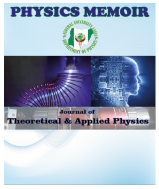

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Original Research

Determination of Electronics and Molecular Structure of Nateglinine Anti-Diabetic Drug Using DFT

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Abstract

Diabetes mellitus is a metabolic disease characterized by high blood glucose level and result from defects in insulin secretion, insulin action or both. Gaussian 09 software package which uses density functional theory was used to search for conformers, optimize the structure, and calculate the electronic properties of the Nateglinide anti-diabetic drugs. It was found that, C_{20}-C_{18}-C_{16}-H_{45} isomer has the lowest energy of −2762.448518 eV and transition energy of 400.8615826 eV. Also it was found that the dipole moment increases as the basis set increases while the total energy decreases. Information on bond lengths, bond angles and dihedral angles of the optimized structure were reported. It was observed that the strongest bond is O_3-C_{17} with a bond length of 0.9728Å and the weakest bond is C_{15}-C_{16} with a bond length of 1.5511Å. Finally the Homo-Lumo formations reveals that there are more free non-bond electron in the homo site due to higher ionization potential.

Keywords: DFT; Anti-diabetic drugs; Conformational search; Dipole moment; Homo-Lumo

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1. Introduction

Diabetes mellitus; is a metabolic disease characterized by high blood glucose level resulting from defects in insulin secretion, insulin action or both [3]. Nateglinide has been exploited as a new class of oral hypoglycemic agent with the chemical name [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine], and the structure is shown in the Fig. 1. Nateglinide is a D-phenylalanine derivative recently approved for the management of type II diabetes that can stimulate the release of insulin by inhibiting ATP- potassium channels present in pancreatic -cells in the incidence of elevated blood glucose levels after oral administration [1]. Diabetes is a clinically and genetically heterogeneous

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group of disorders/metabolic disorder affecting the metabolism of carbohydrates, lipids, and proteins [1]. Type-2 diabetes is a metabolic disorder where the body is unable to automatically regulate blood glucose levels, resulting in hyperglycemia because the pancreatic β-cell does not produce enough insulin. This produces the classical symptoms of Polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) [2]. The characteristic feature of diabetes is an abnormal elevation in blood glucose levels (Hyperglycemia), and this is due to a deficiency of insulin secretion caused by pancreatic β-cell dysfunction and/or insulin resistance in liver and muscle. Diabetes is a syndrome in which chronic hyperglycemia leads to long-term damage to various organs including the heart, eyes, kidneys, nerves, and vascular system [2]. This high blood sugar produces the classical symptoms of Polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) [2]. This metabolic dysregulation is often associated with alterations in adipocyte metabolism. The current classification of diabetes is based upon the pathophysiology of each form of the disease [2]. Type-1 diabetes results from cellular mediated autoimmune destruction of pancreatic b-cells, usually leading to total loss of insulin secretion. Type-1 diabetes is usually present in children and adolescents, although some studies demonstrated 15% to 30% of all cases being diagnosed after 30 years of age [2]. The lack of insulin production in patients with type-1 diabetes makes the use of exogenous insulin necessary to sustain life, hence the former name insulin-dependent diabetes. In the absence of insulin, these patients develop ketoacidosis, a life-threatening condition [2]. Type-2 diabetes, previously called non-insulin dependent diabetes, results from insulin resistance, which alters the use of endogenously produced insulin at the target cells. Type-2 patients have altered insulin production as well; however, autoimmune destruction of b-cells does not occur as it does in type-1, and patients retain the capacity for some insulin production. Because the type-2 patient still produces insulin, the incidence of ketoacidosis is very low compared to type-1 as insulin secretion becomes insufficient to compensate for insulin resistance. Although type-2 patients do not need insulin treatment to survive, insulin is often taken as part of the medical management of type-2 diabetes [2].

Nateglinide is a metglinide short-acting, pancreatic, beta-cell-selective, KATP potassium channel blocker that improves overall glycemic control in type-2 diabetes. Nateglinide is a novel oral glucose regulator for the treatment of type II diabetes mellitus. It is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas [2, 3]

Although nateglinide's mechanism of action is similar to that of sulphonyl-ureas,but little and important differences do exist between the two. Nateglinide binds rapidly to the sulfonylurea SUR1 receptor with a relatively low affinity, and it dissociates from it extremely rapidly in a manner of seconds. This rapid association and dissociation give nateglinide a unique "fast on-fast off" effect. Thus, nateglinide has a rapid onset and short duration of action on beta cells in stimulating insulin secretion in vivo and providing good control of postprandial hyperglycemia when taken immediately before meals. This hypoglycemic effect of nateglinide leads to improved glycemic control, while the short duration avoids delayed hyperinsulinemia and hypoglycemia after meals. Nateglinide is not a sulfonylurea, but it shares the mechanism of action of commonly used oral hypoglycemic agents such as glibenclamide and glipizide. Like the recently introduced, short-acting agent, repaglinide, it does not incorporate a sulfonylurea moiety. Compounds with such a profile should achieve not only overall glucose control but also reduce the risk of vascular complications which is the most important feature of nateglinide. Nateglinide is both effective and well tolerated in the treatment of type-2 diabetes. The reported overall profile of adverse effects appears to be superior to that of other KATP potassium channel blockers, the glucose modulator metformin and PPAR-gamma agonists such as troglitazone. Clinical comparisons of these agents have shown nateglinide to be more effective in attenuating postprandial glucose than any other oral hypoglycemic agent, and that treatment with nateglinide provides effects that afford improved control of plasma glucose levels. The administration regimen for nateglinide, immediately before meals, also facilitates patient compliance [2].

Several studies have reported on controlled drug delivery systems in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, and topical routes. Nateglinide is made available as many forms in the market like conventional and simple sustained release tablets, but microencapsulation is a technique used to deliver the medicament a controlled rate by targeting. Microcapsules have more advantages over conventional and simple sustained release tablet formulations, such as targeting, less dosing frequency, zero-order release and high margin of safety, which are not possible with the existing formulations. Amongst the polymers used for microencapsulation, alginate has gained much attention since it is non toxic, biodegradable and can be prepared by a safe technique avoiding organic solvents. Hence orifice-ionic gelation technique was developed as an alternative approach even though so many other techniques are available like single and double emulsification techniques, normal and interfacial polymerization,

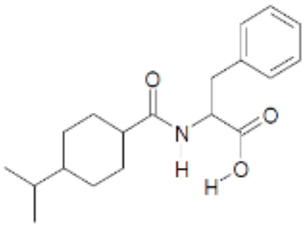

Figure 1. Chemical Structure of Nateglinide.

coacervation phase separation, spray drying, spray congealing, etc. [2].

Remko [4] performed a theoretical study on the molecular structure, pKa, lipophilicity, solubility, absorption and polar surface area of some hypoglycemic agents including nateglinide. The geometries and energies of these drugs were computed using ab initio calculations by Hartree-Fock/6-31G(d) and Becke, three-parameter, Lee-Yang-Parr (B3LYP)/6-31G(d) methods in gaseous phase and in the presence of a solvent (water) using conductor-like polarizable continuum model (CPCM) model. Quantum chemical calculations using B3LYP/6-31G (d) level of theory have been performed to study the conformational preferences in nateglinide. Exploring the complete conformational space becomes a prohibitive task, X-ray crystal data were employed as starting point for conformational analysis. The CSD analysis suggested that the conformational problems in nateglinide may be treated as a three-torsional angle problem (C1-C2, C2-C3 and C3-N4). A few important conformations of nateglinide were explored; the task of identifying the global minimum is beyond the scope of this work. In the reported crystal structure of the hydrated nateglinide salt, four different conformations A, B, C, and D are present. After complete optimization at the structural differences among the four conformations become negligible. Hence, the experimentally observed asymmetry can be attributed to packing effect rather than conformational preferences. The analysis shows that Φ (phi) torsion angle of this phenylalanine derivative is responsible for the observed differences in stability among the nateglinide conformations [5].

An attempt was made to study the importance of minimization algorithms on four anti-diabetic molecules, nateglinide inclusive, with different rotatable bonds. In most of the cases, conjugate gradient algorithm represented the best method and further validated using conformation search analysis, resulted in much lower energy values than with energy minimization procedure alone. These studies provided a method to minimize the energy of any molecule irrespective of the number of freely rotatable bonds. And from the analysis, it can be emphasized that the conjugate gradient algorithm represented as the method of choice to achieve the lowest energy state with its most probable geometry for nateglinide, pioglitazone, repaglinide, and glyburide, respectively, which can be further utilized for drug design studies [6].

The purpose of this work is to employ DFT with different basis sets to perform potential energy scan and single point energy calculations in order to obtain the most stable conformer of the nateglinine molecule, calculate its bond parameters such as bond lengths, bond angles and torsion angles, as well as total energy and Homo-Lumo formations.

2. Theoretical Background

Density Functional Theory (DFT) is a computational method that derives properties of the molecules based on a determination of their electron density. DFT methods have become the most widely-spread ab-initio methods in Computational Material Science (CMS) and Solid state Physics, due to their high computational efficiency and very good accuracy for the structure of molecules, crystals, surfaces and their interactions. In DFT methods, the energy of the molecule is a function of the electron density [7, 8, 9]. The basis of DFT is given by two theorems formulated by Hohenberg and Kohn [10]. Regarding the formulation of Quantum Mechanics, a system comprising N electrons and M nuclei is described by a Hamiltonian H as [10].

$$H = \frac{1}{2}\sum_{i=1}^{N}\nabla_i^2 + \sum_{i<j}^{N}\frac{1}{|r_i - r_j|} + \sum_{i=1}^{N}\sum_{I=1}^{M}\frac{Z_I}{|r_i - R_I|} - \frac{1}{2}\sum_{I=1}^{M}\nabla_I^2 + \sum_{I<J}^{M}\frac{Z_I Z_J}{|R_I - R_J|} \quad (1)$$

where

- Z denotes the nuclear charge.
- $|r_i - r_j|$ is the distance between electron number i and electron number j
- $|r_i - R_I|$ is the distance between electron number i and nucleus number I
- $|R_I - R_J|$ is the distance between nucleus number I and nucleus number J
- ∇_i is the kinetic energy term of the electrons
- ∇_I is the kinetic energy term of the nucleus.

Exactly solving a Schrödinger equation with such many-body Hamiltonian is only possible in principle. For any practical system, one has to resort to approximations. First of all, by the Born-Openheimer (or adiabatic) approximation one drops the last two terms in the Hamiltonian above and treats the nuclei separately. The grounds for this treatment are that the nuclei are much heavier; hence move much slower than the electrons. In this approximation, the kinetic energy of the nuclei is neglected, and the interaction between the nuclei is handled classically. Thus, the original problem in Eq. (2) is reduced to one regarding a system of interacting electrons moving in an external potential $V(r)$, formed by a frozen-in ionic configuration as;

$$H = -\frac{1}{2}\sum_{i=1}^{N}\nabla_i^2 + \sum_{i<j}^{N}\frac{1}{|r_i - r_j|} + V(r) \tag{2}$$

For such an inhomogeneous system of interacting electrons, Hohenberg and Kohn [11], proved two theorems about the electron density function $\rho(r)$:

- *Theorem i*: If the number of electrons in the system is conserved, the external potential $V(r)$ uniquely determines the electronic ground state density $\rho_0(r_0)$.

- *Theorem ii*: There exists a universal energy functional of ρ, $E[\rho]$, which is minimized by the ground state density ρ_0.

These two theorems form the basis of DFT. Kohn and Sham carried this theory further and obtained a single-particle Schrodinger-like equation,

$$\left[-\frac{1}{2}\nabla^2 + \int\frac{\rho(r')}{|r - r'|}d^3r' + \frac{\delta E_X C[\rho(r)]}{\delta\rho(r)} + V(r)\right]\psi_i(r) = \epsilon_i\psi_i(r). \tag{3}$$

This is usually referred to as the Kohn-Sham equation. The KS equation maps a many-electron interacting system onto a single electron system within an effective potential formed by the nuclei and other electrons. The first term in the KS Hamiltonian accounts for the kinetic energy and the following three terms which are the Coulomb (or Hartree), the exchange-correlation(xc) and the external potentials respectively. Comparing with the many-body Hamiltonian in Eq. (2), solving the KS equation is much easier for a practical system.

Due to the fact that the potential and the charge density depend on each other, the KS equation has to be solved self-consistently. Starting from an assumed density $\rho(\mathbf{r})$, one first calculates the Coulomb and xc potentials, then solves Eq. (2) for the KS orbitals $\psi_i(\mathbf{r})$. With these orbitals, a new density can be constructed by

$$\rho(r) = \sum|\psi_i(\mathbf{r})|^2\,, \tag{4}$$

where the index i goes over all occupied orbitals. The procedure is repeated until self-consistency, i.e., consistency between the output and input densities is achieved.

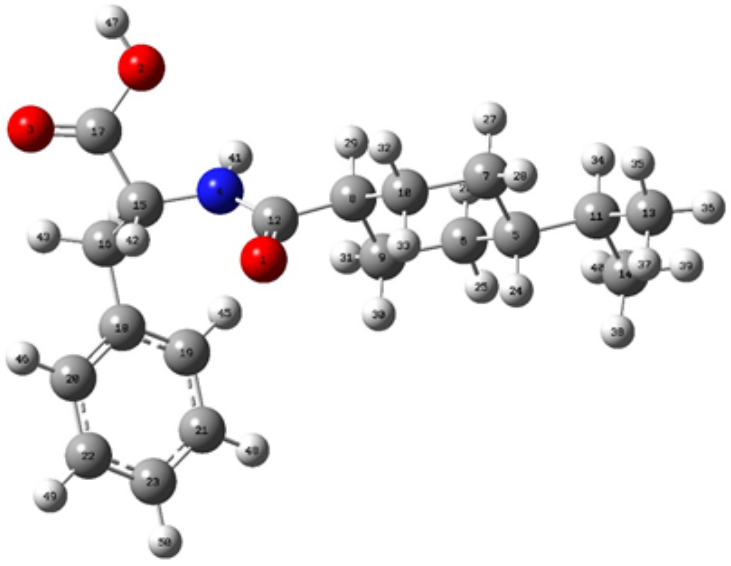

Figure 2. Molecular structure of Nateglinide before optimization.

3. Computational Procedure

Density functional theory calculations were performed using Gaussian09 software package [12]. Potential energy scan was carried out and four conformers with lowest energy were considered for geometry optimization. The structure was optimized with basis set of 3-21G, 6-31G and 6-311G and each time the total energy is recorded. Both the stationary point and the saddle point (transition state) energies were recorded. Single energy calculations were performed on the structure with lowest energy and values of dipole moment, bond lengths, bond angles, torsional angles, and Homo-Lumo energies were also recorded.

4. Results and Discussion

4.1. Potential Energy Scan

Potential energy surface (PES) are important because they aid us in visualizing and understanding the relationship between potential energy and molecular geometry and understanding how computational physics and chemistry programs locate and characterize structures of interest. Potential energy surfaces allow determination of energy minima and transition states [13, 14].

A dihedral angle or torsion angle is the angle between two planes. It defines the conformations around rotatable bonds. The dihedral angle changes only with the distance between the first and fourth atoms; the other inter atomic distances are controlled by the chemical bond lengths and bond angles. Its value range from -180 to +180 degrees. The torsion angle is considered to be positive if a clockwise rotation is performed with the molecule and it will be negative when an anti-clockwise rotation is performed with the molecule in its plane.

The potential energy scans were performed on the conformers of the nateglinide structure as in Figure 2 by rotating through the dihedrals; C_{20}-C_{18}-C_{16}-H_{45}, C_{12}-N_{04}-C_{15}-C_{16}, C_{11}-C_{05}-C_{06}-C_{09} and O_{03}-C_{17}-C_{15}-C_{16} and the energies of each conformer was recorded as shown in the Table.

From Table 1, it was observed that the conformer C_{20}-C_{18}-C_{16}-H_{43} has the lowest energy of −2762.448518 eV when compared with others and hence it's the most stable. However, Figure 3 shows the result of relative energy against torsion angle rotated through 60o degree, and it was found that the lowest energy −415.4805535 eV rotate at 240° and transition state of 400.8615826 eV.

Table 1. Total Energies of conformers of Nateglinide calculate using rB3LYP/3-21G .

s/n	Torsional Angle (ϕ)	Total energy (a.u.)	Total energy (eV)
1	C_{20}-C_{18}-C_{16}-H_{43}	-1015.180593	-2762.448518
2	C_{16} -C_{15} -N_4 -C_{12}	-1015.178926	-2762.443982
3	C_9 -C_6 -C_5 -C_{11}	-1015.180577	-2762.448477
4	O_3-C_{17}-C_{15}-C_{14}	-1015.17888	-2762.443858

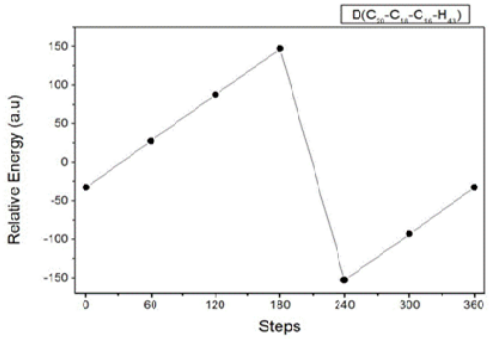

Figure 3. B3LYP/3-21G level PES scan profile of Nateglinide around the torsional angle $\phi(C_{20}–C_{18}–C_{16}–H_{43})$.

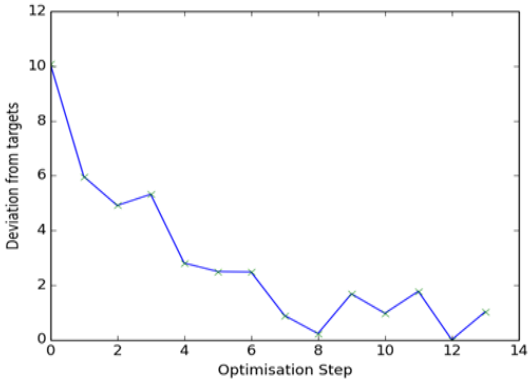

Figure 4. Optimized steps of Nateglinide determined at B3LYP/6-311G(d) level of theory.

Figure 4 shows the optimization process. It was observed that despite the deviation from the target, the optimization was achieved at 12 step. The final geometry of the structure is shown in Figure 5, and it was observed that due to the effect of the optimization, there was increase in bond (double) between the C_{12} and N_4. Dipole moments occur when there is a separation of charge. They can occur between two ions in an ionic bond or between atoms in a covalent bond; dipole moments arise from differences in electronegativity. The larger the difference in electronegativity, the larger the dipole moment. The distance between the charge separations is also a deciding factor into the size of the dipole moment. The dipole moment is a measure of the polarity of the molecule. Table 2 shows the effects of basis sets on dipole moment and total energy. It was observed that as the basis set increases, the electronegativity also increases and so also the dipole moment. This increase in the basis set decreases forced the molecules to approach the ground state as expected.

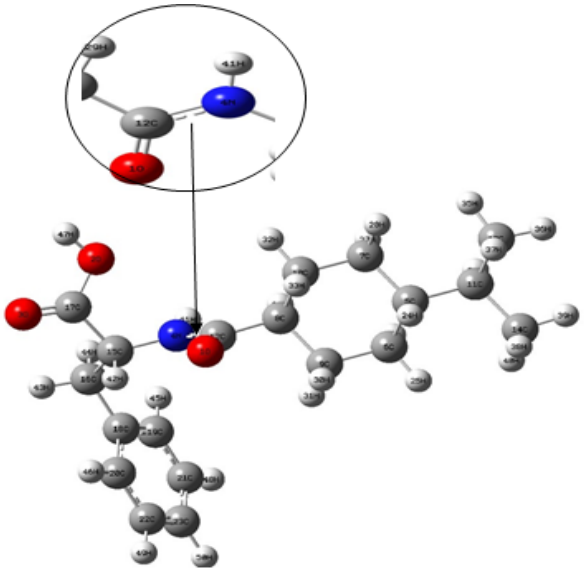

Figure 5. Optimized structure of Nateglinide determined at B3LYP/6-311G(d) level of theory.

Table 2. Total Energies of conformers of Nateglinide calculate using rB3LYP/3-21G .

DFT(RB3LYP)

Basis Set	Dipole (Debye)	Total Energy (a.u.)	Total Energy (eV)
3-21G	4.2444	-1015.300288	-2762.774226
6-31G	4.3288	-1020.839141	-2777.84622
6-311G	4.4325	-1020.839141	-2777.84622

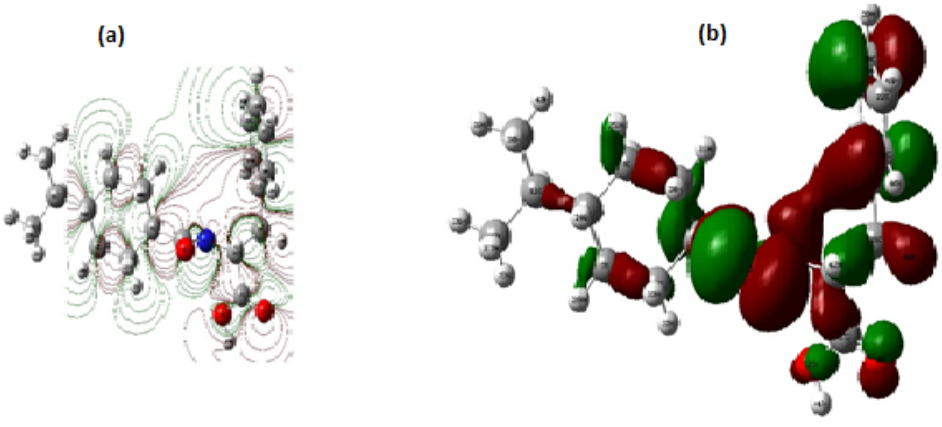

Figure 6. . Nateglinide Structure determined at B3LYP/6-311G(d) level (a) Contour map of Homo (b) Homo Structure.

The HOMO is the outermost (highest energy) orbital containing electrons that could act as an electron donor. The LUMO is the innermost (lowest energy) orbital that has room to accept electrons and can act as the electron

Table 3. Total Energies of conformers of Nateglinide calculate using rB3LYP/3-21G .

S/N	bond	Length (Angstrom)	X-ray[15]	Bond	Angle (Degree)	X-ray [15]	Bond	Dihedral (Degree)	X-ray
1	O1-C12	1.2294	1.213	O1-C12-N4	121.7747	118.982	C15-N4-C12-O1	192.991	189.871
2	O2-C17	1.3531	1.353	C12-N4-C15	122.1466	120.234	C15-N4-C12-C8	-179.3533	-180.367
3	O3-C17	0.9728	0.909	N4-C15-C17	114.3659	113.345	C12-N4-C15-C16	-146.9504	-146.879
4	N4-C12	1.3716	1.447	C15-C17-O2	113.8756	111.223	C12-N4-C15-C17	88.5808	89.234
5	N4-C15	1.4459	1.460	O3-C17-O2	122.8049	119.234	C7-C5-C6-C9	-53.51	55.213
6	C5-C6	1.5437	1.537	N4-C15-C16	111.8985	111.899	C11-C5-C6-C9	-179.2195	-179.321
7	C5-C7	1.544	1.527	C15-C16-C18	113.553	112.999	C6-C5-C7-C10	53.4366	54.678
8	C6-C9	1.5356	1.543	C20-C18-C19	118.4366	117.345	C11-C5-C7-C10	179.1268	178.467
9	C7-C10	1.5362	1.527	C18-C19-C21	120.965	119.345	C6-C5-C11-C13	-179.8546	-178.378
10	C8-C9	1.5424	1.530	C19-C21-C23	120.0419	120.345	C6-C5-C11-C14	-56.2464	-55.876
11	C8-C10	1.5405	1.539	C21-C23-C22	119.5381	119.345	C5-C6-C9-C8	55.8195	56.980
12	C8-C12	1.5252	1.495	C23-C22-C20	120.1936	119.571	C5-C7-C10-C8	-55.6831	-54.654
13	C11-C13	1.5399	1.567	C22-C20-C18	120.8238	112.678	C10-C8-C9-C6	-54.7983	-54.789
14	C11-C14	1.5400	1.588	O1-C12-C8	122.444	122.333	C12-C8-C9-C6	-176.9717	-179.984
15	C15-C16	1.5511	1.345	C10-C8-C9	109.848	110.355	C9-C8-C10-C7	54.7081	54.708
16	C15-C17	1.5322	1.675	C8-C9-C6	111.9009	111.234	C12-C8-C10-C7	176.5285	176.096
17	C16-C18	1.5145	1.524	C9-C6-C5	113.0648	112.365	C9-C8-C12-C1	63.8601	63.731
18	C18-C19	1.4009	1.396	C6-C5-C7	109.1485	110.243	C9-C8-C12-C4	-114.7776	-114.786
19	C18-C20	1.4034	1.345	C5-C7-C10	113.1208	112.890	C10-C8-C12-C1	-57.8049	-57.907
20	C19-C21	1.3983	1.400	C7-C10-C8	111.9258	111.378	C4-C15-C16-C18	61.7229	60.678
21	C20-C22	1.3956	1.401	C6-C5-C11	112.5263	114.213	C17-C15-C16-C18	-170.8342	-170.345
22	C21-C23	1.3962	1.342	C5-C11-C13	112.4621	112.321	N4-C15-C17-C2	13.7476	13.756
23	C22-C23	1.3986	1.341	C13-C11-C14	109.0758	110.000	N4-C15-C17-C3	-168.0431	-168.342
24							C16-C15-C17-C2	-112.2829	-112.753
25							C16-C15-C17-C3	65.9264	65.932
26							C16-C18-C19-C21	-179.8248	-179.346
27							C20-C18-C19-C21	-0.2488	-112.903
28							C16-C18-C20-C22	179.9529	197.345

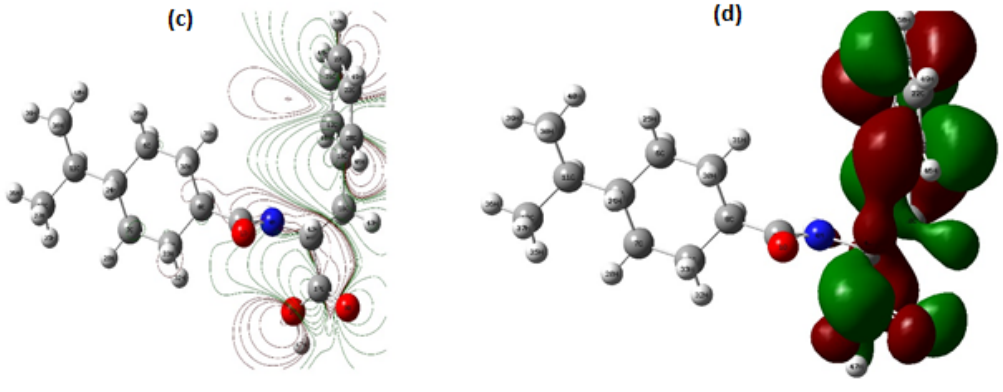

Figure 7. Nateglinide Structure determined at B3LYP/6-311G(d) level (c) Contour map of Lumo (d) Lumo Structure.

acceptor. Formation of the transition state was due to the interaction between the Homo and Lumo as reported by frontier molecular orbital theory [14]. Ionization potential contribute to the formation of Homo energy and electron

affinity for the formation of Lumo energy. Figures 6 and 7 show the formation of Homo and Lumo respectively for the nateglinide structure. It was observed that at Homo, there was tendency of having higher number of non bonded electrons in the region and hence it can donates higer number of ellectron. Also from the Lumo it can be observed that there is tendancy of accepting more electrons ejected from the Homo site.

5. Conclusion

Density function theory calculations was performed using gaussian09 software on the Nategglinide anti-diabetic drug. Conformational search was carried out by rotating through the tortional angles C_{20}-C_{18}-C_{16}-H_{45}, C_{12}-N_{04}-C_{15}-C_{16}, C_{11}-C_{05}-C_{06}-C_{09}, and O_{03}-C_{17}-C_{15}-C_{16}. -2762.448518eV was found to be the lowest energy obtained from the conformer C_{20}-C_{18}-C_{16}-H_{45} and has the transition energy of 400.8615826 eV. Bond lengths, bond angles and dihedral angles values of the optimized structure were reported. However, it was found that there are more non bond electrons in the homo region ready to transfer to the lumo.

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