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Vibrational and Molecular Structural Investigations of Pioglitazone – Combined Study of Experimental and Quantum Chemical Calculations (Density Functional Theory)

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Abstract : The Fourier transform –Raman (FT-Raman) and Fourier transform infrared (FT-IR) spectra of (RS)-5-(4-[2-(5-ethylpyridin-2-yl) ethoxy] benzyl) thiazolidine-2,4-dione (pioglitazone) were studied in the region of 4000-100 cm^{-1} and 4000-400 cm^{-1}respectively. The theoretical spectral investigation of pioglitazone are also carried out by using density functional theory (DFT) with 6-31G (d,p) basis set. Experimental and theoretical values are compared. The entire vibrational assignments were carried out on the basis of the potential energy distribution (PED) of the vibrational modes using VEDA 4 program. The optimized geometry of the compound was calculated from the DFT-B3LYP. HOMO-LUMO energy gap has been calculated. The molecular geometry parameters like bond angle and bond length have been computed. The molecular stability arising from hyper conjugative interaction, charge delocalization has been analyzed using natural bond orbital (NBO) analysis. The Mullikan atomic charges have been computed. The molecular electrostatic potential (MEP) are also carried out to study the molecular interactions in the title molecule.
Key Words : Bond angle & Bond Length, MEP, HOMO-LUMO, Global descriptors.

Introduction:

Pioglitazone is chemically known as(RS)-5-(4-[2-(5-ethylpyridin-2-yl) ethoxy] benzyl) thiazolidine-2,4-dione. The title compound is a diabetes drug (thiazolidinedione-type, also called "glitazone") used to control high blood sugar in patients with type 2 diabetes. It works by helping to restore your body's proper response to insulin, thereby, lowering your blood sugar. Pioglitazone is used either alone or in combination with other diabetes drugs. Its molecular formula is C19 H20 N2 O3 S.

The pioglitazone and its derivatives were studied by several authors. Simultaneous determination of pioglitazone and candesartan in human plasma by LC-MS/MS and its application to a human pharmacokinetic study have been reported by Vijayakumarikarra et al [1]. Pioglitazone: A review of analytical methods was done by N.Satheeshkumar et al[2]. Pioglitazone: A review of its use in type 2 diabetes mellitus was investigated

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by John Waugh etal [3]. HPLC method development, validation and its application to investigate in vitro effect of pioglitazone on the availability of H1 receptor antagonists was reported by Agha zeeshanmirza et al[4]. A study of effects of pioglitazone and rosiglitazone on various parameters in patients of type-2 diabetes mellitus with special reference to lipid profile was done by SK Sharma etal[5].

To the best of our knowledge, literature survey reveals that, the experimental and vibrational calculations of pioglitazone have not been reported so far. In thispresent investigations, the main objectives ofthe work is to study the molecular structure, geometrical parameters, vibrational wave numbers, modes of vibrations and natural bond orbital (NBO). The redistribution of electron density (ED) in various bonding, anti-bonding orbitals and E(2) energies have been calculated by natural bond orbital (NBO) using density functional theory (DFT-B3LYP) with 6-31 G(d,p) basis set. The study of HOMO-LUMO analysis has been used to explain the information concerning charge transfer within the molecule. The molecular electrostatic potential (MEPs) is calculated to interpret the reactivity of pioglitazone molecule. Lastly, electronegativity (χ), chemical hardness (η), softness (s), electron affinity (A), electrophilicity index(ω) and chemical potential (μ) of pioglitazone molecules are estimated with the application of HOMO-LUMO energies.

2. Experimental:

The powder form of pioglitazone was purchased from leading pharmaceutical company in Chennai with a stated purity of 99% and hence used for recording the spectra. The FTIR spectra of the title molecule were recorded in the range of 4000-400 $cm^{-1}$with resolution of 4 cm^{-1} using Perkin Elmerspectrum–two FT-IR spectrophotometer atsaif, St.peter's university,avadi, Chennai, India. TheFT-Raman spectrum of this compound was recorded at saif, IIT-Madras, Chennai, India, using a BRUKER: RFS 27 spectrometer.

3.Method of Calculations

All the calculations were done for the optimized structure in gas phase. The optimized structural parameters were used in the wave number calculations at DFT level to characterize all stationary points as minima. The theoretical vibrational spectra of the title molecule are illustrated by means of potential energy distribution (PED) using VEDA 4 program [7].The optimized geometrical parameters like energy, fundamental vibrational frequencies, Mullikan atomic charges and other molecular properties are calculated theoretically by using Gaussian O3W program package. The natural bond orbital (NBO) calculations[8,9] were executed using NBO 3.1 program as implemented in the Gaussian 03W package. The electronic properties such as HOMO-LUMO energies and molecular electrostatic potential (MEP) were determined by DFT method. Finally the global and local activity descriptors have been calculated by using DFT method.

4. Result and Discussion

4.1 Geometrical Structure Analysis

The molecular structure of pioglitazone belongs to C1 point group symmetry.The optimized molecular structure of title compound is shown in Fig 1.The geometrical parameters like bond lengths and bond angles acquired by the DFT method with 6-31 G(d,p) basis set and results are tabulated in Table1.This label molecule has seventeen C-C bond lengths, Nineteen C-H bond lengths, Three C-N bond lengths, four C-O, two S-C and one N-H bond lengths respectively.

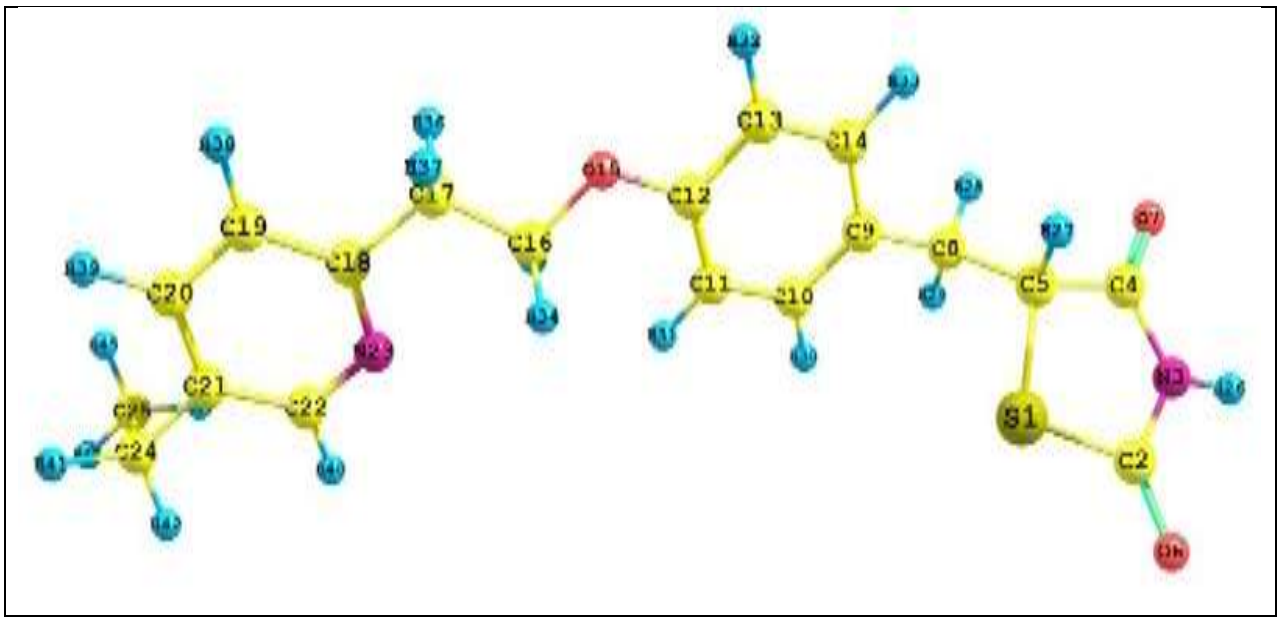


Fig.1 Atom numbering Scheme of Pioglitazone

From this present investigation, the enhanced bond length of S1-C5 (1.8475 A^0) was maximum value and for N3-H26 was minimum (1.0130 A^0). The calculated geometrical parameters show good approximation and they are the basis for calculations of other parameters such as vibrational frequencies.

Table1. Optimized geometricalparameters (Bond Lengths, Bond Angles and Dihedral Angles of Pioglitazone)

Bond Length	B3LYP/6-31G(d,p)	Bond Length	B3LYP/6-31G(d,p)
S_1-C_2	1.799	C_{16}-C_{17}	1.5219
S_1-C_5	1.8475	C_{16}-H_{34}	1.0959
C_2-N_3	1.3948	C_{16}-H_{35}	1.0963
C_2-O_6	1.2054	C_{17}-C_{18}	1.5145
N_3-H_{26}	1.013	C_{17}-H_{36}	1.0974
C_4-C_5	1.5317	C_{17}-H_{37}	1.0976
C_4-O_7	1.2131	C_{18}-C_{19}	1.4028
C_5-C_8	1.5443	C_{18}-N_{23}	1.3401
C_5-H_{27}	1.0946	C_{19}-C_{20}	1.3888
C_8-C_9	1.5121	C_{19}-H_{38}	1.0864
C_8-H_{28}	1.0959	C_{20}-C_{21}	1.4015
C_8-H_{29}	1.095	C_{20}-H_{39}	1.0876
C_9-C_{10}	1.3971	C_{21}-C_{22}	1.3972
C_9-C_{14}	1.405	C_{21}-C_{24}	1.5116
C_{10}-C_{11}	1.3979	C_{22}-N_{23}	1.3396
C_{10}-H_{30}	1.0868	C_{22}-H_{40}	1.09
C_{11}-C_{12}	1.3994	C_{24}-C_{25}	1.5389
C_{11}-H_{31}	1.0832	C_{24}-H_{41}	1.0969
C_{12}-C_{13}	1.404	C_{24}-H_{42}	1.0961
C_{12}-O_{15}	1.3622	C_{25}-H_{43}	1.0947
C_{13}-C_{14}	1.3874	C_{25}-H_{44}	1.0945
C_{13}-H_{32}	1.085	C_{25}-H_{45}	1.0949
C_{14}-H_{33}	1.0878	O_{15}-C_{16}	1.4302

Bond Angle	B3LYP/6-31G(d,p)	Bond Angle	B3LYP/6-31G(d,p)
C_2-S_1- C_5	92.725	C_{10}-C_{11}- C_{12}	119.5693
S-C_2- N_3	109.2981	C_{10}-C_{11}- H_{31}	119.4378
S_1-C_2- O_6	125.6796	C_{12}-C_{11}- H_{31}	120.9927
N_3-C_2- O_6	125.022	C_{11}-C_{12}- C_{13}	119.4125
C_2-N_3- H_{26}	119.3882	C_{11}-C_{12}- O_{15}	124.8425
C_5-C_4- O_7	124.2093	C_{13}-C_{12}- O_{15}	115.7443
S_1-C_5- C_4	106.9392	C_{12}-C_{13}- C_{14}	120.1635
S_1-C_5- C_8	114.1464	C_{12}-C_{13}- H_{32}	118.4915
S_1-C_5- H_{27}	107.8277	C_{14}-C_{13}- H_{32}	121.3439
C_4-C_5- C_8	111.4149	C_9-C_{14}- C_{13}	121.3064
C_4-C_5- H_{27}	107.1664	C_9-C_{14}- H_{33}	119.6117
C_8-C_5- H_{27}	109.0598	C_{13}-C_{14}- H_{33}	119.0797
C_5-C_8- C_9	113.4285	C_{12}-O_{15}- C_{16}	118.6035
C_5-C_8- H_{28}	105.9947	O_{15}-C_{16}- C_{17}	106.4048
C_5-C_8- H_{29}	108.8109	O_{15}-C_{16}- H_{34}	110.5721
C_9-C_8- H_{28}	110.5884	O_{15}-C_{16}- H_{35}	110.578
C_9-C_8- H_{29}	110.5476	C_{17}-C_{16}- H_{34}	110.8977
H_{28}-C_8- H_{29}	107.1902	C_{17}-C_{16}-H_{35}	110.8641
C_8-C_9- C_{10}	121.5286	H_{34}-C_{16}- H_{35}	107.56
C_8-C_9- C_{14}	120.63	C_{16}-C_{17}- C_{18}	113.6686
C_{10}-C_9- C_{14}	117.8334	C_{16}-C_{17}- H_{36}	108.8526
C_9-C_{10}- C_{11}	121.714	C_{25}-C_{24}- H_{42}	109.2915
C_9-C_{10}- H_{30}	119.4884	H_{41}-C_{24}- H_{42}	106.3853
C_{11}-C_{10}- H_{30}	118.7973	C_{24}-C_{25}- H_{43}	110.8572
H_{36}-C_{17}- H_{37}	105.7628	C_{24}-C_{25}- H_{44}	110.9745
C_{17}-C_{18}- C_{19}	120.6214	C_{24}-C_{24}- H_{45}	111.1374
C_{17}-C_{18}- N_{23}	117.7039	H_{43}-C_{25}- H_{44}	108.1296
C_{19}-C_{18}- N_{23}	121.6739	H_{43}-C_{25}- H_{45}	107.9843
C_{18}-C_{19}- C_{20}	119.1882	H_{44}-C_{25}- H_{45}	107.6194
C_{18}-C_{19}- H_{38}	120.0852	C_5-S_1-C_2- N_3	-0.6581
C_{20}-C_{19}- H_{38}	120.726	C_2-S_1-C_5- H_{27}	-113.5772
C_{19}-C_{20}- C_{21}	119.8401	S_1-C_2-N_3- H_{26}	-178.8223
C_{19}-C_{20}- H_{39}	120.1626	O_6-C_2-N_3- H_{26}	0.9902
C_{21}-C_{20}- H_{39}	119.9967	O_7-C_4-C_5- S_1	177.8617
C_{20}-C_{21}- C_{22}	116.3062	O_7-C_4-C_5- C_8	52.4965
C_{20}-C_{21}- C_{24}	122.1025	O_7-C_4-C_5- H_{27}	-66.7311
C_{22}-C_{21}- C_{24}	121.5762	S_1-C_5- C_8- C_9	67.4602
C_{21}-C_{22}- N_{23}	124.6726	S_1-C_5- C_8- H_{28}	-171.0133
C_{21}-C_{22}- H_{40}	119.6238	S_1-C_5- C_8- H_{29}	-56.0246
N_{23}-C_{22}- H_{40}	115.7031	C_4-C_5- C_8- C_9	-171.2886
C_{18}-N_{23}- C_{22}	118.3187	C_4-C_5- C_8- H_{28}	-49.762
C_{21}-C_{24}- C_{25}	113.0468	C_4-C_5- C_8- H_{29}	65.2266
C_{21}-C_{24}- H_{41}	109.4138	H_{27}-C_5- C_8- C_9	-53.1941
C_{21}-C_{24}- H_{42}	109.2689	H_{27}-C_5- C_8- H_{28}	68.3325
C_{25}-C_{24}- H_{41}	109.2164	H_{27}-C_5- C_8- H_{29}	-176.6789
C_5-C_8- C_9- C_{10}	-98.1333	O_{15}-C_{12}- C_{13}- C_{14}	-179.9466
C_5-C_8- C_9- C_{14}	80.8174	O_{15}-C_{12}- C_{13}- H_{32}	-0.3089
H_{28}-C_8- C_9- C_{10}	142.9477	C_{11}-C_{12}- O_{15}- C_{16}	0.9052
H_{28}-C_8- C_9- C_{14}	-38.1016	C_{13}-C_{12}- O_{15}- C_{16}	-179.3837
H_{29}-C_8- C_9- C_{10}	24.3953	C_{12}-C_{13}- C_{14}- C_9	-0.0183
H_{29}-C_8- C_9- C_{14}	-156.654	C_{12}-C_{13}- C_{14}- H_{33}	179.4431
C_8-C_9- C_{10}- C_{11}	178.7517	C_{12}-O_{15}- C_{16}- H_{34}	58.5845
C_8-C_9- C_{10}- H_{30}	-1.4409	C_{12}-O_{15}- C_{16}- H_{35}	-60.4363

C_{14}-C_{9}- C_{10}- C_{11}	-0.2273	O_{15}-C_{16}- C_{17}-C_{18}	-180.037
C_{14}-C_{9}- C_{10}- H_{30}	179.5801	O_{15}-C_{16}-C_{17}-H_{36}	57.2907
C_{8}-C_{9}- C_{14}- C_{13}	-178.7504	O_{15}-C_{16}-C_{17}-H_{37}	-57.4783
C_{8}-C_{9}- C_{14}- H_{33}	1.791	H_{34}-C_{16}-C_{17}-C_{18}	-59.7388
C_{10}-C_{9}- C_{14}- C_{13}	0.2382	H_{34}-C_{16}-C_{17}-H_{36}	177.589
C_{10}-C_{9}- C_{14}- H_{33}	-179.2204	H_{34}-C_{16}-C_{17}-H_{37}	62.8199
C_{9}-C_{10}- C_{11}- C_{12}	-0.0039	H_{35}-C_{16}-C_{17}-C_{18}	59.6767
C_{9}-C_{10}- C_{11}-H_{31}	179.821	H_{35}-C_{16}-C_{17}-H_{36}	-62.9956
H_{30}-C_{10}- C_{11}-C_{12}	-179.8126	H_{35}-C_{16}-C_{17}-H_{37}	-177.7646
H_{30}-C_{10}- C_{11}-H_{31}	0.0122	C_{16}-C_{17}-C_{18}-C_{19}	-178.3762
C_{10}-C_{11}- C_{12}-C_{13}	0.2291	C_{16}-C_{17}- C_{18}-N_{23}	1.9392
C_{10}-C_{11}- C_{12}-O_{15}	179.9304	H_{36}-C_{17}- C_{18}-C_{19}	-56.2078
H_{31}-C_{11}- C_{12}-C_{13}	-179.593	H_{36}-C_{17}- C_{18}-N_{23}	124.1075
H_{31}-C_{11}- C_{12}-O_{15}	0.1083	H_{37}-C_{17}- C_{18}-C_{19}	59.6194
C_{11}-C_{12}- C_{13}-C_{14}	-0.2188	H_{37}-C_{17}- C_{18}-N_{23}	-120.0652
C_{11}-C_{12}- C_{13}-H_{32}	179.4189	C_{17}-C_{18}- C_{19}-C_{20}	-179.8003
C_{17}-C_{18}-C_{19}-H_{38}	-0.0656	C_{20}-C_{21}-C_{24}- C_{25}	80.565
N_{23}-C_{18}-C_{19}-C_{20}	-0.1284	C_{20}-C_{21}-C_{24}- H_{41}	-41.3854
N_{23}-C_{18}-C_{19}-H_{38}	179.6063	C_{20}-C_{21}-C_{24}- H_{42}	-157.4927
C_{17}-C_{18}-N_{23}-C_{22}	179.782	C_{22}-C_{21}-C_{24}- C_{25}	-97.9712
C_{19}-C_{18}-N_{23}-C_{22}	0.1009	C_{22}-C_{21}-C_{24}- H_{41}	140.0784
C_{18}-C_{19}-C_{20}-C_{21}	-0.0136	C_{22}-C_{21}-C_{24}- H_{42}	23.9711
C_{18}-C_{19}-C_{20}- H_{39}	179.7032	C_{21}-C_{22}-N_{23}- C_{18}	0.0713
H_{38}-C_{19}-C_{20}- C_{21}	-179.7465	H_{40}-C_{22}-N_{23}- C_{18}	-179.6435
H_{38}-C_{19}-C_{20}- H_{39}	-0.0297	C_{21}-C_{24}-C_{25}- H_{43}	-179.6351
C_{19}-C_{20}-C_{21}- C_{22}	0.1666	C_{21}-C_{24}-C_{25}- H_{44}	60.1876
C_{19}-C_{20}-C_{21}- C_{24}	-178.4423	C_{21}-C_{24}-C_{25}- H_{45}	-59.5328
H_{39}-C_{20}-C_{21}- C_{22}	-179.5507	H_{41}-C_{24}-C_{25}- H_{43}	-57.574
H_{39}-C_{20}-C_{21}- C_{24}	1.8405	H_{41}-C_{24}-C_{25}- H_{44}	-177.7514
C_{20}-C_{21}-C_{22}- C_{23}	-0.2041	H_{41}-C_{24}-C_{25}- H_{45}	62.5283
C_{20}-C_{21}-C_{22}- H_{40}	179.5003	H_{42}-C_{24}-C_{25}- H_{43}	58.4353
C_{24}-C_{21}-C_{22}- C_{23}	178.4127	H_{42}-C_{24}-C_{25}- H_{44}	-61.742
C_{24}-C_{21}-C_{22}- H_{40}	-1.8829	H_{42}-C_{24}-C_{25}- H_{45}	178.5376
C_{5}-S.C_{2}- O_{6}	179.531	C_{2}-S_{1}-C_{5}- C_{8}	125.0845
C_{2}-S_{1}-C_{5}- C_{4}	1.3866		

4.2 Vibrational Assignments

The label molecule has C1 point group symmetry which possesses 45 atoms and 129 normal modes of vibrations. The noticed FT-Raman and FT-IR bonds with their relative intensities, estimated wave numbers and frequency assignments are given in Table2. The experimental and theoretically simulated FT-IR and FT-Raman spectra of pioglitazone were very well matched, where the calculated IR intensities and Raman intensities are sketched against the vibrational frequencies are shown in Fig 2 and Fig 3 respectively. From the figures 2, 3 and table 2 the slight dispute between theory and experimental could be mentioned that the calculations were made for a free molecule in vacuum, at the same time the experiments were performed for solid samples. The majoritynumber of experimental values are in good coincidence with the theoretical values which is performed by B3LYP/6-31G (d,p) basis set. The vibrational bond assignments were built by using potential energy distribution (PED) analysis with the help of Gaussian view 5.0 program package.

Table 2 Observed and Theoretical Vibrational assignments of Pioglitazone

B3LYP/6-31G(d,p)	EXPT		Vibrational Assignments
	FT-Raman cm-1	FT-IR cm-1	
12			τCCCC(59)+τCOCC(12)
16			τCCOC(22)
21			τCCCC(45)+τOCCC(14)+τNCCC(11)
36			τCCCC(52)
43			τCCCC(26)+τNCCC(12)
47			δOCC(11)+τCCCC(22)
62	68		τCOCC(19)+τCNCC(16)
77			τNCCC(14)+τCOCC(11)
107	115		τCOCC(10)+γCCCC(18)
142			τCNCC(15)
144			δCCN(11)
208			δCCC(15)
223			δCCC(11)+τHCCC(39)
286			δCCC(20)+τSCNC(12)
324	326		δCCC(17)
356			δCCC(22)
370			νSC(13)+δOCS(33)+δCNC(12)
377			δCCC(15)+τCCCC(27)+γCCNC(19)
400			τNCCC(11)+γCCOC(13)
417			δCCN(16)
423			τHCNC(13)+τCNCC(20)+γCCNC(13)
427			τCCCC(26)+τCCCO(21)
465	468		δSCN(44)
506		513	νSC(11)+δOCN(16)+γCCOC(18)
527			γCCCC(15)
596	601	584	νNC(31)+δCNC(30)
616			τHNCC(69)+γONSC(12)
653	640		δCCC(33)
659			νCC(10)+δNCC(26)
670			γOCNC(11)+γONSC(20)
706			νSC(18)+γOCNC(12)
729			τCCCC(12)
736			δNCC(19)
741	742	738	τCCCC(14)+τCNCC(23)
754			νCC(10)
793		790	τHCCC(62)
802			νCC(12)
815			τHCCC(33)
834			τHCCC(68)
844	855	849	τHCCC(53)
862			τHCCC(61)
880	872	872	νCC(24)+δCCC(11)
931		930	νCC(26)
947			τHCCC(13)
952			τHCNC(71)

962			τHCCC(51)
968			τHCCC(11)
976			νCC(65)
987			τHCCC(60)
1029			δCCC(62)
1042	1039	1037	νCC(61)
1045			δCCC(13)
1060	1063		νOC(67)
1075			νCC(22)
1088			νCC(14)+τHCCC(14)
1090			τHCOC(10)
1092			νCC(37)
1138			νCC(12)+δHCC(20)
1145	1150	1147	νNC(39)
1165			δHCC(30)
1174		1175	δHCS(28)+δHCC(27)
1207	1207		δHCC(63)
1221			νCC(13)
1222			δHCO(55)
1232		1230	νCC(31)
1242	1242	1241	νCC(33)
1244			δHCS(20)+τHCSC(41)
1275			δHCC(33)
1296			νOC(39)
1300			δHCC(22)+τHCSC(20)
1309	1306	1310	νCC(12)
1316			τHCCC(17)
1323			νCC(13)+δOCN(20)
1328		1333	νNC(38)+δHCC(10)+δHCN(16)
1343			δHCC(51)
1351			δHCN(13)
1357			τHCCC(12)
1364			τHCCC(29)
1377			τHCCCC(22)
1385	1395	1396	δHNC(50)
1425			τHCOC(11)
1447	1441		δHCH(10)+τHCOC(10)
1468		1460	νCC(16)
1495			δHCH(75)
1496			δHCH(85)
1501			δHCH(77)
1511		1508	δHCH(36)+τHCCC(15)
1521			δHCH(35)
1527			δHCH(83)
1536			δHCN(21)
1561		1552	δHCC(43)
1615	1609	1607	νNC(21)+νCC(11)
1629	1636		νCC(28)+δCCO(10)
1658			νCC(34)

1672	1685	1682	νCC(40)
1822			νOC(51)
1855			νOC(91)
3039	3024		νCH(99)
3041			νCH(95)
3045			νCH(155)
3055			νCH(99)
3068	3062		νCH(37)
3079			νCH(58)
3085			νCH(88)
3095	3100	3092	νCH(46)
3107			νCH(52)
3120			νCH(49)
3123			νCH(65)
3149			νCH(99)
3172			νCH(95)
3173			νCH(79)
3184			νCH(97)
3194			νCH(99)
3211			νCH(95)
3229			νCH(97)
3614			νNH(100)

υ-stretching; δ-in plane bending; γ-Out of plane bending; τ-torsion

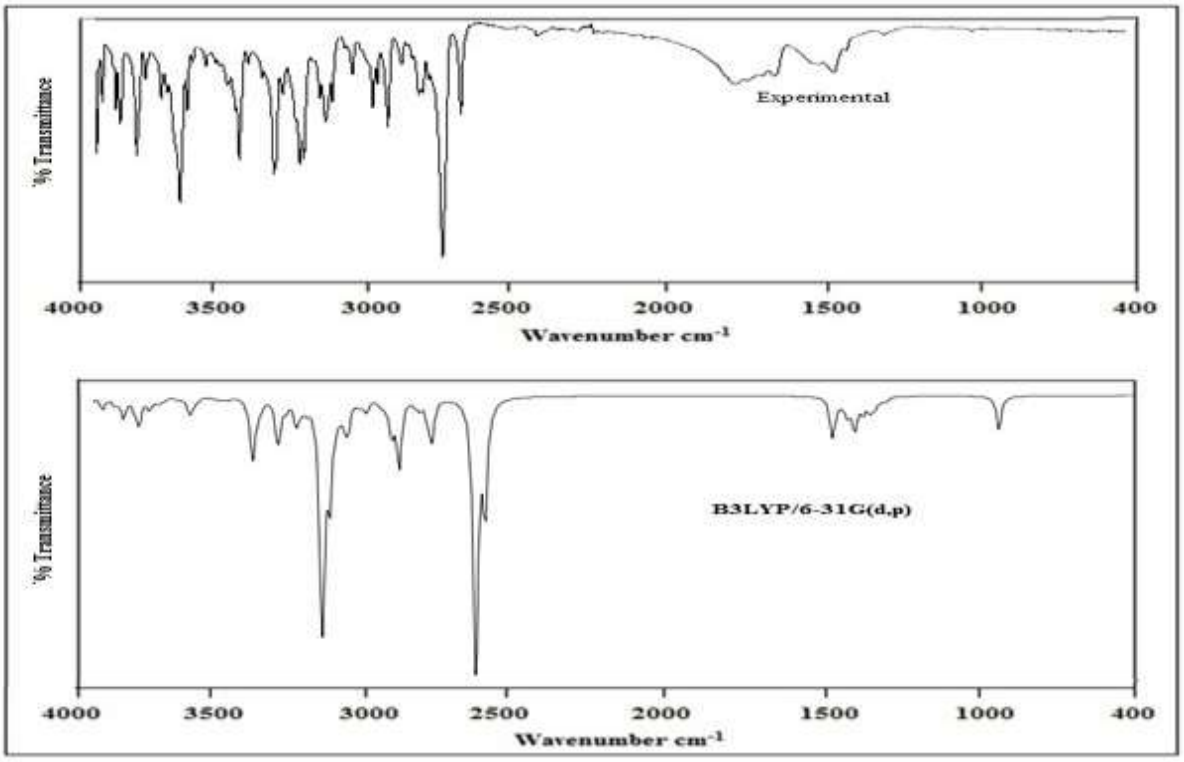


Fig.2 FT-IR spectrum of Pioglitazone

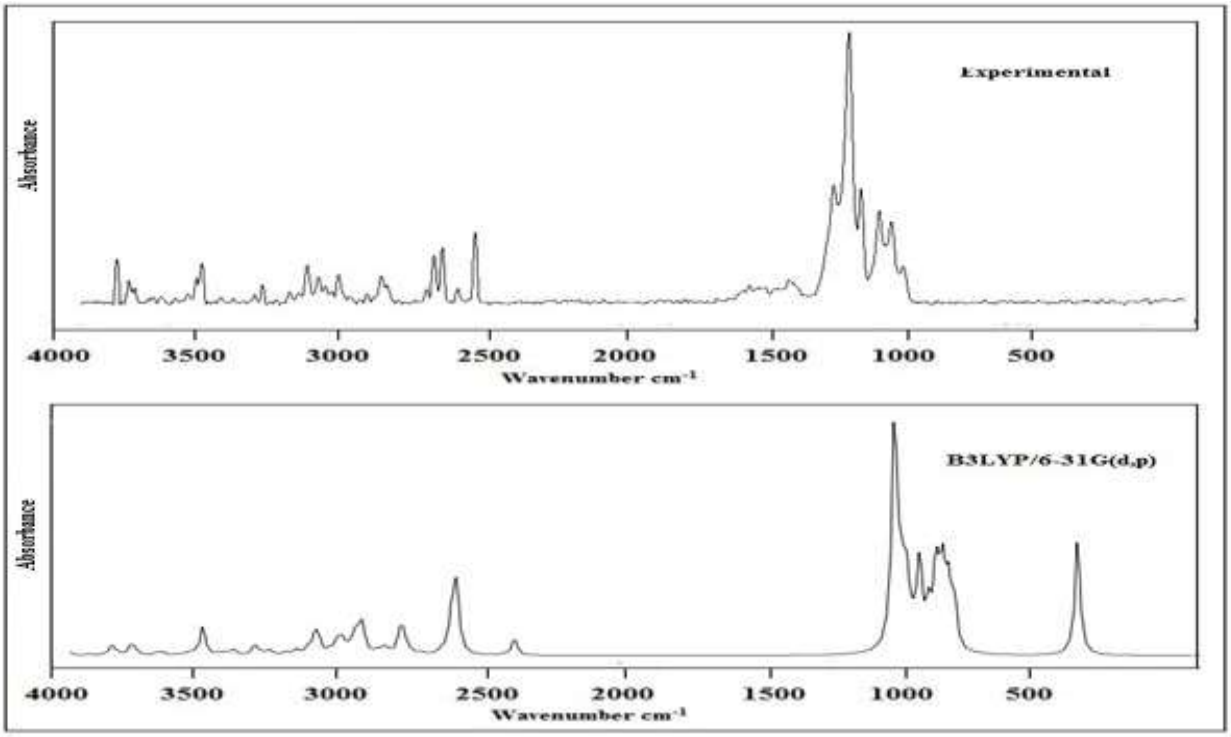


Fig. 3 FT-Raman spectrum of Pioglitazone

4.3 N-H Vibrations

The N-H stretching vibration for aromatic compounds observed in the region of 3500-3220 cm^{-1} [10]. In the spectra of solid samples are obtained near 3350 cm^{-1} to 3180 cm^{-1} because of hydrogen bonding [11]. Generally the N-H stretching vibration occurs in the region of 3500-3000 cm^{-1} for all heterocyclic compounds [12]. In this present investigation, N-H stretching vibrations are observed at 3092 cm^{-1} for FT-IR and at 3024 cm^{-1}, 3062 cm^{-1} and 3100 cm^{-1} for FT-Raman spectra. The above said vibrations were performed in the range of 3614 cm^{-1} to 3024 cm^{-1} by DFT with6-31G(d,p) basis set. The theoretical values by DFT are in good matching with the experimental value.

4.4C-S Vibrations

Generally,the C-S stretching vibrations band assignment is verydifficult for different compounds. Both aliphatic and aromatic sulfides have weak –to- medium bands due to C-S stretching vibration in the region of 750-510 $cm^{-1}$and [13]. In FT-IR spectrum, the band presented at 513 cm^{-1} was assigned to C-S stretching vibrations matched with the experimental values. The in-plane bending vibrations of C-S band of the pioglitazone were found at 324 cm^{-1} in B3LYP/6-31G (d,p) basis set, for experimental value of the above said C-S band for FT-IR is 326 cm^{-1}. According to the literature survey [14]the C-S stretching vibrations were found to be within their characteristic regions.

4.5 C=O Vibrations

The C=O stretching vibration band can be easily identified from the FT-IR and FT-Raman spectrum because of its high intensity [15, 16] degree ofconjugation, the strength and polarizations are increasing. The strong band in the region 1715-1680 cm^{-1} are attributed to C=O stretching vibrations [17]. In this present investigation, the stretching at 1607 cm^{-1} and 1682 cm^{-1} in FT-IR and1609 cm^{-1} ,1636 cm^{-1} and 1685 cm^{-1} in FT-Raman and the theoretical bands by B3LYP at 1615 cm^{-1}, 1629 cm^{-1}, 1658 cm^{-1}, and 1672 cm^{-1} corresponds to C=O stretching. A medium intensity band of in-plane bending of C=O observed at 872 cm^{-1} both experimental FT-IR and FT-Raman spectra which is in good agreement with the calculated frequencies.

4.6 C-H Vibrations

The C-H stretching band vibrations generally occurred in the range of 3100-2950 cm^{-1}[18]. In the present study, the bands appeared at 3092 cm^{-1} in FT-IR spectrum and 3100 cm^{-1} in FT-Raman spectrum are assigned to C-H stretching vibrations. The pioglitazone molecules has eight C-H stretching vibrations appeared at 3039,3041,3045,3055,3068,3079,3085,and 3095 cm^{-1} by DFT method. The C-H out- of- plane bending vibrations appeared at 750-1000 cm^{-1} [19]. For this title molecule, the bands observed at 738,790,849,and 872 cm^{-1} inFT-IR spectrum and at 742,855 and 872 cm^{-1} in FT-Raman spectrum respectively. From DFT methods, the C-Hout-of–planebending vibrations appeared at 729,736,741,754,793,802,815,834,844,862, and 880 cm^{-1}. The C-H in- plane bending vibrations presented at the region of 1000-1300 cm^{-1} [20-24]. In this present investigation, five C-H in–plane bending vibrations identified at 1039,1063,1150,1207 and 1242 cm^{-1}in FT-Raman spectrum and five FT-IR bands observed at 1037,1147,1175,1230 and 1241 cm^{-1}. The theoretical values are in good agreement with the experimental values.

4.7 C-C Vibrations

The C-C bond stretching vibrations identified generally in the region of 1650-1400 cm^{-1}[25]. For this title compound, the wave numbers found at 1511 cm^{-1} and 1615 cm^{-1}in B3LYP methods are assigned to C-C stretching vibrations. The wave numbers appeared at 1460, 1508, 1552, and 1607 cm^{-1}in FT-IR spectrum, 1441 cm^{-1} and 1609 cm^{-1} in FT-Raman spectrum belongs to C-C stretching vibrations of labeled compound. The calculated vibrations are matched with the experimental observations.

4.8C-N Vibrations

The C-N stretching vibrations are commonly in the range of 1600-1200 cm^{-1} for aromatic compounds. The labeling of C-N vibrations is a crucial work [26], the mixing of vibrations is possible in this region. From the literature survey, the bands appeared at 1305 cm^{-1} in FTIR and 1307 cm^{-1} in FT-Raman spectra of 7-choloro-3-methyl-2H-1,2,4-benzothiadiazine 1, 1-dioxide assigned to C-N stretching vibrations by Seshadri etal. [27].The C-N stretching vibrations are observed at 1375 cm^{-1} by Krishnakumar[28]. In this present investigation, the bands appeared at 1037,1147,and 1175 cm^{-1} in FT-IR and 1039,1150 and 1207 cm^{-1} in FT-Raman have been assigned to C-N stretching vibrations. The bands observed at 1042,1060 and 1145 cm^{-1} by B3LYP are in good matching with the experimental values.

5. NBO Analysis

The natural bond orbital (NBO) investigation gives a useful method for studying interesting features of intra and intermolecular bonding and interaction between bonds and also gives a convenient basis for investigating charge transfer in molecular systems [29]. Additional useful aspect of NBO method is that it gives information about interaction in both filled and virtual orbital spaces that could enhance the analysis of intra and intermolecular interactions [30].The NBO analysis is important for understanding the delocalization effect from lone pairs (donor) to anti-bonding orbitals (acceptor) [31].The second order Fock matrix was carried out to evaluate the donor-acceptor interactions in the NBO analysis [32-34].

Table 3. NBO analysis of Pioglitazone

Donor	Acceptor	E(2) Kj/mol	E(j)-E(i) (a.u)	F(I,j) (a.u)
π C_9-C_{10}	π *C_{11}-C_{12}	17.84	0.27	0.063
π C_9-C_{10}	π *C_{13}-C_{14}	21.26	0.28	0.069
π C_{11}-C_{12}	π *C_9-C_{10}	21.28	0.29	0.071
π C_{11}-C_{12}	π *C_{13}-C_{14}	17.54	0.29	0.064
π C_{13}-C_{14}	π *C_9-C_{10}	18.13	0.28	0.065
π C_{13}-C_{14}	π *C_{11}-C_{12}	20.99	0.27	0.069
π C_{18}-N_{23}	π *C_{21}-C_{22}	23.90	0.32	0.078
π C_{19}-C_{20}	π *C_{18}-N_{23}	27.18	0.26	0.076
π C_{19}-C_{20}	π *C_{21}-C_{22}	18.43	0.28	0.065
π C_{21}-C_{22}	π *C_{18}-N_{23}	18.25	0.26	0.062
π C_{21}-C_{22}	π *C_{19}-C_{20}	21.07	0.28	0.069
LP(2) S_1	π *C_2-O_6	26.30	0.21	0.069
LP(1) N_3	π *C_2-O_6	57.13	0.25	0.109

LP(1) N_3	π *C_4-O_7	53.47	0.27	0.111
LP(2) O_6	σ * S_1-C_2	35.71	0.35	0.102
LP(2) O_6	σ * C_2-N_3	24.15	0.64	0.114
LP(2) O_7	σ * N_3-C_4	25.65	0.66	0.118
LP(2) O_7	σ * C_4-C_5	19.91	0.60	0.100
LP(2) O_{15}	π *C_{11}-C_{12}	29.68	0.32	0.093
π *C_{18}-N_{23}	π *C_{19}-C_{20}	170.65	0.02	0.084
π *C_{18}-N_{23}	π *C_{21}-C_{22}	108.50	0.02	0.076

The results of interactions are the loss of occupancy from the localized NBO of the idealized Lewis structure into an empty non-Lewis orbital. For each donor (i) and acceptor(j), the stabilization energy $E^{(2)}$ associated with the delocalization i→ j is estimated as

$$E^{(2)} = E_{ij} = q_i F(i,j)^2 \Big/ (\varepsilon_j - \varepsilon_{i)}$$

Where q_i is the donor orbital occupancy, ε_i, ε_j are diagonal elements and F (i, j) is the offdiagonal NBO Fock matrix element. The perturbation energies of significant donor –acceptor interactions are presented in Table3. In NBO analysis, larger $E^{(2)}$ values shows the intensive interaction between electron donors and electron acceptors and greater the extent of conjugation of the whole system. For this label molecule the interactions π *(C_{18}-N_{23}) → π *(C_{19}-C_{20}) has thehighest $E^{(2)}$value around 170.65 Kcal/mol. π *(C_{18}-N_{23}) → π *(C_{21}-C_{22}), lone pair (N_3) → π *(C_2-O_6) and lone pair (N_3) → π *(C_4-O_7) are the other significant interactions giving stronger stabilization energy to the structure.

6. Mulliken Population Analysis:

The Mullikan charge is directly related to the vibrational properties of the molecule and quantities how the electronic structure changes under atomic displacement. It is therefore related directly to the chemical bonds present in the molecule[35].The Mullikan charge gives net atomic population in the molecule. The total atomiccharges of pioglitazone were obtained by Mullikan population analysis with DFT calculation and 6-31 G(d, p) basis set. The results are tabulated in the Table 4.

Table 4. Mulliken atomic charges of Pioglitazone by B3LYP method

Atoms	Charge (eV)	Atoms	Charge (eV)
S1	0.181294	C24	-0.250760
C2	0.416531	C25	-0.309568
N3	-0.523760	H26	0.293683
C4	0.609369	H27	0.172367
C5	-0.333615	H28	0.137378
O6	-0.436011	H29	0.124445
O7	-0.478177	H30	0.100176
C8	-0.245352	H31	0.106388
C9	0.102075	H32	0.083723
C10	-0.127769	H33	0.075688
C11	-0.134256	H34	0.124409
C12	0.356243	H35	0.115648
C13	-0.118554	H36	0.119025
C14	-0.124472	H37	0.126724
O15	-0.546642	H38	0.078709
C16	0.069798	H39	0.088671
C17	-0.267519	H40	0.100672
C18	0.278972	H41	0.109169
C19	-0.105078	H42	0.116090

C20	-0.087554	H43	0.114504
C21	0.109475	H44	0.114110
C22	0.058059	H45	0.101431
N23	-0.495738		

From the table 4, it shows all the hydrogen atoms have the positive charge. The highest positive charge possessed by H26 atom and the low value atom is H33. Similarly the sulphuratom (S1) also has the positive charge. The nitrogen and oxygen atoms presented in the pioglitazone molecules are negatively charged one.Most of the carbon atoms of title compound are negatively charged except C2, C12, C16, C18, C21 and C22 atoms. The lowest negative charge is -0.0875eV possessed by C20 atom and the highest negative charge is O15 atom (-0.5466eV).

7. Molecular Electrostatic Potential (MEP)

Molecular electrostatic potential are useful quantities to visualize the charge sharing of molecules and used to study the variably charged regions of molecule. MEP is a property that the electron and nuclei of compound create the electrostatic potential surface at each point in the surrounding space [36]. It is broadly used as a reactivity map displaying most probable region for the electrophilicattack of charged point like reagents on organic molecules [37].

The molecular electrostatic potential V(r) is defined by

$$V(r) = \sum_A \frac{Z_A}{(R_A - r)} - \int \frac{\rho(r')}{(r' - r)} dr'$$

Here ZAis the charge of nucleus A, located at RA,ρ(r') is the electron density function for the molecule and r' is the dummy integration variable [38]. MEP is very useful caption for determining sites for electrophilic attack and nucleophilic reactions and hydrogen- bonding interactions [39, 40]. The molecular electrostatic potential map displays the positive sites are nucleophilic regions and the negative sites are electrophilic regions. The electrophilic regions are around oxygen atoms, nucleophilic regions are around carbon atoms (attached with oxygen atoms)and around hydrogen atoms.

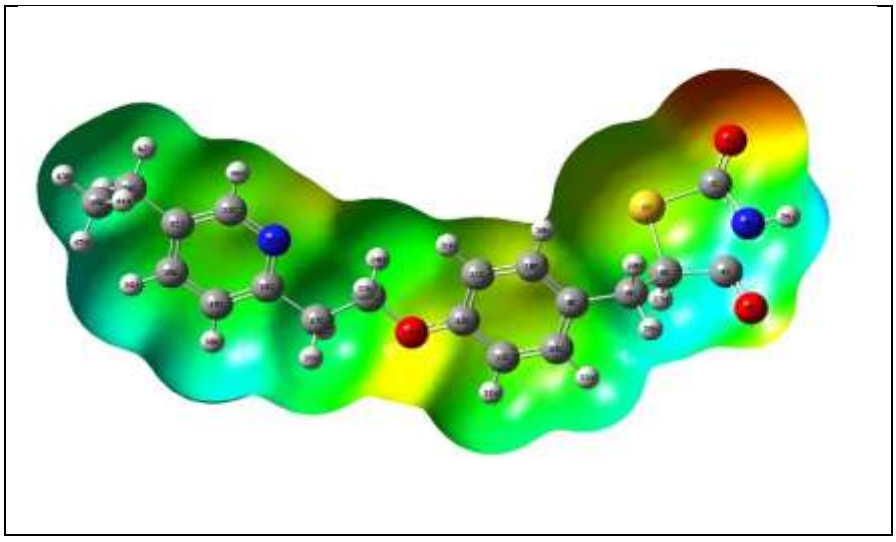


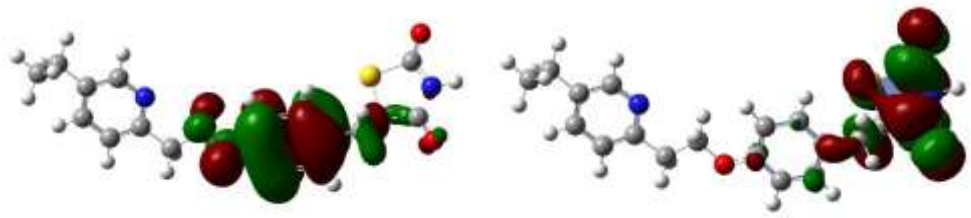
Fig 4. Molecular electrostatic potential Surface of Pioglitazone

For this title compound, the MEPs at the surface represented by different colors. Blue color representsthe regions of positive electrostatic potential, whereas the red colorrepresents the regions of negative electrostatic potential. Also, green color represents the zero potential regions. Corresponding mapped

electrostatic potential surfaces have been plotted for the label compound by using DFT/6-31G(d, p) basis set of the Gaussian view 5.0 software package.The MEP is showed in the Fig 4.

8.Frontier Molecular Orbitals (FMOs)

It plays a vital role in the chemical stability of the molecule [41]. Generally the frontier molecular orbitals (FMOs) such as highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). The HOMO shows the strength to donate an electron and LUMO shows the facility to accept an electron also called electron acceptor. The chemical reactivity, optical polarizability, hardness, softness of the molecule can be determined by the energy gap between HOMO and LUMO[42].



HOMO **LUMO**

Fig 5. 3D Plots of Frontier Molecular Orbital of Pioglitazone

The HOMO-LUMO energies of the title molecule were calculated by DFT/6-31G (d,p) basis set. The molecule have a small orbital gap is more polarizable and is commonly related with a high chemical reactivity, low stability and it is termed as soft molecule [43-45].HOMO can be thought the outermost orbital containing donor electrons and energy of the HOMO is directly related to the ionization potential. Whereas the LUMO can be thought the innermost orbital containing free places to accept electrons and their energy is directly related to the electron affinity [46]. The molecular orbital compositions of the FMOs of pioglitazone molecules are sketched in Fig 5. From the figure the positive regions are denoted by red color and the green color represents the negative phase. The HOMO energy value is 5.8972 eV and 0.8832eV is the energy of LUMO. The energy gap between HOMO-LUMOis 5.0140 eV.

9.Global and Local Reactivity Descriptors

The frontier molecular orbital energies (HOMO and LUMO energy) the energy gap between HOMO and LUMO, chemical potential (μ), electron negativity (χ), global electrophilic index (ω), global hardness (η) and global softness (S) [47-49]of pioglitazone were listed in Table 5.

Table 5. Molecular properties of Pioglitazone

Molecular properties	B3LYP	Molecular properties	B3LYP
E_{HOMO}(eV)	5.8973	Chemical Hardness(η)	-2.5070
E_{LUMO}(eV)	0.8833	Softness(S)	-0.3989
$E_{Homo\text{-}Lumo}$gap(eV)	5.0140	Chemical Potential(μ)	3.3903
Ionisation potential(I) eV	-5.8973	Electronegativity(χ)	-3.3903
Electron affinity (A) eV	-0.8833	Electrophilicity index(ω)	5.7470

The above global quantities are calculated with the help of HOMO-LUMO energies using the below equations.

Chemical potential

$$\mu=\frac{-(I+A)}{2}$$

Chemical hardness

$$\eta=\frac{I-A}{2}$$

Chemical softness

$S=\frac{1}{\eta}$

Electrophilicity index

$\omega=\frac{\mu^2}{2}$

Electronegativity

$\chi=\frac{I+A}{2}$

10. Conclusion

In this present study, spectroscopic properties of pioglitazone have been done with the help of FT-IR and FT-Raman spectroscopies. The vibrational assignments using PED are calculated for the label compound. The vibrational wavenumbers determined experimentally were compared with the theoretical wavenumbers calculated by the help of B3LYP employing 6-31G (d,p) basis set. The geometrical parameters like bond angles and bond lengths are calculated. The theoretical and experimental spectra of FT-IR and FT-Raman are very well matched. HOMO and LUMO energy gaps explain the eventual charge transfer interactions taking place within the molecule. The stability and intra molecular interactions have been done by NBO analysis. The molecular electrostaticpotential map is drawn and the Mulliken population analyses of pioglitazone molecule are also calculated.

References

1. VijayaKumariKarra, NageswaraRao Pilli, Jaswanth Kumar Inamadugu J.V.L.N. SeshagiriRao, J. Pharm. Analysis, 2012, 2(3), 167-173.
2. N. Satheeshkumar, S.Shantikumar, R.Srinivas, J. Pharm. Analysis, 2014, 4(5), 295-302.
3. John Waugh, Gillian M. Keating, Greg L. Plosker, Stephanie Easthope and Dean M. obinson, Drugs, 2006, 66(1), 85-109.
4. Agha ZeeshanMirza , M. SaeedArayne , Najma Sultana, J. Asso. Arab Univ. Basic and Appl. Sci. 2017, 22, 70–75.
5. SK Sharma, SH Verma, J. The Asso. Phy. India, 2016, 64, 24-28.
6. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T.Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. ratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J.Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A.Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A.Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W.Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision A.1, Gaussian Inc, Pittsburgh, PA, 2003.
7. M.H. Jamroz, Vibrational energy Distribution Analysis VEDA 4, Warsaw,Poland, 2004.
8. Y. Wang, S. Saebo, C.U. Pittman Jr., J. Mol. Struct. (THEOCHEM), 1993, 281, 91–98.
9. E.D. Glendening, A.E. Reed, J.E. Carpenter, F. Weinhold, NBO Version 3.1, TCI, University of Wisconsin, Madison, 1998.
10. S. Suresh, S. Gunasekaran, S. Srinivasan, Spectrochim. Acta A, 2014 125, 239–251.
11. S. Gunasekaran, R.K. Natarajan, D. Syamala, R. Rathika, Ind. J. Pure Appl. Phys. 2006, 44, 315.
12. N. Sundaraganesan, S. Ilakiamani, P. Subramani, B.D. Joshua, Spectrochim. Acta. 2007, 67A, 628–635.
13. T. Gnanasambandan, S. Gunasekaran, S. Seshadri, J. Mol. Struc. , 2013, 1052, 38-49.
14. G. Socrates, Infrared and Raman Characteristic Group Frequencies, third ed., Wiley, New York, 2001.
15. D.L. Vein, N.B. Colthup, W.G. Fateley, J.G. Grasselli, The Handbook of Infrared and Raman Characteristic Frequencies of Organic Molecules, Academic Press, San Diego, 1991.
16. S. Gunasekaran, U. Ponnambalam, S. Muthu, ActaCienc. Indica. , 2004, 30, 1015-1020.

17. P. Koczon, J.Cz. Dobrowclski, W. Lewandowski, A.P. Mazurek, J. Mol. Struct., 2003, 655, 89-85.
18. S.Rajesh, S. Gunasekaran, P. Rajesh, Inter. J. Ch. Tech Res. , 2018, 11(07), 107-122.
19. G. Socrates, Infrared Characteristic Group frequencies, Wiley-Interscience, Publication, New York, 1980.
20. S. Ramalingam, S. Periandy, B. Narayanan, S. Mohan, Spectrochim. Acta. , 2010, 7, 84–92.
21. M. Karabacak, D. Karagoz, M. Kurt, J. Mol. Struct. , 2008, 892, 25–31.
22. A. Usha Rani, N. Sundaraganesan, M. Kurt, M. Cinar, M. Karabacak, Spectrochim. Acta. , 2010, 75, 1523–1529.
23. M. Karabacak, M. Kurt, A. Atac, J. Phys. Org. Chem. , 2009, 22, 321–330.
24. P.M. Wojciechowski, D. Michalska, Spectrochim. Acta. , 2007, 68, 948–955.
25. P. Rajesh, S. Gunasekaran, T. Gnanasambandan, S. Seshadri, Spectrochim. Acta. , 2015, 137, 1184–1193.
26. T. Ramya , S. Gunasekaran , G.R. Ramkumaar,Spectrochim. Acta Part A Mol. Biomol. Spectrosc., 2015, 149, 132-142.
27. S. Seshadri, S. Gunasekaran, S. Muthu, J. Raman Spectrosc., 2009, 40, 639.
28. V. Krishnakumar, R. John Xavier, Indian J. Pure Appl. Phys., 2003, 41, 597–601.
29. E. Scrocco, J. Tomasi, Topics in Current Chemistry, vol. 42, Springer-Verlag, Berlin, 1973.
30. P.Govindasamy , S. Gunasekaran, J. Mol. Struct. , 2015, 1081, 96-109.
31. A.E. Reed, P.V.R. Schleye, Inorg. Chem., 1988, 27, 3969.
32. C. James, A. AmalRaj, R. Reghunathan, J. Raman Spectrosc., 2006, 37, 1381–1392.
33. L.J. Na, C.Z. Rang, Y.S. Fang, J. Zhejiang, Univ. Sci. B, 2005, 6, 584–589.
34. M. Szafram, A. Komasa, E.B. Adamska, J. Mol. Struct., 2007, 827, 101–107.
35. M. Prabhaharan , A.R. Prabakaran , S. Srinivasan , S. Gunasekaran, Spectrochim. Acta Part A Mol. Biomol. Spectrosc., 2014, 127, 454-462.
36. K. Golcuk, A. Altun, M. Kumru, Spectrochim. Acta, Part A, 2003, 59A, 1841–1847.
37. P. Politzer, D.G. Truhlar (Eds.), Chemical Application of Atomic and Molecular Electrostatic Potentials, Plenum, New York, 1981.
38. P. Politzer, P.R. Laurence, K. Jayasuriya, Molecular electrostatic potentials: an effective tool for the elucidation of biochemical phenomena, in: J. McKinney (Ed.), Structure Activity Correlation in Mechanism Studies and Predictive Toxicology, Environ. Health Perspect. 1985, 61, 191–202.
39. F.J. Luque, J.M. Lopez, M. Orozco, Theor. Chem. Acc., 2000, 103, 343–345.
40. N. Okulik, A.H. Jubert, J. Mol. Des., 2005, 4, 17–30.
41. S. Gunasekaran, R.A. Balaji, S. Kumaresan, G. Anand, S. Srinivasan, Can. J. Anal.Sci. Spectrosc., 2008, 53, 149–162.
42. B. Kosar, C. Albayrak, Spectrochim. Acta A, 2011, 78, 160–167.
43. A. Rauk, Orbital Interaction Theory of Organic Chemistry, second ed., Wiley-Interscience, New York, 2001.
44. A. Streitwieser Jr., Molecular Orbital Theory for Organic Chemists, Wiley, New York, 1961.
45. B.J. Powell, T. Baruah, N. Bernstein, K. Brake, R.H. McKenzie, P. Meredith,M.R. Pederson, J. Chem. Phys., 2004, 120, 8608-8615.
46. G. Gece, Corros. Sci., 2008, 50, 2981–2992.
47. B. Kosar, C. Albayrak, Spectrochim. Acta, 2011, 78A, 160–167.
48. R.G. Pearson, J. Org. Chem., 1989, 54, 1423–1430.
49. P. Geerlings, F.D. Proft, W. Langenaeker, Chem. Rev., 2003, 103, 1793–1873.

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