Research Article **www.ijcps.com**

International Journal of Chemical and Pharmaceutical Sciences
2017, June., Vol. 8 (2)

ISSN: 0976-9390
IJCPS

Intermolecular interactions of zapizolam molecule with gaba receptor: A molecular docking and quantum chemical calculations

Sathya B, Manikandan M, Prasath M* and Selvapandiyan M.

Department of Physics, Periyar University P.G Extension Centre, Dharmapuri, Tamilnadu, India.

* **Corresponding Author:** E-Mail**:** sanprasath2006@gmail.com

Received: 10th June 2017, Revised and Accepted: 18th June 2017

ABSTRACT

The optimized geometry and various bonding features of Zapizolam have been explored by Hartree-Fock (HF) and density functional B3LYP methods (DFT) with the 6-311G** basis set. A molecular docking, HOMO-LUMO and Electrostatic potential (ESP)analysis has been carried out to identify the conformational change and electrostatic properties of Zapizolam in the active site of GABA-Receptor. The total density of states (TDOS) are used to determine the molecule orbital contributions.

Keywords: Docking, ESP, HOMO-LUMO.

1. INTRODUCTION

The benzodiazepines belongs to the class of psychoactive medications with changing mesmerizing, calming, anxiolytic, anticonvulsant, muscle relaxant and amnesic properties, which are interceded by aid off the central nervous system. It acts as a positive allosteric modulator of GABA receptor. Here the Zapizolam molecule is also a benzodiazepine derivative drug. The IUPAC name of Zapizolam is 8-Chloro-6-(2-chlorophenyl)-4*H*-pyrido[2,3-*f*][1,2,4]triazolo[4,3-*a*][1,4] diazepine and the molecular formula is $C_{15}H_9Cl_2N_5$. Docking analysis is used as a aid to analyze the nearest neighbours, shortest intermolecular contacts between Zapizolam-GABA Receptor and the lowest binding energy of Zapizolam. According to literature survey so far no complete theoretical study has been carried out for the title compound. This shortfall observed in the literature encouraged us to make this theoretical work. As a result, the present study aims to present a complete account of molecular geometry and electronic features of the title compound.

2. COMPUTATIONAL DETAILS

A minimum energy structure optimization was carried out with the help of Hartree-Fock and B3LYP level of theories with 6-311G** basis set were performed to determine the minimum energy structure optimization in Gaussian03 program [1] and to obtain the exact geometry and electronic parameters of the Zapizolam molecule. Autodock software is used to perform Docking analysis. The protein-ligand complex and the intermolecular interactions between GABA receptor and Zapizolam ligand molecules are evaluated and viewed with the aid of Pymol [2] and Chimera [3] programs . The docked ligand molecules were lifted from the active site of GABA receptor, and further a single point energy calculation have been carried out by using the DFT methods (B3LYP/6-311G**). The Gauss view software [4] was used to generate the ESP map of the molecule. The molecular orbital's contribution of the functional group is analysing, the total density of states (TDOS), overlap population density of states (OPDOS) and the partial density of states (PDOS) spectra were analysed by using the software GaussSum 2.2 [5].

3. RESULTS AND DISCUSSION

3.1. Structural aspects

The ball and stick model of Zapizolam molecule in gas phase and in the active site are shown in Figure 1 (a,b). The predicted structural parameters of Zapizolam molecule by HF method are found to be smaller than the DFT method (Table 1). The Zapizolam molecular structure were calculated in gas phase and in the active site by density functional theory to the best knowledge, gas phase and active site geometrical data of Zapizolam molecule has not been published so far.

The bond length values of Zapizolam molecule are not much altered in the active site,

Table - 1: The selected optimized geometrical parameters [bond lengths (Å), bond angles (°), torsion angles (°)] of Zapizolam molecule calculated at HF and DFT levels of theory.

Parameters	Gas phase		Active Site
	HF/6–311G**	DFT/6–311G**	
Bond length(Å			
C(15)–C(16)	1.386	1.398	1.397
C(16)–C(17)	1.381	1.390	1.391
C(17)–C(18)	1.381	1.391	1.390
C(18)–H(29)	1.074	1.083	1.079
C(19)–C(20)	1.380	1.388	1.389
BOND ANGLE(°)			
C(2)–C(3)–H(24)	109.8	110.0	109.1
C(5)–C(15)–C(16)	123.4	123.8	118.4
C(5)–C(15)–C(20)	118.6	118.4	123.8
C(16)–C(15)–C(20)	117.9	117.6	117.6
C(15)–C(16)–C(17)	121.5	121.6	121.3
C(15)–C(16)–Cl(21)	120.7	120.7	119.3
C(17)–C(16)–Cl(21)	117.6	117.5	119.3
C(16)–C(17)–C(18)	119.5	119.5	119.7
C(17)–C(18)–C(19)	119.9	119.9	120.0
C(18)–C(19)–C(20)	119.8	119.8	119.4
C(15)–C(20)–C(19)	121.1	121.3	121.6
TORSION ANGLE(°)			
N(4)–C(5)–C(15)–C(16)	123.2	129.6	119.9
N(4)–C(5)–C(15)–C(20)	-55.3	-48.5	-61.8
C(6)–C(5)–C(15)–C(16)	-60.6	-54.7	-64.4
C(6)–C(5)–C(15)–C(20)	120.8	127.0	113.7
C(5)–C(15)–C(20)–H(31)	-0.4	-0.2	-2.1

when compared with that of gas phase. The C – C bond distances of the aromatic ring ranges from 1.388 to 1.400 Å, the average value is 1.394 Å. On comparing the geometrical parameters in the gas phase and Active site, C–C–C bonds angles of six membered aromatic ring are found to be equal (~119.9°). On comparing the gas phase and active site structure, the aromatic ring has been twisted significantly as shown in Figure 1 (a, b) as it is linear in gas phase. This dissimilarity clearly shows that, when the molecule enters into the active site of protein, the conformation of the Zapizolam molecule changes, owing to the strong intermolecular interactions between the ligand and the amino acid groups of GABA receptor. On comparing gas phase and active site, the bond angles of C(2)–C(3)–H(24), C(5)–C(15)–C(20) and C(17)–C(16)–Cl(21) increases in active site while decreases in gas phase. On comparing gas phase and active site the bond angles of C(5)–C(15)–C(16) and C(15)–C(16)–Cl(21) are increases in gas phase while decreases in active site. The torsion angle of N(4)–C(5)–C(15)–C(16) and C(6)–C(5)–C(15)–C(20) bonds exhibit variations, when the molecule is present in the active site the values slightly decreases; the corresponding gas phase and the active site values are: 129.6/119.6°* and 127.0/113.7°* (* indicates the active site molecule). The torsion angle of N(4)–C(5)–C(15)–C(20), C(6)–C(5)–C(15)–C(16) and C(5)–C(15)–C(20)–H(31) bonds exhibits variation, when the molecule present in the active site; the corresponding gas phase values are decreases while compared with active site. This indicates that when the molecules enter into the active site both the rings are slightly twisted.

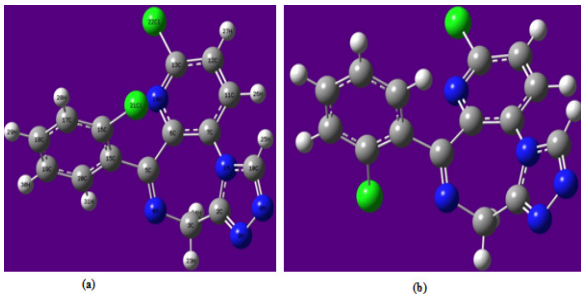

Figure - 1: The optimized structure of Zapizolam molecule (a) gas phase and (b) active site.

3.2. Molecular docking analysis

To identify the intermolecular interactions and binding affinity of Zapizolam in the active site of GABA receptor, a molecular docking analysis has been carried out. The lowest docked energies of Zapizolam and GABA receptor complex are presented in table 2, nearest neighbors of the ligand and shortest intermolecular contacts between ligand and receptor were calculated from the docking analysis (Table 3). The lowest docked energy value is -7.20 kcal/mol.

Table - 2: The lowest binding energy values of 10 different conformers of Zapizolam molecule in the active site of GABA receptor.

Conformation	Binding energy (kcal/mol)
1	-7.20
2	-7.19
3	-7.15
4	-7.03
5	-7.02
6	-6.87
7	-6.84
8	-6.79
9	-6.79
10	-6.69

The structure of Zapizolam-GABA receptor complex shows, how Zapizolam molecule interacts with the nearest amino acid in the active site. Figure 2 shows the intermolecular interactions of GABA receptor. Figure 3 (a,b) shows the surface view of intermolecular interactions of Zapizolam molecule with GABA receptor. The active site residues are: VAL44, TYR216, GLN266, LEU267, ILE42, ARG211 and PHE215. Usually, the intermolecular interactions modify the molecular conformation and the energy of the molecule. In the Zapizolam molecule the aromatic rings are slightly rotated and it fits very well in the active site cavity (Figure 3a, b).

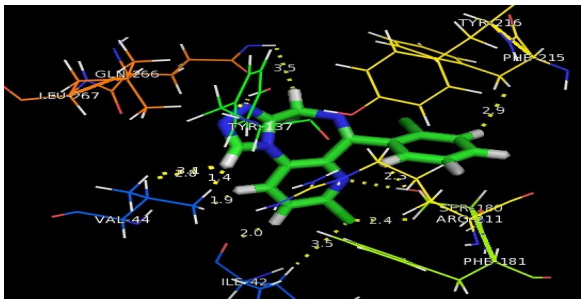

Figure - 2: Intermolecular interactions of Zapizolam molecule in the active site of GABA.

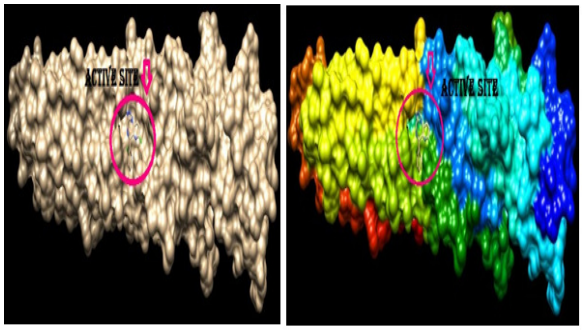

Figure - 3: Surface view of intermolecular interactions (a,b) of Zapizolam molecule with GABA receptor.

Table - 3: Nearest neighbours and intermolecular contact distance (Å) of Zapizolam molecule in the active site of GABA receptor (Conformation-1)

Ligand atom (Zapizolam) ……Atom identifier/ Active site residue (3RHW) protein.	Distance (Å)
N(1)...VAL 44/HG23	3.4
N(1)...TYR 216/HH	3.4
C(2)...TYR 216/HH	3.1
C(2)...GLN 266/OE1	3.2
C(3)...GLN 266/OE1	2.7
C(5)...TYR 216/HH	3.5
N(8)...VAL 44/HG23	3.4
N(8)...LEU 267/HD21	2.7
N(9)...GLN 266/HB3	3.2
N(9)...GLN 266/OE1	3.1
C(10)...VAL 44/HG21	3.4
C(10)...VAL 44/HG23	2.5
C(10)...VAL 44/HB	3.5
C(11)...VAL44/HG21	2.8
C(11)...VAL 44/HG23	3.4
C(11)...VAL 44/H	3.2
C(12)...ILE 42/O	3.0
CL(15)...ILE 42/HB	3.5
C(17)...TYR 216/HE2	2.7
C(17)...ARG 211/HG2	3.4

C(18)...ARG 211/HG2	3.0
C(19)...PHE 215/HB3	3.4
C(20)...PHE 215/HB3	3.3

The N(1) atom forms strong hydrogen bonding interactions with the VAL44 and TYR216 amino acid residue at the distances 3.4 and 3.4 Å respectively. Similarly, the N(8), N(9) and Cl(15) atom forms strong hydrogen bonding interactions with LEU267, GLN266 and ILE42 amino acid residue at the distances of 2.7, 3.1 and 3.5 Å respectively. The C(3), C(10), C(12), C(17) and C(18) atoms forms hydrophobic interaction with GLN266, VAL44, ILE42, TYR216 and ARG211 at the distance 2.7, 2.5, 3.0, 2.7 and 3.0 Å respectively. These interactions enhance the Zapizolam-GABA receptor binding affinity.

3.4. Molecular electrostatic potential

The ESP of the title molecule in gas phase and active site are shown in Figure 4(a,b). On comparing gas phase and active site, both forms are differing significantly. In the C-C bond region of the molecule, the carbon atom bonded with nitrogen atoms are exhibit high electronegative region. In the gas phase, high negative electrostatic potential regions are found at the vicinity of N(1), N(8) and N(9). In the active site, the trend has changed; here N(4) and N(14) atoms exhibit high electronegativity and are found to be merged together. Notably, the ESP region of N(8) and N(9) atoms are reduced [Figure 4b], which displays the difference. The electronegative N(1), N(8) and N(9) atoms are forming hydrogen bonding interaction with VAL44, LEU267 and GLN266 residues, The pictorial representation of interaction of Zapizolam and GABA receptor with ESP shows the strength of interaction in the active site.

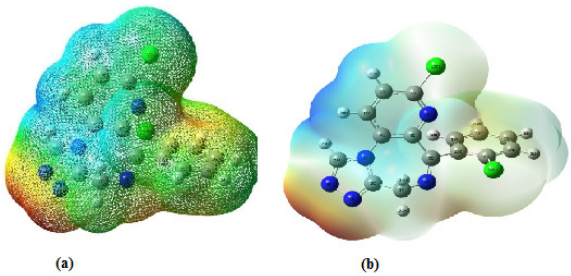

Figure - 4: Electrostatic potential of (a) gas phase and (b) active site for Zapizolam molecule showing the electropositive (blue) and negative (red) regions of the molecule.

3.5. HOMO-LUMO

HOMO - LUMO of the molecule have been plotted using GVIEW to visualize the charge localization and delocalization of the Zapizolam molecule in gas phase and active site as shown in Figure 5 (a-b). The global reactivity descriptors of molecule have been calculated in both gas phase and active site of Zapizolam molecule and are listed in Table 4. According to Pauling the electronegativity is a power of an atom in a molecule to attract electrons to itself [6]. Using finite difference approximation[7] electronegativity may be written as,

$$\chi = (IE + EA)/2$$

Where IE and EA represents the ionization energy and electron affinity respectively. Figure 5(a) and 5(b) provides the HOMO and LUMO of Zapizolam molecule obtained from the gas phase and active site calculations. The calculated molecular electronic property descriptors of Zapizolam are presented in table 4.

Table - 4: Molecular descriptors of Zapizolam molecule

Molecular descriptors	Gas phase	Active site
	Energy (eV)	
HOMO energy	-0.2937	-0.3036
LUMO energy	-0.2211	-0.2102
Ionization potential $I=[-E_{HOMO}]$	0.2937	0.3036
Electron affinity $A=[-E_{LUMO}]$	0.2211	0.2102
Global hardness $\eta=(I-A)/2$	0.0363	0.0467
Electronegativity $\chi=(I+A)/2$	0.2574	0.2569
Electrophilicity $\omega=\mu^2/2\,\eta$	0.9124	0.7061

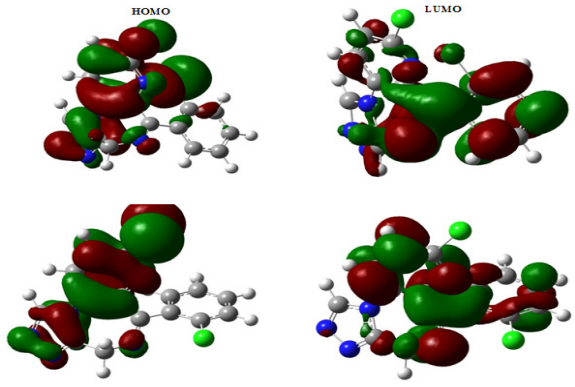

Figure - 5: Displaying (a) gas phase and (b) active site form of HOMO-LUMO of Zapizolam molecule plotted for isosurface value of 0.02au.

The calculated value of ionization potential, electronegativity and the electron

affinity of Zapizolam in gas phase are 0.2937, 0.2574 and 0.2211 eV and in the active site are 0.3036, 0.2569 and 0.2102 eV respectively. The electronegativity and electron affinity of Zapizolam are low when compared with that of ionization potential; hence the title molecule has fewer tendencies to accept electrons. Parr et al. [8,9] introduced the concept of electrophilicity index which is a molecular descriptor and provides information about reactivity and toxicity [7,10,11] of the molecule. This reactivity index measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment [12]. The calculated electrophilicity index (ω) of gas phase and active site are 0.9124 and 0.7061 eV respectively, these values are found to be low which reflects its low toxicity.

The significance of the electron transfer ability between a molecule and a biosystem is large in gaining insights into the overall toxicity (it increases with the increase in electrophilicity index) and it is found to be less; therefore it is speculated that toxicity is also less. Chemical hardness (η) can be used as a tool to assess the kinetic stability or reactivity of molecule[13-15]. The calculated value of chemical hardness of Zapizolam in gas phase and active site values are 0.0363 and 0.0467 eV, reveals that the molecule exhibits high kinetic stability. Hence, it is less reactive. The energy gap between the molecular orbital's is also calculated for gas phase and active site and the values are 0.0726 and 0.0934 eV respectively. The high positive value obtained shows the reactive nature[15] of the compound. This reactivity index is consistent with the presence of the nitrogen atoms in the molecular structure.

3.6. Total, partial and overlap population density of states

In the boundary region, neighbouring orbitals may show quasi degenerate energy levels. In such cases, consideration of only the HOMO and LUMO may not yield a realistic description of the frontier orbitals. For this reason, The total (TDOS), partial (PDOS), and overlap population (OPDOS or COOP (Crystal Orbital Overlap Population)) density of states[16-18] are calculated in terms of Mulliken population analysis and created by convoluting the molecular orbital information with Gaussian curves of unit height and full width at half maximum (FWHM) of 0.3eV by using the Gauss Sum 2.2 program[19]. The TDOS, PDOS and OPDOS of the Zapizolam are plotted in Figures 6 (a-c), respectively.

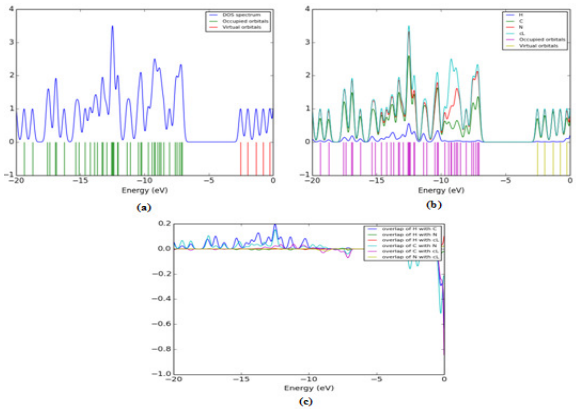

Figure - 6: The calculated (a)TDOS (b) PDOS and (c) OPDOS diagram for Zapizolam molecule.

The most important application of the DOS plots is to demonstrate Molecular Orbital compositions. The OPDOS shows the bonding, anti-bonding and nonbonding nature of the interaction of the two orbitals, atoms or groups. A positive value of the OPDOS indicates a bonding interaction (because of the positive overlap population), negative value means that there is an anti-bonding interaction (due to negative overlap population) and zero value indicates nonbonding interactions [20].

4. CONCLUSION

The structural parameter of Zapizolam molecule has been analyzed in both gas phase and active site. The lowest docked energies of Zapizolam molecule of Gamma-aminobutyric acid (GABA) receptor complex, nearest neighbours of the ligand and the shortest intermolecular contacts between ligand and receptor were calculated from the docking analysis. The structure of Zapizolam-GABA (Gamma-aminobutyric acid) acid receptor complex shows that Zapizolam molecule interacts with the nearest amino acids in the active site. The Iso-surface representations of ESP of the title molecule were investigated in both gas phase and active site.

The HOMO-LUMO calculations are found to be undeviating on comparing with the electrostatic potential surface of Zapizolam molecule. The electrophilicity index (ω) values of Zapizolam in the gas phase and active site are found low, this reports that the molecule has low toxicity. Zapizolam molecule is found to be less reactive because there are not much variation in the values of chemical hardness (η) on comparing the gas phase and active site.

Acknowledgements

Our sincere thanks to Bioinformatics Resources & Applications Facility (**BRAF**)

at **C-DAC**, for supporting this research work by providing high-end supercomputing facility.

5. REFERENCES

1. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Rob MA, Cheeseman JR, Montgomery Jr J. A, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth G. A, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin R. L, Fox D. J, Keith T, Al–Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PM. W, Johnson B, Chen W, Wong MW, Gonzalez C, and Pople J. **A, Gaussian 03 (Gaussian, Inc., Wallingford, CT**, 2003.
2. Delano W.L, PyMol **Molecular Graphics System, Delano Scientific,** San Carlos, CA, USA, 2002.
3. Xin Liul. The structural basis of protein acetylation by the p300/CBP transcriptional coactivator, **Nature Letters**, 451: 846-850, 2008.
4. Jhug A. Stash and Tsirelson V. **J. Appl. Crystallography,** 35: 371 - 373, 2002.
5. O'Boyle NM, Tenderholt AL and Langner KM. **J. Comput. Chem.** 29: 839 - 845, 2008.
6. Sarkar U, Padmanabhan J, Parthasarathi R, Subramanian V and Chattaraj PK. **J.Mol. Struct., THEOCHEM** 758: 119-125, 2006.
7. Parr RG, Szentpaly LV and Liu S. **J. Am. Chem. Soc.** 121: 1922-1924, 1991.
8. Kalyan K. Hazarika, Nabin C. Baruah and Ramesh C. Deka, **Struct. Chem.** 20: 1079 – 1085, 2001.
9. Parthasarathi R, Padmanabhan J, Subramanian V, Maiti B, Chattaraj PK. **J. Phys. Chem. A:** 107: 10346 – 10352, 2007.
10. Parthasarathi R, Padmanabhan J, Subramanian V, Maiti B and Chattaraj PK. **Curr. Sci.** 2004; 86: 535-542.
11. Parthasarathi R, Padmanabhan J, Elango V, Subramanian V and Chattaraj PK. **Chem. Phys. Lett.** 394: 225-230, 2004.
12. Sen KD and Mingos DMP. Chemical Hardness: Structure and Binding, vol. 80, **Springer, Berlin**, 1993.
13. Deva Priyakumar U and Narahari Sastry G, **Organometallics,** 21: 1493-1499, 2001.
14. Ghiasi RJ. **Organomet. Chem.** 690: 4761-4767, 2005.
15. Fazlul Huq. **J. Pharm. Toxic.** 1: 447-450, 2006.
16. Hoffmann R. Solids and Surfaces: A Chemist's View of Bonding in Extended Structures, **VCH Publishers.,** New York, 1988.
17. Hughbanks T and Hoffmann R. **J. Am. Chem. Soc.** 105: 3528-3537, 1983.
18. Małecki JG**. Polyhedron** 29: 1973-1979, 2010.
19. O'Boyle NM, Tenderholt AL and Langner KM. **J. Comp. Chem.** 29: 839-845, 2008.
20. Chen M, Waghmare UV, Friend CM and Kaxiras E. **J. Chem. Phys.** 109: 6680-6854, 1998.