ICC
Iranian Chemical Communication
Original Research Article
Payame Noor University http://icc.journals.pnu.ac.ir

DFT calculations on quetiapine hemifumarate as a pharmaceutical compound for the treatment of schizophrenia

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Received: 20 July 2014, Accepted: 29 September 2015, Published: 29 September 2015

Abstract

In this work, the optimization calculations were carried out on quetiapine hemifumarat, 4, and its analogues, using B3LYP/6-31G(d) level of theory. The DFT calculations clarified a boat structure for dibenzothiazepine moiety of the molecule in which piperazine moiety has a chair conformation. Thermal energies (E), enthalpies (H), and Gibbs free energies (G) of quetiapine and its analogues, were calculated at the B3LYP/6-31G(d) level. The chemical hardness (η), chemical potential (μ), dipole moment (D), electrophilicity (ω) and the maximum amount of electronic charge, ΔNmax, were determined.

Keywords: DFT calculation; quetiapine hemifumarate; pharmaceutical.

Introduction

Quetiapine is described as 2-(2-(4-dibenzo(b,f)(1,4)thiazepine-11-yl-1-piperazinyl) ethoxy)ethanol with molecular formula $C_{21}H_{25}N_3O_{2S}$ and molecular weight 383.51 (Figure 1).

Quetiapine is used for the treatment of schizophrenia and recently has gotten food and drug administration (FDA) approval for treatment of manic depression [1-6]. It is also useable to cure other disorders, such as post-traumatic stress disorder, alcoholism, obsessive compulsive disorder, anxiety disorders, and hallucinations in Parkinson's disease patients who use ropinirole and as a sedative for those with sleep disorders. Quetiapine is the most commonly prescribed antipsychotic drug in America and had been

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used by more than 19 million patients worldwide in 1997. The action mechanism of quetiapine, along with other drugs which have efficacy in the treatment of schizophrenia and acute manic episodes associated with bipolar disorder, is unknown.

Several theoretical calculations have been done on the thiazepine [7,8]. In this work, the optimization calculations were carried out on quetiapine hemifumarat, **4**, which was compared with its obtained X-Ray data (Scheme 1). These calculations were carried out by using B3LYP/6-31G(d) level of theory. The boat structure for dibenzothiazepine part and chair conformation for piperazine section was clarified with DFT calculations.

Method of calculations

All the calculations were performed with the Gaussian 03W program package[9]. The Geometry optimization of **1-5** were done by performing HF and DFT level of theory with 6-31G(d) basis set. The vibrational frequencies were also calculated with these methods. We have used the scaling factor values of 0.9613 for B3LYP method [10]. Harmonic vibrational frequencies have been calculated on optimized structure at B3LYP/6-31G level. Harmonic frequency analysis indicated that all stationary points were found to be true minima.

Model equations

The global electrophilicity power, ω, has been defined by Parr *et al.* [11]. The electrophilicity index has been successfully applied in the theoretical studies of many systems [12] and a useful review has also published by Chattaraj and Roy [13]. It has been successfully used to describe reactivity in the different organic systems.

The global electrophilicity index which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment, has been given in the following expressions [11] in terms of the electronic chemical potential, μ, or the electronegativity, χ, and the chemical hardness, η (Eq. 1).

(Eq. 1) $\omega = \mu^2/2\eta = \chi^2/2\eta$

For an N-electron system with total energy E, χ and η were defined as (Eqs. 2 and 3) [11]:

(Eq. 2) $\chi = -\mu = (I + A)/2)$

(Eq. 3) $\eta = (I - A)$

The I and A are the ionization potential and electron affinity, respectively.

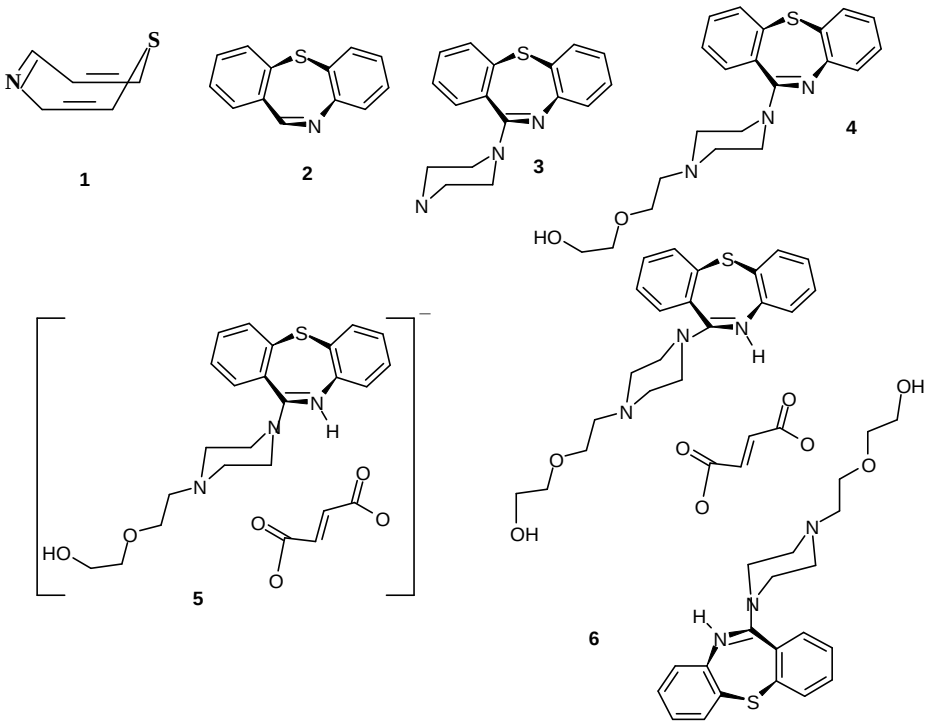

Figure 1. Molecular structure of quetiapine, **4**, and its analogues,**1-3** and **5**,**6**

The global electrophilicity index which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment has been given in the following expressions [11] in terms of the electronic chemical potential, μ, or the electronegativity, χ, and the chemical hardness, η (Eq. 1).

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The ω index establishes an absolute scale of electrophilicity in the sense that the hierarchy of electrophilicity is built up from the electronic structure of molecules, independent of the nucleophilic partner, which is replaced by an unspecified environment viewed as a sea of electrons [11].

Results and discussion

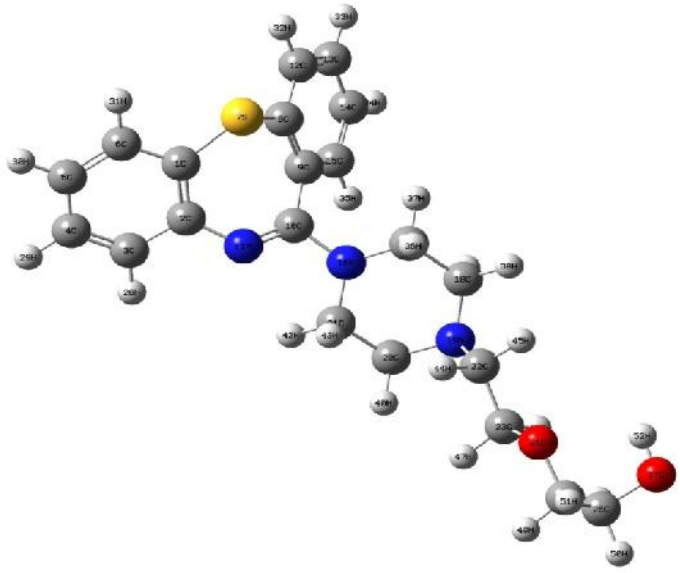
All the enlisted results were made before opening the discussions. The structure of 2-(2-(4-dibenzo(b,f)(1,4)thiazepine-11-yl-1-piperazin-yl) ethoxy)ethanol, quetiapine, **4**, was optimized (Scheme 1).

DFT calculations show that the stable

boat conformation was found for azepine ring in all the studied compounds, **1-6**. The planar conformation is found for azepine ring on going from **1** to **6**. This planar conformation tendency is due to the substitution of two phenyl groups at both sides of azepine ring.

Thermal energies (E), enthalpies (H), and Gibbs free energies (G) of **1-6** were calculated at B3LYP/6-31G* level (Table 1).

The positions of the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO) and dipole moments were presented for quetiapine and its analogues, **1-4** (Table 2). The HOMO-LUMO energy gap has been used as a simple indicator of chemical reactivity and kinetic stability of the molecule. A large HOMO-LUMO gap implies high kinetic stability and low chemical reactivity. The chemical hardness (η), chemical potential (μ), dipole Moment (D), electrophilicity (ω) and the maximum amount of electronic charge, ΔNmax, in atomic unit, also were computed at B3LYP/6-31G* level (Table 2). The least HOMO-LUMO energy gap or the chemical hardness (η) was found for **1** which shows the most chemical reactivity for that. Therefore, we can conclude that the drug chemical activity of **1** is the largest among the other compounds, **2-4**. The chemical potential (μ), electrophilicity (ω) and the maximum amount of electronic charge, ΔN_{max}, in atomic unit, are found to be the most for 1. Most of the chemical potential (μ), electrophilicity (ω) and the maximum amount of electronic charge, ΔN_{max}, for **1** reasonably were attributed to increase the average of electropositive atoms at the azepine ring such as the carbon and hydrogen atoms.



Scheme 1. The optimized structure of 2-(2-(4-dibenzo(b,f)(1,4)thiazepine-11-yl-1-piperazin-yl) ethoxy)ethanol, quetiapine, **4**

Table 1. Zero point energy (ZPE), thermal energies (E), enthalpies (H), and Gibbs free energies (G) of quetiapine, **4**, and its analogues, calculated at B3LYP/6-31G* level

Compound	ZPE Hartree	E Hartree	H Hartree	G Hartree
1	-646.41	-646.40	-646.40	-646.44
2	-953.69	-953.68	-953.68	-953.73
3	-1220.16	-1220.15	-1220.15	-1220.21
4_a	-1528.06	-1528.04	-1528.04	-1528.12
4_X	-1527.70	-1527.67	-1527.67	-1527.76

Table 2. The chemical hardness (η), chemical potential (μ), electrophilicity (ω) the maximum amount of electronic charge, ΔN_{max}, in atomic unit and dipole moment (Deby)

Compound	HOMO	LUMO	η	μ	ω	ΔN_{max}	Dipole Moment
1	-0.2267	-0.0790	0.1477	-0.1528	0.0790	1.03	2.0820
2	-0.2280	-0.0732	0.1548	-0.1506	0.0732	0.97	2.6291
3	-0.1982	-0.0381	0.1601	-0.1181	0.0435	0.73	3.6995
4_a	-0.1943	-0.0356	0.1588	-0.1150	0.0416	0.72	10.3880
4_X	-0.1975	-0.0376	0.1599	-0.11753	0.0432	0.73	5.8407

Table 3. The calculated bond lengths (R, Angstrom) in quetiapine, 4, at B3LYP/6-31G(d) level of theory

Compound	C1-C2	C2-N11	N11-C10	C10-C9	C9-C8	C8-S7	S7-C1	C10-N16	N16-C17
4_a	1.4127	1.3995	1.2806	1.4904	1.4087	1.7123	1.7938	1.4241	1.4639
4_X	1.4159	1.3894	1.2950	1.4982	1.4068	1.7933	1.7933	1.3901	1.4685
	N16-C21	N19-C18	N19-C20	N19-C22	C22-C23	C23-O24	O24-C25	C25-C26	C26-O27
4_a	1.4669	1.5154	1.5225	1.5064	1.5306	1.3983	1.4307	1.5214	14159
4_X	1.4653	1.4662	1.4610	1.4607	1.5339	1.4220	1.4132	1.5232	1.4164

The geometrical parameters including the bond lengths (R) and bond angles (A) were calculated for quetiapine, $\mathbf{4_a}$, at the mentioned level (Tables 3 and 4). The calculated geometrical parameters were compared with the experimental data that achieved through X-Ray, $\mathbf{4_X}$ [14]. The good correlations were found between calculated and experimental geometrical parameters such as bond lengths (R) and bond angles (A) of $\mathbf{4_a}$ and $\mathbf{4_X}$**.** The lowest bond length was observed for N_{11}-C_{10} in 4_a and 4_X that attributed to a more electrongative nitrogen atom in the bond.

Natural bonding orbital (NBO) charge at atoms for quetiapine, **4**, and its analogues, **1-5** were calculated (Table 5). The good correlation was found between calculated and experimental charges on atoms of $\mathbf{4_a}$ and $\mathbf{4_X}$. The highest charges on atoms were observed on C_{10} in $\mathbf{4_a}$ and $\mathbf{4_X}$ attributed to attache to an electrongative nitrogen atom in the molecule.

DFT calculations indicate two conformers for **4** ($\mathbf{4_a}$ and $\mathbf{4_b}$) (Figure 2). Ethoxy ethanol group in $\mathbf{4_a}$ occurs in the horizontal row while ethanol group in $\mathbf{4_b}$ occurs in the vertical row. The conformation of $\mathbf{4_a}$ is more stable (-4.21 kcal/mol) than that of $\mathbf{4_b}$.

The DFT calculations were energetically carried out for molecules, **4-6** (Table 6). There are two interactions in molecules, $\mathbf{5_a}$ and $\mathbf{5_b}$ (Figure 3). In former conformer, the oxygen atom of fumarate ion interacts with hydrogen atom attached to nitrogen atom of piperazidinum ring and in latter, the oxygen atom of fumarate ion interacts with hydrogen atom attached to oxygen atom of ethoxy ethanol. The conformers of $\mathbf{5_a}$ and $\mathbf{5_b}$ are lower in energy (-510.45 and -574.15 kcal/mol), respectively (Table 6). Thus, the conformer 5_b is more stable (-64.30 kcal/mol) than that of 5_b which describes a more stable interaction of fumarate ion interact with hydrogen atom attached to nitrogen atom of piperazidinum ring. Molecule 6 has two quetiapine molecules in the framework which achieves the stability of -910.34 kcal/mol with respect to invididual particles.

Some calculated that the molecular properties of the molecules considered in this study were given in Table 7, which are obtained from DFT/B3LYP/6-31G level.

Log P values, as a descriptor of the hydrophobicity of neutral molecules and indicator of the pharmacetual character, were calculated. Compound **2** has the largest log P value, which means that this molecule is more hydrophobic and high pharmacetual character than the others. The changes in pharmacetual character were in the order: **2** >

3 > **4** > **6**. The hydration energy which indicates the polarity of the molecule was also calculated for the mentioned molecules. Compound **4a** has the largest hydration energy value.

Table 4. The calculated bond angles (A, degree) in quetiapine **4** at B3LYP/6-31G(d) level of theory

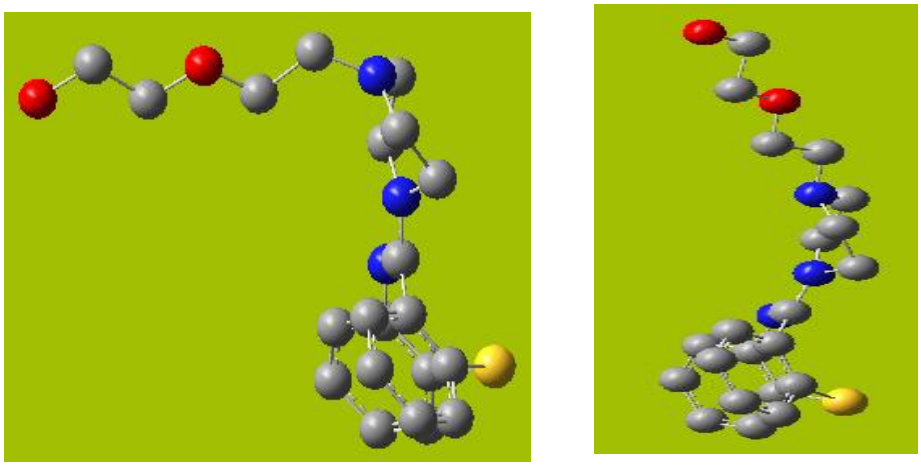
Compound	C1C2N3	C2N3C4	N3C4C5	C4C5C6	C5C6S7	C1C6S7	N3C4N10	C17N10C18
4_a	124.14	126.12	128.83	121.21	120.01	98.01	115.96	111.56
4_x	124.75	126.65	126.09	121.86	119.90	97.57	118.05	111.89
	N10C18C19	C19N20C21	N20C21 C17	N20C38C39	C38C39O40	C39O40C41	O40C41C42	C41C42O43
4_a	108.98	109.42	109.29	113.07	104.77	113.46	108.04	105.49
4_x	110.12	109.60	110.52	113.93	115.66	114.87	109.35	114.16

Table 5. The calculated Natural bonding orbital (NBO) charge at atoms in quetiapine **4** and its analogues, 1-5 at B3LYP/6-31G(d) level of theory

Compound	C1	C2	N3	C4	C5	C6	S7	C8	C9	N10	C12	C13	C14
4_a	-0.12	0.26	-0.54	0.39	0.09	-0.13	0.14	-0.15	-0.14	-0.50	-0.15	-0.11	-0.13
4_b	-0.12	0.27	-0.55	0.41	0.08	-.013	0.11	-0.15	-0.14	-0.45	-0.15	-0.12	-0.13
	C15	C16	C17	C18	C19	N20	C21	C38	C39	O40	C41	C42	O43
4_a	-0.10	-0.13	-0.17	-0.12	-0.19	-0.50	-0.16	-0.17	-0.01	-0.48	-0.04	-0.04	-0.61
4_b	-0.11	-0.13	-0.14	-0.12	-0.14	-0.45	-0.12	-0.13	-0.28	-0.45	-0.03	-0.04	-0.61

Table 6. Total energies (E_T), zero-point energies (ZPE) thermal energies (E,), enthalpies(H) Gibbs free energies(G) in hartree, and relative stability energies, ΔE_T, in kcal/mol for **4-6**

Compound	E_T	ZPE	E	H	G	ΔE_T kcal/mol
Fumarate	-445.6325222	-445.568988	-445.561781	-445.560837	-445.602374	---
4_a	-1502.165455	-1501.658403	-1501.635782	-1501.634838	-1501.714025	0.00
5_a	-1948.6114035	-1948.022259	-1947.993180	-1947.992235	-1948.086426	-510.45
5_b	-1948.7129576	---	---	---	---	-574.15
6	-3451.4141705	---	---	---	---	-910.34

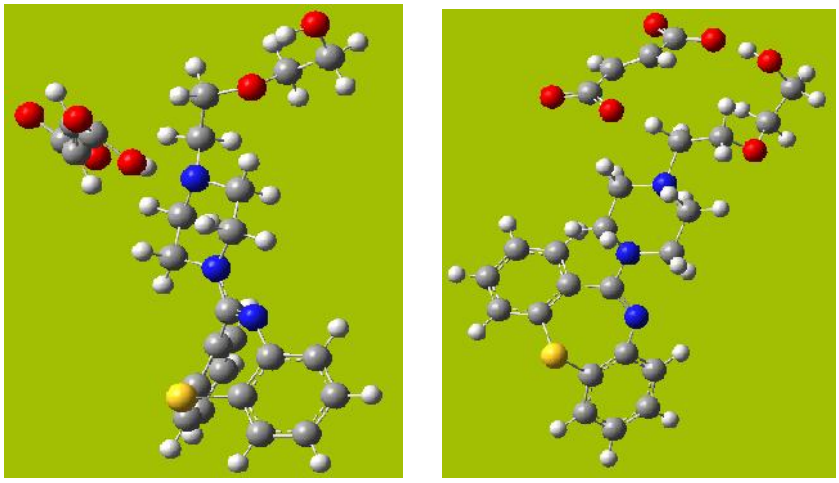


4_a **4_b**

Figure 2. Two conformers of compound **4**

Table 7. Log P, hydration energy (kcal/mol), refractivity (cm^3), polarizability(a.u.), surface area ($A°^2$)and volume(cm^3) of 1-6

Compound	Log P	HydrationEnergy kcal/mol	Refractivity	Polarizability	Surface area	Volume
1	-0.82	-4.88	33.73	12.73	219.18	367.24
2	3.55	-6.18	66.01	25.09	293.72	619.63
3	3.09	-6.10	88.94	34.36	378.05	846.03
4_a	2.12	-10.91	109.48	42.39	555.63	1117.29
4_b	2.52	-10.10	113.97	43.10	527.41	1046.71
6	-1.52	---	231.30	94.66	---	2247.06



5a **5b**

Figure 3. Two conformers of compound **5** with fumarate ion

More hydration energy means that the molecule is more soluble in water. Furthermore, the refractivity and polarizability values of the molecules were calculated whose corresponding values are also given in Table 7. According to DFT calculation, compound 1 has the smallest refractivity and the smallest polarizability value.

Conclusion

DFT calculations indicate that the stable boat conformation was found for azepine ring in all the studied compounds, 1-5. The drug chemical activity of 1 is the largest among of the other compounds, 2-4. It is seemed that the drug chemical activity decreases when the length of a molecule and hence, the carbon and hydrogen atoms increases. The conformation of $\mathbf{4_a}$ is more stable (-4.21 kcal/mol) than that of 4_b. The conformer 5_b is more stable (-64.30 kcal/mol) than that of 5_b which describes a more stable interaction of fumarate ion interact with hydrogen atom attached to nitrogen atom of piperazidinum ring.

Acknowledgments

We are grateful to Payame Noor University for support of this study.

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