Conformational analysis and geometry optimization of apomorphine as an Anti-parkinsonian agent

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Abstract: Apomorphine, a dopamine D_1/D_2 agonist, is an important drug of choice for the treatment of Parkinson's and related disorders. The present study was designed to perform the conformational analysis and geometry optimization of apomorphine. Resultant optimized structure corresponds to a substance as it is found in nature. This could be used for a variety of experimental and theoretical investigations especially in the field of pharmacokinetics. The results indicate that the best conformation of the molecule is present at minimum potential energy -88702.9595 kcal/mol. At this point molecule will be more active as histamine H_1 receptor agonist.

Keywords: Apomorphine, ArgusLab, conformational analysis.

INTRODUCTION

Apomorphine, a non-selective D_1/D_2 receptor agonist with slightly higher affinity for D_2-like dopamine receptors (Wang *et al.,* 2007) is highly effective in treating off episodes associated with the advanced Parkinson's disease (Pahwa *et al.,* 2007). Clinical data demonstrates that apomorphine rapidly and successfully treats the majority of "off" episodes in Parkinson's disease (Dewey *et al.,* 2001; Hagell and Odin, 2001; Stacy and Silver, 2008). However, the major barrier in the treatment of Parkinson's disease with apomorphine is its high abuse potential (Bloise *et al.,* 2007; Haleem *et al.,* 2005). These rewarding effects of apomorphine could be monitored in terms of increased behavioral sensitization (Ikram and Haleem, 2011) and are mediated possibly due to decreased activity of dopaminergic neurons following withdrawal (Ikram *et al.,* 2011; Ikram *et al.,* 2012) and could be attenuated by serotonergic ligands as serotonin negatively regulated dopaminergic release (Ikram *et al.,* 2007; Ikram and Haleem, 2010). Most recently it has also been suggested to act as an antidepressant (Haleem *et al.,* 2013; Haleem and Ikram, 2013).

The present work describes the computer aided conformational analysis that is base on geometry optimization (active conformation) of drug by Argus lab software. Argus is the electronic structure program that is based on the quantum mechanics; it predicts the potential energies, molecular structure, geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angles and reaction pathway (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:
E = E stretching + E bending + E torsion + E Vander Waals + E electrostatic + E hydrogen bond + cross term (Khalida *et al.,* 2010).

These terms are importance for the accurate calculation of geometry properties of molecules. The set of energy functions and the corresponding parameters are called a force field (Fakir *et al.,* 2011). The molecular mechanics method calculates the energy as function of coordinates and energy minimization is an integral part of method. A molecular geometry is constructed by using computer graphics techniques and the atom moved are iteratively moved (without breaking bonds) using an energy minimization technique until the net force on all atoms vanish and the total energy of the molecule reaches a minimum (Merz and Kollaman, 1989). The 3D (3 rotatable bonds) structure of molecule corresponding to this energy is minimum is one of the stable conformations of molecule but not necessarily the most stable one (Still *et al.,* 1990).

MATERIALS AND METHODS

Quantitative structure-activity relationships (QSAR) is used for the development of relationships between physicochemical properties of chemical substances and their biological activities to get the statistical results of the activities of new chemical entities. The fundamental

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principle is that the difference in structural properties are responsible for the variations in biological activities of the compounds (Martin, 1998; Bell and Crighton, 1984). Visualize chemical structures in 2D or 3D to gain more insight into spatial configurations, and relationships to molecular properties Advacement in computational tools generate many softwares which are very usefull to construct models, minimization and representations of molecular structure (Cruciani *et al.*, 1998; Simons *et al.*, 1983).

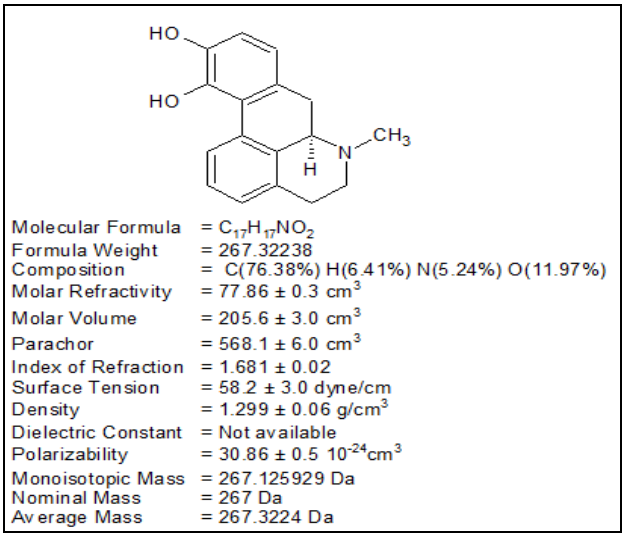


Fig. 1: Prospective view of active conformation of Apomorphine

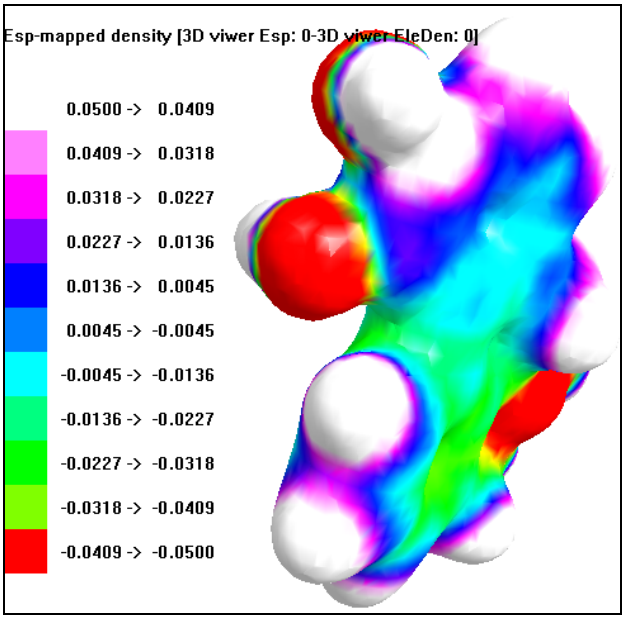


Fig. 2: The complete surface with the map of ESP of Apomorphine

All the conformational analysis and geometry optimization wasperformed by using softwares ACD Chemsketch and Arguslab. The chemical structure (6a*R*)-6-methyl-5,6,6a, 7-tetrahydro-4*H*-dibenzo[de,g]quinoline-10,11-diol was 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 (Khalida *et al.*, 2010; Merz and Kollaman, 1989; Soumendranath, 2011).

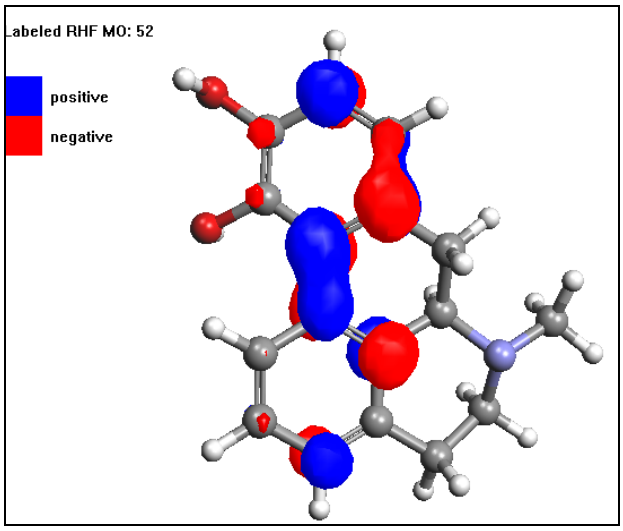
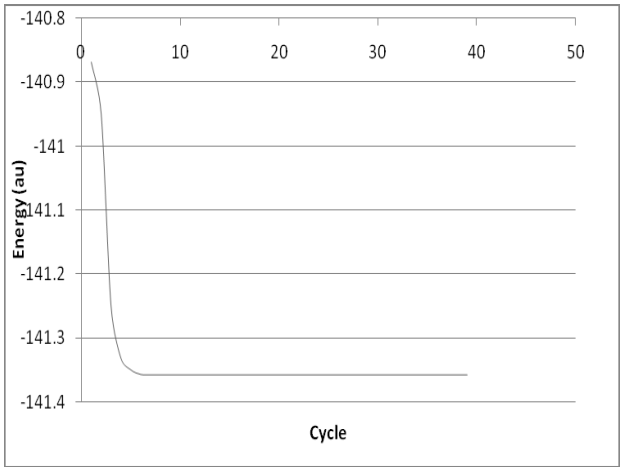


Fig. 3: Visualize the molecular orbital of Apomorphine



Graph1: Potential energy convergence graph of Apomorphine

Surface is 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 (Cruciani *et al.*, 1998; Simons *et al.*, 1983).

RESULTS

Prospective view and calculated properties of Apmorphine molecule are shown in fig. 1. The electron density mapped of Apmorphine by ACDLABS-3D viewer software are shown in fig. 2. Fig. 3 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 black regions represent an increase in electron density and the grey regions show a decrease in electron density. This type of surface representations is useful to discuss drug receptor interaction.

Table 1: Fractional co-ordinates

Atoms	X	Y	Z
C1	-0.15087020	2.87494857	0.40691467
C2	-0.15463094	1.39366063	0.37485424
C3	-1.26195346	3.55814322	0.12290195
C4	-1.30273047	0.72220412	0.12271501
C5	-2.49389161	2.84288803	-0.25760195
C6	-2.51701276	1.49970081	-0.28065945
C7	1.11935134	0.64437357	0.67786027
C8	1.18379712	-0.68022545	-0.12273282
C9	-0.11900186	-1.43910990	0.10701666
C10	-1.29587342	-0.76992342	0.19981755
N1	2.37353539	-1.50704907	0.29544879
C11	2.30107979	-2.77875115	-0.48768233
C12	1.19271449	-3.67083539	0.06469541
C13	-0.10680697	-2.92694164	0.15291557
C14	-1.24834441	-3.59925589	0.36373806
C15	-2.53841361	-1.53685801	0.48762994
C16	-2.51385528	-2.87120724	0.55034775
O1	-3.63052488	3.58172157	-0.65048263
O1	-3.66970275	0.84551431	-0.76737381
C17	3.59873038	-0.82011756	-0.21264920
H1	1.22972764	-0.42885526	-1.21263749
H2	0.75638625	3.41232164	0.66712094
H3	-1.25290362	4.64348264	0.14699027
H4	1.97811446	1.29722018	0.40778883
H5	1.16564782	0.43174194	1.77133820
H6	2.13020641	-2.59266671	-1.57819740
H7	3.25303371	-3.35501721	-0.39088331
H8	1.08127044	-4.56257793	-0.59597827
H9	1.47653204	-4.01940891	1.08492072
H10	-1.24881789	-4.68368437	0.43144265
H11	-3.47056386	-1.03031824	0.70591063
H12	-3.42214360	-3.42204778	0.77429662
H13	-4.16357634	3.73854665	0.22253850
H14	-3.50954449	0.73883432	-1.78428548
H15	3.52149030	-0.54164796	-1.29176741
H16	3.81571769	0.08593087	0.39335294
H17	4.49572716	-1.46943400	-0.07922460

Fractional coordination of molecule is given in table 1 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 apomorphine respectively. Table 5 shows calculated energy of buspirone molecule. Graph 1 illustrates the potential energy geometry convergence map of apomorphine.

Table 2: Bond Length

S.No	Atoms	Bond length
1.	(C1)-(C2)	1.458000
2.	(C1)-(C3)	1.323387
3.	(C1)-(H22)	1.084582
4.	(C2)-(C4)	1.323387
5.	(C2)-(C7)	1.486000
6.	(C3)-(C5)	1.458000
7.	(C3)-(H23)	1.084582
8.	(C4)-(C6)	1.458000
9.	(C4)-(C10)	1.458000
10.	(C5)-(C6)	1.323387
11.	(C5)-(O18)	1.407689
12.	(C6)-(O19)	1.407689
13.	(C7)-(C8)	1.514000
14.	(C7)-(H24)	1.112599
15.	(C7)-(H25)	1.112599
16.	(C8)-(N11)	1.462929
17.	(C8)-(C9)	1.486000
18.	(C8)-(H21)	1.112599
19.	(C9)-(C14)	1.458000
20.	(C9)-(C10)	1.323387
21.	(C10)-(C16)	1.458000
22.	(N11)-(C12)	1.462929
23.	(N11)-(C20)	1.462929
24.	(C12)-(C3)	1.514000
25.	(C12)-(H26)	1.112599
26.	(C12)-(H27)	1.112599
27.	(C13)-(C14)	1.486000
28.	(C13)-(H28)	1.112599
29.	(C13)-(H29)	1.112599
30.	(C14)-(C15)	1.323387
31.	(C15)-(C17)	1.458000
32.	(C15)-(H30)	1.084582
33.	(C16)-(C17)	1.323387
34.	(C16)-(H31)	1.084582
35.	(C17)-(H32)	1.084582
36.	(O18)-(H33)	1.033746
37.	(O19)-(H34)	1.033746
38.	(C20)-(H35)	1.112599
39.	(C20)-(H36)	1.112599
40.	(C20)-(H37)	1.112599

CONCLUSION

The current work resulted that the best conformation of Apomorphine is found to be -88702.9595 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.

Table 3: Bond Angles

S. No.	ATOMS	Angles
1.	(C2)-(C1)-(C3)	120.00
2.	(C2)-(C1)-(H22)	120. 00
3.	(C1)-(C2)-(C4)	120.00
4.	(C1)-(C2)-(C7)	120.00
5.	(C3)-(C1)-(H22)	120.00
6.	(C1)-(C3)-(C5)	120.00
7.	(C1)-(C3)-(H23)	120.00
8.	(C4)-(C2)-(C7)	120.00
9.	(C2)-(C4)-(C6)	120.00
10.	(C2)-(C4)-(C10)	120.00
11.	(C2)-(C7)-(C8)	109.47
12.	(C2)-(C7)-(H24)	109.47
13.	(C2)-(C7)-(H25)	109.47
14.	(C5)-(C3)-(H23)	120.00
15.	(C3)-(C5)-(C6)	120.00
16.	(C3)-(C5)-(O18)	120.00
17.	(C6)-(C4)-(C10)	120.00
18.	(C4)-(C6)-(C5)	120.00
19.	(C4)-(C6)-(O19)	120.00
20.	(C4)-(C10)-(C9)	120.00
21.	(C4)-(C10)-(C16)	120.00
22.	(C6)-(C5)-(O18)	120.00
23.	(C5)-(C6)-(O19)	120.00
24.	(C5)-(O18)-(H33)	104.51
25.	(C6)-(O19)-(H34)	104.51
26.	(C8)-(C7)-(H24)	109.47
27.	(C8)-(C7)-(H25)	109.47
28.	(C7)-(C8)-(N11)	109.47
29.	(C7)-(C8)-(C9)	109.47
30.	(C7)-(C8)-(H21)	109.47
31.	(H24)-(C7)-(H25)	109.47
32.	(N11)-(C8)-(C9)	109.47
33.	(N11)-(C8)-(H21)	109.47
34.	(C8)-(N11)-(C12)	106.70
35.	(C8)-(N11)-(C20)	106.70
36.	(C9)-(C8)-(H21)	109.47
37.	(C8)-(C9)-(C14)	120.00
38.	(C8)-(C9)-(C10)	120.00
39.	(C14)-(C9)-(C10)	120.00
40.	(C9)-(C14)-(C13)	120.00
41.	(C9)-(C14)-(C15)	120.00
42.	(C9)-(C10)-(C16)	120.00
43.	(C10)-(C16)-(C17)	120.00
44.	(C10)-(C16)-(H31)	120.00
45.	(C12)-(N11)-(C20)	106.70
46.	(N11)-(C12)-(C13)	109.47
47.	(N11)-(C12)-(H26)	109.47
48.	(N11)-(C12)-(H27)	109.47
49.	(N11)-(C20)-(H35)	109.47
50.	(N11)-(C20)-(H36)	109.47
51.	(N11)-(C20)-(H37)	109.47
52.	(C13)-(C12)-(H26)	109.47
53.	(C13)-(C12)-(H27)	109.47
54.	(C12)-(C13)-(C14)	109.47
55.	(C12)-(C13)-(H28)	109.47
56.	(C12)-(C13)-(H29)	109.47
57.	(H26)-(C12)-(H27)	109.47
58.	(C14)-(C13)-(H28)	109.47
59.	(C14)-(C13)-(H29)	109.47
60.	(C13)-(C14)-(C15)	120.00
61.	(H28)-(C13)-(H29)	109.47
62.	(C14)-(C15)-(C17)	120.00
63.	(C14)-(C15)-(H30)	120.00
64.	(C17)-(C15)-(H30)	120.00
65.	(C15)-(C17)-(C16)	120.00
66.	(C15)-(C17)-(H32)	120.00
67.	(C17)-(C16)-(H31)	120.00
68.	(C16)-(C17)-(H32)	120.00
69.	(H35)-(C20)-(H36)	109.47
70.	(H35)-(C20)-(H37)	109.47
71.	(H36)-(C20)-(H37)	109.47

Table 4: Dihedrals angles

S. No.	ATOMS	Dihedral Angles
1.	(C4)-(C2)-(C1)-(C3)	2.5
2.	(C7)-(C2)-(C1)-(C3)	2.5
3.	(C2)-(C1)-(C3)-(C5)	9.74
4.	(C2)-(C1)-(C3)-(H23)	9.7
5.	(C4)-(C2)-(C1)-(H22)	2.5
6.	(C7)-(C2)-(C1)-(H22)	2.5
7.	(C1)-(C2)-(C4)-(C6)	9.7
8.	(C1)-(C2)-(C4)-(C10)	9.7
9.	(C1)-(C2)-(C7)-(C8)	0.3
10.	(C1)-(C2)-(C7)-(H24)	0.3
11.	(C1)-(C2)-(C7)-(H25)	0.3
12.	(C5)-(C3)-(C1)-(H22)	9.7
13.	(H23)-(C3)-(C1)-(H22)	9.7
14.	(C1)-(C3)-(C5)-(C6)	2.5
15.	(C1)-(C3)-(C5)-(O18)	2.5
16.	(C6)-(C4)-(C2)-(C7)	9.7
17.	(C10)-(C4)-(C2)-(C7)	9.7
18.	(C4)-(C2)-(C7)-(C8)	0.3
19.	(C4)-(C2)-(C7)-(H24)	0.3
20.	(C4)-(C2)-(C7)-(H25)	0.3
21.	(C2)-(C4)-(C6)-(C5)	2.5
22.	(C2)-(C4)-(C6)-(O19)	2.5
23.	(C2)-(C4)-(C10)-(C9)	2.5
24.	(C2)-(C4)-(C10)-(C16)	2.5
25.	(C2)-(C7)-(C8)-(N11)	0.2
26.	(C2)-(C7)-(C8)-(C9)	0.2
27.	(C2)-(C7)-(C8)-(H21)	0.2

S. No.	ATOMS	Dihedral Angles
28.	(C6)-(C5)-(C3)-(H23)	2.5
29.	(O18)-(C5)-(C3)-(H23)	2.5
30.	(C3)-(C5)-(C6)-(C4)	9.7
31.	(C3)-(C5)-(C6)-(O19)	9.7
32.	(C3)-(C5)-(O18)-(H33)	5.0
33.	(C5)-(C6)-(C4)-(C10)	2.5
34.	(O19)-(C6)-(C4)-(C10)	2.5
35.	(C6)-(C4)-(C10)-(C9)	2.5
36.	(C6)-(C4)-(C10)-(C16)	2.5
37.	(C4)-(C6)-(C5)-(O18)	9.7
38.	(C4)-(C6)-(O19)-(H34)	5.0
39.	(C4)-(C10)-(C9)-(C8)	9.7
40.	(C4)-(C10)-(C9)-(C14)	9.7
41.	(C4)-(C10)-(C16)-(C17)	2.5
42.	(C4)-(C10)-(C16)-(H31)	2.5
43.	(O19)-(C6)-(C5)-(O18)	9.7
44.	(C6)-(C5)-(O18)-(H33)	5.0
45.	(C5)-(C6)-(O19)-(H34)	5.0
46.	(N11)-(C8)-(C7)-(H24)	0.2
47.	(C9)-(C8)-(C7)-(H24)	0.2
48.	(H21)-(C8)-(C7)-(H24)	0.2
49.	(N11)-(C8)-(C7)-(H25)	0.2
50.	(C9)-(C8)-(C7)-(H25)	0.2
51.	(H21)-(C8)-(C7)-(H25)	0.23
52.	(C7)-(C8)-(N11)-(C12)	0.16
53.	(C7)-(C8)-(N11)-(C20)	0.16
54.	(C7)-(C8)-(C9)-(C14)	0.33
55.	(C7)-(C8)-(C9)-(C10)	0.33
56.	(C12)-(N11)-(C8)-(C9)	0.16
57.	(C20)-(N11)-(C8)-(C9)	0.16
58.	(N11)-(C8)-(C9)-(C14)	0.33
59.	(N11)-(C8)-(C9)-(C10)	0.33
60.	(C12)-(N11)-(C8)-(H21)	0.16
61.	(C20)-(N11)-(C8)-(H21)	0.16
62.	(C8)-(N11)-(C12)-(C13)	0.16
63.	(C8)-(N11)-(C12)-(H26)	0.16
64.	(C8)-(N11)-(C12)-(H27)	0.16
65.	(C8)-(N11)-(C20)-(H35)	0.16
66.	(C8)-(N11)-(C20)-(H36)	0.16
67.	(C8)-(N11)-(C20)-(H37)	0.16
68.	(C14)-(C9)-(C8)-(H21)	0.33
69.	(C10)-(C9)-(C8)-(H21)	0.33
70.	(C8)-(C9)-(C14)-(C13)	2.5
71.	(C8)-(C9)-(C14)-(C15)	2.5
72.	(C8)-(C9)-(C10)-(C16)	9.7
73.	(C13)-(C14)-(9)-(C10)	2.5
74.	(C15)-(C14)-(C9)-(C10)	2.5
75.	(C14)-(C9)-(C10)-(C16)	9.7
76.	(C9)-(C14)-(C13)-(C12)	0.33
77.	(C9)-(C14)-(C13)-(H28)	0.33
78.	(C9)-(C14)-(C13)-(H29)	0.33
79.	(C9)-(C14)-(C15)-(C17)	9.7
80.	(C9)-(C14)-(C15)-(H30)	9.7
81.	(C9)-(C10)-(C16)-(C17)	2 .5
82.	(C9)-(C10)-(C16)-(H31)	2.5
83.	(C10)-(C16)-(C17)-(C15)	9.7
84.	(C10)-(C16)-(C17)-(H32)	9.7
85.	(C13)-(C12)-(N11)-(C20)	0.16
86.	(H26)-(C12)-(N11)-(C20)	0.16
87.	(H27)-(C12)-(N11)-(C20)	0.16
88.	(C12)-(N11)-(C20)-(H35)	0.16
89.	(C12)-(N11)-(C20)-(H36)	0.16
90.	(C12)-(N11)-(C20)-(H37)	0.16
91.	(N11)-(C12)-(C13)-(C14)	0.23
92.	(N11)-(C12)-(C13)-(H28)	0.23
93.	(N11)-(C12)-(C13)-(H29)	0.23
94.	(C14)-(C13)-(C12)-(H26)	0.23
95.	(H28)-(C13)-(C12)-(H26)	0.23
96.	(H29)-(C13)-(C12)-(H26)	0.23
97.	(C14)-(C13)-(C12)-(H27)	0.23
98.	(H28)-(C13)-(C12)-(H27)	0.23
99.	(H29)-(C13)-(C12)-(H27)	0.23
100.	(C12)-(C13)-(C14)-(C15)	0.33
101.	(C15)-(C14)-(C13)-(H28)	0.33
102.	(C15)-(C14)-(C13)-(H29)	0.33
103.	(C13)-(C14)-(C15)-(C17)	9.7
104.	(C13)-(C14)-(C15)-(H30)	9.7
105.	(C14)-(C15)-(C17)-(C16)	2.5
106.	(C14)-(C15)-(C17)-(H32)	2.5
107.	(C16)-(C17)-(C15)-(H30)	2.5
108.	(H32)-(C17)-(C15)-(H30)	2.5
109.	(C15)-(C17)-(C16)-(H31)	9.7
110.	(H32)-(C17)-(C16)-(H31)	9.7

Table 5: Improper Torsion Angles

S. No.	Atoms	Torsion
1.	(C3)-(H22)-(C1)-(C2)	2.00
2.	(C4)-(C7)-(C2)-(C1)	2.00
3.	(C5)-(H23)-(C3)-(C1)	2.00
4.	(C6)-(C10)-(C4)-(C2)	2.00
5.	(C6)-(O18)-(C5)-(C3)	2.00
6.	(C5)-(O19)-(C6)-(C4)	2.00
7.	(C9)-(C16)-(C10)-(C4)	2.00
8.	(C12)-(C20)-(N11)-(C18)	7.33
9.	(C14)-(C10)-(C9)-(C8)	2.00
10.	(C13)-(C15)-(C14)-(C9)	2.00
11.	(C17)-(H31)-(C16)-(C10)	2.00
12.	(C17)-(H30)-(C15)-(C14)	2.00
13.	(C16)-(H32)-(C17)-(C15)	2.00

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