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Research Article

Spectroscopic and Theoretical Investigation of Pioglitazone with FT-IR, Raman, UV-Vis. and NMR

Tuba Özdemir ÖGE[1*], Adnan SAĞLAM[2], Firdevs Banu ÖZDEMIR[3], Ali Ünsal KESKINER[4], Mecit ÖGE[5]

[1]Vocational School of Health Services, Bartın University, 74100 Bartın, Turkey;
[2]Faculty of Engineering, Architecture and Design, Department of Electrical and Electronic Engineering, Bartın University, Kutlubey-Yazıcılar Campus, 74100 Bartın, Turkey;
[3]Department of Medical Services and Techniques, Radiotherapy Program, Beykent University Vocational School, , 34500 Istanbul, Turkey;
[4]Pharmacist, Kozcagiz, 74100 Bartın, Turkey
[5]Faculty of Engineering, Architecture and Design, Department of Mechanical Engineering, Bartın University, Kutlubey-Yazıcılar Campus, 74100 Bartın, Turkey;

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Abstract

Geometric structures, bond lengths, bond angles, vibrational frequencies, dipole moments, proton and carbon-13 NMR isotropic chemical shifts, UV-Vis. Parameters, HOMO and LUMO energies of pioglitazone molecules were studied using Gaussian09 program with DFT/B3LYP method at the 6-311G++(2d,2p) basis set. The assignments of theoretical vibrational modes were obtained using VEDA 4 software in terms of potential energy distribution (PED). The spectroscopic characterizations of pioglitazone molecule were performed using FT-IR, Laser-Raman, and NMR chemical shift and UV-vis. experimental methods. Theoretically obtained geometric parameters, vibrational wavenumbers and NMR chemical shifts will also be compared with the experimental results.

Keywords: Pioglitazone, FTIR, Laser-Raman, Proton and Carbon-13 NMR chemical shifts, DFT/B3LYP

Pioglitazon Molekülünün Spektroskopik Özelliklerinin FT-IR, Raman, UV-Vis ve NMR Yöntemleri ile Teorik ve Deneysel Olarak İncelenmesi

Öz

Bu çalışmada pioglitazon molekülünün geometrik yapıları, bağ uzunlukları, bağ açıları, titreşim frekansları, dipol momentleri, proton ve karbon-13 NMR izotropik kimyasal kaymaları, UV-Vis. Parametreleri ile HOMO ve LUMO enerjileri Gaussian09 programı ve DFT/B3LYP yöntemi kullanılarak 6-311G++(2d,2p) temel setinde incelenmiştir. Teorik titreşim modlarının potansiyel enerji dağılımı (PED) üzerinden belirlenmesi VEDA 4 yazılımı ile gerçekleştirilmiştir. Pioglitazon molekülünün spektroskopik karakterizasyonu FT-IR, Lazer-Raman ve NMR kimyasal kayma ve UV-vis deneysel yöntemleri ile gerçekleştirilmiştir. Teorik olarak elde edilen geometrik parametreler, titreşimsel dalgaboyları ve NMR kimyasal kayma değerleri de aynı zamanda deneysel sonuçlarla karşılaştırılmıştır.

*Corresponding Author: tozdemir@bartin.edu.tr

1. Introduction

Pioglitazone is a prescription anti-diabetic drug that reduces insulin resistance. Pioglitazone is in the thiazolidinedione class and used in the treatment of diabetes mellitus type 2. It can be used alone or with other medicines such as insulin, metformin, or sulfonylurea agents (Soni, 2014). Pioglitazone hydrochloride (PGZ), [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]-2,4-] thiazolidine-dione monohydrochloride, is an oral anti-hyperglycemic agent (Sujana et al., 2011). The systemic chemical names are given in Ref (Pioglitazone, 2021; Moffat et al., 2011; Alexandar et al., 2010; Shrivastaval et al., 2008). The chemical formula of pioglitazone used in the present study is C19H20N2O3S. Pioglitazone, 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione, is an insulin sensitizing agent indicated for the treatment of type 2 diabetes. The CAS and MDL numbers are CDS021593 and MFCD00865504, respectively. Al-Majed et al. (2016) reported the elemental analysis of pioglitazone as C:64.02%, H:5.66%, N:7.86%, O:13.47%, S:9.00%; and pioglitazone hydrochloride as C:58.08%, H:5.39%, N:7.13%, O:12.22%, S:8.16%, Cl:9.02% (Al-Majed et al. 2016). The empirical formula of pioglitazone hydrochloride is $C_{19}H_{20}N_2O_3S.HCl$. The melting points of pioglitazone and pioglitazone hydrochloride are 183-184^{0}C and 193-194^{0}C, respectively (O'Neil, 2013). Investigation of pioglitazone by various analytical methods such as spectrophotometric method has been reported in literature (Patil et al., 2011; Kulkarni et al., 2012; Adhikari et al., 2012; Ulu and Elmalı, 2009; Dubey et al., 2013). Satheeshkumar, et al. (2014) reported a review on the analytical methods used in the investigation of pioglitazone (Satheeshkumar et al., 2014). Appana Chowdary K., et al. investigated the formulation and characterization of pioglitazone hydrochloride nanoparticles and found the average particle size of pioglitazone hydrochloride in the range of 100-500 nm (Appana Chowdary K. et al., 2015). Attia, et al. (2013) studied the thermal analysis of some antidiabetic pharmaceutical compounds such as pioglitazone hydrochloride (PTZ), rosiglitazone maleate (RGZ), glibenclamide (GBD) and glimepiride (GMP) (Attia et al., 2013). Few studies on the density functional theory study (DFT) of pioglitazone haVE been encountered in the related literature (Rajesh et al., 2018; Thirunavukkarasu et al., 2018). The theoretical spectral investigation of pioglitazone were performed using density functional theory (DFT) with 6-31G (d,p) basis set by Rajesh et al. (2018). The vibrational frequencies of $C_{19}H_{20}N_2O_3S$ were obtained theoretically with 6-31G(d,p) and 6-311G(d,p) basis sets for optimized geometry by Thirunavukkarasu et al. (2018). In the present study, DFT study was theoretically carried out to obtain the vibrational wavenumbers, FT-IR, Laser-Raman, and NMR chemical shifts and UV-vis of pioglitazone molecule. The recorded experimental data were then supported using theoretical methods at DFT/B3LYP/6-311G++(2d,2p) level. The obtained theoretical and experimental results were used to give detailed information of the molecular electronic structure of the pioglitazone molecule.

2. Materials and Methods

Pioglitazone was purchased from Sigma-Aldrich Corporation in powder form. The molecular weight is 356.44 g/mol. The other geometric parameters such as bond lengths, bond angles and torsion angles with the corresponding literature information, are given in Table 1.

Table 1. The optimized molecular geometric parameters for pioglitazone.

Bond	**Bond lengths (Å) (Yathirajan et al., 2005)**	**Bond lengths (Å) (This study)**	**Bond angles (°) (This study)**	**Values**	**Bond angles (°) (This study)**	**Values**
C25-H43	0.9800	1.090	H41-C24-H42	106.44	C10-C9-S6	113.88729
C25-H45	0.9800	1.091	H41-C24-C22	109.21	C8-C9-H36	107.30289
C25-H44	0.9800	1.090	H43-C25-C24	110.80	O3-C8-C9	124.15027
C24-C25	1.465	1.537	H43-C25-H45	108.01	C9-C8-N7	111.58730
C24-H42	0.9900	1.092	H42-C24-C25	109.28	C8-N4-C7	119.54272
C24-H41	0.9900	1.092	C24-C22-C23	121.39	O3-C8-N4	124.26149
C22-C24	1.509	1.509	C24-C22-C21	122.29	C8-N4-H37	120.84280
C21-C22	1.399	1.393	C24-C25-H44	111.00	C7-N4-H37	119.61430
C22-C23	1.366	1.396	H45-C25-H44	107.68	N4-C7-O2	124.87430
C21-H39	0.9500	1.083	C22-C21-H39	120.15	N4-C7-S6	109.45330
C23-H40	0.9500	1.085	C21-C22-C23	116.31	O2-C7-S6	125.67239
C20-C21	1.380	1.388	C22-C23-H40	119.63	C7-S6-C9	92.84309
C20-H38	0.9500	1.081	C22-C21-C20	119.82	C8-C9-S6	106.56953
C19-C20	1.378	1.395	C21-C20-H38	120.56	Dihedral angles (°)	Values
C19-N5	1.336	1.339	C19-C20-H38	120.10	O2-C7-S6-C9	179.75216
C23-N5	1.343	1.332	C20-C19-N5	121.43	O2-C7-N4-C8	179.86520
C18-C19	1.505	1.510	C19- N5-C23	118.51	C16-C11-C10-H34	158.90416
C18-H28	0.9900	1.091	N5-C23-H40	115.78	C16-C11-C12-H31	-179.48708
C18-H29	0.9900	1.090	N5-C19-C18	116.69	C14-C13-C12-H31	179.78987
C17-C18	1.510	1.523	C19-C18-H29	110.34	C15-C14-C13-H30	179.39385
C17-H26	0.9900	1.091	C19-C18-H28	109.30	C11-C12-C13-H30	-179.67615
C17-H27	0.9900	1.094	H28-C18-H29	107.68	C12-C13-C14-O1	-179.94377
C17-O1	1.434	1.429	H28-C18-C17	108.37	C16-C15-C14-O1	179.93942
C14-O1	1.379	1.362	C19-C18-C17	111.71	C22-C21-C20-H38	-179.72963
C13-C14	1.381	1.394	C18-C17-H27	110.71	C23-N5-C19-C18	179.97008
C12-C13	1.390	1.394	C18-C17-H26	109.96	C23-C22-C21-H39	-179.38656
C11-C12	1.398	1.391	H27-C17-H26	108.67	N5-C19-C20-H38	179.58700
C11-C16	1.366	1.401	H26-C17-O1	110.40	N5-C19-C18-H29	-174.55014
C14-C15	1.385	1.399	C17-O1-C14	118.61	C21-C20-C19-C18	-179.86146
C15-C16	1.370	1.383	O1-C14-C15	115.92	C14-C15-C16-H32	-179.24535
C13-H30	0.9500	1.079	C14-C15-H33	118.68	C11-C16-C15-H33	179.60380
C15-H33	0.9500	1.081	C14-C13-H30	121.07	C11-C12-C13-H30	-179.67615
C12-H31	0.9500	1.082	C15-C16-H32	118.91	C12-C11-C16-H32	178.97222
C16-H32	0.9500	1.083	C13-C12-H31	118.67	C12-C11-C10-H35	-139.76195
C10-C11	1.531	1.510	C14-C15-C16	120.18	C16-C11-C10-H34	158.90416
C9-C10	1.524	1.541	C13-C14-C15	119.32	C9-C8-N4-H37	-179.61566
C9-H36	1.0000	1.089	C12-C13-C14	119.64	O3-C8-N4-C7	-179.79800
C10-H34	0.9900	1.090	C11-C12-C13	121.75	C21-C22-C23-H40	179.25679
C10-H35	0.9900	1.091	C12-C11-C16	117.73	C21-C20-C19-C18	-179.86146
C8-C9	1.546	1.528	C11-C16-C15	121.38	C19-N5-C23-H40	-179.41725
C9-S6	1.823	1.846	C11-C16-H32	119.70	C16-C11-C10-H34	158.90416
C9-H36	1.0000	1.089	C11-C12-H31	119.59	C22-C24-C25-H43	-179.77640
N4-H37	0.93	1.010	C11-C10-H35	110.36	C24-C22-C21-C20	-178.59025
C7-S6	1.760	1.790	C11-C10-H34	110.23	C24-C22-C23-N5	178.70058
C7-O2	1.208	1.200	C9-C10-H35	106.40	C19-N5-C23-H40	-179.41725
		R^2=0.98	C9-C10-H34	108.86	C21-C22-C24-H41	-154.18076
			C10-C9-H36	109.50	H41-C24-C25-H45	178.42640
					H42-C24-C25-H44	-177.84920

Table 2. The experimental and computed vibrational wavenumbers and their vibrational assignments of pioglitazone results.

	Exp. freq. (cm^{-1})		**The computed parameters**		
Assignment (PED%) Molecular Formula: $C_{19}H_{20}N_2O_3S$	IR	Raman	Freq.	IIR	SRaman
$\tau C_{14}O_1C_{17}C_{18}(13)+ \tau C_{17}C_{18}C_{19}C_{20}(13)+ \tau C_8C_9C_{10}C_{11}(38)$		22	21.3	0.50	2.53
$\delta C_{17}C_{18}C_{19}(13)+ \tau C_{17}C_{18}C_{19}C_{20}(10)+ \tau C_{18}C_{19}N_5C_{20}(12)$		31	29.4	0.24	1.70
$\delta C_9C_{10}C_{11}(13)+ \tau C_{14}O_1C_{17}C_{18}(17)+ \rho CH_3$		67	70.4	0.17	0.55
$\delta O_1C_{17}C_{18}(10)+ \delta C_8C_9C_{10}(10)+ \tau S_6C_7N_4C_8(10)+ \rho CH_2$		157	156.0	0.22	1.82
$\gamma C_{18}C_{20}N_5C_{19}(21)+ \rho CH_3$		175	173.2	0.49	2.39
$\tau N_4C_8C_9C_{10}(11)+ \tau S_6C_7N_4C_8(10)+\tau CH_3$		283	282.6	0.15	1.32
$\nu_s S_6C_7(12)+ \delta O_2C_7S_6(33)+ \delta N_4C_8C_9(16)+ \rho CH_2$		373	363.3	15.44	2.25
$\tau N_4C_8C_9C_{10}(10)+ \gamma C_{15}C_{13}O_1C_{14}(11)+wCH_2$		400	404.0	1.56	0.40
$\tau H_{30}C_{13}C_{12}C_{11}(25)+ \tau C_{11}C_{12}C_{13}C_{14}(44)$	434.79		421.4	0.16	0.03
$\delta O_2C_7S_6(17)+ \delta N_4C_8C_9(18)+ \delta N_4C_8C_9(10)+ \delta S_6C_7N_4(31)+ \nu sC_9S_6$	465.56		455.0	4.05	6.80
$\delta S_6C_7N_4+ \delta O_1C_{14}C_{15}$		463	465.2	2.34	1.93
$\nu_s S_6C_7(12)+ \delta O_3C_8N_4(15)+ \gamma C_{15}C_{14}O_1C_{13}(21)$		499	499.6	10.55	0.26
$\delta C_{14}O_1C_{17}(10)+ \gamma C_{10}C_{11}C_{12}C_{16}(10) + \gamma C_{15}C_{13}O_1C_{14}(13)$	516.23		528.6	37.79	0.28
$\delta C_9C_{10}C_{11}(12)+ \tau H_{37}N_4C_8C_9(10)$	562.86		574.7	28.52	1.37
$\delta C_{25}C_{24}C_{22}(12)+ \tau C_{18}C_{20}N_5C_{19}(25)$	596.55		593.8	10.71	0.65
$\tau H_{37}N_4C_8C_9(66)$		598	601.0	49.02	2.13
$\delta C_{11}C_{12}C_{13}(10)+ \delta C_{11}C_{12}C_{13}(56)+ \delta C_{11}C_{12}C_{13}(12)$	641.40		643.2	1.79	5.09
$\delta C_{21}C_{20}C_{19}(12)+ \gamma O_2N_4S_6C_7(37)$	657.28		651.6	15.18	4.68
$\delta N_4C_8C_9(19)+ \delta S_6C_7N_4(15)+\gamma O_2N_4S_6C_7(12)+ \rho CH_2$	715.21		714.5	10.05	1.81
$\tau C_{11}C_{12}C_{13}C_{14}(18)+ \gamma C_{10}C_{16}C_{12}C_{11}(17)$	737.44		731.7	5.33	2.40
$\tau H_{41}C_{24}C_{22}C_{21}(28)+ \rho CH_2+ \rho CH_3$	778.77		779.2	0.91	0.09
$\nu_s C_8C_9(10)+ \delta C_{20}C_{19}N_5(10)$			792.6	5.70	6.64
$\tau H_{30}C_{13}C_{12}C_{11}(56)+ \tau H_{26}C_{17}O_1C_{14}(28)$	822.73		816.4	1.14	0.56
$\tau H_{38}C_{20}C_{21}C_{22}(18)+ \tau H_{38}C_{20}C_{21}C_{22}(21)$	839.41		841.9	2.69	20.46
$\nu_s N_5C_{19}(11)+ \nu_s C_{20}C_{19}(10)+ \nu sC_{18}C_{19}$	903.04		869.6	13.54	41.14
$\nu_s C_8C_9(11)+ \nu_s C_8C_9(18)$	925.83		914.0	7.07	5.70
$\tau H_{30}C_{13}C_{12}C_{11}(61)+ \tau H_{30}C_{13}C_{12}C_{11}(15)$	960.18		963.1	0.19	0.10
$\nu_s C_9C_{10}(28)+ \delta C_{11}C_{12}C_{13}(28)$	1015.02		1015.2	2.88	11.94
$\delta H_{28}C_{18}C_{19}(17)+ \delta C_{23}N_5C_{19}(12)+ \delta C_{21}C_{20}C_{19}(13)$	1038.07		1039.0	18.63	0.88
$\delta H_{28}C_{18}C_{19}(11)+\tau H_{41}C_{24}C_{22}C_{21}(10)+ \tau H_{45}C_{25}C_{24}C_{22}(19)+ \tau C_{25}C_{24}C_{22}C_{21}(10)$	1070.75		1068.5	5.12	8.64
$\nu_s C_{11}C_{12}(16)+ \delta H_{36}C_9C_{10}+ \rho CH_2$	1107.46		1115.3	7.24	6.41
$\nu_s N_4C_7(53)+ \delta H_{37}N_4C_8(10)$		1138	1120.7	124.88	1.26
$\delta H_{36}C_9S_6(33)+ \delta H_{34}C_{10}C_{11}(21)+ \rho CH_2$	1157.53		1151.0	17.16	5.65
$\nu_s C_{11}C_{12}(13)+ \delta H_{30}C_{13}C_{12}(24)$	1178.87	1174	1182.5	72.12	13.21
$\nu_s C_{10}C_{11}+ \nu_s C_8C_9(19)+ \nu_s C_8C_9(16)$		1210	1205.9	9.04	80.19
$\nu_s C_{18}C_{19}(22)+ \nu_s C_{22}C_{24}+ \delta C_{17}H_{27}H_{26}+ \delta C_{24}H_{41}H_{42}$		1228	1228.1	40.19	0.37
$\nu_s O_1C_{14}(42)$	1249.82		1251.5	450.52	14.01
$\delta H_{36}C_9S_6(10)+ \delta H_{41}C_{24}C_{25}(16)+ \tau H_{34}C_{10}C_{11}C_{16}(20)+ \tau H_{34}C_{10}C_{11}C_{16}(13)$		1273	1277.2	18.91	3.87
$\nu_s N_4C_7(37)+ \delta O_3C_8N_4(21)$	1296.45	1300	1294.4	203.95	3.02
$\nu_s C_{11}C_{12}(13)+ \nu_s C_{15}C_{14}(11)$	1316.85	1318	1313.2	37.85	10.03
$\delta H_{30}C_{13}C_{12}(12)+ \delta H_{30}C_{13}C_{12}(12)+ \delta H_{30}C_{13}C_{12}(10)+ \tau H_{34}C_{10}C_{11}C_{16}(29)+ \rho CH_2$	1328.61		1324.0	3.68	19.43
$\delta H_{34}C_{10}C_{11}(27)+ \tau H_{34}C_{10}C_{11}C_{16}(16)+ \delta C_{10}H_{35}H_{11}+ \delta C_9H_{36}H_{10}$		1345	1347.6	14.69	51.25
$\nu O_2C_7(11)+ \nu N_4C_7(18)+ \delta H_{37}N_4C_8(61)+ \nu C_8{=}O_3(18)$		1372	1367.4	28.65	6.81
$\nu C_{24}C_{25}+ \delta_s H_{42}C_{24}H_{41}(77)+ \delta C_{25}H_{44}H_{45}+$	1384.17		1392.0	2.54	2.18

$\delta C_{25}H_{43}H_{44}$ $\tau H_{26}C_{17}O_1C_{14}(13)+ \tau H_{26}C_{17}O_1C_{14}(49)+$ $wC_{17}H_{27}H_{26}$			1395.4	14.95	4.48
$\tau H_{26}C_{17}O_1C_{14}(15)+ \gamma C_{22}C_{24}H_{41}H_{42}+$ $wC_{17}H_{27}H_{26}$		1417	1407.1	34.25	10.60
$\nu_s C_{11}C_{12}(26)+ \nu_s C_{15}C_{16}+ \nu_s C_{12}C_{13}+$ $\delta_s H_{30}C_{13}C_{12}(12)+ \delta_s H_{30}C_{13}C_{12}(10)$	1454.00		1433.5	0.65	3.40
$\delta_s H_{35}C_{10}H_{34}(87)$	1466.92		1467.2	6.66	8.96
$\delta_s H_{42}C_{24}H_{41}(62)+ \delta_s H_{42}C_{24}H_{41}(10)+$ $\delta sH_{29}C_{18}H_{28}+ \gamma C_{25}H_{43}H_{45}H_{44}$			1470.2	1.45	13.27
$\delta_s H_{27}C_{17}H_{26}(58)+ \delta_s H_{27}C_{17}H_{26}(22)+$ $\delta sH_{29}C_{18}H_{28}$		1498	1498.1	65.30	2.05
$\delta_s H_{30}C_{13}C_{12}(15)+ \delta_s H_{30}C_{13}C_{12}(12)+$ $\delta_s H_{30}C_{13}C_{12}(11)+ \delta_s H_{30}C_{13}C_{12}(13)+ \delta_s H_{33}C_{15}C_{14}$	1513.23		1523.1	139.60	3.51
$\nu_s C_{20}C_{19}(36)+ \nu_s C_{20}C_{19}(24)+ \delta_s H_{38}C_{20}C_{21}(12)$	1573.43		1574.8	16.53	2.59
$\nu N_5C_{23}+ \nu C_{20}C_{21} + \delta C_{21}C_{22}C_{23}(16)$	1608.66		1607.7	25.32	98.75
$\nu C_{15}C_{16}+ \nu C_{12}C_{13}+ \nu C_{10}C_{11}+ wCH_2$		1633	1623.4	82.56	140.70
$\nu_s O_2C_7(85)+ \nu_s O_3C_8+ \delta_s C_8N_4H_{37}$	1699.51		1696.1	834.44	8.87
$\nu_s O_2C_7(90)+ \nu_s O_3C_8$	1737.54		1729.7	272.45	55.44
$\nu_s CH_2(34)+ \nu_s CH_2(53)+ \nu C_{18}H_{28}$	2868.13		2886.1	19.14	122.82
$\nu_s CH_2(59)+ \nu_s CH_2(38)+ \nu_s CH_2$	2925.51		2924.3	16.05	126.44
$\nu_s C_9H_{36}(94)+ \nu_{as} CH_2$	2961.42		2965.7	6.13	25.19
$\nu_s C_{12}H_{31}(13)+ \nu_s C_{12}H_{31}(15)+ \nu_s C_{16}H_{32}+ \nu_s C_{15}H_{33}$		3046	3027.9	12.23	74.45
$\nu_s C_{20}H_{38}(76)+ \nu_s C_{20}H_{38}(19)+ \nu_s C_{21}H_{39}$		3100	3029.0	12.49	84.39
$\nu_s C_{12}H_{31}(36)+ \nu_s C_{12}H_{31}(30)+ \nu_s C_{12}H_{31}(18) +$ $\nu_s C_{12}H_{31}(15)+ \nu_s C_{13}H_{30}$		3136	3038.4	11.76	48.83
$\nu_s C_{20}H_{38}(48)+ \nu_s C_{20}H_{38}(24)+ \nu_s C_{20}H_{38}(28)+$ $\nu sC_{21}H_{39}$		3163	3051.9	10.47	137.50
$\nu_s C_{12}H_{31}(13)+ \nu_s C_{12}H_{31}(16)+ \nu_s C_{12}H_{31}(34)+$ $\nu_s C_{12}H_{31}(37)+ \nu_s C_{15}H_{33} + \nu_s C_{16}H_{32}$		3199	3062.7	4.28	135.79
$\nu_s C_{12}H_{31}(16)+ \nu_s C_{12}H_{31}(18)+ \nu_s C_{12}H_{31}(32)+$ $\nu_s C_{12}H_{31}(34)+ \nu_s C_{13}H_{30}$		3217	3081.4	6.75	96.72
$\nu_s N_4H_{37}(100)$		3595	3447.4	81.89	237.20
				R^2=0.9997 for IR	

s, symmetric; as, asymmetric; ν, stretching; δ, in-plane bending; τ, torsion; γ, out-of-plane bending; δ_s, scissoring and symmetric bending; ρ, rocking; t, twisting; w, wagging; I_{IR}, IR intensity (km/mol); S_{Raman}, Raman scattering activity; PED, potential energy distribution; W, Wavenumber (cm^{-1}); T, Transmittance (%).

Table 3. The experimental and computed ^{1}H NMR isotropic chemical shifts (with respect to TMS, all values in ppm) of pioglitazone.

^{1}H NMR Locations (δ) and Correspondences (Al-Majed et al., 2016)	**^{1}H NMR Locations (δ) and Correspondences (Gadape and Parik, 2011)**	**$\delta_{exp.}$ (in DMSO-d_6) (This study)**	**$\delta_{cal.}$ (in DMSO) (This study)**
12.05	12.05; N-H-imide	11.97	8.93-H40
8.72-8.73	8.71; 1H/ 2-pyridine	8.48	-
8.40-8.42	8.39-8.41-1H/ 2-pyridine	8.34	-
7.97-7.99	7.95-7.98; 1H/ 2-pyridine	7.93	8.01-H39
7.13-7.17	7.11-7.14; 2CH-Benzene	7.10-7.12	7.13-H30
6.86-6.90	6.84-6.87; 2 CH-Benzene	6.83-6.85	-
4.85-4.89	4.83-4.87-methine-CH	4.82-4.84	4.77-H36
4.40-4.41	4.36-4.40; 2H-methylene-CH_2	4.27	4.13-H27 4.35-H26
3.49-3.51	3.47-3.51; methylene-CH_2	3.58	3.38-H28
3.27-3.32	3.24-3.30; methylene-CH_2	3.28-3.29	3.36-H29
3.03-3.10	3.02-3.07; 1H-methylene-CH_2	3.02	2.95-H34
2.51-2.82	2.73-2.81; 2H-methylene-CH_2	2.75	2.82-H41 2.81-H42
1.23-1.26	1.18-1.23; 3H-methyl-CH3	1.15	1.11-H44 1.19-H45 1.51-H43
			R^2=0.94 and RMSD=0.97 ppm

Table 4. The experimental and computed ^{13}C NMR isotropic chemical shifts (in ppm) of pioglitazone.

^{13}C NMR Locations (δ) and Correspondences (Al-Majed et al., 2016)	**^{13}C NMR Locations (δ) and Correspondences (Gadape and Parik, 2011)**	**$\delta_{exp.}$ (in DMSO-d_6) (This study)**	**$\delta_{cal.}$ (in DMSO) (This study)**
176.15-C-O	175.72-C	175.83	181.64-C8
172.12- C-O	171.71- C	171.79	181.37-C7
151.74-C	151.08-C	155.56	165.34-C14 162.43-C19
157.49-C	157.03-C	157.63	155.93-C23
141.71-C	141.45-C	136.78	141.93-C21
140.67-CH	139.86-CH	135.80	135.55-C12 135.21-C11
145.46-CH	145.44-CH	148.66	145.12-C22
130.88-CH	130.46-CH	130.46	134.75-C16
129.56-C	129.09-C	128.72	127.30-C20
127.53-CH	127.30-CH	123.14	121.15-C15
114.90-CH	114.46-CH	114.46	112.87-C13
65.91-CH_2	65.49-CH2	66.83	71.83-C17
-	-	-	66.46-C9
-	-	40.07	42.07-C18
-	-	39.23	41.85-C10
36.67-CH_2	36.261-CH_2	36.90	30.23-C24
32.79-CH_2	32.185-CH_2	36.41	-
25.07-CH_2	24.643-CH_2	25.08	-
14.08-CH_3	14.062-CH_3	15.51	18.72-C25
		R^2=0.99 and RMSD=4.56 ppm	

Table 5. The experimental and computed UV-Vis. parameters and electronic transitions in methanol of pioglitazone.

Experimental parameters	**Calculated parameters**			
$\lambda_{exp.}$ (nm)	$\lambda_{cal.}$ (nm)	Excitation energy (eV)	Oscillator strength	Major contributions (O'boyle et al., 2008)
285	281.26	4.4081	0.0422	HOMO->LUMO (98%)
-	260.66	4.7566	0.0155	HOMO->L+1 (95%)
275	255.12	4.8598	0.0324	HOMO->L+2 (80%) -
-	252.05	4.9190	0.0057	H-3->L+1 (95%)
-	245.82	5.0437	0.0006	H-5->LUMO (89%),%)
268	241.06	5.1434	0.1582	HOMO->L+4 (80%) -
-	239.41	5.1788	0.0519	H-1->L+1 (55%), HOMO->L+3 (22%), HOMO->L+4 (10%)
-	238.41	5.2005	0.0359	H-1->L+1 (23%), HOMO->L+3 (68%), -
-	236.26	5.2477	0.0720	H-4->LUMO (64%), H-2->LUMO (32%)
-	231.36	5.3590	0.0010	H-3->L+3 (92%)

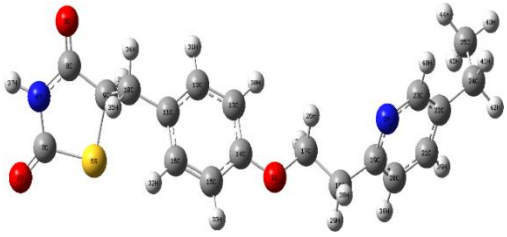
The FT-IR spectrum of pioglitazone molecule was recorded within 400-4000 cm^{-1} region at the room temperature, using potassium bromide (KBr) pellet, on a Fourier Transform Infrared spectrometer in solid phase of the sample as shown in Table 2. The Laser-Raman spectrum was recorded at room temperature in 100-4000 cm^{-1} region as shown in Table 2. B3LYP (Becke, three-parameter, Lee-Yang-Parr) level with 6-311G++(2d,2p) basis set was used to compute the electronic structure properties of pioglitazone molecule (Becke, 1993; Lee et al.,1988). Vibrational wavenumbers, geometric parameters and molecular properties were calculated using Gaussian 09W software and GaussView5 molecular visualization program on a computing system (Frish et al., 2001; Frisch et al., 2009; Gaussian, 2016). VEDA 4 program was used to compute the potential energy distribution of vibrational wavenumbers as given in Table 2 (Jamr'oz, 2004).

The ^{1}H and ^{13}C NMR chemical shift spectra of the compound solved in dimethyl sulfoxide (DMSO-d6) were recorded with TMS as internal standard using Premium Compact NMR device at 600 MHz frequency and 14.1 Tesla field power. The chemical shifts were reported at ppm level as given in Table 3 and Table 4. The ultraviolet visible spectrum of pioglitazone dissolved in DMSO was recorded using a UV Spectrophotometer in 200-400 nm region at room temperature as given in Table 5. The spectral bandwidth is 2 nm.

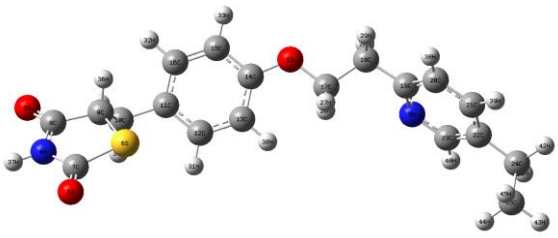
3. Results and Discussions

3.1. Geometric Structure

The optimized molecular structures of conformer I (E= -1469.82995425 a.u.) and conformer II (E= -1469.83019029 a.u) are given in Figure 1.



E(Conformer I)= -1469.82995425 a.u.



E(Conformer II)= -1469.83019029 a.u.

Figure 1. The optimized molecular conformational form of pioglitazone molecule

The calculated C8-C9, C9-S6, C7-S6, C7-N4 and C8-N4 bond lengths for pioglitazone are 1.528 Å, 1.846 Å, 1.790 Å, 1.391 Å and 1.378 Å. The calculated bond angles of C8-C9-S6, C7-S6-C9, N4-C7-S6, C8-N4-C7 and N4-C8-C9 are 106.570, 92.840, 109.450, 119.540 and 111.590 in this study. The experimental bonds lengths and bond angles are given as 1.546 (5) Å, 1.823 (5) Å, 1.760 (3) Å, 1.366 (4) Å, 1.362 Å, 104.30 (3), 92.440 (18), 111.20 (2), 117.40 (3) and 112.00 (3), respectively (Yathirajan et al., 2005). The linear correlation coefficient (R^2) between the experimental Yathirajan et al. (2005) and computed bond lengths were found as 0.9821.

3.2. Vibrational Frequency Analyses

The vibrational analyses were calculated based on the characteristic vibrations of the molecule with Gaussian09 Program. The computations of harmonic wavenumbers, IR intensities and Raman activities were performed at the DFT/B3LYP/6-311G++(2d,2p) level. The scaling factors of 0.983 (for values less than 1700 cm^{-1}) and 0.958 (for values greater than 1700 cm^{-1}) were used to eliminate the systemic difference (Gökçe and Bahçeli, 2013; Sundaraganesan et al., 2007; Chebbi et al., 2016).

Pioglitazone consists of forty-five atoms, and accordingly it has 129 modes of vibrations. The computed vibrational wavenumbers, their assignments, IR and Raman activities and measured infrared and Raman band positions are given to identify the vibrational modes in detail in comparison with literature (AIST, 2017). The graphs of experimental and simulated IR spectra and vibrational assignments of pioglitazone molecule are given in Figure 2 and Table 2. The graphs of experimental and simulated Raman spectra of pioglitazone are given in Figure 3. The linear correlation coefficient (R^2) between the experimental and computed vibration frequencies for IR was found as 0.9997.

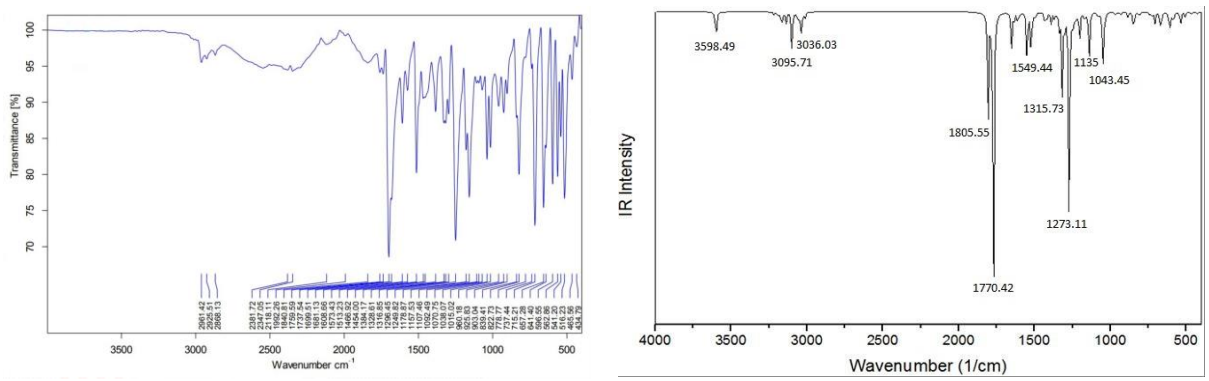


Figure 2. The experimental (top) and simulated (bottom) IR spectra of pioglitazone

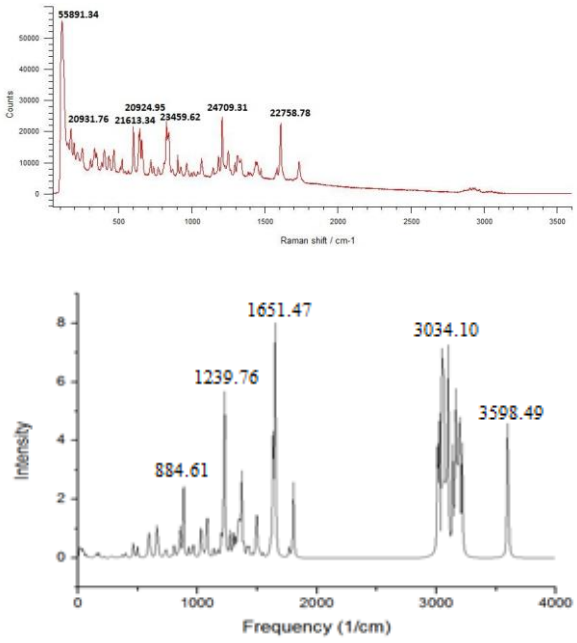


Figure 3. The experimental (top) and simulated (bottom) Raman spectra of pioglitazone

Reportedly, the IR absorption spectrum of pioglitazone showed two carbonyl functions in the range of 1684–1743 cm^{-1} and the NH absorption band appeared at 3258 cm^{-1} (Al-Majed et al., 2016). In the present study, the NH absorption band is observed at 3595 cm^{-1} (R) and calculated at 3447 cm^{-1}.

Gowrav et al. (2014) observed the prominent peaks of pioglitazone HCl in the region of 3084 cm^{-1} due to the (aromatic C-H stretching), one at 2996 cm^{-1} due to the aliphatic C-H stretching, another at 1743 cm^{-1} due to the C=O stretching, in addition to the peak at 1610 cm^{-1} due to C=C stretching and at 1243 cm^{-1} due to C-S stretching (Gowrav et al., 2014). In this research, the peaks corresponding to aromatic C-H stretching vibration were observed in the range of 3046-3217 cm^{-1} for Raman, in addition to the peak which was observed at 2868.13 cm^{-1} for IR. The peaks arising from C=O stretching vibrations were observed at 1372 cm^{-1} (R), 1249.82 cm^{-1} (IR), 1699.51 cm^{-1} (IR) and 1737.54 cm^{-1} (IR). The peaks arising from C=C stretching vibrations were observed at 903.04 cm^{-1} (IR), 925.83 cm^{-1} (IR), 1015.02 cm^{-1} (IR), 1107.46 cm^{-1} (IR), 1178.87 cm^{-1} (IR) and 1174 cm^{-1} (R), 1210 cm^{-1} (R), 1316.85 cm^{-1} (IR) and 1318 cm^{-1} (R). The peaks arising from νS_6C_7 stretching vibrations were calculated at 694.98 cm^{-1}, 661.56 cm^{-1}, 499.36 cm^{-1} and 361.71 cm^{-1} for IR; and observed at 373 cm^{-1} and 499 cm^{-1} for Raman.

3.3. NMR

NMR analysis, used in organic structure determination, is associated with the spin orientation direction. In NMR analysis, chemical shifts are measured in parts per million (ppm). The proton and carbon-13 NMR chemical shifts for pioglitazone molecule were calculated at DFT/B3LYP/6-311G++(2d,2p) in DMSO-d_6. The experimental ^{1}H and ^{13}C NMR chemical shift spectra are summarized in Figures 4 and 5.

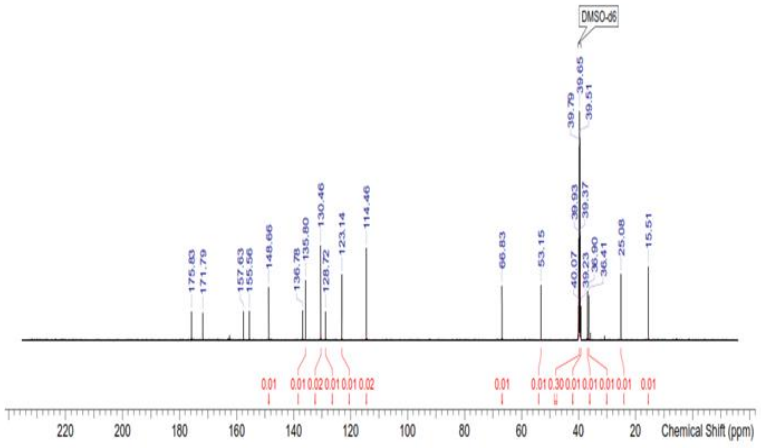


Figure 4. The experimental 13C NMR chemical shift spectra of pioglitazone

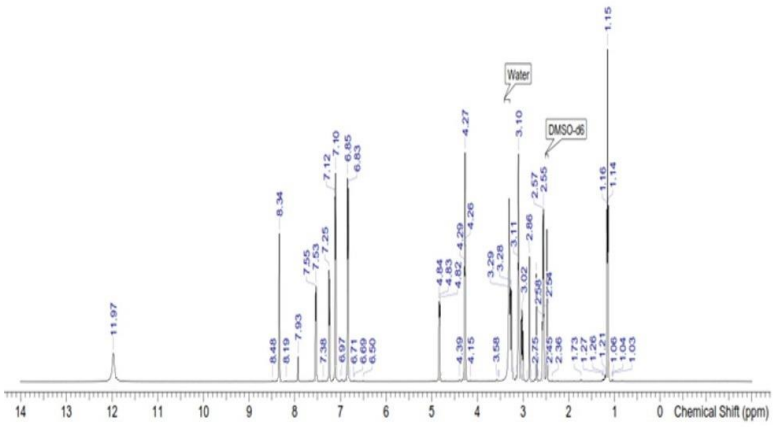


Figure 5. The experimental 1H NMR chemical shift spectra of pioglitazone

The experimental and computed ^{1}H and ^{13}C NMR chemical shift spectra are summarized in Tables 3 and 4 along with corresponding literature information (Al-Majed et al., 2016; Gadape and Parik, 2011). The linear correlation coefficient (R^2) and root-mean-square deviation (RMSD) values between the experimental and computed vibrational frequencies were found as 0.9939 and 4.56 ppm for ^{13}C NMR chemical shifts and 0.9370 and 0.97 ppm for ^{1}H NMR chemical shifts, respectively.

^{1}H chemical shift values were computed at the intervals of 1.1124-8.9261 ppm and were measured in the range of 1.15-11.97 ppm in DMSO-d_6. The largest deviation between the calculated and experimental ^{1}H NMR chemical shifts ($\delta_{exp.}$-$\delta_{cal.}$) is observed for H40 with 3.0439 ppm, N-H-imide, whereas the smallest deviation is found for H30 with 0.0256 ppm, 2CH-Benzene.

The ^{13}C chemical shifts are calculated in the range of 18.7206-181.639 in DMSO ppm, while they are experimentally recorded in the range of 15.51-175.83 ppm. The largest deviation between the calculated and experimental ^{13}C NMR chemical shifts ($\delta_{exp.}$-$\delta_{cal.}$) is obtained for C14 with 9.781 ppm, C, whereas the smallest deviation is found for C12 with 0.25 ppm, CH.

3.4. UV Analyses

The experimental ultraviolet (UV) absorption spectrum of pioglitazone in DMSO is given in Figure 6.

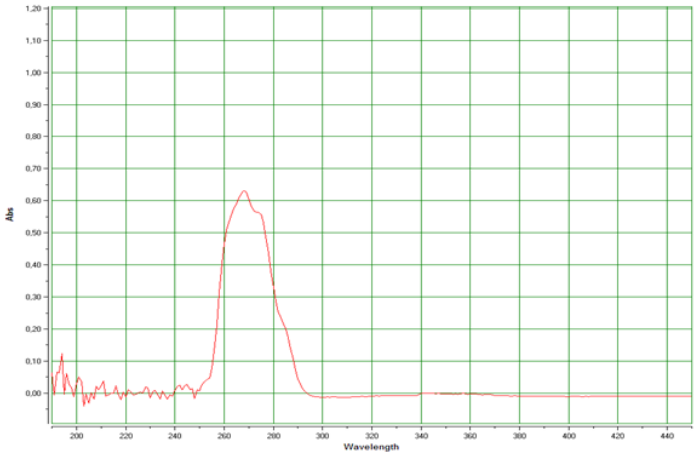


Figure 6. UV-Vis analysis of pioglitazone in DMSO

The absorption spectra of the reference and test solutions were carried out in the range of 100–460 nm. The absorption value of pioglitazone at 268 nm is 0.65 a.u. TD-SCF/DFT/6-311G++(2d,2p) method was used to determine the electronic absorption and emission energies of pioglitazone, in DMSO solvent, as shown in Figure 7.

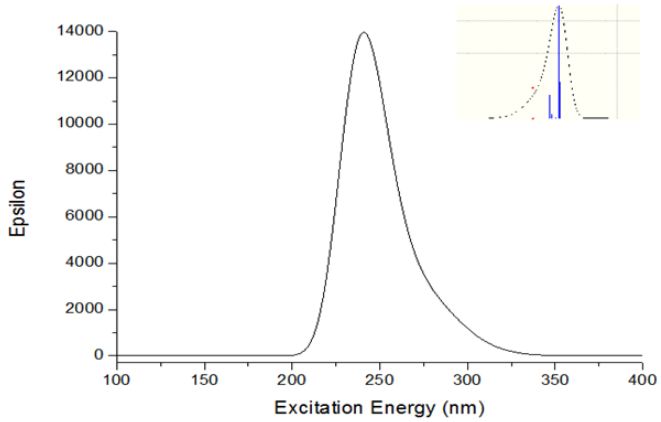


Figure 7. The simulated UV-Vis analysis of pioglitazone in DMSO

The absorption spectra of the reference and test solutions were carried out in the range of 100–400 nm. The excitation energy value (nm) and oscillator strength of pioglitazone were

calculated as 281.26nm/0.0422, 260.66nm/0.0155, 255.12nm/0.0324, 252.05 nm/0.0057, 241.06 nm/0.1582, 239.41 nm/0.0519, 238.41 nm/0.0359, 236.26 nm/0.072 and 231.36 nm/0.001, respectively as given in Table 5. The calculated E(TD-HF/TD-KS) energy value with 6-311++G(2d,2p) basis set of pioglitazone is -1469.6860 a.u. and dipole moment is 4.8133 debye. Additionally, the experimental and computed electronic absorption wavelengths, electronic transitions, oscillator strengths, excitation energies and major contributions are listed Table 5. The major contributions for the computed electronic wavelengths were obtained by GaussSum 3.0 program (O'boyle et al., 2008).

3.5. HOMO-LUMO Analyses

The highest and the lowest occupied molecular orbitals (HOMO and LUMO) are also referred to as the frontier molecule orbitals (Fukui, 1982). The simulated HOMO and LUMO surfaces, energy values and their shapes for the title molecule are given in Figure 8. The calculated HOMO, HOMO-1, LUMO and LUMO+1 energy values were computed as -6.3248 eV, -7.0320 eV, -1.3791 eV and -1.1173 eV at the DFT/B3LYP/6-311G++(2d,2p) level, respectively.

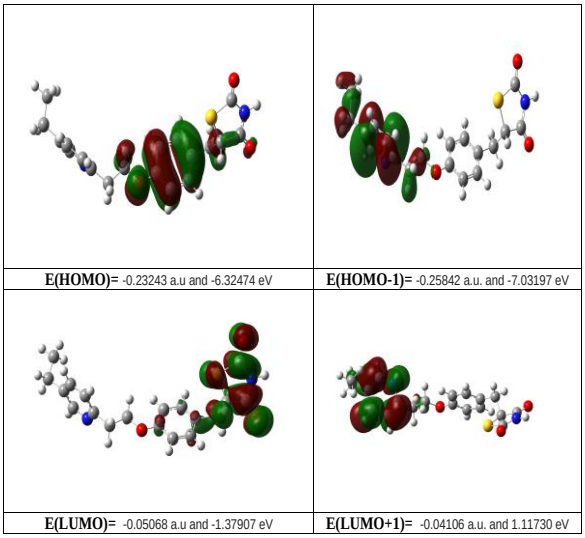


Figure 8. The HOMO and LUMO energy plots for pioglitazone molecule

4. Conclusion

The experimental and theoretical spectroscopic analyses of pioglitazone were studied by using FT-IR, Raman, UV-Vis. and NMR methods. Quantum chemical computations were performed with DFT/B3LYP/6-311G++(2d,2p) basis level using Gaussian/Gaussview program. The computed molecular energy for the conformer I and conformer II was obtained as E= -1469.82995425 a.u. and E= -1469.83019029 a.u. By considering conformer II, the structural, spectroscopic (IR, Raman, NMR and UV-Vis.) and HOMO-LUMO analyses for pioglitazone were performed using theoretical computational methods. The observed and calculated broad bands of FT-IR spectrum are given in the region of 435-2961 cm^{-1} and 475-

3598 cm^{-1} in Figure 2, respectively. The experimental and computed ^{13}C NMR isotropic chemical shifts of pioglitazone are given in the region of 15.51-175.783 ppm and 18.72-181.639 ppm, in DMSO, respectively. The experimental and computed ^{1}H NMR isotropic chemical shifts of pioglitazone are given in the region of 1.15-11.97 ppm and 1.1124-8.93 ppm, in DMSO, respectively. The electronic transitions in UV-Vis. spectra supported with charge transfers in the HOMO and LUMO analyses of the molecule were determined. The experimental and theoretical studies were found to be agreeable as verified by the spectroscopic analyses.

Ethics in Publishing

There are no ethical issues regarding the publication of this study

Acknowledgement

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References

Adhikari, L., Jagadev, S., Sahoo, S., Murthy, P., Mishra, U.S., 2012. "Development and Validation of UV-Visible Spectrophotometric Method for Simultaneous Determination of Pioglitazone Hydrochloride, Metformin Hydrochloride and Glipizide in its Bulk and Pharmaceutical Dosage Form (Tablet)", International Journal of ChemTech Research. Vol.4, No.2 625-630.

Alexandar, S., Diwedi, R., Chandrasekar, M., 2010. "A RP-HPLC method for simultaneous estimation of metformin and pioglitazone in pharmaceutical formulation", Res. J. Pharm. Biol. Chem. Sci. 1 (4) 858–866.

Al-Majed, A., Bakheit, A.H.H., Abdel Aziz, H.A., Alharbi, H., Al-Jenoobi, F.I., 2016. "Profiles of Drug Substances, Excipients, and Related Methodology", Volume 41, Elsevier Inc. ISSN 1871-5125.

Appana Chowdary K., Navya Lakshmi Raju Suravarapu., Swathi Meddala., 2015. "Formulation and Characterization of Pioglitazone Hydrochloride Nanoparticles", World Journal of Pharmacy and Pharmaceutical Sciences. Volume 4, Issue 04, 1638-1648.

Attia, A. K., Ibrahim, M. M., El-Ries, M. Abdel-Nabi., 2013. "Thermal Analysis of Some Antidiabetic Pharmaceutical Compounds", Advanced Pharmaceutical Bulletin, 3 (2), 419-424.

AIST, (2017). National Institute of Advanced Industrial Science and Technology Spectral Database for Organic Compounds, SDBS. http://sdbs.db.aist.go.jp/sdbs/cgibin/cre_index.cgi, (Accessed on 02 February 2018).

Becke, A. D., 1993. "Density- functional thermochemistry. III. The role of exact Exchange", J. Chem. Phys., 98, 5648.

Chebbi H, Chebbi M, Guesmi A, Arfaoui Y., 2016. "Crystal Structure Determination, and DFT Calculations of Dichlorobis (Dimethylsulfoxide-O)Copper(II)", Journal of Structural Chemistry, 57 (6) 1104-1110.

Dubey, S., Kashyap, P., Pandey, A., Thakur, D., 2013. "A Validated Method Development For Estimation of Pioglitazone By First Order Derivative Spectroscopy", International Journal of PharmTech Research. Vol.5, No.4 1451-1455.

Frish, A., Nielsen, A. B., Holder, A. J., 2001. "Gauss View User Manual", Gaussian Inc., Pittsburg, PA.

Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A. et al. 2009. Gaussian 09, Revision, A.1, Gaussian Inc., Wallingford CT.

Fukui, K., 1982. "Role of frontier orbitals in chemical reactions", Science 218 747-754.

Gadape, H. H., Parikh, K. S., 2011. "Quantitative Determination and Validation of Pioglitazone in Pharmaceutical using Quantitative Nuclear Magnetic Resonance Spectroscopy", J. Chem. Pharm. Res., 3(1): 649-664.

Gaussian website, Visualizing Molecules&Reactions with Gaussview 5. http://www.gaussian.com/g_prod/gv5.htm (Son erişim tarihi: 10.08.2016).

Gowrav M.P., Shivakumar H.G., Vishal Gupta N., 2014. "Design and evaluation of pH sensitive multi-particulate systems for chronotherapeutic delivery of pioglitazone hydrochloride", World J Pharm Sci, 2(12): 1813-1821.

Gökce H., Bahçeli S. 2013. "Analysis of molecular structure, spectroscopic properties (FT-IR, micro-Raman and UV–vis) and quantum chemical calculations of free and ligand 2-thiopheneglyoxylic acid in metal halides (Cd, Co, Cu, Ni and Zn)", Spectrochim. Acta. A. Mol. Biomol. Spectrosc. 116, 242-250.

Jamr'oz, M.H., 2004. "Vibrational Energy Distribution Analysis", VEDA4.

Kulkarni, A.P., Mohd, S., Zaheer, Z., Dehghan, M.H., 2012. "Spectroscopic Estimation of Pioglitazone Hydrochloride". Global Journal of Medical Research Volume XII Issue II 57-61.

Lee, C., Yang, W., Parr, R. G., 1988. "Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density", Phys. Rev. B., 37, 785.

Moffat, A.C., Osselton, M.D., Widdop, B., 2011. "Clarke's Analysis of Drugs and Poisons", Vol. 3, Pharmaceutical Press, London.

O'Neil, M.J., 2013. "The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals", Merck and Co, Whitehouse Station, NJ.

O'boyle, M., Tenderholt, A.L., Langner, K.M., 2008. "cclib: a library for package-independent computational chemistry algorithms", J. Comput. Chem. 29 839-845.

Patil, S., Dwivedi, S., Bagade, S., 2011. "Development of Spectrophotometric Method for the Estimation of Pioglitazone HCL from Two Different Marketed Brands", American Journal of Pharmtech Research. Volume 1, Issue 4 264-275.

Pioglitazone, Compound Summary
https://pubchem.ncbi.nlm.nih.gov/compound/Pioglitazone#section=Synonyms
Son erişim tarihi: 16.03.2021.

Rajesh, S., Gunasekaran, S., Rajesh P., 2018. "Vibrational and Molecular Structural Investigations of Pioglitazone-Combined Study of Experimental and Quantum Chemical Calculations (Density Functional Theory)". International Journal of ChemTech Research. 11 (10). 10.20902/IJCTR.2018.111015.

Soni, H., 2014. "Martindale: the complete drug reference", Emerg. Nurse, 22 (5) 12.

Sujana, K., Abdulu, K., Bala Souri, O. Archana, B., Sindu, M., Swathi Rani, G., 2011. "Difference Spectrophotometric Methods for Pioglitazone Hydrochloride and Metformin Hydrochloride", J. Pharm. Sci. & Res. Vol. 3(4) 1122-1126.

Shrivastaval, P., Basniwala, P.K., Jainz, D., 2008. "Alkaline hydrolysis of pioglitazone hydrochloride by RP-HPLC: stress stability study", Acta Pharm. Sci. 50 41–46.

Satheeshkumar, N., Shantikumar, S., Srinivas, R., 2014. "Pioglitazone: A review of analytical methods", Journal of Pharmaceutical Analysis. 4(5) 295-302.

Sundaraganesan N., Joshua B.D., Settu K. 2007. "Vibrational spectra and assignments of 5-amino-2-chlorobenzoic acid by ab initio Hartree-Fock and density functional methods", Spectrochim. Acta. A. Mol. Biomol. Spectrosc. 66 (2), 381-388.

Thirunavukkarasu, K., Rajkumar, P., Selvaraj, S., Gunasekaran, S., Kumaresan, S., 2018. "Electronic Structure, Vibrational (FT-IR and FT-Raman), UV–Vis and NMR analysis of 5-(4-(2-(5-ethylpyridin-2-yl) ethoxy) benzyl) thiazolidine-2,4-dione by Quantum Chemical method". Chemical Data Collections. 17-18. 263-275. 10.1016/j.cdc.2018.09.006.

Ulu, S. T., Elmalı, F.T., 2009. "UV-Second Derivative Spectrophotometric and Colorimetric Methods for the Determination, Validation and Thermogravimetric Analysis of New Oral Antidiabetic Pioglitazone in Pure and Pharmaceutical Preparations", Analytical Letters. 42 2254-2270.

Yathirajan, Hemmige S., Nagaraj, B., Nagaraja, P., Bolte, M., 2005. "Pioglitazone hydrochloride", Acta Cryst. E61, 154-155.