Acta Scientific Pharmaceutical Sciences

Volume 1 Issue 2 2017

Research Article

Electrostatic Potential-Mapped Electron Density Surface and Conformation Analysis of an Antidepressant, Mirtazapine

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Received: May 31, 2017; Published: July 01, 2017

Abstract

Mirtazapine (methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1]pyrido [2,3][2]benzazepine) is a medication with noradrenergic and specific serotonergic activity. Electrostatic potential-mapped electron density surface and conformation analysis of mirtazapine was carried out using ArgusLab 4.0.1 software. Electrostatic potential-mapped electron density surface showed the areas of the molecule that would be susceptible to nucleophilic and electrophilic attack. The geometry convergence curve predicted the minimum energy of the molecule. The predicted geometry energy was -90.575172 au (-56836.830000 kcal/mol). At this potential energy, mirtazapine will be able to interact effectively with the receptor.

Keywords: Mirtazapine; Arguslab; Conformation Analysis; Electrostatic Potential; Receptor

Abbreviations

ESP: Electrostatic Potential

Introduction

Mirtazapine (methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1] pyrido[2,3][2]benzazepine) is a medication with noradrenergic and specific serotonergic activity [1]. It inhibits the α2 adrenergic auto- and heteroreceptors (enhancing 5-hydroxytryptamine release), and by selection antagonizes the 5-HT2 5-hydroxytryptamine receptors within the central and peripheral systema nervosum. It additionally enhances 5-hydroxytryptamine neurotransmission at the 5-HT1 receptor and blocks the histaminergic (H1) and muscarinic receptors. This antidepressant is not a 5-hydroxytryptamine or catecholamine uptake substance however it has the ability to increase 5-hydroxytryptamine and catecholamine by alternative mechanisms of action [2]. Mirtazapine was introduced by Organon International in the United States in 1996 [3] as a noradrenergic and specific serotonergic medication (NaSSA). It is employed primarily for treatment of depression, major depressive disorder and other mood disorders [4,5]. It can also act as a medicament for anxiolytic, hypnotic and appetency stimulant. Structurally, it is the 6-aza analogue of mianserin [6] and can be classified as a tetracyclic medication (TeCA). The comparison of the efficacy and tolerability of 12 second-generation antidepressants was studied in 2009 [6]. It was discovered that mirtazapine was superior to other selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [6].

However, it has additionally been found helpful in assuaging generalized anxiety disorder [7,8], low appetite/underweight [9-11], nausea and vomiting [12-14], social anxiety disorder [15,16], obsessive-compulsive disorder [15,17], and post-traumatic stress disorder [15]. Mirtazapine and its derivatives might cause a discontinuance syndrome when the medication is stopped abruptly [18,19]. A gradual and slow reduction in dose is usually recommended to reduce discontinuance symptoms [20]. Effects of abrupt stoppage of treatment with mirtazapine might embody depression, anxiety, panic attacks, vertigo, restlessness, irritability, reduced appetency, insomnia, diarrhea, nausea, vomiting, flu-like symptoms like allergies and itching, headaches and typically hypomania or mania [20]. The structure of mirtazapine is shown in Figure 1.

In conformation analysis, energy is decreased so as to induce rock bottom energy. The conformation with rock bottom energy is the most stable. In nature, low energy level is favourable. Understanding the electrostatic potential-mapped density surface and conformation of a molecule is important because it permits us to predict the re-

activity of the molecule. The aim of conformation analysis is to work out atomic orientations that are the most stable. ArgusLab [21] is a molecular modelling graphics and drug style program for windows package. It is a software package for conformation analysis, single purpose energy calculations, electronic spectrum predictions, molecular orbital surfaces and molecular docking.

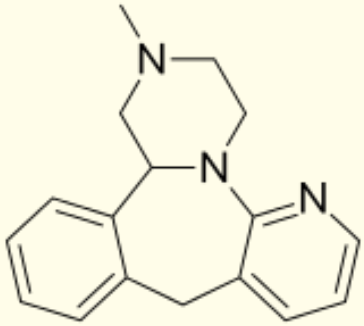

Figure 1: Structure of mirtazapine.

We hereby present electrostatic potential-mapped electron density surface and conformation analysis of an antidepressant, mirtazapine.

Materials and Methods

Geometry optimization study was performed on a window primarily based computer using ArgusLab and ACD laboratory ChemSketch software package. The chemical structure of mirtazapine was generated by ArgusLab. Diminution was performed with Parameterized Model three (PM3) semi-empirical using ArgusLab 4.0.1 software. The minimum potential energy was calculated by geometry convergence operation in ArgusLab software package. Electrostatic potential mapped on negatron density surface of mirtazapine was created. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map.

Results and Discussion

The electrostatic potential-mapped electron density surface and geometry convergence curve of mirtazapine are shown in Figures 2 and 3 respectively. Final geometry optimized coordinates, geometry optimized bond length and geometry optimized bond angles of mirtazapine are presented in Tables 1 - 3 respectively.

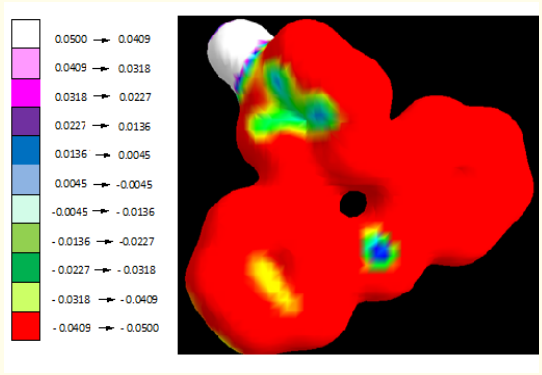

Figure 2: Electrostatic potential-mapped electron density surface of mirtazapine.

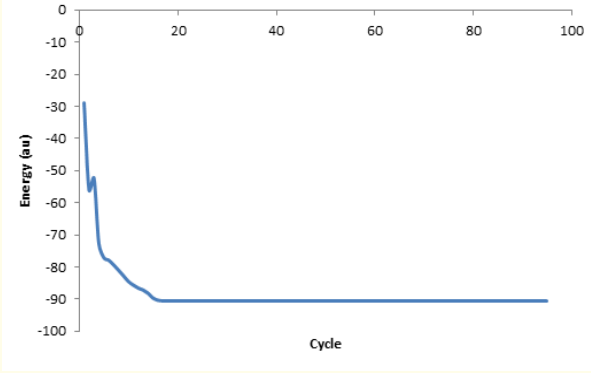

Figure 3: Geometry convergence curve of mirtazapine.

Atom	X	Y	Z
C	16.549701	10.132548	0.003997
C	16.961337	8.708667	0.124094
C	17.487689	11.285460	0.141336
N	18.143823	8.174487	0.527106
C	18.937676	11.200564	0.119797
C	19.819033	10.056703	0.075609
C	19.474461	8.625286	0.174592
C	15.231331	10.402526	0.025517
C	14.713674	11.781813	0.056375
C	17.006128	12.536591	0.195900
C	15.561094	12.803683	0.153275
C	21.077653	10.368091	0.402055
C	22.109495	9.329014	0.536827
N	20.428527	7.721903	0.058697
C	21.784353	8.059266	0.308131

C	15.975604	7.740665	0.654381
N	16.060883	6.349686	0.299243
C	18.048771	6.854942	1.126927
C	16.991907	5.929555	0.712034
C	15.109748	5.416241	0.836185

Table 1: Final geometry optimized coordinates of mirtazapine.

Atoms	Bond Length (Å)
1 2 (C)-(C)	1.458000
1 8 (C)-(C)	1.323387
1 3 (C)-(C)	1.458000
2 16 (C)-(C)	1.458000
2 4 (C)-(N)	1.433804
3 5 (C)-(C)	1.458000
3 10 (C)-(C)	1.323387
4 7 (N)-(C)	1.433804
4 18 (N)-(C)	1.433804
5 6 (C)-(C)	1.458000
6 12 (C)-(C)	1.323387
6 7 (C)-(C)	1.458000
7 14 (C)-(N)	1.301961
8 9 (C)-(C)	1.458000
9 11 (C)-(C)	1.323387
10 11 (C)-(C)	1.458000
12 13 (C)-(C)	1.458000
13 15 (C)-(C)	1.323387
14 15 (N)-(C)	1.433804
16 17 (C)-(N)	1.433804
17 19 (N)-(C)	1.433804
17 20 (N)-(C)	1.436817
18 19 (C)-(C)	1.458000

Table 2: Geometry optimized bond length of Mirtazapine.

Atoms	Bond angles (°)	Alternate bond angle (°)
2 1 8 (C)-(C)-(C)	120.000000	216.488007
2 1 3 (C)-(C)-(C)	120.000000	188.442082
1 2 16 (C)-(C)-(C)	120.000000	188.442082
1 2 4 (C)-(C)-(N)	120.000000	257.053574
8 1 3 (C)-(C)-(C)	120.000000	216.488007
1 8 9 (C)-(C)-(C)	120.000000	216.488007
1 3 5 (C)-(C)-(C)	120.000000	188.442082
1 3 10 (C)-(C)-(C)	120.000000	216.488007
16 2 4 (C)-(C)-(N)	120.000000	257.053574
2 16 17 (C)-(C)-(N)	120.000000	257.053574
2 4 7 (C)-(N)-(C)	120.000000	198.144139
2 4 18 (C)-(N)-(C)	120.000000	198.144139
5 3 10 (C)-(C)-(C)	120.000000	216.488007
3 5 6 (C)-(C)-(C)	120.000000	188.442082
3 10 11 (C)-(C)-(C)	120.000000	216.488007
7 4 18 (C)-(N)-(C)	120.000000	198.144139
4 7 6 (N)-(C)-(C)	120.000000	257.053574
4 7 14 (N)-(C)-(N)	120.000000	402.764879
4 18 19 (N)-(C)-(C)	120.000000	257.053574
5 6 12 (C)-(C)-(C)	120.000000	216.488007
5 6 7 (C)-(C)-(C)	120.000000	188.442082
12 6 7 (C)-(C)-(C)	120.000000	216.488007
6 12 13 (C)-(C)-(C)	120.000000	216.488007
6 7 14 (C)-(C)-(N)	120.000000	294.480480
7 14 15 (C)-(N)-(C)	120.000000	227.506158
8 9 11 (C)-(C)-(C)	120.000000	216.488007
9 11 10 (C)-(C)-(C)	120.000000	216.488007
12 13 15 (C)-(C)-(C)	120.000000	216.488007
13 15 14 (C)-(C)-(N)	120.000000	295.980973
16 17 19 (C)-(N)-(C)	120.000000	198.144139
16 17 20 (C)-(N)-(C)	120.000000	197.520556
19 17 20 (C)-(N)-(C)	120.000000	197.520556
17 19 18 (N)-(C)-(C)	120.000000	257.053574

Table 3: Geometry optimized bond angles of mirtazapine.

Mapped surface was generated using ArgusLab software. This is a surface where one property is superimposed onto a surface created by another property. The foremost well-liked example of this is often to map the electrostatic potential (ESP) onto a surface of the negatron density. In ESP-mapped density surface, the negatron density surface offers the form of the surface whereas the ESP offers the colours. The potential energy felt by a positive test charge at a selected purpose in area is known as electrostatic potential. A negative ESP, is often a vicinity of stability for test charge. Conversely, a positive ESP, is often a vicinity of relative instability for the positive test charge. Thus, the favorability of a molecule to nucleophilic or electrophilic attack can be seen using ESP-mapped density surface. This surface is helpful for qualitative interpretations of chemical reactivity. In a different

way to think about ESP-mapped density a surface is that it shows where the frontier negatron density for the molecule is greatest (or least) relative to the nuclei. In the ESP-mapped density surface of mirtazapine (Figure 2), the colours show the ESP on the negatron density surface. The red colour on the surface shows region of high electron density. Nucleophilic attack is likely to occur at these regions. The white portion on the surface is the methyl group. Electrophillic attack will occur at this region.

The geometry convergence curve of mirtazapine (Figure 2) shows a reduction in energy from. The lowest energy obtained was -90.575172 au (-56836.830000 kcal/mol). At this point, the drug will be stable. At this point the drug will be able to interact with the receptor. The geometry optimized coordinates, bond length and bond angles (Table 1- 3) will give a conformation with the lowest potential energy and most stable conformation. Previous studies [22, 23] have shown that Arguslab software is reliable for the prediction of ESP-mapped density surface and minimum energy of a molecule.

Conclusion

Arguslab software is reliable for the prediction of ESP-mapped density surface and minimum energy of a molecule. The most feasible conformation mirtazapine to interact with the receptor is -90.575172 au (-56836.830000 kcal/mol). The ESP-mapped density surface was used in the prediction of molecular reactivity.

Acknowledgements

We are grateful for the research grant from Abia State Government, Nigeria.

Conflict of Interest

No conflict of interest.

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