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Quantum Chemical Calculation and DFT Study of Sitagliptin: Insight from Computational Evaluation and Docking Approach

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Abstract

This study aims to explore the structural and chemical behavior of sitagliptin using density functional theory (DFT). The chemical reactivity has been studied in terms of MEP, HOMO-LUMO energy gap, Hirshfeld charge, and global and local reactivity descriptors. Thermodynamic parameters like entropy, enthalpy and specific heat capacity and, nonlinear optical (NLO) properties have been analysed. Higher value of the first hyperpolarizability than that of urea show its potential use as NLO material. Intra-molecular Hydrogen bonding and topological parameters at the bond critical point (BCP) of title molecule have been studied by using the quantum theory of atoms in molecules (QTAIM) approach. The bond of 2.3777 Å between H42⋯N11 is noticed to be strongest one. The pharmacological behavior and protein-ligand interaction of the title molecule have been investigated in terms of drug-likeness and molecular docking which motivates that the amine and carbonyl group bind with the amino acid of the protein.

Keywords: Sitagliptin, Chemical reactivity, DFT, Hydrogen bonding, Molecular docking, NLO.

1. INTRODUCTION

Sitagliptin, (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-1,2,4-triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one, chemically named as Xelevia (or trade name Januvia) is an orally active member of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. It is used against type-2 diabetes and has low side effects in hypoglycemia to control the blood glucose level in humans by increasing insulin secretion [1], lowering HbA1c and fasting as well as postprandial glucose in monotherapy and insulin secretion [2]. Zerilli and Pyon [3] studied its pharmacology and clinical efficacy. Desai [4] analyzed its manufacturing evolution through three generations of process research and development. Similarly, Stofella et al. [5] carried out the solid-state characterization of its different crystalline forms.

Rajesh et al. [6] performed the DFT study of sitagliptin by using the Gaussian 03 package program incorporating B3LYP functional with the implementation of 6-31G(d,p) basis set. However, the properties regarding chemical reactivity, drug-likeness, nonlinear optical (NLO) properties, thermodynamic properties, atoms in the molecule (AIM), and molecular docking have not been performed by any research group so far. In this continuation, we have focused on these properties. DFT has broad spectrum to study hydrogen bonding, chemical reactivity, and electronic properties of pharmaceutical compounds [7-9]. AIM study reveals hydrogen bonding (H-bonding) whereas molecular docking explains the binding of drugs molecule with the target protein. NLO study tells whether the title molecule can be used further as NLO material and, the local reactivity descriptor justifies which particular site is active for further reaction with surrounding sites.

2. MATERIALS AND METHOD

2.1 Computational Details

Quantum chemical calculation and geometry optimization of the title molecule have been performed by using density functional theory (DFT) [10] with the support of Gaussian 09 package [11] at B3LYP/6-311++G(d, p) [12-14]
level of theory. Output files obtained from Gaussian 09 program are visualized with Gauss View 05 [15]. The formation of intramolecular hydrogen bonding in the molecule has been studied with AIMALL software [16] by implementing the quantum theory of atoms in the molecule (QTAIM) [17-20]. The molecular docking (ligand-protein) simulation of the investigated molecule has been performed to check its biological activity by using AutoDock 1.5.4 software [21]. Discovery Studio Visualizer 4.5 software [22] was used to analyze the active site in the molecule. The initial structure of sitagliptin was obtained from PubChem [23].

2.2 Theoretical Details

The global reactivity descriptors: electronegativity ($\chi$), chemical potential ($\mu$), global hardness ($\eta$), global electrophilicity index ($\omega$) and global softness ($S$) are calculated from the energies of frontier molecular orbitals $E_{HOMO}$ and $E_{LUMO}$ and, are given by [24, 25]:

\[
\chi = -\frac{1}{2} (E_{HOMO} + E_{LUMO})
\]

\[
\mu = -\chi = \frac{1}{2} (E_{HOMO} + E_{LUMO})
\]

\[
\eta = \frac{1}{2} (E_{LUMO} - E_{HOMO})
\]

\[
S = \frac{1}{2\eta}
\]

\[
\omega = \frac{\mu^2}{2\eta}
\]

The local reactivity descriptor reveals that which particular site in the molecular system is capable of further chemical reaction with surrounding molecules. This is studied by using Fukui function (FF) [26-29] calculation and is given by the equations:

\[
f_k^+ = [q_k(N+1) - q_k(N)] \quad \text{for nucleophilic attack}
\]

\[
f_k^- = [q_k(N) - q_k(N-1)] \quad \text{for electrophilic attack}
\]

\[
f_k^0 = [q_k(N+1) - q_k(N-1)] \quad \text{for radical attack}
\]

Where $N$, $N-1$, $N+1$ are total electrons present in neutral, cation and anion state of molecule respectively. $+$, $-$ and $0$ represents for nucleophilic, electrophilic, and radical attack respectively. Besides FF, Local softness ($s_k^+$, $s_k^-$, $s_k^0$) and local electrophilicity indices ($\omega_k^+$, $\omega_k^-$, $\omega_k^0$) is also used to check the local reactivity behavior and is given by the equations:

\[
s_k^+ = Sf_k^+, s_k^- = Sf_k^-, s_k^0 = Sf_k^0
\]

\[
\omega_k^+ = \omega f_k^+, \omega_k^- = \omega f_k^-, \omega_k^0 = \omega f_k^0
\]

The first hyperpolarizability ($\beta_0$) is a third-ranked tensor which can be explained by a $3X3X3$ matrix. The 27 components of the 3D-matrix can be reduced to 10 components from the Kleinman symmetry [30]. The lower part of the $3X3X3$ matrix is tetrahedral. The components of ($\beta_k$) can be defined as the coefficients in the Taylor series expansion of the energy in the external electric field. For weak and homogenous electric field this expansion becomes:

\[
E = E^0 - \mu_i F_i - \frac{1}{2} \alpha_{ij} F_i F_j - \frac{1}{6} \beta_{ijk} F_i F_j F_k
\]

Where $E^0$ is the energy of the unperturbed molecules, $F_i$ is the field at the origin and $\mu_i$, $\alpha_{ij}$ and $\beta_{ijk}$ are the components of dipole moment, polarizability and first hyperpolarizability respectively.

Total static dipole moment ($\mu_0$), the first hyperpolarizability ($\beta_0$), mean polarizability ($\Delta\alpha_0$) and anisotropy of polarizability $|\alpha_0|$ of the molecular system have been calculated by using DFT at B3LYP/6-311++G(d, p) level of theory and are given by the equations [31].
3. RESULTS AND DISCUSSION

3.1 Geometry Optimization

The optimized structure of sitagliptin with the numbering scheme used in this study is presented in Fig. 1. The calculated bond length, bond angle, and dihedral angles are found similar to the results by Rajesh et al. [6]. The ground state optimized energy obtained is -1567.1989 Hartree.

![Fig. 1: Optimized structure of sitagliptin and the atom numbering scheme adopted in this study.](image)

3.2 Molecular Electrostatic Potential (MEP)

The distribution of partial charges in space around the molecule, which infer about the reactive site of the molecule, is examined, and explained in terms of MEP [32-34]. The values of electrostatic potential are given in terms of distinct colors: red region identified the negative electrostatic potential; blue region recognized the positive electrostatic potential and green region represents the zero potential. Potential increases in the order red<orange<yellow<green<blue. The color code of MEP for title molecule is in the range -4.986e-2 a.u to +4.986e-2 a.u. The MEP mapped structure is presented in Fig. 2.

![Fig. 2: Molecular electrostatic potential (MEP) formed by mapping of total density over the electrostatic potential of sitagliptin.](image)

The negative charge is mostly concentrated across N10 and N12 of ring R3 and behaves as an electrophilic center but the partial negative charge is localized across carbonyl group (C19=O7) whereas the positive charge is concentrated across N11H2, C17H2 and the ring R2 which are the major nucleophilic centers.

3.3 Frontier Orbital Analysis

The highest molecular orbital (HOMO) and lowest molecular orbital (LUMO) are the main frontier orbitals which take part in chemical reaction for the chemical stability of the molecule [35]. The energy of HOMO (E_{HOMO}) is related to ionization potential whereas the energy of LUMO (E_{LUMO}) is related to electron affinity. Their gap energy (\Delta E = E_{LUMO} - E_{HOMO}) is the stability index that determines the electron transport properties [36]. This energy gap for sitagliptin is found to be 5.6714 eV. The HOMO-LUMO orbitals and their energies are presented in Fig. 3.

![Fig. 3: HOMO-LUMO plot of sitagliptin.](image)

3.4 Global Reactivity Descriptors

The calculated E_{HOMO}, E_{LUMO} and their energy gap (\Delta E) and \chi, \mu, \eta, S, and \omega values for sitagliptin are listed in Table 1. The HOMO–LUMO energy gap of the examined molecule is obtained as 5.6714 eV but the global softness is found to be 4.0836 eV. Small value of the energy gap represents the more chemically reactive molecule and softer whereas the high value of the energy gap stands for a harder molecule with more stable.
3.4 Drug-Likeness
When a chemical compound has definite biological/pharmacological activity, for the orally active drug in humans, Lipinski’s ‘rule of five’ evaluates drug-likeness. In an experiment for a better forecast of drug-likeness, the rules have generated many developments. Out of these developed rules, three of them state that the compound should have (i) a molar refraction (MR) from 40 to 130 (ii) a molecular weight from 180 to 500 and (iii) its number of atoms from 20 to 70.

The value of molar refraction (MR) is responsible for the binding property and lipophilicity of the studied system which is calculated from the Lorenz-Lorentz formula [37-39]. The values of MR, molecular weight, and the number of atoms for sitagliptin are 80 esu, 407.32 g/mol, and 43 respectively. All the above-mentioned values lie within the normal range. So, sitagliptin can be orally used for humans.

3.5 Local Reactivity Descriptors
The highest value of \((f_k^+, s_k^+, \omega_k^+)\) gives the idea of the most nucleophilic site whereas the peak value of \((f_k^-, s_k^-, \omega_k^-)\) infer about the electrophilic region in the molecule respectively. The local reactivity properties of sitagliptin are calculated by using Hirshfeld derived charges at B3LYP/6-311++G(d,p) level and their values are presented in Table 2 and, the atoms N11 and H33 are the most responsible for the nucleophilic and electrophilic attack respectively.

### Table 2: Calculated local reactivity properties of Sitagliptin using Hirshfeld [B3LYP/6-311++G(d,p)] derived charges.

| Site | \(f_k^+\) | \(s_k^+\) | \(\omega_k^+\) | \(f_k^-\) | \(s_k^-\) | \(\omega_k^-\) | \(f_k^0\) | \(s_k^0\) | \(\omega_k^0\) |
|------|----------|----------|---------------|----------|----------|---------------|----------|----------|---------------|
| F1   | 0.0092   | 0.0016   | 0.0271        | 0.0101   | 0.0018   | 0.0298        | -0.3195  | -0.0563  | -0.9394       |
| F2   | 0.0079   | 0.0014   | 0.0232        | 0.0091   | 0.0016   | 0.0268        | -0.3569  | -0.0629  | -1.0493       |
| F3   | 0.0069   | 0.0012   | 0.0204        | 0.0084   | 0.0015   | 0.0248        | -0.3550  | -0.0626  | -1.0437       |
| F4   | 0.0495   | 0.0087   | 0.1456        | 0.0023   | 0.0004   | 0.0067        | -0.3322  | -0.0586  | -0.9768       |
| F5   | 0.0537   | 0.0095   | 0.1580        | 0.0096   | 0.0017   | 0.0283        | -0.3168  | -0.0559  | -0.9316       |
| F6   | 0.0538   | 0.0095   | 0.1582        | 0.0144   | 0.0025   | 0.0424        | -0.3150  | -0.0555  | -0.9263       |
| O7   | 0.0377   | 0.0066   | 0.1107        | 0.0188   | 0.0033   | 0.0553        | -0.6190  | -0.1091  | -1.8202       |
| N8   | 0.0328   | 0.0058   | 0.0964        | 0.0020   | 0.0004   | 0.0059        | -0.5045  | -0.0889  | -1.4833       |
| N9   | 0.0067   | 0.0012   | 0.0196        | 0.0077   | 0.0014   | 0.0226        | -0.4128  | -0.0728  | -1.2137       |
| N10  | 0.0517   | 0.0091   | 0.1520        | 0.0185   | 0.0033   | 0.0545        | -0.2888  | -0.0509  | -0.8491       |
| N11  | 0.1036   | 0.0183   | 0.3046        | 0.0187   | 0.0033   | 0.0550        | -0.8055  | -0.1420  | -2.3685       |
| N12  | 0.0450   | 0.0079   | 0.1324        | 0.0307   | 0.0054   | 0.0904        | -0.2426  | -0.0428  | -0.7134       |
| C13  | -0.0024  | -0.0004  | -0.0070       | 0.0099   | 0.0017   | 0.0291        | -0.1967  | -0.0347  | -0.5783       |
| C14  | -0.0024  | -0.0004  | -0.0069       | 0.0032   | 0.0006   | 0.0093        | -0.1790  | -0.0316  | -0.5262       |
| C15  | -0.0046  | -0.0008  | -0.0136       | 0.0224   | 0.0039   | 0.0658        | -0.2194  | -0.0387  | -0.6451       |
| C16  | -0.0005  | -0.0001  | -0.0015       | 0.0127   | 0.0022   | 0.0373        | 0.3715   | 0.0655   | 1.0923        |
| C17  | 0.0082   | 0.0014   | 0.0241        | 0.0298   | 0.0053   | 0.0877        | -0.4933  | -0.0870  | -1.4506       |
| C18  | -0.0056  | -0.0010  | -0.0164       | 0.0060   | 0.0011   | 0.0177        | -0.0275  | -0.0048  | -0.8080       |
| C19  | -0.0062  | -0.0011  | -0.0183       | 0.0016   | 0.0003   | 0.0048        | 0.6996   | 0.1233   | 2.0571        |
The calculated values of dipole moment ($\mu_0$), the mean polarizability ($\alpha_0$), and first hyperpolarizability ($\beta_0$) of Sitagliptin at B3LYP/6-311++G(d, p).

| Dipole moment (Debye) | Polarizability ($\alpha$ *10^{-24}$esu) | First Hyperpolarizability ($\beta$ *10^{-30}$esu) |
|-----------------------|------------------------------------------|-----------------------------------------------|
| $\mu_x$              | $-0.4527$                                 | $43.8660$                                     | $\beta_{xxx}$ | $-0.4350$ |
| $\mu_y$              | $-0.4270$                                 | $-2.0511$                                     | $\beta_{xyy}$ | $0.0164$  |
| $\mu_z$              | $-1.9397$                                 | $31.1093$                                     | $\beta_{yyy}$ | $-0.9051$ |
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\[
\begin{align*}
\mu_0 & \quad 2.0371 \quad \alpha_{xz} & \quad 2.3298 \quad \beta_{yyy} & \quad 0.5594 \\
\mu_0 \text{ (Urea)} & \quad 1.7410 \quad \alpha_{yz} & \quad 0.0706 \quad \beta_{xxz} & \quad -0.1117 \\
\quad & \quad \alpha_{zz} & \quad 24.9932 \quad \beta_{xyz} & \quad 0.2994 \\
\quad & \quad \beta_{axy} & \quad 33.3228 \quad \beta_{yyz} & \quad -0.4786 \\
\Delta \alpha & \quad 77.9074 \quad \beta_{xzz} & \quad -0.5016 \\
\Delta \alpha \text{ (Urea)} & \quad 9.7710 \quad \beta_{yzz} & \quad 0.4545 \\
\quad & \quad \beta_{zz} & \quad -1.2093 \quad \beta_{0} & \quad 2.7733 \\
\quad & \quad \beta_{0} \text{ (Urea)} & \quad 0.9279
\end{align*}
\]

Fig. 4: Correlation graph of enthalpy \( (H_m^0) \) (kcal/mol), specific heat \( (C_{p,m}^0) \) (cal/mol-K), entropy \( (S_m^0) \) (cal/mol-K) and temperature for sitagliptin. (Colour online).

3.7 Thermodynamic Properties

Important thermodynamic properties of solids are entropy, enthalpy, heat capacity, specific heat capacity, and many more. Thermodynamics is used to analyze the effect of temperature on chemical reactions, the stability of the molecule, binding properties of biologically active molecules with protein, and physicochemical properties [43-45]. In this study, we have focused on the variation of thermodynamic parameters: heat capacity \( (C_{p,m}^0) \), entropy \( (S_m^0) \) and enthalpy \( (H_m^0) \) as a function of temperature in the range 50K to 400K. Total energy, zero-point vibrational energy, enthalpy, specific heat, entropy, and rotational constant of title molecule calculated at room temperature (298.15K) and normal pressure are listed in Table 4. The graphic correlation of enthalpy \( (H_m^0) \), specific heat \( (C_{p,m}^0) \) and entropy \( (S_m^0) \) is presented in Fig. 4 and is given by the relations:

\[
H_m^0 = 196.44911 + 0.0125 T + 1.35119 \times 10^{-4} T^2 \quad (R^2 = 0.9999)
\]

\[
C_{p,m}^0 = 9.99089 + 0.2291 T - 6.45992 \times 10^{-5} T^2 \quad (R^2 = 0.9997)
\]

\[
S_m^0 = 67.25107 + 0.44544 T - 2.13619 \times 10^{-4} T^2 \quad (R^2 = 0.9996)
\]

Fig. 4 reveals that the values of \( H_m^0 \), \( C_{p,m}^0 \) and \( S_m^0 \) increase with the rise in temperature which is due to an increase in molecular vibrational intensities with an increase in temperature.

Table 4: Theoretically computed total energy (eV), zero-point energy (J/mol), enthalpy (kcal/mol), specific heat (cal/mol-K), entropy (cal/mol-K) and rotational constants(GHz) at 298.15 K at the B3LYP/6-311++G(d,p) level of sitagliptin.

| Parameters | Values |
|------------|--------|
| Total energy (eV) | -42645.6718 |
| Zero point energy (J/mol) | 822583.6 |
| Enthalpy (kcal/mol) | 212.213 |
| Specific heat (cal/mol-K) | 93.322 |
| Entropy (cal/mol-K) | 180.323 |
| Rotational constant (GHz) | 0.51921 |
3.8 Atom In Molecule (AIM) Calculation

The Quantum theory of atoms in the molecule (QTAIM) explains the strength and nature of inter and intra-molecular hydrogen bonding [46]. The molecular graph of sitagliptin using the AIM program at B3LYP/6-311++G(d,p) level is presented in Fig. 5. The calculated topological and energy parameters for the intramolecular H-bonds of interacting atoms of sitagliptin is reported in Table 5. The geometrical parameters for the H-bonds of sitagliptin are given in Table 6. All the H-bonds have an electron density in the range 0.0020-0.0400 a.u., predicted by Koch and Popelier [47] criteria. In this study, the bond H42…N11 has the smallest bond length, as given in Table 5, so it is a strong intra-molecular H-bond. However, the distance between the interacting atoms H31…F2 is greater than the sum of their Van der Waals radii, so this H-bond is weak. The AIM result explores \( \nabla^2 \rho_{\text{BCP}} > 0 \) and \( H_{\text{BCP}} < 0 \) so the nature of the bond is medium as suggested by Rozas et al. [48].

Table 5: Topological parameters for intramolecular interaction in sitagliptin: ED \( (\rho_{\text{BCP}}) \), Laplacian of ED \( (\nabla^2 \rho_{\text{BCP}}) \), electron kinetic energy density \( (G_{\text{BCP}}) \), electron potential energy density \( (V_{\text{BCP}}) \), total electron energy density \( (H_{\text{BCP}}) \), interaction energy \( (E_{\text{int}}) \) at BCP.

| Interactions | Bond Length (Å) | \( \rho_{\text{BCP}} \) (a.u) | \( \nabla^2 \rho_{\text{BCP}} \) (a.u) | \( G_{\text{BCP}} \) (a.u) | \( V_{\text{BCP}} \) (a.u) | \( H_{\text{BCP}} \) (a.u) | \( E_{\text{int}} \) (kcal/mol) |
|--------------|-----------------|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| H31…F2      | 3.0634          | 0.0065           | 0.0268          | -0.0010         | -0.0046         | -0.0057         | -1.4482         |
| H34…C17     | 2.4989          | 0.0130           | 0.0558          | -0.0025         | -0.0089         | -0.0114         | -2.7961         |
| H42…N11     | 2.3777          | 0.0150           | 0.0468          | -0.0017         | -0.0084         | -0.0100         | -2.6290         |

Fig. 5: Molecular graph of sitagliptin: bond critical points (small red spheres), ring critical points (small yellow spheres), bond paths (pink lines).

Table 6: Geometrical parameters for intramolecular hydrogen bonds in sitagliptin: bond length (Å), bond angle (°) and the sum of Van der Waals radii of interacting atoms \( (r_H + r_A) \) in Å.

| D-H…A       | D-H (Å) | H…A (Å) | D-H…A (°) | \( (r_H + r_A) \) (Å) |
|--------------|---------|---------|-----------|----------------------|
| C14-H31…F2  | 1.09055 | 3.0634  | 115.81191 | 2.67                 |
| C15-H34…C17 | 1.08699 | 2.4989  | 103.25822 | 2.60                 |
| C25-H42…N11 | 1.08261 | 2.3777  | 123.21447 | 2.75                 |

3.9 Molecular Docking

Molecular docking has become an important tool in drug discovery with the study of the ligand-protein interaction mechanism. To examine the biological activity of sitagliptin, docking simulation has been performed using AutoDock software [22]. The active site of the enzyme was explained within the grid size 60ÅX60ÅX60Å to incorporate the residues of the active sites. Proteins were prepared by removing co-crystallized ligands and water molecules using Discovery Studio Visualizer 4.5 software [49]. It is a dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs and works by increasing the production of insulin and decreasing the production of glucagon by the pancreas. Therefore, DPP-4 was chosen as a target for sitagliptin which is predicted by Swiss Dock software and given in Fig. 6. The crystal structure of target protein DPP-4 (PDB
code: 1J2E and 1U8E) was downloaded from the RSCB PDB website [50]. The binding energy of ligand with the target and the bond length of the hydrogen bond formed between them are shown in Table 7. Out of many docked conformations, one which well-bounded the active sites was taken into consideration and is drawn in Fig. 7. 1J2E shows the formation of one hydrogen bond (2.49 Å, THR A: 251) with the carbonyl group, two hydrogen bonds (1.77 Å, GLU B: 237, 1.95 Å, PRO B: 249) with NH$_2$ group and one (2.21Å, ARG B:253 ) with the CF$_3$ group attached to the ring having binding energy −7.25 kcal/mol. Another interaction was also found with 1U8E in which two hydrogen bonds were observed with the NH$_2$ group having bond length and residues: 1.81 Â, ASP B:709, and 2.03 Â, ASP B:739 respectively. One hydrogen bond was also present with the C=O group (2.36 Å, LYS B: 122). The binding energy was −7.17 kcal/mol. The above discussed molecular docking study of sitagliptin explores its ligand-target interaction mechanism.

Table 7: Bond length, Binding energy and Ligand efficiency of sitagliptin against two protein targets.

| Ligand     | protein              | PDB code | Bond length (Å) | Amino acid | Binding energy (kcal/mol) | Ligand efficiency |
|------------|----------------------|----------|-----------------|------------|--------------------------|------------------|
| Sitagliptin| Dipeptidyl Peptidase-4 (DPP-4) | 1J2E     | 1.77            | GLU B:237  | −7.25                    | −0.26            |
|            |                      |          | 1.95            | PRO A:249  |                          |                  |
|            |                      |          | 2.49            | THR A:251  |                          |                  |
|            |                      |          | 2.21            | ARG A: 253 |                          |                  |
|            |                      |          | 1.81            | ASP B:709  |                          |                  |
|            |                      | 1U8E     | 2.03            | ASP B:739  | −7.17                    | −0.26            |
|            |                      |          | 2.36            | LYS B:122  |                          |                  |

**Fig. 6:** Swiss Dock used to suggest different target proteins to perform the molecular docking simulation.
4. CONCLUSION

Theoretical investigations on sitagliptin molecule, a novel oral hypoglycemic drug of the dipeptidyl peptidase-4 inhibitor (DPP-4) class, have been done by DFT method. The optimized ground state energy is -1567.1989 Hartree. From the molecular electrostatic potential (MEP) map, it is found that the negative charge is concentrated across N10 and N12 of ring R3 while the positive charge is concentrated across N11H$_2$, C17H$_2$, and ring R2. The HOMO-LUMO energy gap is found to be 5.6714eV which explains that the title molecule is chemically more reactive. From local reactivity descriptor analysis N11 and H33 are the key atoms responsible for the nucleophilic and electrophilic attack, respectively. The dipole moment ($\mu_0$) and first hyperpolarizability ($\beta_0$) of title molecule are found to be 2.7733X10$^{-30}$ esu, respectively which are higher than the standard values of urea, its potential as NLO material. The enthalpy, specific heat, and entropy of title molecule at room temperature are found to be 212.213 kcal/mol, 93.322 cal/mol-K and 180.323 cal/mol-K respectively. The QTAIM infer that the title molecule has three intra-molecular hydrogen bonding with $\nabla^2\rho_{\text{BCP}} > 0$ and $H_{\text{BCP}} < 0$. So, there is medium H-bond with partially covalent bond H42…N11 and has the smallest bond length which is the strongest one in nature. Molecular docking has been explored that the investigated molecule can be used as against type-2 diabetes.

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