



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 4000-450 cm^{-1} with resolution of 4 cm^{-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 15,798 cm^{-1} was used as an excitation source, over the region of 4000-100 cm^{-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-Lumo are 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 03W 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 bond 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 (7.0973 Å) were maximum and for N-H was minimum (1.0172 Å).

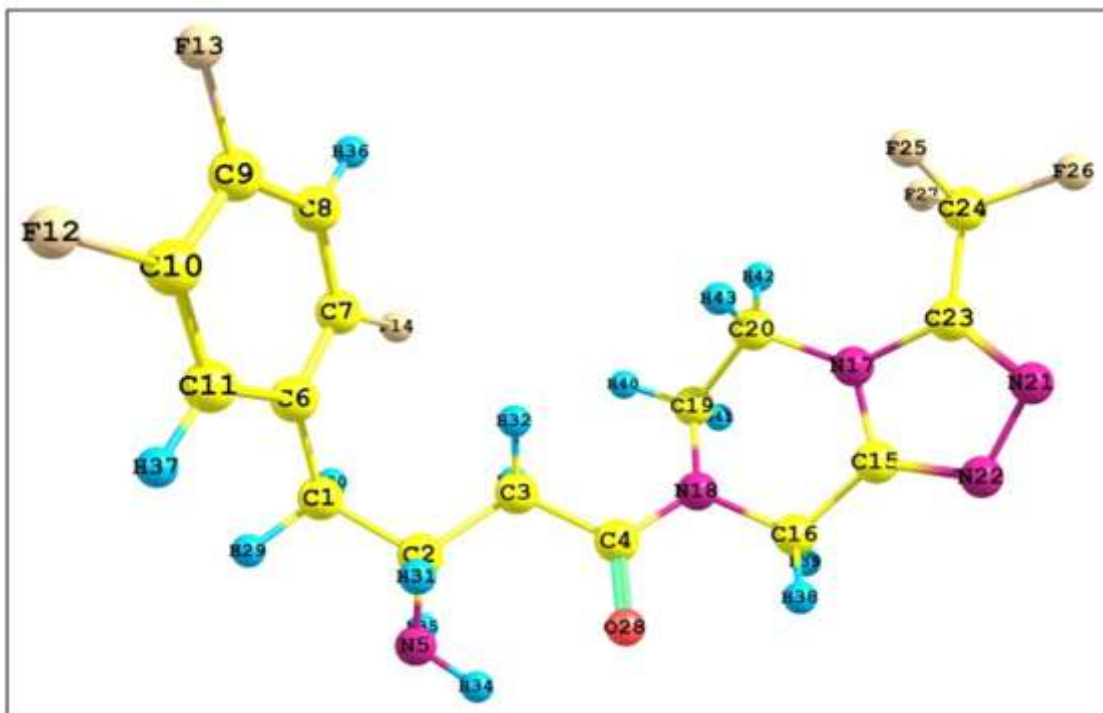


Fig.1 Optimized structure of Sitagliptin

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 |

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| 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 |

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| 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 | | | τ CNCC(33)+ τ CCCC(19)+ τ CCCN(18) |
| 20 | | | τ CCCC(53)+ τ CCNC(21) |
| 25 | | | τ CCCC(46) |
| 34 | | | δ CCC(11)+ τ FCCN(18) |
| 43 | | | τ FCCN(50)+ γ CNNC(13) |
| 57 | | | δ CCC(11)+ τ FCCN(12)+ τ CCCN(21) |
| 79 | | | τ CCCN(21) |
| 96 | | | γ CCNC(13) |
| 110 | 105 | | τ CCCC(13) |
| 114 | | | τ NCCN(13) |
| 138 | 140 | | δ CCN(37)+ γ FCFC(10) |
| 167 | | | τ CCCC(14)+ τ CCNC(20) |
| 197 | 205 | | γ CCCN(22)+ γ CNNC(11) |
| 265 | 270 | | γ CNNC(17) |
| 277 | | | δ FCC(31) |
| 280 | | | τ CCCC(15) |
| 300 | | | δ CCC(29) |
| 348 | | | δ FCC(25)+ τ HNCC(11) |
| 355 | 367 | | δ CNC(11)+ γ CCCN(11) |
| 383 | | | δ FCF(14) |
| 392 | | | τ HNCC(10)+ γ FCCC(28) |
| 406 | 403 | | δ FCF(24)+ τ NCNC(12) |
| 445 | | | δ CCN(16)+ δ FCF(11) |
| 447 | | | δ NCC(22) |
| 448 | 457 | 463 | γ FCCC(13) |
| 482 | | | τ CCCC(16) |
| 502 | | 505 | δ CNC(15) |
| 539 | | 529 | δ CCN(10)+ γ OCNC(11) |
| 548 | | | δ CCC(23) |
| 552 | | | δ FCF(11)+ τ NCNC(16) |
| 605 | | | δ CCN(11) |

| | | | |
|------|------|------|---|
| 635 | | | $\delta\text{OCC}(22)$ |
| 681 | | | $\tau\text{CCCC}(12)+\gamma\text{FCCC}(10)$ |
| 702 | | | $\nu\text{NC}(22)$ |
| 723 | 724 | 725 | $\nu\text{FC}(13)+\delta\text{CCC}(23)$ |
| 732 | | | $\tau\text{NCNC}(43)+\gamma\text{FCFC}(18)$ |
| 744 | 754 | 746 | $\nu\text{FC}(27)$ |
| 777 | | 769 | $\nu\text{CC}(24)$ |
| 786 | | | $\delta\text{NCN}(19)$ |
| 810 | | | $\nu\text{CC}(22)$ |
| 834 | | | $\tau\text{HCCC}(79)$ |
| 849 | | 844 | $\nu\text{CC}(19)$ |
| 876 | 881 | 880 | $\nu\text{NC}(12)+\nu\text{CC}(12)$ |
| 893 | | | $\tau\text{HCCC}(63)$ |
| 902 | 901 | 912 | $\tau\text{HNCC}(23)$ |
| 920 | | | $\tau\text{HCCC}(10)$ |
| 954 | | | $\nu\text{NC}(13)$ |
| 971 | | 977 | $\delta\text{CNC}(11)$ |
| 988 | 980 | | $\nu\text{CC}(12)+\delta\text{HNC}(10)$ |
| 1018 | 1017 | 1010 | $\delta\text{HCC}(10)$ |
| 1075 | | | $\delta\text{HCC}(19)$ |
| 1080 | | | $\nu\text{NC}(10)+\delta\text{NCN}(57)$ |
| 1101 | | 1102 | $\gamma\text{CCCN}(16)$ |
| 1120 | | | $\nu\text{NC}(26)$ |
| 1135 | | | $\nu\text{FC}(13)+\nu\text{CC}(22)$ |
| 1158 | 1148 | 1147 | $\nu\text{FC}(42)$ |
| 1172 | | | $\delta\text{HCN}(12)$ |
| 1177 | | | $\nu\text{FC}(11)+\delta\text{HCC}(54)$ |
| 1182 | | | $\nu\text{NC}(11)$ |
| 1191 | | | $\delta\text{HCN}(11)+\delta\text{HCC}(23)$ |
| 1236 | 1238 | | $\delta\text{HCC}(10)$ |
| 1243 | | | $\delta\text{HCC}(33)$ |
| 1247 | | | $\nu\text{FC}(16)+\delta\text{HCN}(31)$ |
| 1264 | 1278 | 1274 | $\nu\text{FC}(13)+\nu\text{NC}(15)$ |
| 1311 | | | $\nu\text{FC}(19)$ |
| 1325 | | | $\delta\text{HCC}(15)$ |
| 1349 | 1338 | 1340 | $\nu\text{CC}(10)+\tau\text{HCCN}(10)$ |
| 1368 | | | $\tau\text{HCCC}(23)$ |
| 1373 | | | $\nu\text{NC}(11)+\tau\text{HCNC}(18)$ |
| 1377 | 1375 | 1370 | $\nu\text{FC}(37)+\nu\text{CC}(12)$ |
| 1388 | | | $\nu\text{CC}(15)+\delta\text{HCN}(17)$ |
| 1407 | | | $\tau\text{HCNC}(40)$ |
| 1419 | | | $\delta\text{HCN}(28)$ |
| 1434 | | 1426 | $\nu\text{NC}(15)$ |
| 1458 | 1445 | | $\delta\text{HCH}(56)$ |
| 1460 | | | $\delta\text{CNC}(15)$ |
| 1489 | | | $\nu\text{NC}(26)$ |

| | | | |
|------|------|------|-----------------------------------|
| 1505 | | | δ HCH(136) |
| 1511 | 1518 | 1514 | δ HCH(62) |
| 1530 | | | ν NC(10)+ δ HCH(53) |
| 1543 | | | ν NC(46)+ δ CNC(17) |
| 1564 | | 1556 | ν CC(10) |
| 1577 | | | ν NC(28) |
| 1657 | | | ν CC(37) |
| 1667 | 1668 | 1669 | δ HNH(68)+ τ HNCC(13) |
| 1680 | | | ν CC(42) |
| 1749 | | | ν OC(85) |
| 3020 | | | ν CH(97) |
| 3030 | | | ν CH(93) |
| 3031 | | | ν CH(95) |
| 3050 | | | ν CH(99) |
| 3065 | | 3060 | ν CH(65) |
| 3071 | 3077 | | ν CH(98) |
| 3084 | | | ν CH(74) |
| 3114 | | | ν CH(78) |
| 3132 | | | ν CH(76) |
| 3149 | | | ν CH(97) |
| 3172 | | | ν CH(96) |
| 3212 | | | ν CH(100) |
| 3238 | | | ν CH(99) |
| 3478 | | | ν NH(100) |
| 3576 | | | ν NH(71) |

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

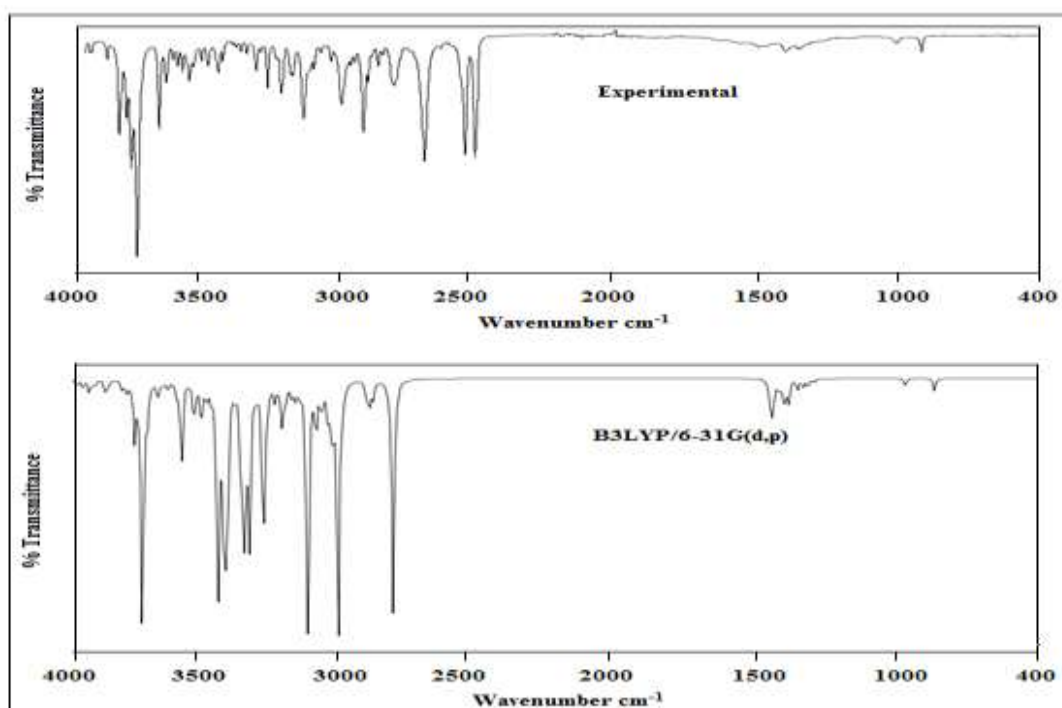


Fig.2 FT-IR spectrum of Sitagliptin

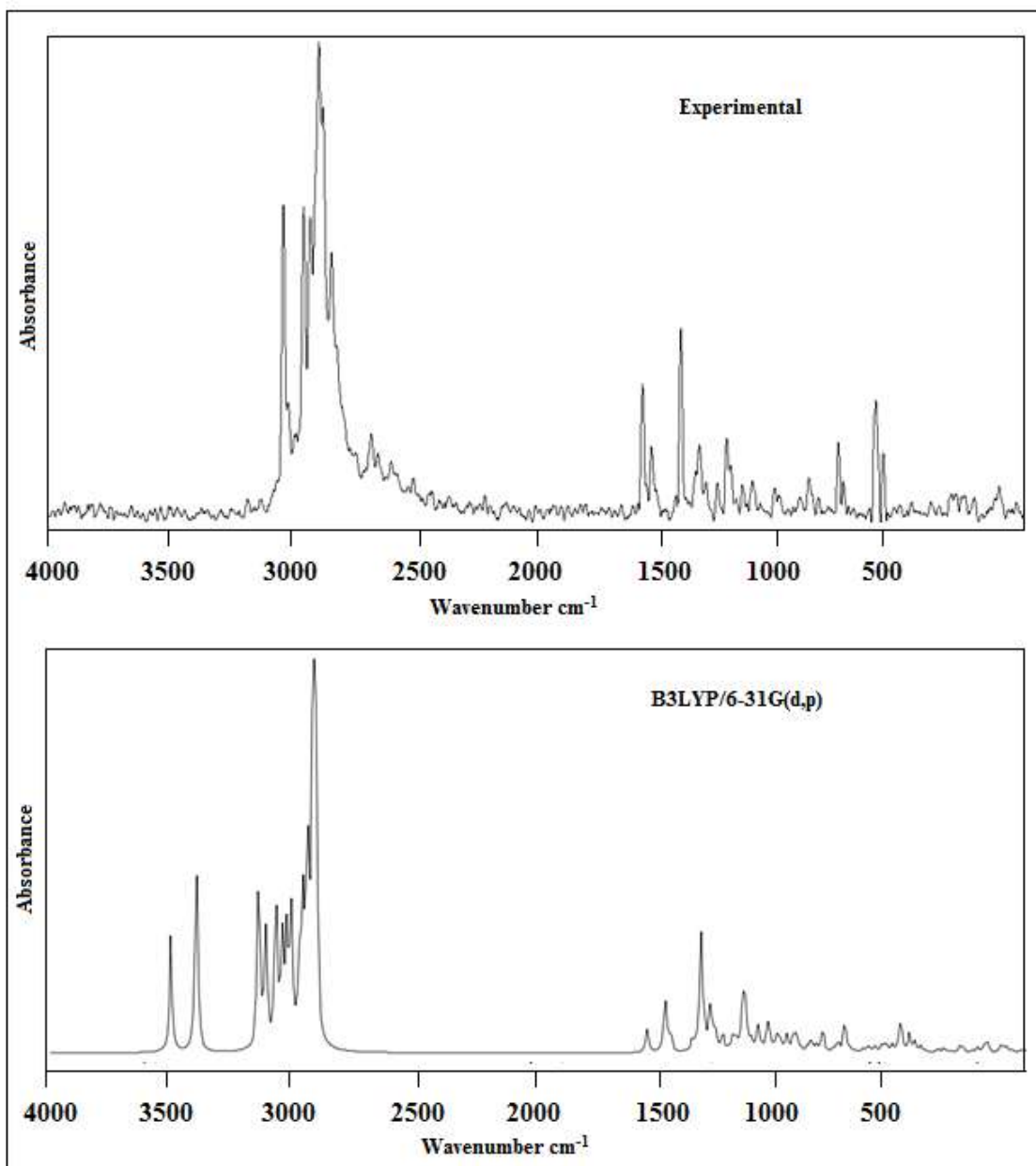


Fig. 3 FT-Raman spectra of Sitagliptin

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 3077 cm^{-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 3084 cm^{-1} by B3LYP method. The theoretical vibrations by B3LYP method also show good agreement with experimentally recorded data. The bands appeared at 900-675 cm^{-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 901 cm^{-1} in FT-Raman spectrum. From B3LYP methods the C-H out-of-plane bending vibrations at 723, 744 and 876 cm^{-1} . The C-H in plane bending vibrations observed in the region of 1000-1300 cm^{-1} [17-21]. In this present study the four C-H in plane bending vibrations identified at 1010, 1102, 1147 and 1274 cm^{-1} in FT-IR and at 1017, 1148, 1238 and 1278 cm^{-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 1650-1400 cm^{-1} [22]. In this present work the wave numbers found at 1511, 1667 cm^{-1} in B3LYP/6-31G(d,p) methods are assigned to C-C stretching vibrations. The C-C stretching wave number is established at 1426 cm^{-1} 1514 cm^{-1} and 1556 cm^{-1} in FT-IR spectra and 1445 cm^{-1} , 1518 cm^{-1} and 1634 cm^{-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 902 cm^{-1} and 971 cm^{-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 1700-1660 cm^{-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 1669 cm^{-1} in FT-IR and 1668 cm^{-1} in FT-Raman and the theoretical bands by B3LYP at 1667 cm^{-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 1266 cm^{-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 1415 cm^{-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 1575 cm^{-1} in FTIR and 1540 cm^{-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 1180-1280 cm^{-1} [28]. Kahovec and Kohlresuch et al. [32] identified the stretching wave number of C-N band in salicylaldehyde at 1617 cm^{-1} .

In this present study the C-N stretching vibrations of sitagliptin are identified at 1668, 1634, 1518 and 1445 cm^{-1} in FT-Raman and the FT-IR bands at 1669, 1556, 1514 and 1426 cm^{-1} . The FT-IR bands observed at 1274 cm^{-1} and the Raman band at 1278 cm^{-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 3520 cm^{-1} to 3480 cm^{-1} for dilute solutions. In the spectra of solid samples are observed near 3350 cm^{-1} to 3180 cm^{-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 3060 cm^{-1} in FT-IR and at 3077 cm^{-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 1120 cm^{-1} [28]. Also the above same highest fundamental frequency vibrations of the CF₃ group which occurs between 1050 and 1225 cm^{-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 CF₃ group, it follows, 3 stretching, 3 bending, 2 rocking and 1 torsional mode. The CF₃ symmetric stretching frequencies are observed at 1102 and 1147 cm^{-1} in FT-IR and at 1148 cm^{-1} in FT-Raman for the title molecule. The CF₃ in plane bending vibration is observed at 463 and 505 cm^{-1} in FT-IR and 457 cm^{-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⁻¹in FT-IR. The out-of-plane modes were calculated at 552,548,539 and 502cm⁻¹by 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 $i \rightarrow j$ is estimated as

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

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/mol to 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 wavelength is 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 |
| | λ_{cal} | 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].

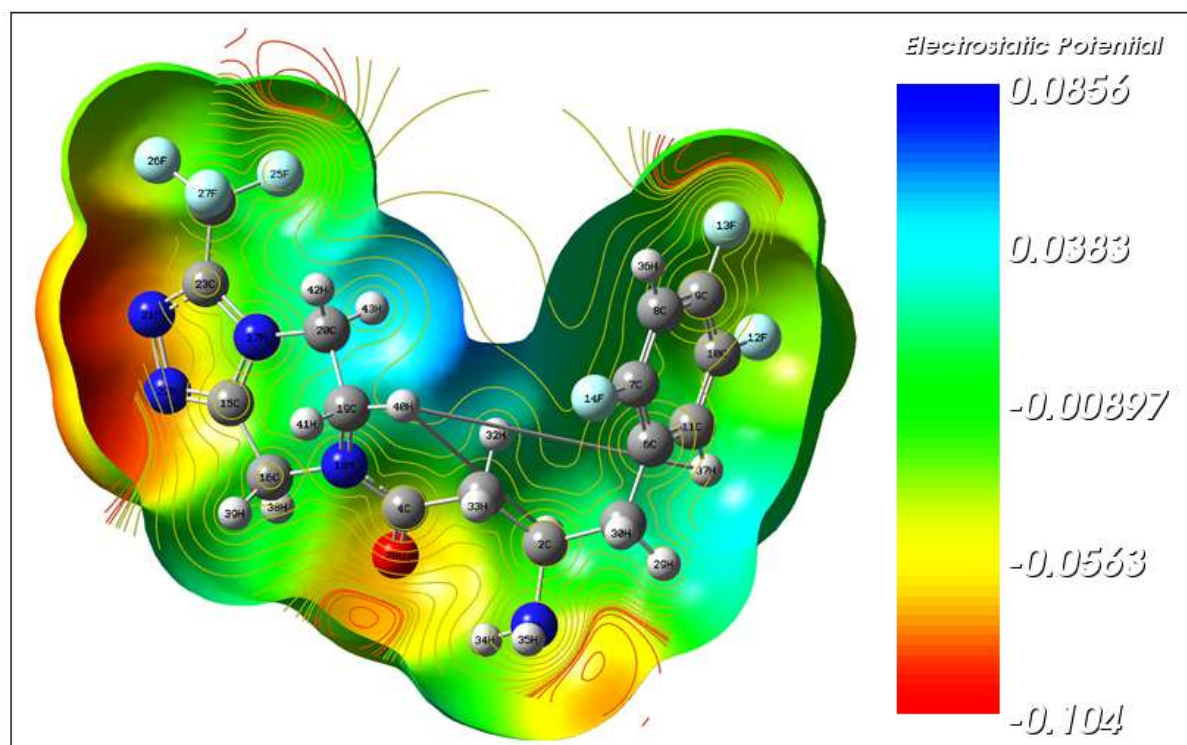


Fig.4 Molecular electrostatic potential of Sitagliptin

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 π 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.

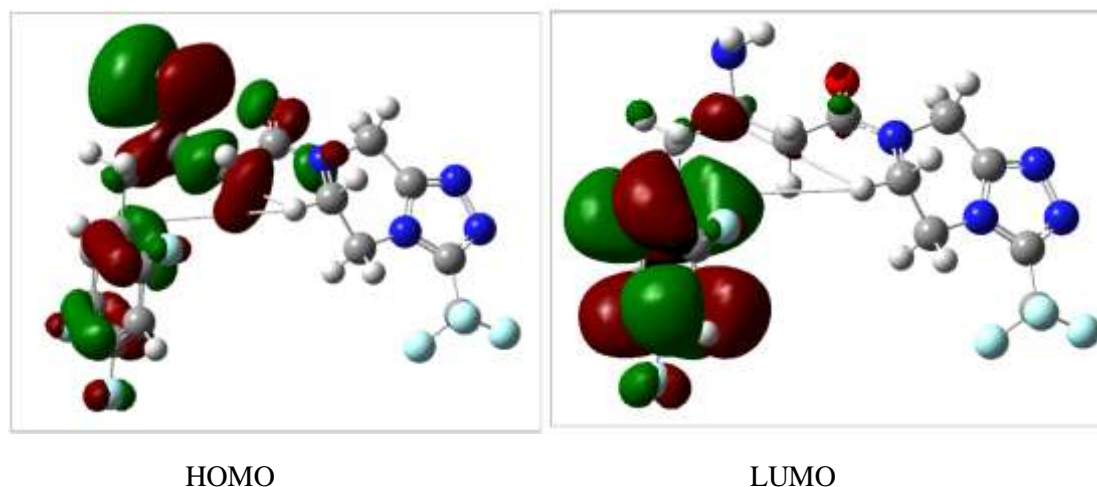


Fig. 5 Frontier molecular orbitals of Sitagliptin

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(ω), Chemical potential (μ), Electronegativity (χ), 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 |
| $E_{\text{Homo-Lumo}}$ 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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