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HOMO-LUMO, NBO and Vibrational analysis of Sitagliptin by using DFT calculations and Experimental Study (FT-IR, FT-Raman and UV-Visible Spectroscopies)

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Abstract : The vibrational spectra analysis of Sitagliptin was calculated using density functional theory method(B3LYP) by employing 6-31G (d, p) basis set, compared with experimental FT-IR and FT-Raman spectra in the region of 4000-400 cm^{-1} and 4000-100 cm^{-1}. The electronic properties like Homo-Lumo energies and molecular electrostatic potential (MEP) have been computed. The experimental FT-IR and FT-Raman spectra were compared with theoretical spectrograms. The Mullikan atomic charges were also calculated. The inter and intramolecular interactions of title molecule has been visualized using NBO analysis. Electronic stability of the title compound arising from hyper conjugative interactions and charge delocalization were also investigated based on NBO analysis.
Keywords : Sitagliptin, UV-Vis, NBO,FT-IR, FT-Raman.

1. Introduction

Sitagliptin is a novel oral hypoglycemic drug of the dipeptidyl peptidase 4 inhibitor class (DPP-4). This enzyme-inhibiting drug is used either alone or in combination with other oral anti hyperglycemic agents for treatment of type-2 diabetes mellitus. Sitagliptin increased in certain levels (GLP-1 and GIP)which inhibit glucagon release, which decreases blood glucose levels towards normal. This inturn increases insulin secretion. Chemically, Sitagliptin is (R)-4-oxo-4[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine. The molecular formula is C16H15F6N5O.Sitagliptin is available in the market in the trade name of Januvia.

The Sitagliptin and its derivatives are studied by several authors. Simultaneous quantitation of metformin and Sitagliptin from mouse and human dried blood spots using laser diode thermal desorption tandem mass spectrometry was investigated by swales et al[1]. Practical, asymmetric route to sitagliptin and derivatives, development and origin of diastereoselectivity was done by OsvaldoGutierrez et al [2]. Liquid chromatographic determination of Sitagliptin either alone or in ternary mixture with metformin and Sitagliptin degradation product have been reported by El-Bagary et al [3].Review of Sitagliptin phosphate a

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novel treatment for type 2 diabetes was reported by Baptist Gallwitz et al [4]. Bio-analytical method development and validation of sitagliptin phosphate by RP-HPLC and its application to pharmacokinetic study was done by Anil Dubala et al [5]. Formulation and evaluation of sitagliptin phosphate gastro retentive tables were investigated by Krishna Keerthi et al [6].

A Literature survey reveals that no complete theoretical and experimental study is available for sitagliptin has been reported so far. In this present work, FT-IR and FT-Raman spectral investigation of sitagliptin molecule have been performed using DFT/B3LYP calculations. Also this study mainly focusing on the various molecular properties of sitagliptin like electronic absorption spectra, Mullikan atomic charges, NBO, HOMO-LUMO and potential energy distribution (PED) by using density functional theory (DFT). Natural bond orbital (NBO) is used to calculate the redistribution of electron density(ED) in various bonding, antibonding orbitals and E (2) energies. The HOMO-LUMO study has been used to interpret the information of charge transfer within the molecule. Vibrational spectral analysis have been carried out on the basis of calculated potential energy distribution. Electronic absorption properties are explained and clarified from the frontier molecular orbitals. Mullikan atomic charge calculation has a substantial role in the application of DFT to molecular systems.

2. Experimental methods

The spectroscopic pure sample of sitagliptin was obtained from a leading pharmaceutical concern in Chennai with a stated purity of 99% and used as such to record the FTIR, FT-Raman and UV-Visible spectra. The Fourier transform infrared (FTIR) spectra of the label molecule was recorded in the region of 4000-450cm^{-1} with resolution of 4cm^{-1}using PerkinElmer spectrum- two FT-IR spectrophotometer at saif, St.peter`s university avadi, Chennai,India. The FT-Raman spectra was recorded at saif, IIT-Madras, Chennai, India, using a BRUKER: RFS 27 spectrometer. A laser wavenumber of 15,798cm^{-1}was used as an excitation source, over the region of 4000-100cm^{-1}. The UV-Visible absorption spectrum of sitagliptin was examined in the region of 200-400nm using Perkin Elmer UV-Vis Lambda 35 spectrophotometer at saif, St.peter`s university avadi, Chennai, India.

3. Computational details

The molecular structure optimization of sitagliptin, matching energy and vibrational harmonic frequencies are calculated using Gaussian 03w software package [7], Becke`s three parameter hybrid exchange functional[8] with Lee-yang-Parr correlation functional[9,10] standard 6-31G(d,p) basis set. The optimized geometrical parameters like energy, fundamental vibrational frequencies, Mulliken atomic charges and other molecular properties are calculated theoretically by using Gaussian 03W program package. Homo-Lumoare also calculated. The potential energy distribution (PED) corresponding to each of the observed frequencies is calculated using VEDA4 software program [11]. The natural bond orbital (NBO) calculations [12, 13] were performed using NBO 3.1 Program as implemented in the Gaussian O3W package. In order to understand the various second order interactions between the filled orbital of one subsystem and vacant orbital of another subsystem. This is a measure of the inter-molecular and intra molecular delocalization or hyper conjugation[14].

4. Results and discussion

4.1 Molecular geometry

The optimized geometrical structure of title compound with atom numbering scheme is shown in Fig. 1. The geometrical parameter of sitagliptin like bond angle and bond length was calculated by using density functional theory (DFT). From the geometrical structure, the molecules of sitagliptin belongs to C1 point group symmetry. The Table 1 shows the optimized geometrical parameter of title molecule, which is calculated from DFT computations B3LYP level with 6-31G (d, p) basis set. This title molecule has thirteen C-C bond lengths, fourteen C-H band lengths, nine C-N, six C-F, two N-H, two H-H, one C-O and one N-N bond lengths respectively. In this present work the optimized bond length of C-H (7.0973A^0)were maximum and for N-H was minimum (1.0172A^0).

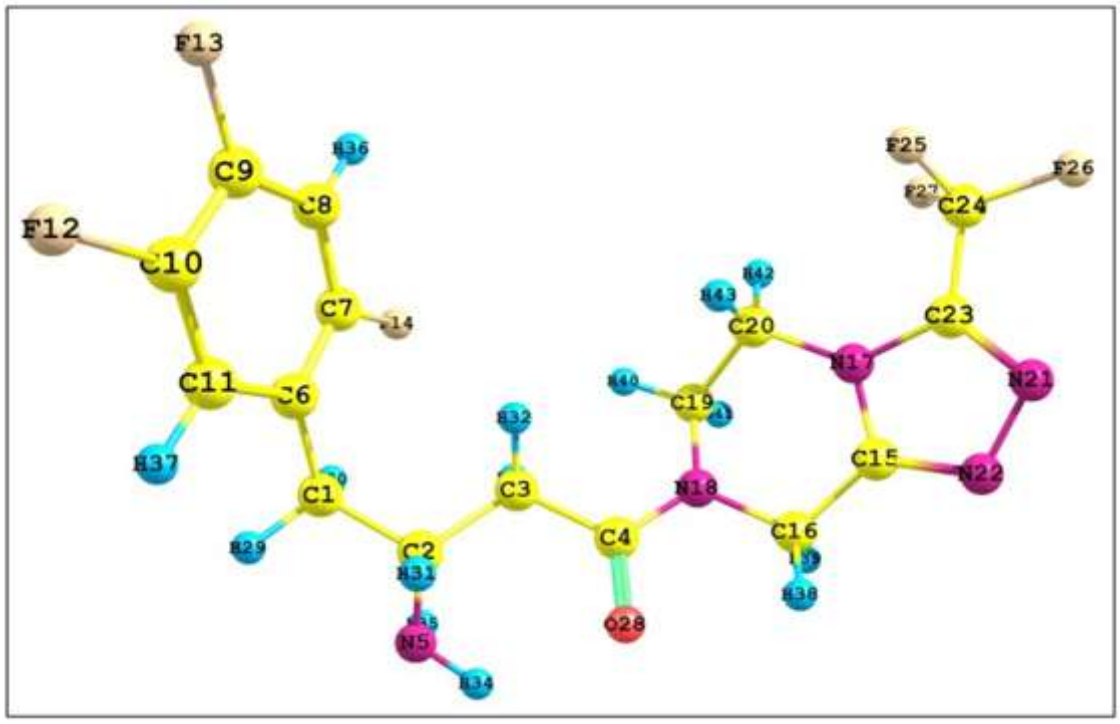


Fig.1 Optimized structure of Sitagliptin

Table1. Geometrical parameters - Bond Length and Bond Angles of Sitagliptin

Bond Length	**B3LYP/6-31G(d,p)**	**Bond Length**	**B3LYP/6-31G(d,p)**
C_1-C_2	1.5476	C_{10}-F_{12}	1.3435
C_1-C_6	1.5113	C_{11}-C_{37}	1.0852
C_1-H_{29}	1.0934	C_{15}-C_{16}	1.4992
C_1-H_{30}	1.0966	C_{15}-N_{17}	1.3681
C_2-C_3	1.5446	C_{15}-N_{22}	1.3153
C_2-N_5	1.4621	C_{16}-N_{18}	1.4653
C_2-H_{31}	1.0963	C_{16}-H_{38}	1.0905
C_3-C_4	1.5263	C_{16}-H_{39}	1.0998
C_3-H_{32}	1.0961	N_{17}-C_{20}	1.4632
C_3-H_{33}	1.0986	N_{17}-C_{23}	1.3711
C_4-N_{18}	1.3811	N_{18}-C_{19}	1.4583
C_4-O_{28}	1.2280	C_{19}-C_{20}	1.5333
N_5-H_{34}	1.0172	C_{19}-H_{37}	7.0973
N_5-H_{35}	1.0192	C_{19}-H_{40}	1.0883
C_6-C_7	1.3961	C_{19}-H_{41}	1.0989
C_6-C_{11}	1.4031	C_{20}-H_{42}	1.0925
C_7-C_8	1.3907	C_{20}-H_{43}	1.0948
C_7-F_{14}	1.3586	N_{21}-N_{22}	1.3773
C_8-C_9	1.3875	N_{21}-C_{23}	1.3109
C_8-H_{36}	1.0832	C_{23}-C_{24}	1.4939
C_9-C_{10}	1.3948	C_{24}-F_{25}	1.3575
C_9-F_{13}	1.3413	C_{24}-F_{26}	1.3304
C_{10}-C_{11}	1.3870	C_{24}-F_{27}	1.3589
H_{31}-H_{40}	4.5087	H_{37}-H_{40}	6.4634
Bond Angle	**B3LYP/6-31G(d,p)**	**Bond Angle**	**B3LYP/6-31G(d,p)**
C_2-C_1- C_6	115.4824	C_1-C_6- C_7	122.0483
C_2-C_1- H_{29}	106.514	C_1-C_6- C_{11}	121.4453

C_2-C_{1-} H_{30}	108.8411	C_7-C_{6-} C_{11}	116.5053
C_6-C_{1-} H_{29}	109.425	C_6-C_{7-} C_8	123.6607
C_6-C_{1-} H_{30}	109.36	C_6-C_{7-} F_{14}	118.7334
H_{29}-C_{1-} H_{30}	106.8572	C_8-C_{7-} F_{14}	117.6032
C_1-C_{2-} C_3	111.2059	C_7-C_{8-} C_9	118.0729
C_1-C_{2-} N_5	108.0244	C_7-C_{8-} H_{36}	121.1833
C_1-C_{2-} H_{31}	108.2832	C_9-C_{8-} H_{36}	120.7428
C_3-C_{2-} N_5	114.9531	C_8-C_{9-} C_{10}	120.2322
C_3-C_{2-} H_{31}	107.5874	C_8-C_{9-} F_{13}	120.3209
N_5-C_{2-} H_{31}	106.5082	C_{10}-C_{9-} F_{13}	119.4469
C_2-C_{3-} C_4	113.0539	C_9-C_{10-} C_{11}	120.3785
C_2-C_{3-} H_{32}	109.9332	C_9-C_{10-} F_{12}	119.057
C_2-C_{3-} H_{33}	109.1123	C_{11}-C_{10-} F_{12}	120.5631
C_4-C_{3-} H_{32}	108.7882	C_6-C_{11-} C_{10}	121.1497
C_4-C_{3-} H_{33}	109.615	C_6-C_{11-} H_{37}	120.3733
H_{32}-C_{3-} H_{33}	106.1026	C_{10}-$C_{11-}$$H_{37}$	118.4756
C_3-C_{4-} N_{18}	117.3081	C_{16}-C_{15-} N_{17}	121.829
C_3-C_{4-} O_{28}	122.1342	C_{16}-C_{15-} N_{22}	127.4475
N_{18}-C_{4-} O_{28}	120.5571	N_{17}-C_{15-} N_{22}	110.6957
C_2-N_{5-} H_{34}	108.0873	C_{15}-C_{16-} N_{18}	110.2828
C_2-N_{5-} H_{35}	110.0793	C_{15}-C_{16-} H_{38}	110.8261
H_{34}-N_{5-} H_{35}	107.1327	C_{15}-C_{16-} H_{39}	109.5623
N_{18}-C_{16-} H_{38}	108.1856	C_{15}-N_{22-} N_{21}	107.3418
N_{18}-C_{16-} H_{39}	110.595	N_{17}-C_{23-} N_{21}	110.9311
H_{38}-C_{16-} H_{39}	107.3412	N_{17}-C_{23-} C_{24}	122.7656
C_{15}-N_{17-} C_{20}	125.116	N_{21}-C_{23-} C_{24}	126.2992
C_{15}-N_{17-} C_{23}	103.8549	C_{23}-C_{24-} F_{25}	110.6211
C_{20}-N_{17-} C_{23}	130.9813	C_{23}-C_{24-} F_{26}	111.9203
C_4-N_{18-} C_{16}	118.5114	C_{23}-C_{24-} F_{27}	110.8087
C_4-N_{18-} C_{19}	126.1622	F_{25}-C_{24-} F_{26}	108.6826
C_{16}-N_{18-} C_{19}	115.2966	F_{25}-C_{24-} F_{27}	106.1244
N_{18}-C_{19-} C_{20}	110.5644	F_{26}-C_{24-} F_{27}	108.4800
N_{18}-C_{19-} H_{37}	67.3993	C_2-H_{31-} H_{40}	54.9042
N_{18}-C_{19-} H_{40}	110.6736	C_{11}-H_{37-} C_{19}	53.7428
N_{18}-C_{19-} H_{41}	109.3105	C_{11}-H_{37-} H_{40}	48.3041
C_{20}-C_{19-} H_{37}	101.3629	C_{19}-H_{40-} H_{31}	102.8124
C_{20}-C_{19-} H_{40}	109.2743	H_{31}-H_{40-} H_{37}	25.0946
C_{20}-C_{19-} H_{41}	109.3783	C_6-C_{1-} C_{2-} C_3	-63.3528
H_{37}-C_{19-} H_{41}	147.6131	C_6-C_{1-} C_{2-} N_5	169.6252
H_{40}-C_{19-} H_{41}	107.5805	C_6-C_{1-} C_{2-} H_{31}	54.6510
N_{17}-C_{20-} C_{19}	108.0431	H_{29}-C_{1-} C_{2-} C_3	174.9409
N_{17}-C_{20-} H_{42}	109.0198	H_{29}-C_{1-} C_{2-} N_5	47.9189
N_{17}-C_{20-} H_{43}	109.3511	H_{29}-C_{1-} C_{2-} H_{31}	-67.0553
C_{19}-C_{20-} H_{42}	110.9823	H_{30}-C_{1-} C_{2-} C_3	60.0587
C_{19}-C_{20-} H_{43}	110.7766	H_{30}-C_{1-} C_{2-} N_5	-66.9633
H_{42}-C_{20-} H_{43}	108.6736	H_{30}-C_{1-} C_{2-} H_{31}	178.0624
N_{22}-N_{21-} C_{23}	107.1709	C_2-C_{1-} C_{6-} C_7	92.1523
C_2-C_{1-} C_{6-} C_{11}	-88.2382	H_{32}-C_{3-} C_{4-} O_{28}	124.2703
H_{29}-C_{1-} C_{6-} C_7	-147.7181	H_{33}-C_{3-} C_{4-} N_{18}	60.1558
H_{29}-C_{1-} C_{6-} C_{11}	31.8914	H_{33}-C_{3-} C_{4-} O_{28}	-120.1188
H_{30}-C_{1-} C_{6-} C_7	-30.9853	C_3-C_{4-} N_{18-} C_{16}	-179.4582
H_{30}-C_{1-} C_{6-} C_{11}	148.6241	C_3-C_{4-} N_{18-} C_{19}	-1.5426
C_1-C_{2-} C_{3-} C_4	175.1344	O_{28}-C_{4-} N_{18-} C_{16}	0.8119
C_1-C_{2-} C_{3-} H_{32}	53.3536	O_{28}-C_{4-} N_{18-} C_{19}	178.7275

C_1-C_2- C_3- H_{33}	-62.6171	C_1-C_6- C_7- C_8	179.4924
N_5-C_2- C_3- C_4	-61.7311	C_1-C_6- C_7- F_{14}	-1.1208
N_5-C_2- C_3- H_{32}	176.4881	C_{11}-C_6- C_7- C_8	-0.1353
N_5-C_2- C_3- H_{33}	60.5174	C_{11}-C_6- C_7- F_{14}	179.2516
H_{31}-C_2- C_3- C_4	56.7109	C_1-C_6- C_{11}- C_{10}	-179.6718
H_{31}-C_2- C_3-H_{32}	-65.0699	C_1-C_6- C_{11}- H_{37}	-0.1219
H_{31}-C_2- C_3- H_{33}	178.9594	C_7-C_6- C_{11}- C_{10}	-0.0417
C_1-C_2- N_5- H_{34}	-175.1997	C_7-C_6- C_{11}- H_{37}	179.5081
C_1-C_2- N_5- H_{35}	68.0989	C_6-C_7- C_8- C_9	0.0921
C_3-C_2- N_5- H_{34}	59.9831	C_6-C_7- C_8- H_{36}	-179.5599
C_3-C_2- N_5- H_{35}	-56.7184	F_{14}-C_7- C_8- C_9	-179.3012
H_{31}-C_2- N_5- H_{34}	-59.0623	F_{14}-C_7- C_8- H_{36}	1.0468
H_{31}-C_2- N_5- H_{35}	-175.7638	C_7-C_8- C_9- C_{10}	0.1293
C_1-C_2- H_{31}- H_{40}	-113.2386	C_7-C_8- C_9- F_{13}	-179.9072
C_3-C_2- H_{31}- H_{40}	7.0502	H_{36}-C_8- C_9- C_{10}	179.7829
N_5-C_2- H_{31}- H_{40}	130.7976	H_{36}-C_8- C_9- F_{13}	-0.2536
C_2-C_3- C_4- N_{18}	-177.8772	C_8-C_9- C_{10}- C_{11}	-0.302
C_2-C_3- C_4- O_{28}	1.8482	C_8-C_9- C_{10}- F_{12}	-179.8807
H_{32}-C_3- C_4- N_{18}	-55.455	F_{13}-C_9- C_{10}- C_{11}	179.7341
F_{13}-C_9- C_{10}- F_{12}	0.1554	H_{39}-C_{16}- C_{18}-C_{19}	-79.1371
C_9-C_{10}- C_{11}- C_6	0.2575	C_{15}-N_{17}- C_{20}-C_{19}	-21.6869
C_9-C_{10}- C_{11}- H_{37}	-179.3007	C_{15}-N_{17}- C_{20}-H_{42}	-142.3933
F_{12}-C_{10}- C_{11}- C_6	179.8298	C_{15}-N_{17}- C_{20}-H_{43}	98.9645
F_{12}-C_{10}- C_{11}- H_{37}	0.2716	C_{23}-N_{17}- C_{20}-C_{19}	161.2476
C_6-C_{11}- H_{37}- C_{19}	45.7868	C_{23}-N_{17}-C_{20}-H_{42}	40.5412
C_6-C_{11}- H_{37}- H_{40}	39.1567	C_{23}-N_{17}-C_{20}-H_{43}	-78.101
C_{10}-C_{11}- H_{37}- C_{19}	-134.6515	C_{15}-N_{17}-C_{23}-N_{21}	0.7118
C_{10}-C_{11}- H_{37}- H_{40}	-141.2816	C_{15}-N_{17}-C_{23}-C_{24}	-179.9872
N_{17}-C_{15}- C_{16}- N_{18}	-11.7277	C_{20}-N_{17}-C_{23}-N_{21}	178.2398
N_{17}-C_{15}- C_{16}- H_{38}	-131.5008	C_{20}-N_{17}-C_{23}-C_{24}	-2.4592
N_{17}-C_{15}- C_{16}-H_{39}	110.2311	C_4-N_{18}-C_{19}-C_{20}	118.2769
N_{22}-C_{15}- C_{16}-N_{18}	170.3729	C_4-N_{18}-C_{19}-H_{37}	24.1616
N_{22}-C_{15}- C_{16}-H_{38}	50.5998	C_4-N_{18}-C_{19}-H_{40}	-2.9471
N_{22}-C_{15}- C_{16}-H_{39}	-67.6683	C_4-N_{18}- C_{19}-H_{41}	-121.2609
C_{16}-C_{15}- C_{17}-C_{20}	3.3344	C_{16}-N_{18}- C_{19}-C_{20}	-63.749
C_{16}-C_{15}- C_{17}-C_{23}	-178.9469	C_{16}-N_{18}- C_{19}-H_{37}	-157.8642
N_{22}-C_{15}- C_{17}-C_{20}	-178.4483	C_{16}-N_{18}- C_{19}-H_{40}	175.027
N_{22}-C_{15}- C_{17}-C_{23}	-0.7296	C_{16}-N_{18}- C_{19}-H_{41}	56.7132
C_{16}-C_{15}- N_{22}-N_{21}	178.5831	N_{18}-C_{19}- C_{20}-N_{17}	49.1314
N_{17}-C_{15}- N_{22}-N_{21}	0.4909	N_{18}-C_{19}-C_{20}-H_{42}	168.6049
C_{15}-C_{16}- N_{18}-C_4	-139.6519	N_{18}-C_{19}-C_{20}-H_{43}	-70.6256
C_{15}-C_{16}- C_{18}-C_{19}	42.2094	H_{37}-C_{19}-C_{20}-N_{17}	119.0549
H_{38}-C_{16}- C_{18}-C_4	-18.2949	H_{37}-C_{19}-C_{20}-H_{42}	-121.4717
H_{38}-C_{16}- C_{18}-C_{19}	163.5664	H_{37}-C_{19}-C_{20}-H_{43}	-0.7021
H_{39}-C_{16}- C_{18}-C_4	99.0016	H_{40}-C_{19}-C_{20}-N_{17}	171.181
H_{40}-C_{19}-C_{20}-H_{42}	-69.3455	N_{22}-N_{21}-C_{23}-C_{24}	-179.7105
H_{40}-C_{19}-C_{20}-H_{43}	51.424	N_{17}-C_{23}-C_{24}-F_{25}	55.5882
N_{18}-C_{19}-H_{37}-C_{11}	172.0082	N_{17}-C_{23}-C_{24}-F_{26}	176.944
C_{20}-C_{19}-H_{37}-C_{11}	64.2843	N_{17}-C_{23}-C_{24}-F_{27}	-61.8278
H_{41}-C_{19}-H_{37}-C_{11}	-97.2782	N_{21}-C_{23}-C_{24}-F_{25}	-125.2218
N_{18}-C_{19}-H_{40}-H_{31}	15.0515	N_{21}-C_{23}-C_{24}-F_{26}	-3.866
C_{20}-C_{19}-H_{40}-H_{30}	-106.9324	N_{21}-C_{23}-C_{24}-F_{27}	117.3622
H_{41}-C_{19}-H_{40}-H_{31}	134.4133	C_2-H_{31}-H_{40}-C_{19}	-128.7119
C_{23}-N_{21}-N_{22}-C_{15}	-0.031	C_2-H_{31}-H_{40}-H_{37}	89.2417

N_{22}-N_{21}-C_{23}-N_{17}	-0.4398	C_{11}-H_{37}-H_{40}-H_{31}	179.2854
H_{41}-C_{19}-C_{20}-N_{17}	-71.2903	H_{41}-C_{19}-C_{20}-H_{43}	168.9527
H_{41}-C_{19}-C_{20}-H_{42}	48.1832		

4.2 Vibrational Frequencies Assignments

The title compound has 43 atoms and 123 normal modes of vibrations, also it belongs to C1 point group symmetry. The experimental and theoretical vibrational frequencies of the title molecule have been arranged in the Table 2. The observed and calculated FT-IR and FT-Raman spectra of sitagliptin were showed in Fig. 2 and Fig. 3 respectively. The maximum number of experimental values is in good agreement with the theoretical values which is calculated by B3LYP/6-31 G (d, p) basis set. The Table2 also shows the potential energy distribution (PED) values of the title molecule.

Table2. Vibrational assignments of Sitagliptin

B3LYP/6-31G(d,p)	**EXPT**		**Vibrational Assignments**
	FT-Raman cm-1	**FT-IR cm-1**	
9			τCNCC(33)+τCCCC(19)+τCCCN(18)
20			τCCCC(53)+τCCNC(21)
25			τCCCC(46)
34			δCCC(11)+τFCCN(18)
43			τFCCN(50)+γCNNC(13)
57			δCCC(11)+τFCCN(12)+τCCCN(21)
79			τCCCN(21)
96			γCCNC(13)
110	105		τCCCC(13)
114			τNCCN(13)
138	140		δCCN(37)+γFCFC(10)
167			τCCCC(14)+τCCNC(20)
197	205		γCCCN(22)+γCNNC(11)
265	270		γCNNC(17)
277			δFCC(31)
280			τCCCC(15)
300			δCCC(29)
348			δFCC(25)+τHNCC(11)
355	367		δCNC(11)+γCCCN(11)
383			δFCF(14)
392			τHNCC(10)+γFCCC(28)
406	403		δFCF(24)+τNCNC(12)
445			δCCN(16)+δFCF(11)
447			δNCC(22)
448	457	463	γFCCC(13)
482			τCCCC(16)
502		505	δCNC(15)
539		529	δCCN(10)+γOCNC(11)
548			δCCC(23)
552			δFCF(11)+τNCNC(16)
605			δCCN(11)

635			δOCC(22)
681			τCCCC(12)+γFCCC(10)
702			νNC(22)
723	724	725	νFC(13)+δCCC(23)
732			τNCNC(43)+γFCFC(18)
744	754	746	νFC(27)
777		769	νCC(24)
786			δNCN(19)
810			νCC(22)
834			τHCCC(79)
849		844	νCC(19)
876	881	880	νNC(12)+νCC(12)
893			τHCCC(63)
902	901	912	τHNCC(23)
920			τHCCC(10)
954			νNC(13)
971		977	δCNC(11)
988	980		νCC(12)+δHNC(10)
1018	1017	1010	δHCC(10)
1075			δHCC(19)
1080			νNC(10)+δNCN(57)
1101		1102	γCCCN(16)
1120			νNC(26)
1135			νFC(13)+νCC(22)
1158	1148	1147	νFC(42)
1172			δHCN(12)
1177			νFC(11)+δHCC(54)
1182			νNC(11)
1191			δHCN(11)+δHCC(23)
1236	1238		δHCC(10)
1243			δHCC(33)
1247			νFC(16)+δHCN(31)
1264	1278	1274	νFC(13)+νNC(15)
1311			νFC(19)
1325			δHCC(15)
1349	1338	1340	νCC(10)+τHCCN(10)
1368			τHCCC(23)
1373			νNC(11)+τHCNC(18)
1377	1375	1370	νFC(37)+νCC(12)
1388			νCC(15)+δHCN(17)
1407			τHCNC(40)
1419			δHCN(28)
1434		1426	νNC(15)
1458	1445		δHCH(56)
1460			δCNC(15)
1489			νNC(26)

1505			δHCH(136)
1511	1518	1514	δHCH(62)
1530			νNC(10)+δHCH(53)
1543			νNC(46)+δCNC(17)
1564		1556	νCC(10)
1577			νNC(28)
1657			νCC(37)
1667	1668	1669	δHNH(68)+τHNCC(13)
1680			νCC(42)
1749			νOC(85)
3020			νCH(97)
3030			νCH(93)
3031			νCH(95)
3050			νCH(99)
3065		3060	νCH(65)
3071	3077		νCH(98)
3084			νCH(74)
3114			νCH(78)
3132			νCH(76)
3149			νCH(97)
3172			νCH(96)
3212			νCH(100)
3238			νCH(99)
3478			νNH(100)
3576			νNH(71)

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

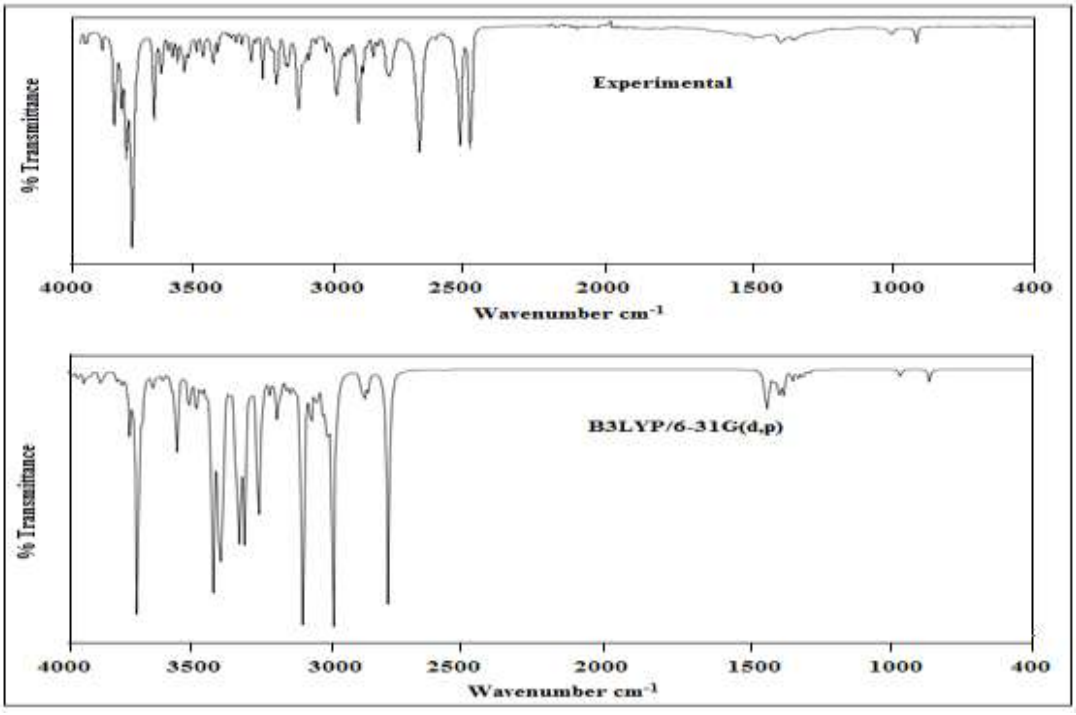


Fig.2 FT-IR spectrum of Sitagliptin

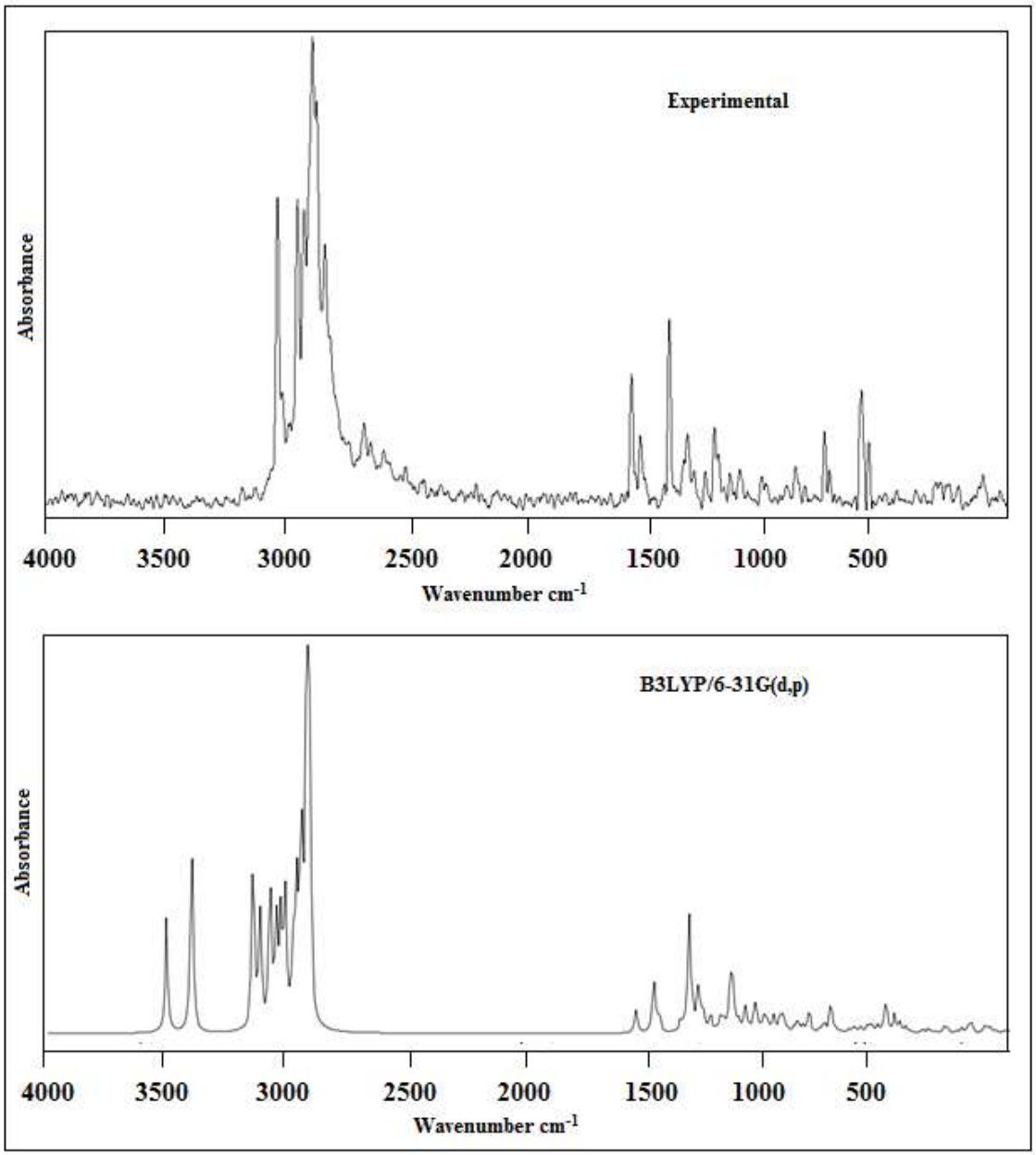


Fig. 3 FT-Raman spectra of Sitagliptin

4.3 C-H vibrations

The bands due to C-H stretching vibrations commonly exhibit in the region of 3100-2950 cm^{-1}[15]. In the present case, the bands appeared at 3060 cm^{-1} in FT-IR Spectrum and 3077cm^{-1} in FT-Raman spectrum are assigned to C-H stretching vibrations. According to sitagliptin seven C-H stretching vibrations appeared at 3020, 3030, 3031, 3050, 3065, 3071, and 3084cm^{-1} by B3LYP method. The theoretical vibrations by B3LYP method also show good agreement with experimentally recorded data. The bands appeared at 900-675cm^{-1} due to C-H out-of–plane bending vibrations [16]. For this compound the C-H out of plane bending vibrations appeared at 725,746,769,844, and 880 cm^{-1}in FT-IR Spectrum, and at 724,754,881 and 901cm^{-1}in FT-Raman spectrum.From B3LYP methods the C-H out-of-plane banding vibrations at 723,744 and 876cm^{-1}. The C-H in plane bending vibrations observed in the region of 1000-1300cm^{-1}[17-21]. In this present study the four C-H in plane bending vibrations identified at 1010, 1102, 1147 and 1274cm^{-1}in FT-IR and at 1017, 1148,1238 and 1278cm^{-1} in FT-Raman. The C-H vibrations are in good agreement with theoretical and experimental values.

4.4 C-C vibrations

The carbon–carbon bond stretching appeared usually in the range of 1650-1400cm^{-1}[22]. In this present work the wave numbers found at 1511, 1667cm^{-1}in B3LYP/6-31G(d,p) methods are assigned to C-C stretching vibrations. The C-C stretching wave number is established at 1426cm^{-1} 1514$cm^{-1}$and 1556cm^{-1} in FT-IR spectra and 1445cm^{-1},1518$cm^{-1}$and 1634cm^{-1} in FT-Raman spectra have been assigned to C-C stretching vibrations of the title molecule. In this study two strong bands appeared at 902cm^{-1} and 971cm^{-1} in B3LYP/6-31G (d, p)are assigned to C-C-C in plane bending vibrations [23]. Hence in the present investigation theoretically calculated wave numbers are correlated with the experimental observation.

4.5 C=O vibrations

The carbonyl group shows a strong absorption band due to C=O stretching vibration and is observed in the region 1700-1660cm^{-1}. The C=O stretching vibration band can be easily identified from the FT-IR and FT-Raman spectrum because of its high intensity [24,25], degree of conjugation, the strength and polarizations are increasing. In this present work, the stretching at 1669cm^{-1} in FT-IR and 1668cm^{-1} in FT-Raman and the theoretical bands by B3LYP at 1667cm^{-1} corresponds to the C=O stretching. The theoretically observed frequencies are in good agreement with the experimental frequencies. These C=O vibrations are also shown fairly good coherent in literature survey [26, 27].

4.6 C-N vibrations

From the literature survey, Silverstein et al [28] observed the frequency between 1382 and 1266cm^{-1} are belongs to C-N stretching vibrations. The C-N stretching vibrations are very difficult to identify comparing with other vibration [29]. Muthu et al. [30] assigned the band at 1415cm^{-1} in FTIR spectrum to C-N stretching vibration for the 8-chloro-1-methyl-6-phenyl-4H-[1,2,4] triazolo[4,3-a][1,4] benzodiazepine molecule. Prabhavathi et al. [31] reported that the band in at 1575cm^{-1} in FTIR and 1540cm^{-1} both in FTIR and Raman spectrum to C=N stretching vibrations. The identification of C-N vibration is a very difficult task,since the mixing of several bands is possible in this region. The C-N stretching vibrations generally occur in the region 1180-1280cm^{-1}[28]. Kahovec and Kohlresuch et al. [32] identified the stretching wave number of C-N band in salicylicaldoxinne at 1617cm^{-1} .

In this present study the C-N stretching vibrations of sitagliptin are identified at 1668, 1634, 1518 and 1445cm^{-1} in FT-Raman and the FT-IR bands at 1669, 1556, 1514 and 1426cm^{-1}. The FT-IR bands observed at 1274cm^{-1} and the Raman band at 1278cm^{-1} are assigned to C-N bending modes of vibrations. These assignments are made in accordance with the assignments proposed by Roy [33].

4.7 N-H vibrations

The N-H stretching vibrations observed at 3520cm^{-1} to 3480cm^{-1} for dilute solutions. In the spectra of solid samples are observed near 3350cm^{-1} to 3180cm^{-1} because of hydrogen bonding [34].Normally in all the heterocyclic compounds, the N-H stretching vibration occurs in the region of 3500-3000 cm^{-1} [35].In this present work, N-H stretching vibrations are observed at 3060cm^{-1} in FT-IR and at 3077cm^{-1} in FT-Raman spectrum. The above said vibrations were calculated in the range of 3576$cm^{-1}$to 3020$cm^{-1}$by B3LYP(6-31G/d,p) basis set. The calculated theoretical value by B3LYP are in good agreement with the experiment value for the corresponding mode of vibrations.

4.8 CF3-Vibrations

The trifluoromethyl group (CF3) has a set of fairly well defined group frequencies associated with it. The highest fundamental frequency vibration of the CF3 group is the CF3 stretch which occurs between 1350 and 1120cm^{-1}[28].Also the above same highest fundamental frequency vibrations of the CF3 group which occurs between 1050 and 1225cm^{-1} [36-38]. These vibrations were observed to give rise to extremely intense IR absorption and rather weak Raman scattering. The nine fundamental vibrations can be described the motion of the CF3group,it follows, 3 stretching, 3bending, 2rocking and 1 torsional mode. The CF3 symmetric stretching frequencies are observed at 1102 and 1147cm^{-1} in FT-IR and at 1148cm^{-1} in FT-Raman for the title molecule. The CF3in plane bending vibration is observed at 463 and 505cm^{-1} in FT-IR and 457cm^{-1} in FT-Raman for sitagliptin respectively. These vibrational modes are also confirmed by their PED values. The CF out-of-plane

bending mode of vibration observed at 529cm^{-1}in FT-IR. The out-of-plane modes were calculated at 552,548,539 and 502cm^{-1}by using B3LYP 6-31G (d, p) basis set are presented in the Table 2.

5. NBO analysis

By using Gaussian 09w Program package at B3LYP level the natural bond orbital (NBO) calculations were performed. A useful feature of the NBO method is that it gives information about interactions in filled and virtual orbital spaces that could improve the analysis of intra and intermolecular interactions [39-41].NBO also provides a convenient basis for studying transfer of charge [42] to determine the interaction between acceptor and donor for which the second order Fock matrix is used [43].The results of interactions is 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

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i}$$

Where q_i is the donor orbital occupancy, ε_i, ε_j are diagonal elements and F (i, j) is the off-diagonal NBO Fock matrix element. The second order micro-disturbance theory [44-45] were reported that some of the electron donor orbital, acceptor orbital and the interacting stabilization energy. Higher the $E^{(2)}$value, the intensive is the interaction between electron donors and electron acceptors i.e., the more donating tendency from electron donors to electron acceptors and greater is the extent of conjugation of the whole system. Delocalization of electron density between occupied Lewis type NBO orbitals and formally unoccupied non –Lewis NBO orbitals corresponds to a stabilizing donor –acceptor interaction [46]. The perturbation energies of significant donor – acceptor interaction are presented in Table 3. In the title molecule, the interactions between the BD*(2) C8-C9 and BD*(2) C6-C7 have the highest $E^{(2)}$(stabilization energy) value around 333.63 kcal/mol. The other significant interactions giving stronger $E^{(2)}$value of 67.52 kcal/molto the structure are the interactions between first lone pair of N18 and BD*(2)C4-O28.

Table 3. NBO analysis of Sitagliptin

Donor	Acceptor	E(2) kj/mol	E(j)-E(i) (a.u)	F(I,j) (a.u)
π C_6-C_7	π *C_8-C_9	21.64	0.27	0.070
π C_6-C_7	π *C_{10}-C_{11}	19.71	0.28	0.067
π C_8-C_9	π *C_6-C_7	19.49	0.29	0.069
π C_8-C_9	π *C_{10}-C_{11}	19.32	0.29	0.068
π C_{10}-C_{11}	π *C_6-C_7	18.52	0.29	0.067
π C_{10}-C_{11}	π *C_8-C_9	21.62	0.28	0.071
LP(3) F13	π *C_8-C_9	18.43	0.39	0.083
LP(1) N17	π *C_{15}-N_{22}	46.03	0.28	0.104
LP(1) N17	π *N_{21}-C_{23}	44.02	0.27	0.099
LP(1) N18	π *C_4-O_{28}	67.52	0.25	0.116
LP(2) O28	σ * C_4-N_{18}	23.22	0.68	0.114
π *C_8-C_9	π *C_6-C_7	333.63	0.01	0.082

6. UV-Vis spectral analysis

The UV-Vis absorption spectrum of the title compound was recorded within the range of 200-800nm. To understand the nature of electronic, transitions, positions of experimental and calculated absorption peaks(λ_{max}) and Vertical excitation energies (E) [47-49] of the sitagliptin molecule were calculated and the results are tabulated in the Table 4. From the TD-DFT calculations, the absorption bands were appeared at 246,237 and 227nm for various S1, S2 and S3 states respectively. The excited energy values in eV for the above wavelengths are 5.0340, 5.2265 and 5.4551 Ev respectively. The calculated theoretical absorption wavelengthis in good agreement with the experimental absorption wavelength in the UV-Visible spectrum.

Table 4.The UV–vis excitation energy of Sitagliptin

States	TD-B3LYP/6-31G(d,p)		
	Gas Phase		Expt
	λcal	E(ev)	λ_{obs}
S1	246	5.0340	245
S2	237	5.2265	238
S3	227	5.4551	226

7. Mullikan atomic charges

Mullikan atomic charge distribution plays an important role in the application of quantum chemical calculations of the molecule systems. The Mullikan charges gives net atomic population in the molecule. The natural charges of antidiabetic drug of sitagliptin was obtained by Mullikan [50] using B3LYP method with 6-31G (d, p) basis set. The natural charge affects dipole moment, polarizability, electronic structure and many properties of molecular systems. The calculated atomic charge values and the atom numbers are listed in the Table5. From the Table5, all the hydrogen atoms have positive Mullikan charges and all the nitrogen and fluorine atoms are the negative charges. The single oxygen atom also negative in nature. The charges of carbon atom are positive in the DFT level. The C24 atom has the highest positive Mullikan charge value (0.832) compared with other atoms. The smallest positive Mullikan charge value (0.061432) was obtained for C2atom.The N5 atom was much more negative than any other atoms which contribute in sitagliptin molecular structure.

Table 5.Mullikan's atomic charges of Sitagliptin by B3LYP method

Atoms	Charge (eV)	Atoms	Charge (eV)
C1	-0.240926	C23	0.352416
C2	0.061432	C24	0.831922
C3	-0.285167	F25	-0.272631
C4	0.602075	F26	-0.236511
N5	-0.601384	F27	-0.265087
C6	0.056101	O28	-0.521836
C7	0.318497	H29	0.127906
C8	-0.199072	H30	0.112663
C9	0.308383	H31	0.107163
C10	0.307473	H32	0.121037
C11	-0.183604	H33	0.127604
F12	-0.285038	H34	0.262270
F13	-0.278520	H35	0.228898
F14	-0.303683	H36	0.133188
C15	0.479250	H37	0.115370
C16	-0.081565	H38	0.186293
N17	-0.513153	H39	0.153295
N18	-0.481973	H40	0.147896
C19	-0.096953	H41	0.143094
C20	-0.037607	H42	0.152966
N21	-0.337501	H43	0.148188
N22	-0.363166		

8. Molecular electrostatic potential

The molecular electrostatic potential (MEPs) are used to study the molecular interactions in the molecule. Also MEPs at a point in the space around a molecule gives an indication of the net electrostatic effect produced at that point by the total charge distribution (electron + nuclei) of the molecule and correlated with the dipole moment, electronegativity partial charges and chemical reactivity of the molecules [51].Recently the

MEPs have been used for interpreting and predicting relative reactivities sites for electrophilic and nucleophilic attack, investigation of biological recognition, hydrogen bonding interactions, molecular cluster, crystal behavior, correlation and prediction of a wide range of macroscopic properties [52-53].

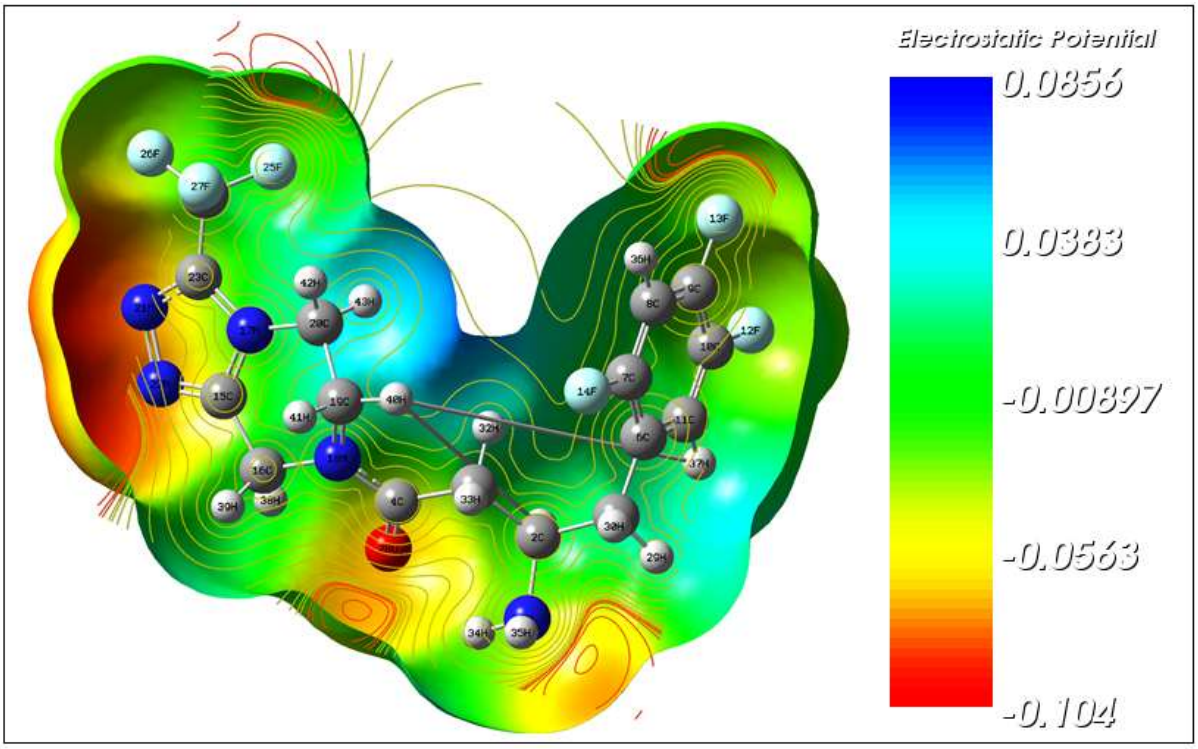


Fig.4 Molecular electrostatic potential of Sitagliptin

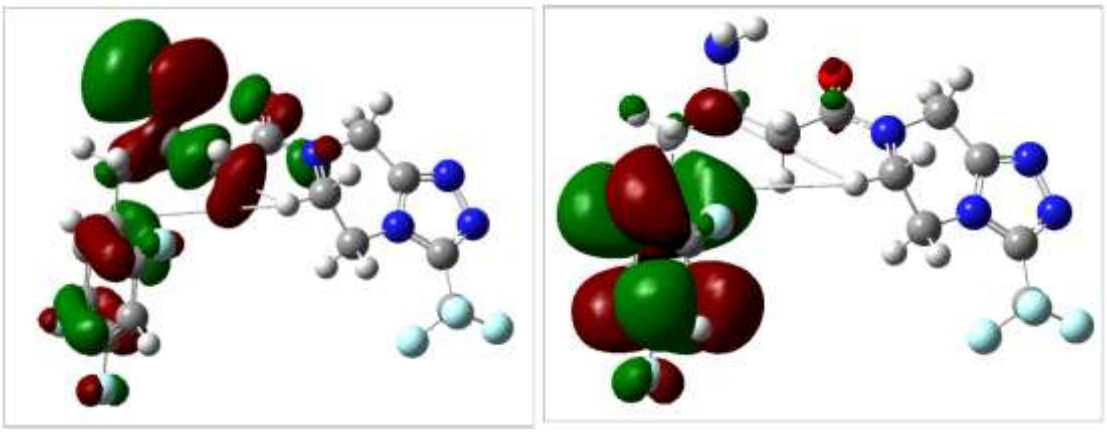
Molecular electrostatic potential map is commonly used as reactivity map [54]. The importance of total electron density surface mapped with the electrostatic potential lies in the fact that it simultaneously display molecular size, shape, positive or negative electrostatic potential regions in terms of color coding and is very useful in research of molecular structure with its physiochemical property relationship [55].

The different values of the electrostatic potential represented by different colors. The regions of the most negative electrostatic potential is represented by red colors, blue color represents the regions of the most positive electrostatic potential and the zero potential region was represented by the green color. Potential increases in the order of red<orange<yellow<green<blue. The negative regions of V(r) potential are related to electrophilic reactivity, while the positive ones are related to nucleophilic reactivity. Such mapped electrostatic potential surfaces have been plotted of the title compound by using B3LYP-6-31G (d, p) basis set of the computer software Gauss view 5.0. Projections of these surfaces along the molecular plane and a perpendicular plane are given in Fig. 4. The figure provides a visual representation of the chemically active sites and comparative reactivity of atoms. From the figure4, the contour map provides a simple way to predict how different geometries could interact.

9. Frontier molecular orbitals (FMOS)

Several organic molecules that containing conjugated ∏ electrons are characterized and investigated by means of vibrational spectroscopy [56-57]. The most important orbitals in molecules are the Highest Occupied Molecular Orbital (HOMO) and Lowest un Occupied Molecular Orbital (LUMO) are called as frontier molecular orbitals (FMOs). These HOMO and LUMO are very convincing parameters for quantum chemistry. The interaction of molecules with other breeds can be determined by these parameters. The frontier orbital gap helps to characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbitals gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability is also termed as soft molecule [58-60]. The HOMO and LUMO energies of the title compound were

calculated by B3LYP/6-31G (d, p) basis set. The HOMO is the orbital that mainly act as an electron donor and the LUMO is the orbital that primarily acts as the electron acceptor.



HOMO LUMO

Fig. 5 Frontier molecular orbitals of Sitagliptin

HOMO energy is directly associated with the ionization potential and the LUMO energy is directly related to the electron affinity[61]. The energy gap between HOMO and LUMO is a critical parameter in describing molecular electrical transport properties [28]. In recent times the energy gap between HOMO and LUMO were used to prove the bioactivity from intermolecular charge transfer [62-63]. In this present study, the 3D structure of the HOMO and LUMO for the title molecule are shown in Fig. 5. The red color is the positive phase and the green is negative one. The energy value of HOMO is 6.5599 eV and the LUMO is 0.9110 eV, the band gap between HOMO-LUMO is equal to 5.6488 eV. Also energies of HOMO and LUMO are used for the determination of Ionization potential (I), Electron affinity (A), Electrophilicity(w), Chemical potential (μ), Electronegativity (x), Chemical hardness (η), and softness (s) and their values are tabulated in the Table 6.

Table 6. Molecular properties of Sitagliptin

Molecular properties	**B3LYP**	**Molecular properties**	**B3LYP**
E_{HOMO}(eV)	6.5599	Chemical Hardness(η)	-2.8244
E_{LUMO}(eV)	0.9110	Softness(S)	-0.3540
$E_{Homo-Lumo}$gap(eV)	5.6488	Chemical Potential(μ)	3.73545
Ionisation potential(I) eV	-6.5599	Electronegativity(χ)	-3.73545
Electron affinity (A) eV	-0.9110	Electrophilicity index(ω)	6.9767

10. Conclusions

In this present investigation, the vibrational spectroscopic details of sitagliptin have been analyzed by FT-IR, FT-Raman and UV-visible spectroscopic techniques. The vibrational assignments using potential Energy distribution (PED) are determined for the title molecule. Theoretical and experimental wave numbers are compared which is in good agreement with each other. The complete molecular structural parameters like bond length and bond angle have been calculated by DFT-B3LYP/6-31G(d, p) basis sets. Various quantum chemical calculations helps us to see the structural and symmetry properties of the title compound. The intramolecular interactions have been interpreted by NBO analysis. The Mullikan atomic charges of sitagliptin are calculated. The frontier molecular orbitals have been visualized and the HOMO-LUMO energy gap explain the eventual charge transfer interactions taking place within the molecule.

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