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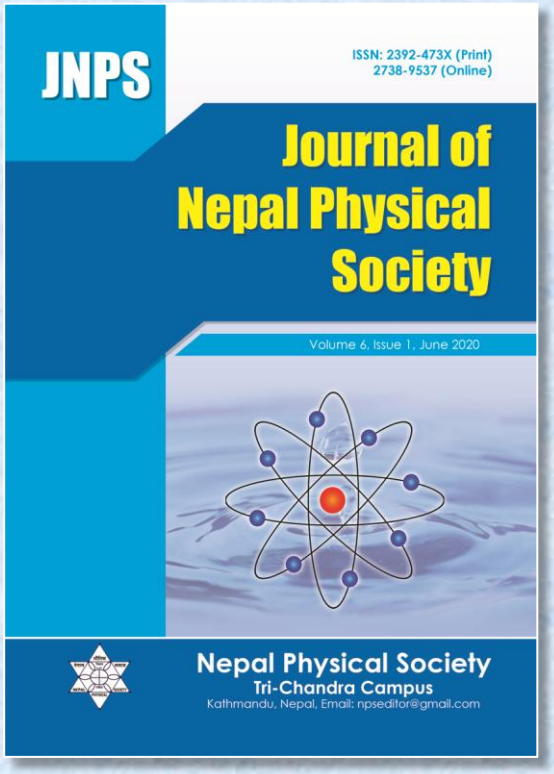

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Quantum Chemical Calculation and DFT Study of Sitagliptin: Insight from Computational Evaluation and Docking Approach

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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, (3*R*)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5*H*-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 (χ), chemical potential (μ), global hardness (η), global electrophilicity index (ω) 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:

$f_k^+ = [q_k(N+1)-q_k(N)]$ *for nucleophilic attack*

$f_k^- = [q_k(N)-q_k(N-1)]$ *for electrophilic attack*

$f_k^0 = [q_k(N+1) - q_k(N-1)]$ *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 (ω_k^+, ω_k-, ω_k^0) is also used to check the local reactivity behavior and is given by the equations:

$s_k^+ = Sf_k^+$, $s_k- = Sf_k-$, $s_k^0 = Sf_k^0$

for local softness

$\omega_k^+ = \omega f_k^+$, $\omega_k- = \omega f_k-$, $\omega_k^0 = \omega f_k^0$

for local electrophilicity indices

The first hyperpolarizability (β_o) 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 (β_o) 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:

$$E = E^0 - \mu_i F_i - \frac{1}{2}\alpha_{ij}F_iF_j - \frac{1}{6}\beta_{ijk}F_iF_jF_k$$

Where E^0 is the energy of the unperturbed molecules, F_i is the field at the origin and μ_i, α_{ij} and β_{ijk} are the components of dipole moment, polarizability and first hyperpolarizability respectively.

Total static dipole moment (μ_0), the first hyperpolarizability (β_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].

$$\mu_0 = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2}$$

$$|\alpha_0| = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$$

$$\Delta\alpha = 2^{-1/2}\left[(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2 + 6\alpha_{xx}^2\right]^{1/2}$$

$$\beta_0 = \left[(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{xxy} + \beta_{yzz})^2 + (\beta_{zzz} + \beta_{xxz} + \beta_{yyz})^2\right]^{1/2}$$

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 rsults by Rajesh *et al*. [6]. The ground state optimized energy obtained is -1567.1989 Hartree.

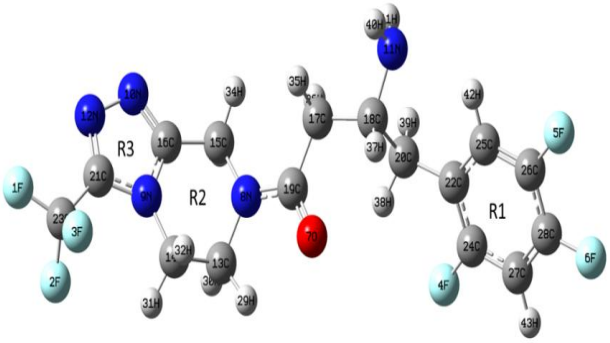

Fig. 1: *Optimized structure of sitagliptin and the atom numbering scheme adopted in this study.*

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.

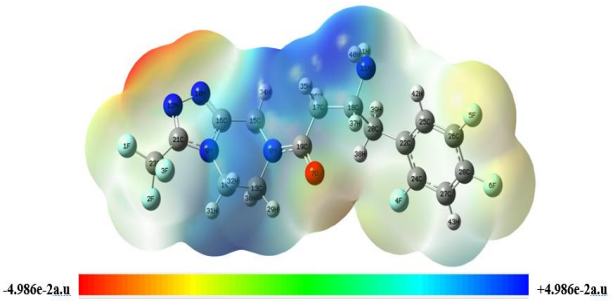

Fig. 2: *Molecular electrostatic potential (MEP) formed by mapping of total density over the electrostatic potential of sitagliptin.*

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 $N11H_2$, $C17H_2$ 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.

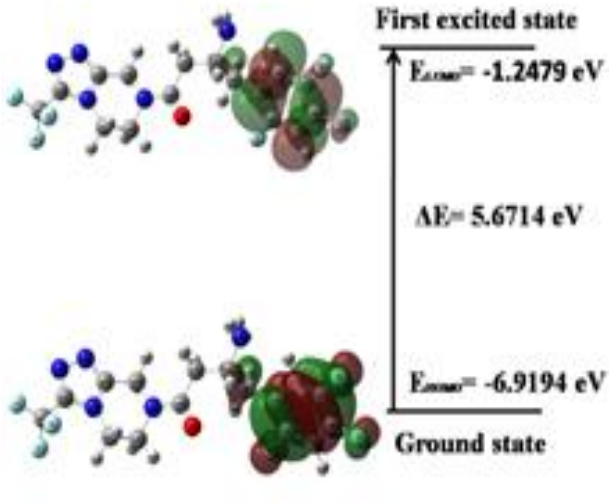

Fig. 3: *HOMO-LUMO plot of sitagliptin.*

3.4 Global Reactivity Descriptors

The calculated E_{HOMO}, E_{LUMO} and their energy gap (ΔE) and χ, μ, η, S, and ω 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.

Table 1: Calculated E_{HOMO}, E_{LUMO}, energy ban gap (E_L–E_H), chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S) and global electrophilicity index (ω) for sitagliptin.

E_H (eV)	E_L(eV)	$E_L - E_H$ (eV)	χ (eV)	μ (eV)	η (eV)	S $(eV)^{-1}$	ω (eV)
-6.9194	- 1.2479	5.6714	4.0836	- 4.0836	2.8357	0.1763	2.9404

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 refractivity (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 refractivity (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^+, ω_k^+) gives the idea of the most nucleophilic site whereas the peak value of (f_k-, s_k-, ω_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^+	ω_k^+	f_k-	s_k-	ω_k-	f_k^0	s_k^0	ω_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	−0.0808
C19	−0.0062	−0.0011	−0.0183	0.0016	0.0003	0.0048	0.6996	0.1233	2.0571

C20	−0.0175	−0.0031	−0.0514	0.0104	0.0018	0.0304	-0.4158	-0.0733	−1.2227
C21	0.0224	0.0039	0.0659	0.0375	0.0066	0.1102	0.2439	0.0430	0.7170
C22	0.0918	0.0162	0.2700	−0.0015	−0.0003	−0.0043	−0.0338	−0.0060	−0.0994
C23	−0.0005	−0.0001	−0.0014	0.0067	0.0012	0.0196	1.0379	0.1830	3.0520
C24	0.0761	0.0134	0.2237	0.0005	0.0001	0.0016	0.4523	0.0797	1.3299
C25	−0.0069	−0.0012	−0.0203	0.0291	0.0051	0.0855	−0.2586	−0.0456	−0.7602
C26	0.0825	0.0146	0.2427	0.0076	0.0013	0.0223	0.3824	0.0674	1.1245
C27	0.0068	0.0012	0.0199	0.0302	0.0053	0.0887	−0.3218	−0.0567	−0.9461
C28	0.0775	0.0137	0.2278	0.0218	0.0038	0.0641	0.3926	0.0692	1.1543
H29	0.0024	0.0004	0.0070	0.0206	0.0036	0.0606	0.2478	0.0437	0.7287
H30	0.0144	0.0025	0.0423	0.0515	0.0091	0.1513	0.1783	0.0314	0.5242
H31	0.0138	0.0024	0.0407	0.0198	0.0035	0.0581	0.2206	0.0389	0.6488
H32	0.0063	0.0011	0.0186	0.0463	0.0082	0.1363	0.1962	0.0346	0.5768
H33	0.0164	0.0029	0.0483	0.1047	0.0185	0.3079	0.1714	0.0302	0.5041
H34	−0.0003	0.0000	−0.0008	0.0434	0.0077	0.1276	0.2176	0.0384	0.6397
H35	0.0149	0.0026	0.0438	0.0764	0.0135	0.2245	0.1949	0.0344	0.5731
H36	0.0120	0.0021	0.0354	0.0900	0.0159	0.2647	0.1721	0.0303	0.5061
H37	0.0124	0.0022	0.0365	0.0119	0.0021	0.0349	0.2109	0.0372	0.6201
H38	0.0164	0.0029	0.0481	0.0066	0.0012	0.0195	0.2364	0.0417	0.6951
H39	0.0315	0.0056	0.0926	0.0353	0.0062	0.1037	0.2046	0.0361	0.6017
H40	0.0196	0.0035	0.0577	0.0408	0.0072	0.1198	0.3461	0.0610	1.0178
H41	0.0156	0.0028	0.0459	0.0631	0.0111	0.1854	0.3243	0.0572	0.9537
H42	0.0160	0.0028	0.0471	0.0002	0.0000	0.0005	0.2639	0.0465	0.7758
H43	0.0312	0.0055	0.0917	0.0114	0.0020	0.0334	0.2490	0.0439	0.7320

3.6 Nonlinear Optical (Nlo) Properties

NLO phenomena are used to investigate the interaction of the applied magnetic field with organic materials which generate the new magnetic field altered in frequency, amplitude, phase, and many more physical phenomena which has the practical applications in optical sensing, data storage, optical communication, *etc.* [40-42].

The calculated values of dipole moment (μ_0), the first hyperpolarizability (β_0), mean polarizability ($\Delta\alpha_0$) and anisotropy of polarizability $|\alpha_0|$ of the investigated molecule are listed in Table 3. The values of the dipole moment (μ_0) and the first hyperpolarizability (β_0) of title molecule are obtained as 2.03714 Debye and $2.7733X10^{-30}$ esu, respectively. The dipole moment and first hyperpolarizability of the investigated molecule are greater than that of urea, hence this molecule can be considered as NLO active material.

Table 3: The calculated dipole moment (μ_0), mean polarizability$|\alpha_0|$ anisotropy of polarizability ($\Delta\alpha$) and first hyperpolarizability (β_0) of Sitagliptin at B3LYP/6-311++G(d, p).

Dipole moment (Debye)		**Polarizability ($*10^{-24}$esu)**		**First Hyperpolarizability ($*10^{-30}$esu)**	
μ_x	−0.4527	α_{xx}	43.8660	β_{xxx}	−0.4350
μ_y	−0.4270	α_{xy}	−2.0511	β_{xxy}	0.0164
μ_z	−1.9397	α_{yy}	31.1093	β_{xyy}	−0.9051

μ_0	2.0371	α_{xz}	2.3298	β_{yyy}	0.5594
μ_0 (Urea)	1.7410	α_{yz}	0.0706	β_{xxz}	−0.1117
		α_{zz}	24.9932	β_{xyz}	0.2994
		$\lvert\alpha_0\rvert$	33.3228	β_{yyz}	−0.4786
		$\Delta\alpha$	77.9074	β_{xzz}	−0.5016
		$\Delta\alpha$ (Urea)	9.7710	β_{yzz}	0.4545
				β_{zzz}	−1.2093
				β_0	2.7733
				β_0 (Urea)	0.9279

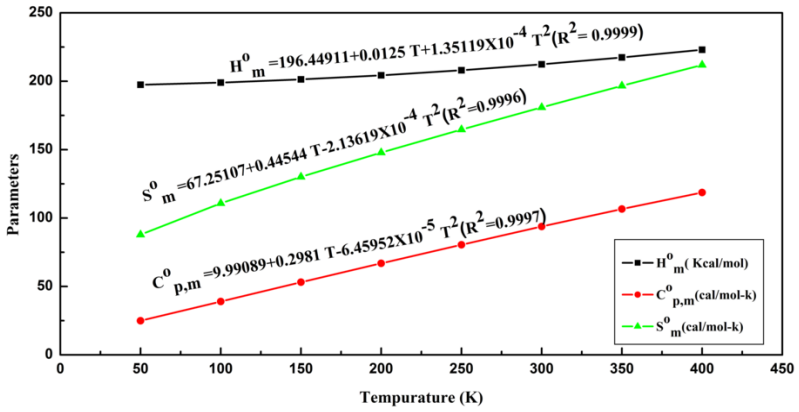

Fig. 4: *Correlation graph of enthalpy (H_m^o) (kcal/mol), specific heat ($C_{p,m}^o$) (cal/mol-K), entropy (S_m^o) (cal/mol-K) and temperature for sitagliptin. (Colour online).*

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 ($C_{p,m}^o$), entropy (S_m^o) and enthalpy (H_m^o) 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^o), specific heat ($C_{p,m}^o$) and entropy (S_m^o) is presented in Fig. 4 and is given by the relations:

H_m^o = 196.44911+0.0125 T+1.35119X10^{-4} T^2

(R^2 = 0.9999)

$C_{p,m}^o$ = 9.99089+0.2981 T–6.45952X10^{-5} T^2

(R^2 = 0.9997)

S_m^o = 67.25107+0.44544 T–2.13619X10^{-4} T^2

(R^2 = 0.9996)

Fig. 4 reveals that the values of H_m^o, $C_{p,m}^o$ and S_m^o 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 Popeliar [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 week. The AIM result explores $\nabla^2\rho_{BCP} > 0$ and $H_{BCP} < 0$ 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 (ρ_{BCP}), Laplacian of ED ($\nabla^2\rho_{BCP}$), electron kinetic energy density (G_{BCP}), electron potential energy density (V_{BCP}), total electron energy density (H_{BCP}), interaction energy (E_{int}) at BCP.

Interactions	Bond Length (Å)	ρ_{BCP} (a.u)	$\nabla^2\rho_{BCP}$ (a.u)	G_{BCP} (a.u)	V_{BCP} (a.u)	H_{BCP} (a.u)	E_{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

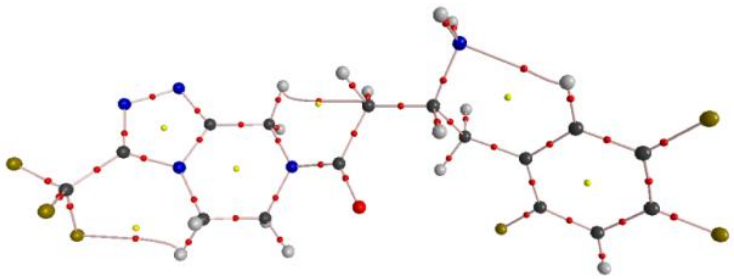

Fig. 5*: Molecular graph of sitagliptin: bond critical points (small red spheres), ring critical points (small yellow spheres), bond paths (pink lines).*

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 Å, ASP B:709, and 2.03 Å, 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 1.95 2.49 2.21	GLU B:237 PRO A:249 THR A:251 ARG A: 253	−7.25	−0.26
		1U8E	1.81 2.03 2.36	ASP B:709 ASP B:739 LYS B:122	−7.17	−0.26

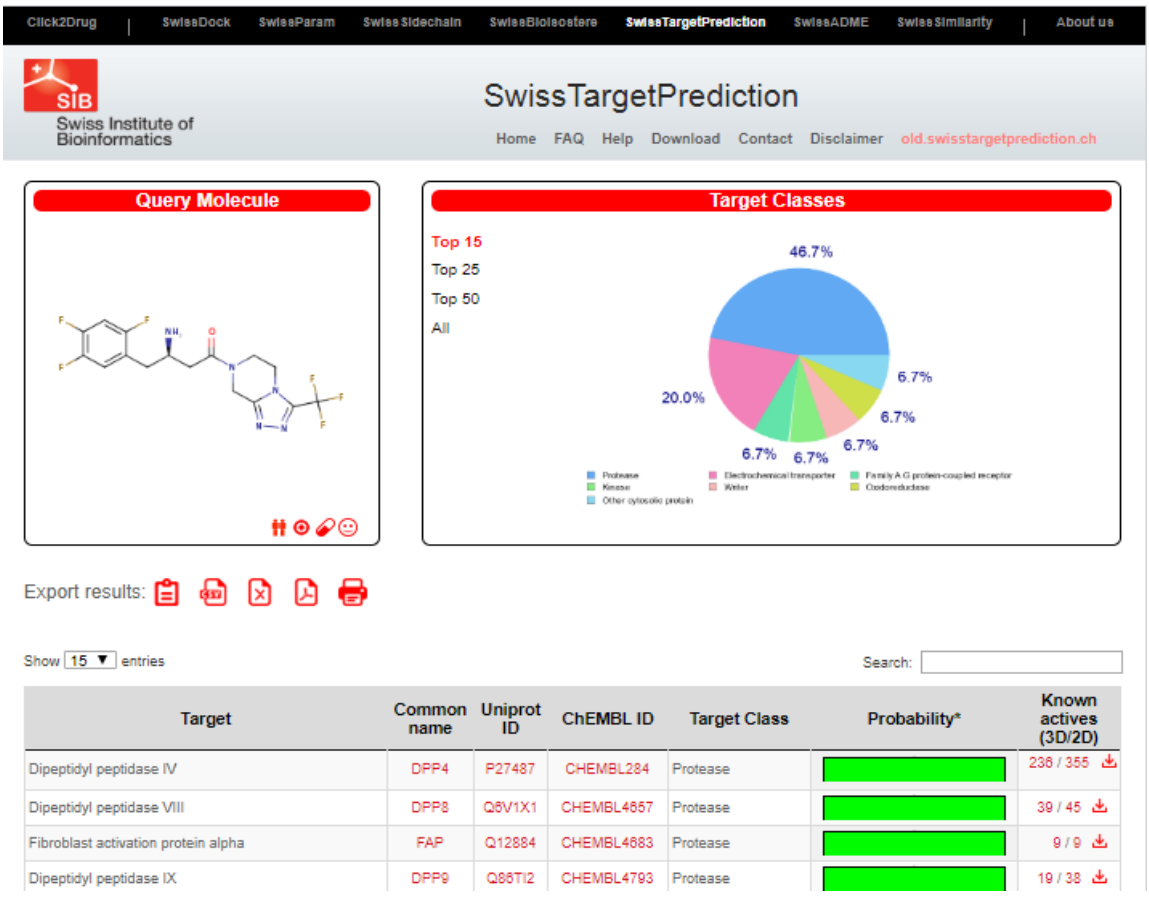

***Fig. 6**: Swiss Dock used to suggest different target proteins to perform the molecular docking simulation.*

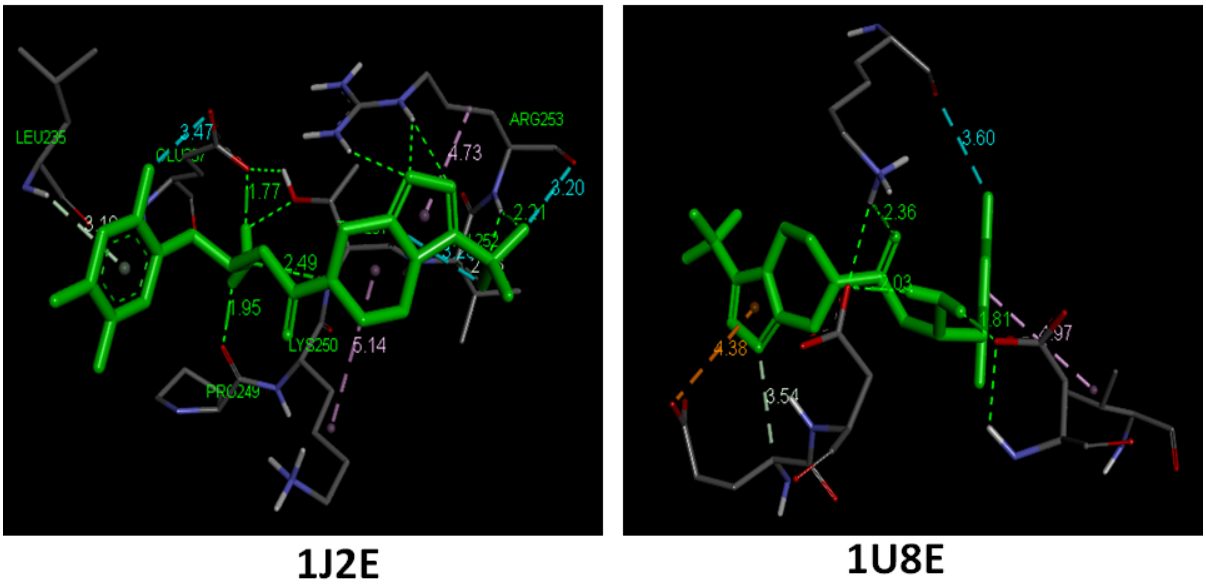

***Fig. 7**: Docking of sitagliptin with the molecular target.*

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 (μ_0) and first hyperpolarizability (β_0) of title molecule are found to be and $2.7733X10^{-30}$ 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 $\nabla^2\rho_{BCP} > 0$ and $H_{BCP} < 0$. 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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