title molecule is found to be 0.717 * 10^{-30} e.s.u. and 1.545* 10^{-30} e.s.u. respectively and are presented in Table III. Urea (β_{total} =0.1947 *10^{-30}e.s.u.) is supposed to be a yardstick compound for NLO properties because it does not have particularly strong nonlinearity, therefore the results are compared with urea. The calculated value of hyperpolarizability of the title compound is ***eight times*** to that of urea so it is a good claimant as a NLO material.

Table III: Electric Parameters of DHMC by B3LYP/6-311G(d,p) method
(1 a.u.=8.3693*10^-33 e.s.u)

Polarizability	Values (a.u)	Hyperpolarizability	Values (a.u)
α_{XX}	-93.9252	β_{XXX}	-103.4627
α_{XY}	6.1407	β_{XXY}	81.7553
α_{YY}	-79.1558	β_{XYY}	-32.2518
α_{YZ}	0.0067	β_{YYY}	45.5651
α_{ZZ}	-84.0873	β_{XXZ}	-0.003
α_{XZ}	-0.0098	β_{XYZ}	-0.0073
<α>	**-85.722**	β_{YYZ}	0.0048
Dipole Moment(Debye)	Values	β_{XZZ}	-1.4356
		β_{YZZ}	-3.679
μ_x	-4.0993	β_{ZZZ}	0.0061
μ_y	8.27	**β_{Total}**	**184.6547**
μ_z	0.0007		
μ_{total}	**9.2302**		

3.6 Thermodynamic Properties

On the basis of statistical thermodynamics and vibrational analysis, the standard thermodynamic functions: heat capacity (C), entropy (S), enthalpy (H), for the title compound 6,7-Dihydroxy-4-Methylcoumarin ($C_{10}H_8O_4$) [DHMC] were calculated in the temperature range 100-500 and are listed in Table IV below. It is evident that these thermodynamic functions increase with increasing temperature because the intensities of molecular vibrational increase with temperature.

Table IV : Thermodynamic parameters of DHMC

	E (Thermal) KCal/Mol	CV Cal/Mol-Kelvin	S Cal/Mol-Kelvin
Total	117.412	43.154	102.522
Electronic	0.000	0.000	0.000
Translational	0.889	2.981	41.663
Rotational	0.889	2.981	31.614
Vibrational	115.634	37.192	29.245

3.8 Molecular Docking

Molecular docking is a technique which finds the best orientation position of ligand to fit with its target protein. The ligand generally fits into the target protein cavity which is predicted by search technique. The molecular binding of a ligand to its receptor may alter its function, thereby enabling the use of ligand molecule for development of a drug [18]. We have used the Autodock tools, which is a graphical user interface (GUI) program, for the preparation, execution and analyzing docking simulations. For docking simulation, Kollman charges and polar hydrogens were added to the receptor. The docking calculations have been performed using Autodock Vina 4.2.6 program provided with Auto Grid and Auto dock tools were used to prepare grid maps [19].The target protein has been obtained from Protein Data Bank (PDB) database (PDB ID = 6IUA).2D protein-ligand interaction profile image has been generated using PYMOL software and is presented in Fig 5 in which the residue with maximum interaction energy -6.3 Kcal/mol is highlighted with blue color and the high negative interaction energy predicts that there is strong docking between 6IUA protein and the title molecule 6,7-Dihydroxy-4-Methylcoumarin (C10H8O4) [20].

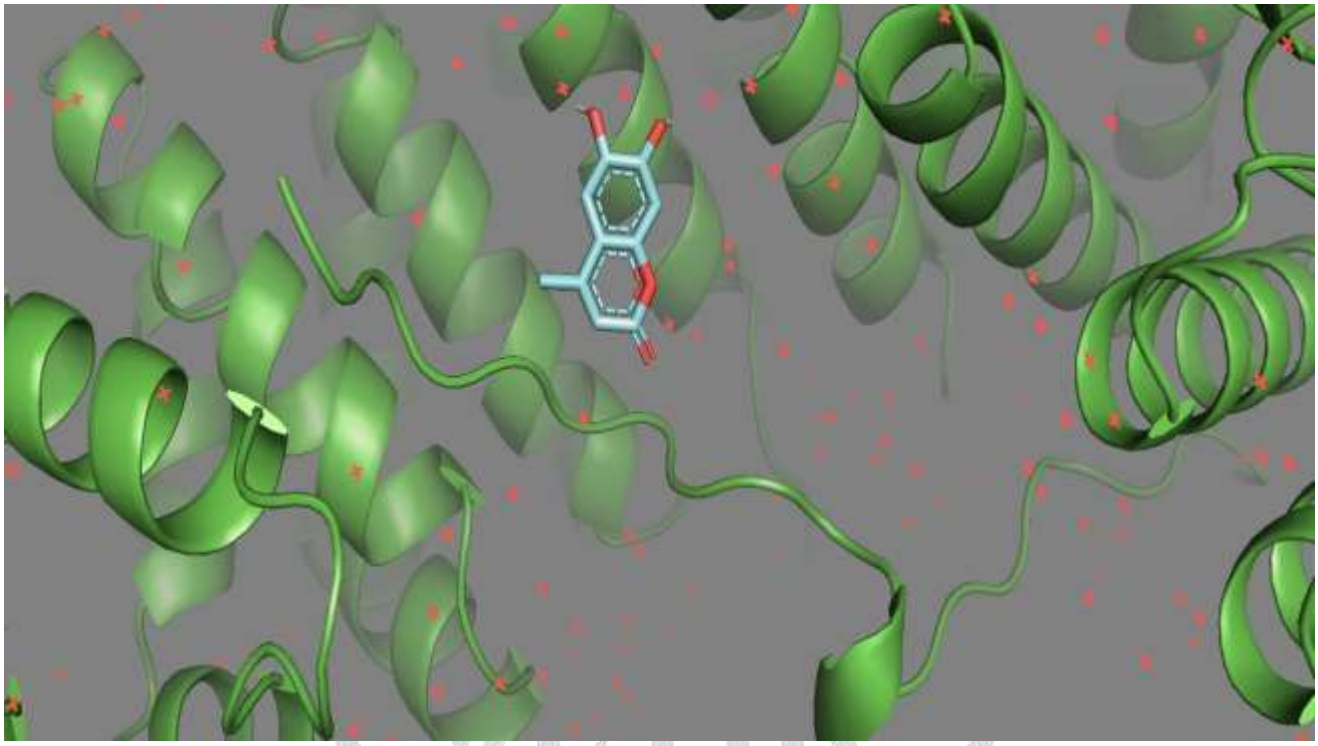


Fig 4: Molecular docking of the title compound DHMC with the protein 6IUA using Pymol

4. Conclusion

Present work deals with a thorough study of spectroscopic assignments (FTIR, NMR & UV-Vis), NLO behavior, electric parameters, electronic properties and Fukui functions, calculated with B3LYP/6-311++G(d,p) method on 6,7-Dihydroxy-4-Methylcoumarin (C10H8O4) [DHMC]. Theoretically calculated FTIR with DFT method are in accordance with the reported literature spectral values. HOMO-LUMO plot has been obtained to find the charge transfer in the molecule and their energy gap is 10.18 eV indicates that the molecule bears high polarizability and low chemical reactivity. The calculated value of hyperpolarizability of the title compound is eight times to that of urea so it should serve as a good NLO material. The molecular docking analysis of title molecule 6,7-Dihydroxy-4-Methylcoumarin (C10H8O4) [DHMC] has been performed with target protein 6IUA. We have obtained a strong interaction of title compound with the protein receptor 6IUA supporting its claim for the anti-inflammatory properties.

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