Conformational analysis and geometry optimization of buspirone-A 5-HT_{1A} receptor agonist

Huma Ikram*[1], Muhammad Azhar[2], Muhammad Jameel[2] and Khalida Bano[1]
[1]Department of Biochemistry, University of Karachi, Karachi, Pakistan
[2]Department of Physics, University of Karachi, Karachi, Pakistan

Abstract: Buspirone, a partial 5-HT_{1A} receptor agonist, is a clinically prescribed anxiolytic. In the present study, conformational analysis and geometry optimization of buspirone were done as per Hartree-Fock (HF) calculation method by Argus Lab 4.0.1 software. The minimum potential energy was calculated by geometry convergence function by Argus Lab software. The results indicate that the best conformation of molecule is present at minimum potential energy of-100679.5513 kcal/mol. At this point, buspirone will be more active.

Keywords: Buspirone, geometry optimization, conformational analysis, Arguslab 4.0.1.

INTRODUCTION

Buspirone(chemically 8-[4-(4-pyrimidin-2-ylpiperazin-1-yl)butyl]-8-azaspiro[4.5]decane-7,9-dione), is the member of the azapironegroup. Clinically, it is prescribed for the treatment of generalized anxiety disorders of mild to moderate intensity (Ortiz *et al*., 1987, Trivedi *et al*., 2006; Appelberg *et al*., 2001). Anxiolytic and antidepressant effects are mediated via partial agonistic affinity of buspirone towards serotonergic 5-HT_{1A} receptors (Bordukalo-Niksic *et al*., 2010; Blier *et al*., 1997).It also functions as presynaptic dopamine D_2agonist as well (Blier *et al*., 1997; McMillen *et al*.,1983)At micro doses,theability of buspirone to selectively block presynaptic mesolimbic D_2auto-receptorsappears to result in increased dopamine synthesis and release (Jadhav *et al*., 2008; Dhavalshankh *et al*., 2007). It has also been suggested that combination of buspirone and melatonin stimulates neurogenesis (Fava *et al*., 2012; Grabiec *et al*., 2009; Mareš *et al*., 2012).

In the present study, Argus lab software was used for the computer aided geometry optimization (active conformation) and conformational analysis of buspirone. Prediction of reaction pathway, bond angles, bond lengths, vibration frequencies of coordinates of atoms, geometry optimization of structure and potential energies, can be predicted by this electronic structure program (Peng *et al*., 1996; Soumendranath *et al*., 2011).

Geometry optimization is fundamental component of molecular modeling. The determination of a low-energy conformation for a given force field can be the final objective of the computation. Alternatively, the minimum for the system on the specified potential energy surface, in a local or globe sense can serve as starting or reference point for subsequent calculation.

The energy (E) of molecule is calculated as a sum of terms as in equation vibration frequencies of coordinates of atoms (Khalida *et al*., 2010; Cramer *et al*., 1992; Bell and Crighton, 1984):

$$E= E_{\text{stretching}} + E_{\text{bending}} + E_{\text{torsion}} + E_{\text{VanderWaals}} + E_{\text{electrostatic}} + E_{\text{hydrogenbond + crossterm}}$$

Accurate calculation of geometry properties of molecules involves these terms. The set of energy functions and the corresponding parameters are called a force field (Fakir *et al*., 2011).An integral part of method is calculation of molecular mechanics as a function of coordinates and energy minimization.

Computer graphics techniques are used to construct a molecular geometry. Usingan energy minimization technique, atoms are iteratively moved (without breaking bonds) until total energy of the molecule reaches a minimum and net force on all atoms vanishes (Merz and Kollaman, 1989; Simons *et al*., 1983). Stable conformations of 3D (3 rotatable bonds) structure of molecule but not necessarily the most stable ones correspond to this minimumenergy (Still *et al*., 1990).

MATERIALS AND METHODS

The three dimensional quantitative structural activity relationships (3D- QSAR) important to understand the detailed interactions of the ligand with its receptor protein. It describes the biological activity of molecule with pharmacological potential as a function of their structure properties (Singh *et al*., 2006; Bell and Crighton, 1984; Merz and Kollaman, 1989). Computational advances have generated many tools, which are widely used to construct models, minimization and representations of molecular structure (Martin, 1998; Cruciani *et al*., 1998; Soumendranath, 2011).

**Corresponding author:* e-mail: huma_biochemist@yahoo.com

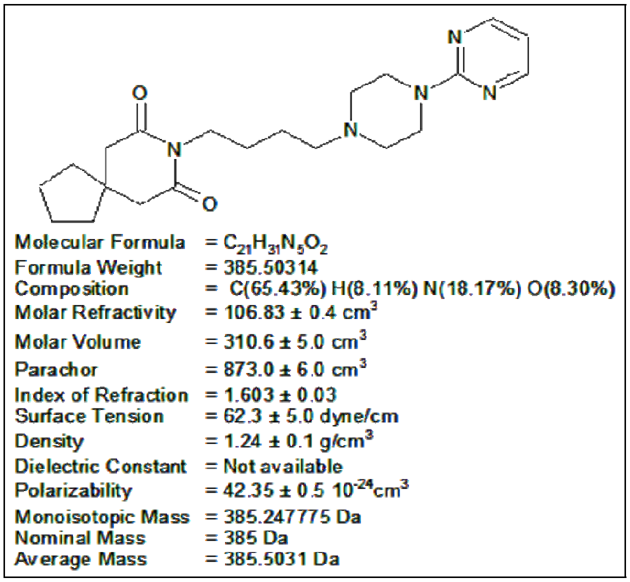
All conformational analysis and geometry optimization study was performed using software's ACD Chemsketch and Arguslab. The chemical structure of 8-{4-[4-(pyrimidin-2-yl) piperazin-1-yl]butyl}-8-azaspiro [4.5] decane-7,9-dionewas refined by X-ray crystallography technique.

The minimum potential energy was calculated with the help of geometry convergence function in Arguslab software. In order to determine the allowed conformation the contact distance between atoms in adjacent residues examined using the criteria for minimum Vander Waal contact distance (Soumendranath *et al*., 2011; Khalida *et al*., 2010; Simons *et al*., 1983).

Surface created by using Arguslab to visualize ground state properties as well as excited state properties and orbital, electron densities, electrostatic potential (ESP), spin densities generated and to make the molecular orbital surface and visualized the molecular orbital and making an electrostatic potential map and electron density surface grid data was used.. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map (Martin, 1998; Cruciani *et al*., 1998).

RESULTS

Prospective view and calculated properties of Buspirone molecule are shown in fig. 1. The active conformation and electron density mapped of Buspirone by ACDLABS-3D viewer software are shown in fig. 2 and 3 respectively. fig. 4 shows Electrostatic potential of molecular ground state mapped onto the electron density surface for the ground state.



Molecular Formula = $C_{21}H_{31}N_5O_2$
Formula Weight = 385.50314
Composition = C(65.43%) H(8.11%) N(18.17%) O(8.30%)
Molar Refractivity = 106.83 ± 0.4 cm^3
Molar Volume = 310.6 ± 5.0 cm^3
Parachor = 873.0 ± 6.0 cm^3
Index of Refraction = 1.603 ± 0.03
Surface Tension = 62.3 ± 5.0 dyne/cm
Density = 1.24 ± 0.1 g/cm^3
Dielectric Constant = Not available
Polarizability = 42.35 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass = 385.247775 Da
Nominal Mass = 385 Da
Average Mass = 385.5031 Da

Fig. 1: Properties of Buspirone.

Fig 5 shows the occupied molecular orbital of molecule calculated with the Zindo method and rendered a mesh the positive and negative phases of the orbital are represented by two colors, the blue regions represent an increase in electron density and the red regions shows a decrease in electron density. This type of surface representations is useful to discuss drug receptor interaction.

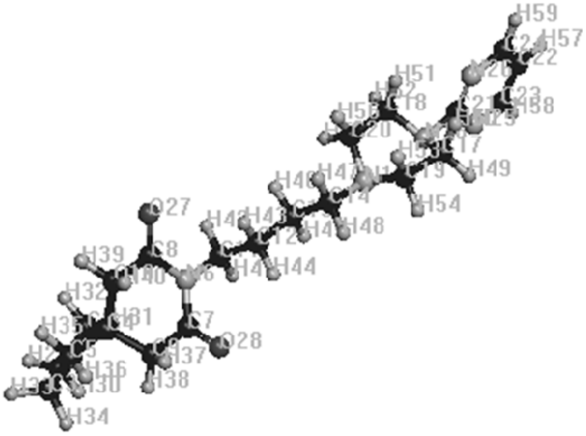


Fig. 2: Prospective view of active conformation of Buspirone

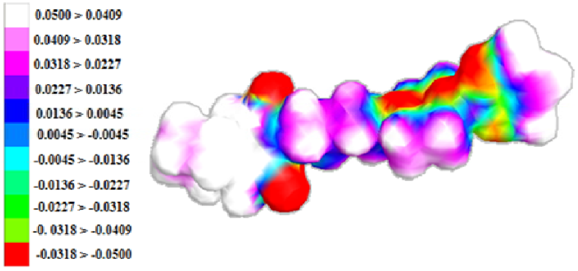


Fig. 3: The complete surface of ESP of Buspirone.

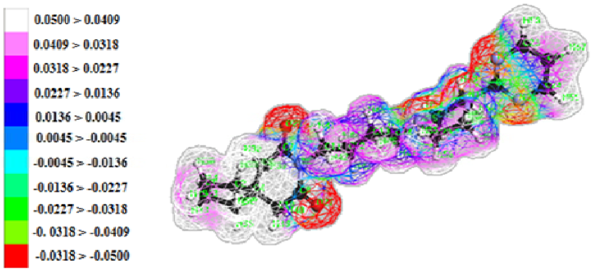


Fig. 4: Electrostatic potential of Buspirone

Fractional coordination of molecule is given in table1 and bond length and bond angles are given in table 2 and 3 respectively, which are calculated after geometry optimization of molecule from ARGUS LAB by using molecular mechanics calculation.

Tables 4 and 5 show the dihedral angles and improper torsion angles of Buspirone respectively. table 5 shows calculated energy of Buspirone molecule. Graph 1 illustrate the potential energy geometry convergence map of Buspirone.

Table 1: Fractional co-ordinates

Atoms	x	y	z
C1	2.81592011	-13.56649299	-0.85470696
C2	3.65099306	-12.28961560	-0.87033651
C3	2.74021286	-14.03109457	0.59789917
C4	4.42075818	-12.26063395	0.46319164
C5	3.47738225	-12.98996204	1.43068859
N1	6.69755243	-10.84883001	-0.64252649
C6	6.76913497	-12.28283328	-0.49490604
C7	5.67549703	-10.11041868	0.05941193
C8	5.76704832	-13.02391356	0.35195576
C9	4.68929952	-10.81799266	0.94850739
C10	7.71668220	-10.13385989	-1.42068465
C11	8.88730067	-9.73721148	-0.51617066
C12	9.93240590	-8.91775441	-1.28334114
C13	11.08328525	-8.49126707	-0.35911528
N2	12.18965518	-7.84220681	-1.13204385
N3	14.14316037	-6.44940544	-2.17349052
C14	14.52002563	-6.97270784	-0.82808049
C15	12.94545683	-5.58855558	-1.96250108
C16	13.33630280	-7.72437933	-0.17959682
C17	11.76576286	-6.43482360	-1.43237483
C18	15.22992808	-5.57705854	-2.60851912
C19	17.33034460	-3.95845178	-3.48649046
C20	16.92667940	-5.14851765	-4.25414994
C21	16.67387266	-3.66550759	-2.36168128
N4	15.93844236	-5.89965623	-3.82946594
N5	15.58865706	-4.51277110	-1.91658541
O1	5.62843677	-8.85032060	-0.02027763
O2	7.70676130	-12.93430572	-1.03586966
H1	1.79626754	-13.37226681	-1.26252854
H2	3.30690902	-14.35001237	-1.47859499
H3	4.32482189	-12.26338906	-1.75826720
H4	2.95960718	-11.41598143	-0.93926017
H5	1.68107261	-14.12714867	0.93338016
H6	3.24134357	-15.02188540	0.70534721
H7	2.72520559	-12.27915132	1.85032989
H8	4.01762588	-13.46246924	2.28454898
H9	6.21253246	-13.15386485	1.36564390
H10	5.60200905	-14.04070145	-0.07605577
H11	3.73804388	-10.23605798	0.98538362
H12	5.10856419	-10.84270151	1.98136526
H13	8.08494161	-10.77157705	-2.25814801
H14	7.27206457	-9.22515756	-1.89015797
H15	8.50116737	-9.13356301	0.33842412
H16	9.36086875	-10.66096797	-0.10851738
H17	10.34117933	-9.52799746	-2.12260997
H18	9.43409667	-8.01682194	-1.70695473
H19	10.69304283	-7.83565724	0.45832938
H20	11.46717209	-9.42144364	0.12710397
H21	15.37748976	-7.67788038	-0.94373063
H22	14.84701826	-6.16024347	-0.13196887
H23	13.14777892	-4.76162154	-1.23613675
H24	12.65036462	-5.11782476	-2.93123847
H25	13.03403589	-7.19403420	0.75891803
H26	13.68849864	-8.74279430	0.11204298
H27	10.98009583	-6.45013257	-2.22162086
H28	11.33356162	-5.92396987	-0.53630142
H29	18.14733403	-3.33190373	-3.83022964
H30	17.44576859	-5.40540737	-5.17128727
H31	16.95145915	-2.79392391	-1.77784861

Table 2: Bond Length

S. No.	Atom	Bond length
1.	(C1)-(C2)	1.514
2.	(C1)-(C3)	1.514
3.	(C1)-(H29)	1.112
4.	(C1)-(H30)	1.112
5.	(C2)-(C4)	1.514
6.	(C2)-(H31)	1.112
7.	(C2)-(H32)	1.112
8.	(C3)-(C5)	1.514
9.	(C3)-(H33)	1.112
10.	(C3)-(H34)	1.112
11.	(C4)-(C5)	1.514
12.	(C4)-(C9)	1.514
13.	(C4)-(C10)	1.514
14.	(C5)-(H35)	1.112
15.	(C5)-(H36)	1.112
16.	(N6)-(C7)	1.422
17.	(N6)-(C8)	1.422
18.	(N6)-(C11)	1.44
19.	(C7)-(C9)	1.489
20.	(C7)-(O28)	1.260
21.	(C8)-(C10)	1.489
22.	(C8)-(O27)	1.260
23.	(C9)-(H37)	1.112
24.	(C9)-(H37)	1.112
25.	(C10)-(H39)	1.112
26.	(C10)-(H40)	1.112
27.	(C11)-(C12)	1.514
28.	(C11)-(H41)	1.112
29.	(C11)-(H42)	1.112
30.	(C12)-(C13)	1.514
31.	(C12)-(H43)	1.112
32.	(C12)-(H44)	1.112
33.	(C13)-(C14)	1.514
34.	(C13)-(H45)	1.112
35.	(C13)-(H46)	1.112
36.	(C14)-(N15)	1.462
37.	(C14)-(H47)	1.112
38.	(C14)-(H48)	1.112
39.	(N15)-(C19)	1.462
40.	(N15)-(C20)	1.462
41.	(N16)-(C17)	1.462
42.	(N16)-(C18)	1.462
43.	(N12)-(C21)	1.434

S. No.	Atom	Bond length
44.	(C17)-(C19)	1.514
45.	(C17)-(H49)	1.112
46.	(C17)-(H50)	1.112
47.	(C18)-(C20)	1.514
48.	(C18)-(H51)	1.112
49.	(C18)-(H52)	1.112
50.	(C19)-(H53)	1.112
51.	(C19)-(H54)	1.112
52.	(C20)-(H55)	1.112
53.	(C20)-(H56)	1.112
54.	(C21)-(N25)	1.433
55.	(C21)-(N26)	1.301
56.	(C22)-(C23)	1.458
57.	(C22)-(C24)	1.323
58.	(C22)-(H57)	1.084
59.	(C23)-(N25)	1.301
60.	(C23)-(H58)	1.084
61.	(C24)-(N26)	1.433
62.	(C24)-(H59)	1.084

Table3: Bond Angles

S. No.	Atoms	Angles
1.	(C2)-(C1)-(C3)	109.47
2.	(C2)-(C1)-(H29)	109.47
3.	(C2)-(C1)-(H30)	109.47
4.	(C1)-(C2)-(C4)	109.47
5.	(C1)-(C2)-(H31)	109.47
6.	(C1)-(C2)-(H32)	109.47
7.	(C3)-(C1)-(H29)	109.47
8.	(C3)-(C1)-(H30)	109.47
9.	(C1)-(C3)-(C5)	109.47
10.	(C1)-(C3)-(H33)	109.47
11.	(C1)-(C3)-(H34)	109.47
12.	(H29)-(C1)-(H30)	109.47
13.	(C4)-(C2)-(H31)	109.47
14.	(C4)-(C2)-(H32)	109.47
15.	(C2)-(C4)-(C5)	109.47
16.	(C2)-(C4)-(C9)	109.47
17.	(C2)-(C4)-(C10)	109.47
18.	(H31)-(C2)-(H32)	109.47
19.	(C5)-(C3)-(H33)	109.47
20.	(C5)-(C3)-(H34)	109.47
21.	(C3-)(C5)-(C4)	109.47
22.	(C3)-(C5)-(H35)	109.47
23.	(C3)-(C5)-(H36)	109.47
24.	(H33)-(C3)-(H34)	109.47
25.	(C5)-(4C)-(C9)	109.47
26.	(C5)-(C4)-(C10)	109.47
27.	(C4)-(C5)-(H35)	109.47
28.	(C4)-(C5)-(H36)	109.47
29.	(C9)-(C4)-(C10)	109.47
30.	(C4)-(C9)-(C7)	109.47
31.	(C4)-(C9)-(H37)	109.47
32.	(C4)-(C9)-(H38)	109.47
33.	(C4)-(C10)-(C8)	109.47
34.	(C4)-(C10)-(H39)	109.47
35.	(C4)-(C10)-(H40)	109.47
36.	(H35)-(C5)-(H36)	109.47
37.	(C7)-(N6)-(C8)	120.00
38.	(C7)-(N6)-(C11)	120.00
39.	(N6)-(C7)-(C9)	120.00
40.	(N6)-(C7)-(O28)	120.00
41.	(C8)-(N6)-(C11)	120.00
42.	(N6)-(C8)-(C10)	120.00
43.	(N6)-(C8)-(O27)	120.00
44.	(N6)-(C11)-(C6)	109.47
45.	(N6)-(C11)-(H41)	109.47
46.	(N6)-(C11)-(H42)	109.47
47.	(C9)-(C7)-(O28)	120.00
48.	(C7)-(C9)-(H37)	109.47
49.	(C7)-(C9)-(H38)	109.47
50.	(C10)-(C8)-(O27)	120.00
51.	(C8)-(C10)-(H39)	109.47
52.	(C8)-(C10)-(H40)	109.47
53.	(H37)-(C9)-(H38)	109.47
54.	(H39)-(C10)-(H40)	109.47
55.	(C12)-(C11)-(H41)	109.47
56.	(C12)-(C11)-(H42)	109.47
57.	(C11)-(C12)-(C13)	109.47
58.	(C11)-(C12)-(H43)	109.47
59.	(C11)-(C12)-(H44)	109.47
60.	(H41)-(C11)-(H42)	109.47
61.	(C13)-(C12)-(H43)	109.47
62.	(C13)-(C12)-(H44)	109.47
63.	(C12)-(C13)-(C14)	109.47
64.	(C12)-(C13)-(H45)	109.47
65.	(C12)-(C13)-(H46)	109.47
66.	(H43)-(C12)-(H44)	109.47
67.	(C14)-(C13)-(H45)	109.47
68.	(C14)-(C13)-(H46)	109.47
69.	(C13)-(C14)-(N15)	109.47
70.	(C13)-(C14)-(H47)	109.47
71.	(C13)-(C14)-(H48)	109.47
72.	(H45)-(C13)-(H46)	109.47
73.	(N15)-(C14)-(H47)	109.47
74.	(N15)-(C14)-(H48)	109.47
75.	(C14)-(N15)-(C19)	106.70
76.	(C14)-(N15)-(C20)	106.70
77.	(H47)-(C14)-(H48)	109.47
78.	(C19)-(N15)-(C20)	106.70
79.	(N15)-(C19)-(C17)	109.47
80.	(N15)-(C19)-(H53)	109.47
81.	(N15)-(C19)-(H54)	109.47
82.	(N15)-(C29)-(C18)	109.47
83.	(N15)-(C20)-(H55)	109.47
84.	(N15)-(C20)-(H56)	109.47
85.	(C17)-(N16)-(C18)	106.70

S. No.	Atoms	Angles
86.	(C17)-(N16)-(C21)	106.70
87.	(N16)-(C17)-(C19)	109.47
88.	(N16)-(C17)-(H49)	109.47
89.	(N16)-(C17)-(H50)	109.47
90.	(C18)-(N16)-(C21)	106.70
91.	(N16)-(C18)-(C20)	109.47
92.	(N16)-(C18)-(H51)	109.47
93.	(N16)-(C18)-(H52)	109.47
94.	(N16)-(C21)-(N25)	120.00
95.	(N16)-(C21)-(N26)	120.00
96.	(C19)-(C17)-(H49)	109.47
97.	(C19)-(C17)-(H50)	109.47
98.	(C17)-(C19)-(H53)	109.47
99.	(C17)-(C19)-(H54)	109.47
100.	(H49)-(C17)-(H50)	109.47
101.	(C20)-(C18)-(H51)	109.47
102.	(C20)-(C18)-(H52)	109.47
103.	(C18)-(C20)-(H55)	109.47
104.	(C18)-(C20)-(H56)	109.47
105.	(H51)-(C18)-(H52)	109.47
106.	(H53)-(C19)-(H54)	109.47
107.	(H55)-(C20)-(H56)	109.47
108.	(N25)-(C21)-(N26)	120.00
109.	(C21)-(N25)-(C23)	120.00
110.	(C21)-(N26)-(C24)	120.00
111.	(C23)-(C22)-(C24)	120.00
112.	(C23)-(C22)-(H57)	120.00
113.	(C22)-(C23)-(N25)	120.00
114.	(C22)-(C23)-(H58)	120.00
115.	(C24)-(C22)-(H57)	120.00
116.	(C22)-(C24)-(N26)	120.00
117.	(C22)-(C24)-(H59)	120.00
118.	(N25)-(C23)-(H58)	120.00
119.	(N26)-(C24)-(H59)	120.00

Table 4: Dihedrals angles

S. No.	Atoms	Dihedrals angles
1.	(C4)-(C2)-(C1)-(C3)	0.23
2.	(H31)-(C2)-(C1)-(C3)	0.23
3.	(H32)-(C2)-(C1)-(C3)	0.23
4.	(C2)-(C1)-(C3)-(C5)	0.23
5.	(C2)-(C1)-(C3)-(H33)	0.23
6.	(C2)-(C1)-(C3)-(H34)	0.23
7.	(C4)-(C2)-(C1)-(H29)	0.23
8.	(H31)-(C2)-(C1)-(H29)	0.23
9.	(H32)-(C2)-(C1)-(H29)	0.23
10.	(C4)-(C2)-(C1)-(H30)	0.23
11.	(H31)-(C2)-(C1)-(H30)	0.23
12.	(H32)-(C2)-(C1)-(H30)	0.23
13.	(C1)-(C2)-(C4)-(C5)	0.23
14.	(C1)-(C2)-(C4)-(C9)	0.23
15.	(C1)-(C2)-(C4)-(C10)	0.23
16.	(C5)-(C3)-(C1)-(H29)	0.23
17.	(H33)-(C3)-(C1)-(H29)	0.23
18.	(H34)-(C3)-(C1)-(H29)	0.23
19.	(C5)-(C3)-(C1)-(H30)	0.23
20.	(H33)-(C3)-(C1)-(H30)	0.23
21.	(H34)-(C3)-(C1)-(H30)	0.23
22.	(C1)-(C3)-(C5)-(C4)	0.23
23.	(C1)-(C3)-(C5)-(H35)	0.23
24.	(C1)-(C3)-(C5)-(H36)	0.23
25.	(C5)-(C4)-(C2)-(H31)	0.23
26.	(C9)-(C4)-(C2)-(H31)	0.23
27.	(C10)-(C4)-(C2)-(H31)	0.23
28.	(C5)-(C4)-(C2)-(H32)	0.23
29.	(C9)-(C4)-(C2)-(H32)	0.23
30.	(C10)-(C4)-(C2)-(H32)	0.23
31.	(C2)-(C4)-(C5)-(C3)	0.23
32.	(C2)-(C4)-(C)5-(H35)	0.23
33.	(C2)-(C4)-(C5)-(H36)	0.23
34.	(C2)-(C4)-(C9)-(C7)	0.23
35.	(C2)-(C4)-(C9)-(H37)	0.23
36.	(C2)-(C4)-(C9)-(H38)	0.23
37.	(C2)-(C4)-(C10)-(C8)	0.23
38.	(C2)-(C4)-(C10)-(H39)	0.23
39.	(C2)-(C4)-(C10)-(H40)	0.23
40.	(C4)-(C5)-(C3)-(H33)	0.23
41.	(H35)-(C5)-(C3)-(H33)	0.23
42.	(H36)-(C5)-(C3)-(H33)	0.23
43.	(C4)-(C5)-(C3)-(H34)	0.23
44.	(H35)-(C5)-(C3)-(H34)	0.23
45.	(H36)-(C5)-(C3)-(H34)	0.23
46.	(C3)-(C5)-(C4)-(C9)	0.23
47.	(C3)-(C5)-(C4)-(C10)	0.23
48.	(H35)-(C5)-(C4)-(C9)	0.23
49.	(H36)-(C5)-(C4)-(C9)	0.23
50.	(C5)-(C4)-(C9)-(C7)	0.23
51.	(C5)-(C4)-(C9)-(H37)	0.23
52.	(C5)-(C4)-(C9)-(H38)	0.23
53.	(H35)-(C5)-(C4)-(C10)	0.23
54.	(H36)-(C5)-(C4)-(C10)	0.23
55.	(C5)-(C4)-(C10)-(C8)	0.23
56.	(C5)-(C4)-(C10)-(H39)	0.23
57.	(C5)-(C4)-(C10)-(H40)	0.23
58.	(C7)-(C9)-(C4)-(C10)	0.23
59.	(H37)-(C9)-(C4)-(C10)	0.23
60.	(H38)-(C9)-(C4)-(C10)	0.23
61.	(C9)-(C4)-(C10)-(C8)	0.23
62.	(C9)-(C4)-(C10)-(H39)	0.23
63.	(C9)-(C4)-(C10)-(H40)	0.23
64.	(C4)-(C9)-(C7)-(N6)	0.33
65.	(C4)-(C9)-(C7)-(O28)	0.33
66.	(C4)-(C10)-(C8)-(N6)	0.33
67.	(C4)-(C10)-(C8)-(O27)	0.33
68.	(C9)-(C7)-(N6)-(C8)	2.50

S. No.	Atoms	Dihedrals angles
69.	(O28)-(C7)-(N6)-(C8)	2.50
70.	(C7)-(N6)-(C8)-(C10)	2.50
71.	(C7)-(N6)-(C8)-(O27)	2.50
72.	(C9)-(C7)-(N6)-(C11)	2.50
73.	(O28)-(C7)-(N6)-(C11)	2.50
74.	(C7)-(N6)-(C11)-(C12)	0.33
75.	(C7)-(N6)-(C11)-(H41)	0.33
76.	(C7)-(N6)-(C11)-(H42)	0.33
77.	(N6)-(C7)-(C9)-(H37)	0.33
78.	(N6)-(C7)-(C9)-(H38)	0.33
79.	(C10)-(C8)-(N6)-(C11)	2.50
80.	(O27)-(C8)-(N6)-(C11)	2.50
81.	(C8)-(N6)-(C11)-(C12)	0.33
82.	(C8)-(N6)-(C11)-(H41)	0.33
83.	(C8)-(N6)-(C11)-(H42)	0.33
84.	(N6)-(C8)-(C10)-(H39)	0.33
85.	(N6)-(C8)-(C10)-(H40)	0.33
86.	(N6)-(C11)-(C12)-(C13)	0.23
87.	(N6)-(C11)-(C12)-(H43)	0.23
88.	(N6)-(C11)-(C12)-(H44)	0.23
89.	(H37)-(C9)-(C7)-(O28)	0.33
90.	(H38)-(C9)-(C7)-(O28)	0.33
91.	(H39)-(C10)-(C8)-(O27)	0.33
92.	(H40)-(C10)-(C8)-(O27)	0.33
93.	(C13)-(C12)-(C11)-(H41)	0.23
94.	(H43)-(C12)-(C11)-(H41)	0.23
95.	(H44)-(C12)-(C11)-(H41)	0.23
96.	(C13)-(C12)-(C11)-(H42)	0.23
97.	(H43)-(C12)-(C11)-(H42)	0.23
98.	(H44)-(C12)-(C11)-(H42)	0.23
99.	(C11)-(C12)-(C13)-(C14)	0.23
100.	(C11)-(C12)-(C13)-(H45)	0.23
101.	(C11)-(C12)-(C13)-(H46)	0.23
102.	(C14)-(C13)-(C12)-(H43)	0.23
103.	(H45)-(C13)-(C12)-(H43)	0.23
104.	(H46)-(C13)-(C12)-(H43)	0.23
105.	(C14)-(C13)-(C12)-(H44)	0.23
106.	(H45)-(C13)-(C12)-(H44)	0.23
107.	(H46)-(C13)-(C12)-(H44)	0.23
108.	(C12)-(C13)-(C14)-(N15)	0.23
109.	(C12)-(C13)-(C14)-(H47)	0.23
110.	(C12)-(C13)-(C14)-(H48)	0.23
111.	(N15)-(C14)-(C13)-(H45)	0.23
112.	(H47)-(C14)-(C13)-(H45)	0.23
113.	(H48)-(C14)-(C13)-(H45)	0.23
114.	(N15)-(C14)-(C13)-(H46)	0.23
115.	(H47)-(C14)-(C13)-(H46)	0.23
116.	(H48)-(C14)-(C13)-(H46)	0.23
117.	(C13)-(C14)-(N15)-(C19)	0.16
118.	(C13)-(C14)-(N15)-(C20)	0.16
119.	(C19)-(N15)-(C14)-(H47)	0.16
120.	(C20)-(N15)-(C14)-(H47)	0.16
121.	(C19)-(N15)-(C14)-(H48)	0.16

S. No.	Atoms	Dihedrals angles
122.	(C20)-(N15)-(C14)-(H48)	0.16
123.	(C14)-(N15)-(C19)-(C17)	0.16
124.	(C14)-(N15)-(C19)-(H53)	0.16
125.	(C14)-(N15)-(C19)-(H54)	0.16
126.	(C14)-(N15)-(C20)-(C18)	0.16
127.	(C14)-(N15)-(C20)-(H55)	0.16
128.	(C14)-(N15)-(C20)-(H56)	0.16
129.	(C17)-(C19)-(N15)-(C20)	0.16
130.	(H53)-(C19)-(N15)-(C20)	0.16
131.	(H54)-(C19)-(N15)-(C20)	0.16
132.	(C19)-(N15)-(C20)-(C18)	0.16
133.	(C19)-(N15)-(C20)-(H55)	0.16
134.	(C19)-(N15)-(C20)-(H56)	0.16
135.	(N15)-(C19)-(C17)-(N16)	0.23
136.	(N15)-(C19)-(C17)-(H49)	0.23
137.	(N15)-(C19)-(C17)-(H50)	0.23
138.	(N15)-(C20)-(C18)-(N16)	0.23
139.	(N15)-(C20)-(C18)-(H51)	0.23
140.	(N15)-(C20)-(C18)-(H52)	0.23
141.	(C19)-(C17)-(N16)-(C18)	0.16
142.	(H49)-(C17)-(N16)-(C18)	0.16
143.	(H50)-(C17)-(N16)-(C18)	0.16
144.	(C17)-(N16)-(C18)-(C20)	0.16
145.	(C17)-(N16)-(C18)-(H51)	0.16
146.	(C17)-(N16)-(C18)-(H52)	0.16
147.	(C19)-(C17)-(N16)-(C21)	0.16
148.	(H49)-(C17)-(N16)-(C21)	0.16
149.	(H50)-(C17)-(N16)-(C21)	0.16
150.	(C17)-(N16)-(C21)-(N25)	0.50
151.	(C17)-(N16)-(C21)-(N26)	0.50
152.	(N16)-(C17)-(C19)-(H53)	0.23
153.	(N16)-(C17)-(C19)-(H54)	0.23
154.	(C20)-(C18)-(N16)-(C21)	0.16
155.	(H51)-(C18)-(N16)-(C21)	0.16
156.	(H52)-(C18)-(N16)-(C21)	0.16
157.	(C18)-(N16)-(C21)-(N25)	0.50
158.	(C18)-(N16)-(C21)-(N26)	0.50
159.	(N16)-(C18)-(C20)-(H55)	0.23
160.	(N16)-(C18)-(C20)-(H56)	0.23
161.	(N16)-(C21)-(N25)-(C23)	5.00
162.	(N16)-(C21)-(N26)-(C24)	19.48
163.	(H53)-(C19)-(C17)-(H49)	0.23
164.	(H54)-(C19)-(C17)-(H49)	0.23
165.	(H53)-(C19)-(C17)-(H50)	0.23
166.	(H54)-(C19)-(C17)-(H50)	0.23
167.	(H55)-(C20)-(C18)-(H51)	0.23
168.	(H56)-(C20)-(C18)-(H51)	0.23
169.	(H55)-(C20)-(C18)-(H52)	0.23
170.	(H56)-(C20)-(C18)-(H52)	0.23
171.	(C23)-(N25)-(C21)-(N26)	5.00
172.	(N25)-(C21)-(N26)-(C24)	19.48
173.	(C21)-(N25)-(C23)-(C22)	19.48
174.	(C21)-(N25)-(C23)-(H58)	19.48

S. No.	Atoms	Dihedrals Angles
175.	(C21)-(N26)-(C24)-(C22)	5.00
176.	(C21)-(N26)-(C24)-(H59)	5.00
177.	(N25)-(C23)-(C22)-(C24)	2.50
178.	(H58)-(C23)-(C22)-(C24)	2.50
179.	(C23)-(C22)-(C24)-(N26)	9.74
180.	(C23)-(C22)-(C24)-(H59)	9.74
181.	(N25)-(C23)-(C22)-(H57)	2.50
182.	(H58)-(C23)-(C22)-(H57)	2.50
183.	(N26)-(C24)-(C22)-(H57)	9.74
184.	(H59)-(C24)-(C22)-(H57)	9.74

Table 5: Improper torsion angles

S. No.	Atoms	Torsion
1.	(C8)-(C11)-(N6)-(C7)	2.00
2.	(C9)-(O28)-(C7)-(N6)	16.66
3.	(C10)-(O27)-(C8)-(N6)	16.66
4.	(C19)-(C20)-(N15)-(C14)	7.33
5.	(C18)-(C21)-(N16)-(C17)	7.33
6.	(N25)-(N26)-(C21)-(N16)	2.00
7.	(C24)-(H57)-(C22)-(C23)	2.00
8.	(N25)-(H58)-(C23)-(C22)	2.00
9.	(N26)-(H59)-(C24)-(C22)	2.00

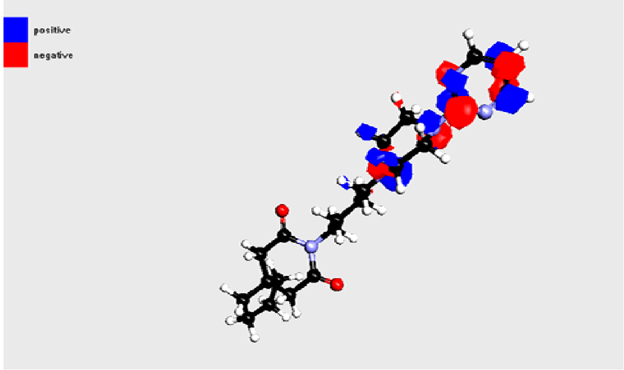
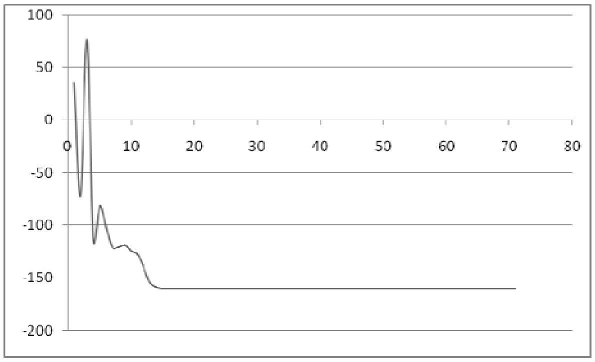


Fig. 5: Visualize the molecular orbital of Buspirone.



Graph 1: Potential energy convergence graph of Buspirone.

DISCUSSION

Buspironeis a drug of choice for the treatment of generalized anxiety disorder (GAD). Side effects of include nausea, vomiting, dizziness, drowsiness and gastric distress. A conformational analysis is global method of software-aided geometry optimization, which yields multiple structurally stable conformational geometries (i.e. equilibrium geometries). The best possible geometry is the one, which is closest to minimum/ equilibrium conformation for a given structure (conformer). Findings are helpful in further studies at molecular level such as molecular docking etc. Computational blind docking approach is usually used for mapping of possible binding sites of the conformer/drug and modification/s in the conformation could be used for the improved drug-receptor interactions. Therefore, conformational analysis can help us in improving the stability of the ligand in the first hand. Processing further, information gathered from conformational analysis can be used to perform docking studies to increase '*functionality*' of the drug by improving receptor-drug interaction.

Although buspirone is used for treating generalized anxiety disorders (Boerner *et al*., 2003), its antioxidant (Ferreira *et al*., 2012) activities are also reported. Previously, NMR studies on buspirone as carried out by (Szelejewska-Woźniakowska *et al*., 1999) have suggested that for free bases the two bands corresponding to piperazine hydrogen atoms in the spectra broaden considerably with an increase in temperature to divide into four separate bands, indicating the presence of a dynamic exchange process. In the present study, the best possible conformation of Buspironeas obtained by Argus Lab software was found to be -100679.5513 kcal/mol. This reflects minimum potential energy needed for stability of the structure of buspirone.

CONCLUSION

The best conformation of Buspirone is found to be -100679.5513 kcal/mol, which is the minimum potential energy by using Argus Lab software. Finally all geometric variables were completely optimized and lowest energy conformations were used in molecular modeling studies.

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