Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2016, 5, 12:203-207

Theoretical study on the interaction of pregabalin and olanzapine with DNA

ZibaHooshiarSodagar[1], Mohammad Reza Bozorgmehr[1]*, Ali Morsali[1]

[1] *Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran*
**Corresponding Email:bozorgmehr@mshdau.ac.ir*

ABSTRACT

This paper aims is to study the interaction of two drugs including pregabalin and olanzapine with DNA. For this purpose, density functional theory calculations and docking were used. The structure of pregabalin and olanzapine using B3Lyp theory level and the basis set 6-311 G(d,p) was optimized. Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) calculated for each drugs. The obtained results showed that olanzapine is more reactive than pregabalin. Docking of drugs with DNA was performed and the results showed that binding affinity of olanzapine is higher than pregabalin. Also, the graphical results revealed that olanzapine interact with DNA via 5-terminal major groove of DNA, whereas pregabalin interact with DNA via 3-termind major groove.

Keywords: Olanzapine, pregabalin, drug- dna interaction, groove binding, Docking

INTRODUCTION

Pregabalin, ((s)-3-(amino methyl)-5- methyl hexanoic acid (Fig.1) binds with high affinity to the $\alpha 2\delta$ subunit of voltage- gated calcium channels and exerts analgestic, anxiolytic, and antiseizure activities. Renal excertion is the primary route of elimination. Pregabalin can establish hydrogen bond through carboxyl group (-COOH) and amine ($-NH_2$)- [1,2].

Olanzapine (Fig.2) is 2-methyl -4- (4-methyl-1- piperazinyl)- 10H- thieno [2,3-b] [1,5] benzodiazepine and its empirical formula is $C_{17}H_2O\ N_4S$. This drug is structurally and pharmacologically similar to the atypical antipsychotic clozapine, and is an antipsychotic medication that affects chemicals in the brain. Olanzapine has been evaluated as an adjunctive medication for the prevention and treatment of chemotherapy- induced nausea and vomiting (CINV) in patients with cancer [3,4]. Drug- DNA interaction affects DNA replication and division, causes strand breaks, and mutations [5].

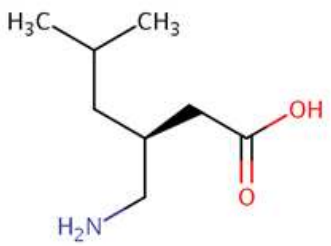

Figure 1.Chemical structure of Pregabalin

Figure 2. Chemical structure of Olanzapine

The study of the interaction of drug and dna plays a key role in pharmacology and it is of great significance for designing and synthesizing the new drugs targeted to DNA and their effectiveness depends on the mode and affinity of the binding [6]. During the past decades, molecules binding with DNA have been seriously taken into concern [7-13].
A lot of investigation on the interaction of drug molecules with dna have been studied [14-20]. By identifying the mechanism of interaction between different combinations with dna, It is possible to design new drugs that prevent from replicating of dna in cancer cells [21]. Computational chemistry methods, have widely been applied in chemotherapy studies of dna- drug binding. DFT molecular methods are a group of specific and reliable quantum mechanical calculations for computational studies [22-30].

The binding of small molecules to DNA involves electrostatics interaction, intercalation between base pairs and minor and major DNA groove binding interaction. There are two modes of drug- DNA binding, covalent and non covalent. The non- covalent mode of drug- DNA binding is further classified into tree types, intercalation, groove binding and internal binding (on the outside of the helix) [31,32].

In the present study the interaction of two drugs, pregabalin and olanzapine with dna was investigated using DFT method. The docking between drugs and DNA were performed in order to determine the dna- drug binding site.

MATERIALS AND METHODS

The ground state optimizations of compound have been carried out using DFT with becke-3- lee- Yang- parr (B_3LyP) exchange- correlation function [33] in combination with 6-311 G (d,p) basis sets using Gaussian 09 package [34]. B-DNA molecule was obtained from the protein data bank (available online on http://www.rcsb.org/pdp).The energy gap between the highest occupied (HOMO) and the lowest unoccupied molecular orbital (LUMO) were calculated for each drug by DFT method. The docking studies were performed by hex server [35] and the binding site of drugs with dna were determined.

RESULTS AND DISCUSSION

The optimized structure of pregabalin, olanzapine and B-DNA is presented in Fig 3.

Molecular orbitals

The energy gap between the highest occupied and the lowest unoccupied molecular orbital is an important quantum chemical parameter that determines molecular electrical transport properties and is a measure of electron conductivity. The HOMO energy characterizes electron ability to give while the LUMO energy characterizes electron ability to accept, and the gap between the HOMO and LUMO molecular orbital characterizes the chemical reactivity and kinetic stability of the molecule. A molecule with a small energy gap is more polarizable and is generally associated with high chemical reactivity, low kinetic stability and is also termed as a soft molecule. [36]

Table 1. The HOMO - LUmO gap energy of drugs

Drug molecule	$\Delta E_{HOMO-LUMO}$ (ev)
Olanzapine	0.11295
Pregabalin	0.21548

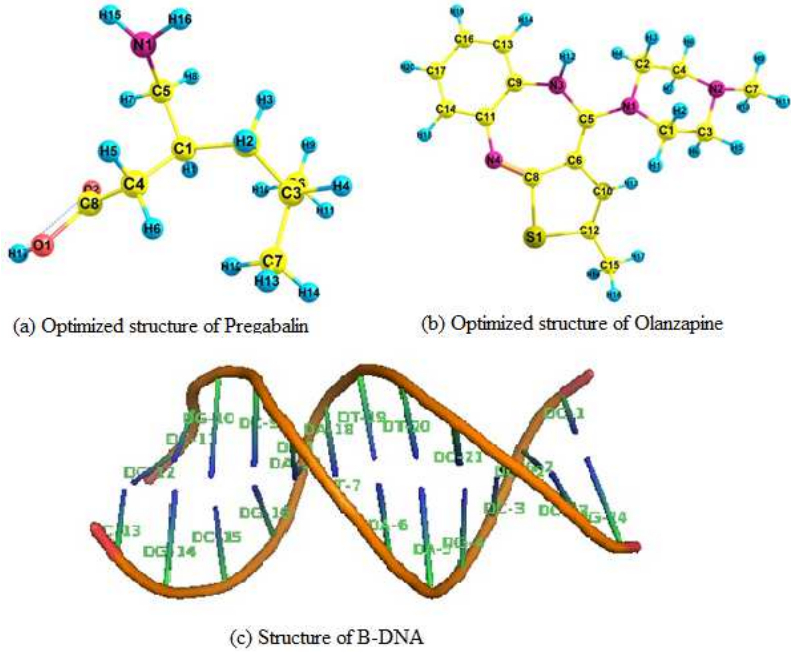

Figure 3. Optimized structure of Compounds

TheHOMO - LUMO gap energy for each drug were calculated and is presented in table 1.The HOMO - LUMO gap energy for olanzapine is lower than pregabalin, so olanzapine is more reactive than pregabalin. The HOMO and LUMO plot for drugs is presented in Fig.4 and Fig.5:

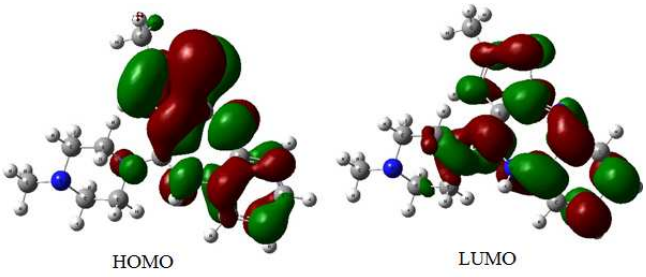

Figure 4. Molecular orbital of Olanzapine

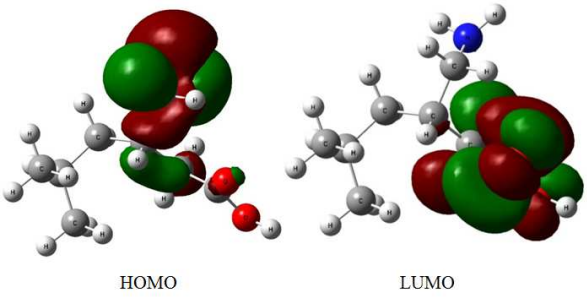

Figure 5. Molecular orbital of Pregabaline

Molecular docking study

The interaction of drugs with dna were studied using DFT and Hex server. In order to run a docking calculation, it is necessary to provide two protein structures, and specify a few parameters that control the calculation. Hex calls the two proteins to be docked the receptor and ligand, respectively. These can be uploaded from PDB files. The Hex server removes all water molecules and other heteroatoms from the input files. During the main docking calculation, Hex rotates each protein about its own coordinate origin, and varies the separation between the two origins.

A score is calculated for each orientation and the highest- scoring orientations are saved and returned to the user.

In general PDB files may be downloaded from the RCSB protein data bank. The correlation type entry box is used to specify the type of docking calculation to be performed (shape- only, or shape+ electrostatics).Requesting electrostatics can be beneficial if the protein have complementary formal charges. The calculation device entry box is used to request that the calculation will be performed by a graphics processor unit (Gpu) or the central processor (cpu). The final search entry box is used to specify the main expansion order N, although the defult value of N=25 is usually sufficient for most purpose. However, performing the full docking calculation with N=25 is time-consuming. In practice, almost identical results are achieve by using a fast initial scan of the orientational search space using N=16 and then rescoring only the top 10,000 orientations with N=25.

The docking studies were performed for drugs using hex server and the binding energy of drugs were determined. The binding energy values is presented in table 2.

Table 2. The binding energy values of drug

Drug molecule	E (ev)
Olanzapine	- 2.276
Pregabalin	-1.622

According to the binding energy values, it is specified that binding affinity of olanzapine to DNA is higher than pregabalin. The binding sites of drugs with dna is presented in Fig.6 and Fig.7.

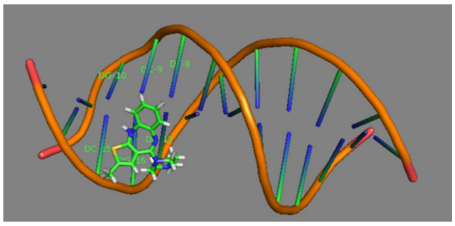

Figure 6. Molecular docked model of Olanzapine with DNA

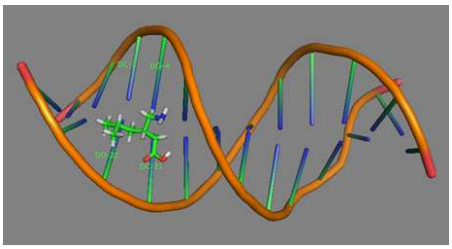

Figure 7. Molecular docked model of Pregabalin with DNA

Concerning figures, it is observed that pregabalin binds to the starting point of DNA and olanzapine binds to the ending point of DNA. In addition, the interacting couple of bases in interaction of pregabalin and DNA are: (C_{21}, G_4) and (G_{22}, C_3), while the interacting couple of bases in interaction of olanzapine and DNA are: (G_{10}, C_{15}), (C_9, G_{16}) and (G_8, C_{17}). From the results, we could find that, olanzapine interacts with higher number of DNA base couples and these finding are consistent with the results related to the HOMO - LUMO gap energy and the binding energy values.

CONCLUSION

This study investigated theoretical interaction of two drugs including pregabalin and olanzapine with DNA using density functional theory computations (DFT) and docking. The calculation of the HOMO -LUMO gap energy of drugs showed that olanzapine is more reactive than pregabalin. Docking results of drugs showed that binding affinity of olanzapine is higher than pregabalin and also olanzapine bears interaction from the ending major groove of DNA whereas pregabalin bears interaction from the starting point of the major groove of DNA.

REFERENCES

[1] Shahabadi, N.; Amiri, S. spectrochim. Acta part A 2015; 138: 840-845.
[2] Meyler's side effects of drugs (sixteenth Edition) 2016;PP. 907-917.
[3] Shahabadi, N.; Bagheri, S.; spectrochim. Acta part A 2015; 136: 1454-1459.
[4] Meyler's side effects of drugs (sixteenth Edition) 2016;PP. 297-328.

[5] Hasan zadeh, M.; Shdjou, N. 2015;PP. 16.
[6] Zhou, Y.L.; Li, Y.Z. Biophys. Chem. 2004; 107: 273-281.
[7] Amirani, M.C.; Tang, T.; Cuervo, J. physical E 2013; 54: 65-71.
[8] Neog, B.; Sinha, S.; Bhattacharyya, p.k. comp. theoretical. Chem. 2013; 1018: 19-25.
[9] Spinello, A.; Terenzi, A.; Barone, G.J. inorg. Biochem. 2013; 124: 63-69.
[10] Balakrishan, C. spectrochim. Acta part A 2015; 150: 671-681.
[11] Wang, S.; peng, T.; yang, C.F.J. Biophys. Chem. 2003; 104: P. 239.
[12] Bren. V.; Hodoscek, M.; Koller. J.J. Chem. Inf. Model. 2005; 45: 1546.
[13] Dolenc, J.; Borstnik, U.; Hodoscek, M.; Koller. J.; Jane zic, D.; J.Mol. struct. (TEOCHEM) 2005; 718: 77.
[14] Krishna, A. G.; Kumar, D.V.; Khan. B.M.; Rawal, S.K.; Ganesh, K.N. Biochem. Biophys. Acta 1998; 1381: 104.
[15] Qu, X.G. ; Wan, C.Z. ; Becker. H.C. ;Zhong. O.P. ;Zewail. A.H. Proc. Natl. Acad. Sci.U.S.A 2001; 98: 14212.
[16] Pyle, A. M; Rehman, J.P; Mechoyree, R. ;Jumer. C.V; Turro. N.J. Barton, J.K. J.Am. cehm. Soc. 1989; 111: 3051.
[17] Kumar, C.V.; Asuncion. E.H. J.Am. chem. Soc. 1993; 115: 8547.
[18] Kumar, G.S.; Mussers, S.M.; Cummings, J.; Tomas, Z.M. J.Am. Chem. Soc 1996; 118: 9209.
[19] Leng, F.F; Priebe. W.; Chires. J.B. Biochem. 1998; 37: 1743.
[20] Maeda, Y.; Nunomura, K.; Ohtsubo, E. J.Mol. Biol. 1990; 215: P. 321.
[21] Sirajuddin, M.; Ali, S.; Badshah, A. Photochem. Photobiol. 2013; 124: 1-79.
[22] Riahi, S.; Ganjali, M.R.; Norouzi, P.; Theor, J. Comput. chem. (JTCC) 2008; 7: P. 317.
[23] Riahi, S.; Moghaddam. A.B.; Ganjali, M.R.; Norouzi, P.; Theor, J. Comput. chem. (JTCC) 2007; 6: P. 331.
[24] Riahi, S.; Ganjali. M.R.; Moghaddam, A.B.; Norouzi, P.; HosseinyDavarani, S.S. Spectro chem.Acta. 2008; 70:P. 94.
[25] Riahi, S.; Faridbod, F.; Ganjali, M.R; Sensor let. 2009; 7: P. 42.
[26] Ganjali. M.R. ;Norouzi, P. ; Sadat Mirnaghi, F. ; Riahi, S. ; Faridbod, F. IEEE.Sens.J. 2007; 7: P. 1138.
[27] Riahi, S.; Ganjali. M.R.; Moghaddam, A.B.; Norouzi, P.; Spectrochim.ActaA 2008; 71: P. 1390.
[28] Riahi, S.; Ganjali. M.R.; Norouzi, P.; Jafari, F. Sens. Actuators. B 2008; 132: P. 13.
[29] Faridbod, F.; Ganjali, M.R.; Larijani, B.; Norouzi, P.; Riahi, S.; Sadat Mirnaghi, F. Sensors 2007; 7: P. 3119.
[30] Faridbod, F.; Ganjali, M.R.; Dinarvand, R.; Norouzi, P.; Riahi, S.; Sensors 2008; 8: P. 1645.
[31] Li, H; Mei, W.J.; Xu, Z.H. ; Pang, D.W; Ji, L.N.; Lin, Z.H.J. Electroanal. Chem. 2007; 600: 243-250.
[32] Li, C; Liu, S.L.; Guo, L.H.; Chen, D.P. Electrochem.Commun. 2005; 7: 23-28.
[33] Becke, A.D. phys. Rev. A 1988; 386: 3098-3100.
[34] Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Sucseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scoolmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A. Gaussian 09, Gaussian, Inc,. Wallingford, CT, 2010, Revission 401 Bot.
[35] Mustard, D.; Rtchie, D.W. Proteins 2005; 60: 269-274.
[36] Gil, D.M.; Tuttolomondo, M.E.; Altabef, A.B.Spectrochim. ActaA 2015; 149: 408-418.