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Conformational analysis of Ciproxifan as a histamine H_3 receptor antagonist

Khalida Bano, Amber Yaseen, Syed Shah Wali and Naheed Akhter*
Biophysics Research Unit, Department of Biochemistry, University of Karachi, Karachi, Pakistan

Abstract: Conformational analysis, geometry optimization and energy minimization of cyclopropyl-(4-(3-1H-imidazol-4-yl) propyloxy) phenyl) ketone, Ciproxifan was preformed according to the Hartree-Fock (HF) calculation method by ArgusLab software. The minimum potential energy is calculated by geometry convergence function by ArgusLab software and energy minimization programs. The most feasible position and energy for the drug to interact with the receptor were found to be -71096.6641 k.cal/mol at this point molecule will be more active as HISTAMINE H_3 antagonist.

Keywords: ArgusLab 4.0.1, H_3 receptor antagonist, Ciproxifan.
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***Author for Correspondence**: khalidabano@hotmail.com

INTRODUCTION

An H_3-receptor antagonist is a classification of drugs used to block the action of histamine at the H_3 receptor [1]. Unlike the H_1 and H_2 receptors which have primarily peripheral actions, but cause sedation if they are blocked in the brain, H_3 receptors are primarily found in the brain and are inhibitory autoreceptors located on histaminergic nerve terminals, which modulate the release of histamine[2]. Histamine release in the brain triggers secondary release of excitatory neurotransmitters such as glutamate and acetylcholine via stimulation of H_1 receptors in the cerebral cortex [3]. Consequently unlike the H_1 antagonist antihistamines which are sedating, H_3 antagonists have stimulant and nootropic effects, and are being researched as potential drugs for the treatment of neurodegenerative conditions such as Alzheimer's disease e.g., A - 349, 821, ABT - 239,Ciproxifan , Clobenpropit, Thioperamide[4].

Ciproxifan, i.e., cyclopropyl-(4-(3-1H-imidazol-4-yl)propyloxy) phenyl) ketone, belongs to a novel chemical series of histamine H3-receptor antagonists[5]. In vitro, it behaved as a competitive antagonist at the H3 autoreceptor controlling H3 histamine release from synaptosomes[3,6] . Histamine has an excitatory effect in the brain via H_1 receptors in the cerebral cortex, and so drugs such as ciproxifan which block the H_3 receptor and consequently allow more histamine to be released have an alertness-promoting effect[7].

Ciproxifan produces wakefulness and attentiveness in animal studies, and produced cognitive enhancing effects without prominent stimulant effects at relatively low levels of receptor occupancy, and pronounced wakefulness at higher doses[8]. It has therefore been proposed as a potential treatment for sleep disorders such as narcolepsy and to improve vigilance in old age, particularly in the treatment of conditions such as Alzheimer's disease[9]. It also potentiated the effects of antipsychotic drugs, and has been suggested as an adjuvant treatment for schizophrenia[10].

Methods of geometry optimization and potential energy calculation

The three dimensional quantitative structure activity relationship (3D-QSAR) describe the biological activity of molecule with pharmacological potential as a function of their structural properties[11,12].

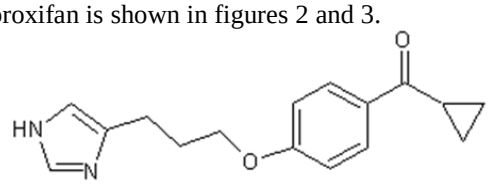
Computational advances have generated many tools which are widely used to construct models, minimization and representation of molecular structure[13- 15].

All conformational analysis (geometry optimization) study was performed on window based computer using Argus and ACD Lab chem. Sketch softwares. ACDS/CHEMSKETCH is an integrated software package from advanced chemistry development for drawing chemical structures, reactions and to plot best projection with minimum energy. The chemical structure of Ciproxifan was refined by X-ray crystallography technique[16]. The Ciproxifan molecule is utilized to determine the 3D structure of molecule. Several computer programs are used infer the shape of molecule from geometry optimization calculations. The Ciproxifan structure[17] is generated by argues Lab, and minimization was performed with the semi-empirical Austin model 1(AMI) parameter[18]. Argus is an 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 angle , bond length , and reaction pathways . The set of energy function and the corresponding parameters are called as force field. The molecular mechanics method calculates the energy as the function of the coordinates and energy minimization is an integral part of the method.

Conformation search method random no are used to determine, how many and which torsion angle to be incremented and how much (torsion space) and in which direction x, y, z, coordinates of each atom are to be translated. The minimum potential energy is calculated by using geometry convergence function in Argus Lab software .In order to determine the allowed conformation the contact distance between the atoms in adjacent residues is examined using criteria for minimum Vander wall contact distance [19].Surfaces created to visualize ground state properties such as orbital , electron densities , electrostatic potentials (ESP)spin densities and generated grid data used to make molecular orbital surfaces and visualized the molecular orbital and making an electrostatic potential mapped electron density surface[20] .Electron density shows the location of electrons . Large values will reveal the atomic positions and the smaller values will indicate over all molecule size .An ESP map gives information about the distribution and delocalization of charge in a molecule. ESP mapped density surface, the electron density surface gives the shape of surface while the values of the ESP on that surface gives the colors[21]. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map.

RESULTS AND DISCUSSION

Properties calculated by ACD chemsketch of Ciproxifan is shown in figure 1. Prospective view of Ciproxifan is shown in figures 2 and 3.



cyclopropyl{4-[3-(1*H*-imidazol-4-yl)propoxy]phenyl}methanone

Molecular Formula	= $C_{16}H_{18}N_2O_2$
Formula Weight	= 270.32632
Composition	= C(71.09%) H(6.71%) N(10.36%) O(11.84%)
Molar Refractivity	= 76.43 ± 0.3 cm^3
Molar Volume	= 219.5 ± 3.0 cm^3
Parachor	= 601.9 ± 4.0 cm^3
Index of Refraction	= 1.613 ± 0.02
Surface Tension	= 56.5 ± 3.0 dyne/cm
Density	= 1.231 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 30.30 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 270.136828 Da
Nominal Mass	= 270 Da
Average Mass	= 270.3263 Da
M+	= 270.136279 Da
M-	= 270.137376 Da
[M+H]+	= 271.144104 Da
[M+H]-	= 271.145201 Da
[M-H]+	= 269.128454 Da
[M-H]-	= 269.129551 Da

Figure 1: Properties calculated by ACD chemsketch of Ciproxifan.

The electron density mapped of atoms by ACD LABS 3D Viewer software in figure 4. Figures 5 and 6 shows Electrostatic potential of molecule ground state mapped on to the electron density surface for the ground state and with the color map.

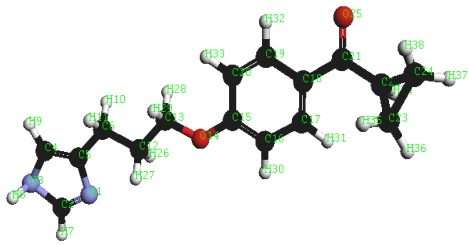


Figure 2: Prospective view of Ciproxifan after geometry optimization.

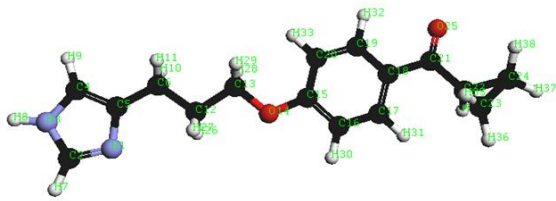


Figure 3: Prospective and label view of Ciproxifan.

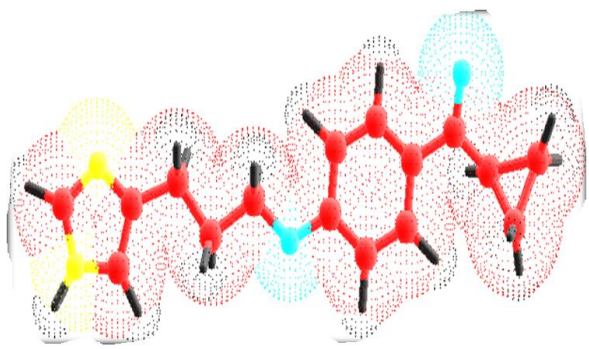


Figure 4: Electron density map of Ciproxifan.

Figures 5 and 6 used a clipping plane showing a cutaway of the same surface revealing the underlying molecular structure. The color map shows Esp. energy (in hartess) for the various colors. The red end of the spectrum show regions of highest stability for a positive test charge, magenta / blue show the regions of least stability for a positive test charges.

Figure 7 show 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 the two colors. The blue region represents an increase in a density the red region a represent a decrease in electron density.

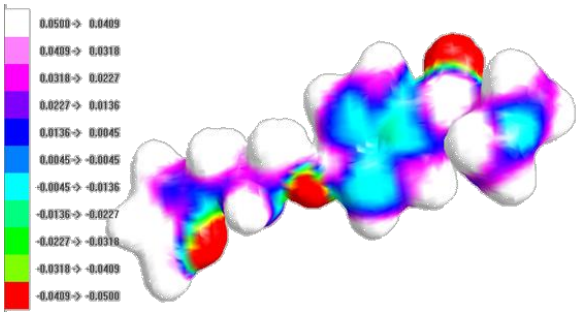


Figure 5: The electrostatic potential of Ciproxifan.

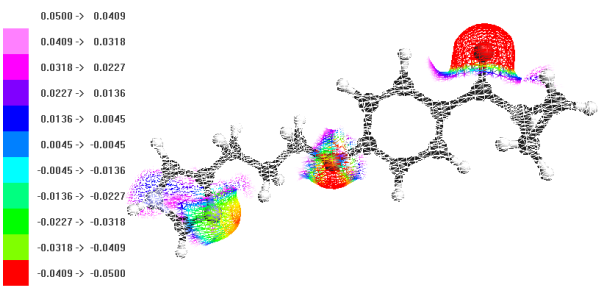


Figure 6: The electrostatic potential of Ciproxifan (mesh).

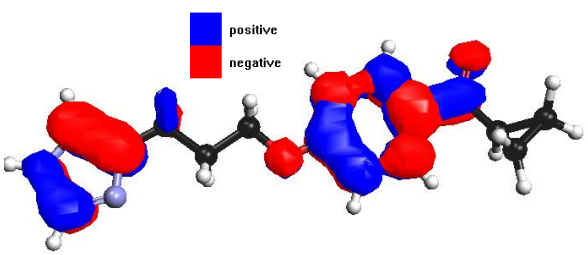


Figure 7: The occupied molecular orbital of Ciproxifan.

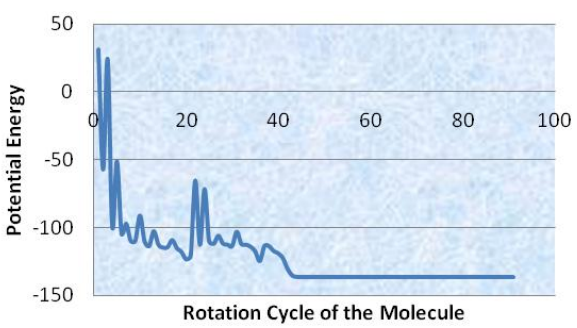


Figure 8: Potential energy geometry convergence map of Ciproxifan.

The minimum potential energy shows for drug receptor interactive via the geometry convergence map in figure 8. Fractional coordinates of molecule are given in table 1 and bond length and bond angles are given in table 2 which are taken after geometry optimization of molecular from Argus lab by using molecular mechanics calculation.

Table 1: Coordinate of Ciproxifan as a histamine H_3 receptor antagonist.

Atom No.	X	Y	Z
N1	-4.819	1.095	-1.549
C2	-6.077	0.882	-1.821
N3	-7.030	1.437	-0.877
C4	6.092	2.037	0.038
C5	-4.847	1.844	-0.343
C6	-3.631	2.330	0.367
H7	-6.387	0.315	-2.693
H8	-7.330	0.567	-0.340
H9	-6.385	2.570	0.937
H10	-3.623	3.443	0.382
H11	-3.626	1.945	1.412
C12	-2.396	1.831	-0.351
C13	-1.159	2.301	0.394
O14	0.006	1.837	-0.271
C 15	1.313	2.084	0.153
C16	2.32	1.592	-0.567
C17	3.728	1.827	-0.154
C18	4.005	2.533	0.957
C19	2.876	3.086	1.752
C20	1.609	2.873	1.376
C21	5.405	2.789	1.396
C22	6.584	2.137	0.719
C23	6.695	0.636	0.946
C24	7.642	1.581	1.662
O25	5.623	3.605	2.336
H26	-2.390	2.232	-1.390
H27	-2.417	0.718	-0.387
H28	-1.159	3.415	0.427
H29	-1.189	1.898	1.432
H30	2.130	1.014	-1.465
H31	4.518	1.418	-0.775
H32	3.069	3.663	2.652
H33	0.805	3.286	1.977
H34	6.952	2.514	-0.261
H35	5.921	0.183	1.608
H36	7.162	0.077	0.103
H37	8.676	1.577	1.248
H38	7.437	1.672	2.754

CONCLUSION

In the present potential energy of non-bonded interactive for Ciproxifan is calculated. Total potential energies were calculated by Arguslab software at PM3. Contours are plotted for visual understanding. The result indicates that the best conformation of Ciproxifan is found to be 71096.66kcal/mol, which is minimum potential energy. At this point molecule will be more active as Histamine H_3 antagonist.

Table 2: Bond length of Ciproxifan as a histamine H_3 receptor antagonist.

S. No.	Atoms	Bond Length (A^o)
1	(N1)-(C2)	1.301
2	(C2)-(N3)	1.434
3	(N3)-(C4)	1.434
4	(C4)-(C5)	1.323
5	(N1)-(C5)	1.433
6	(C5)-(C6)	1.486
7	(C12)-(C13)	1.514
8	(C6)-(C12)	1.514
9	(C13)-(O14)	1.411
10	(O14)-(C15)	1.383
11	(C15)-(C16)	1.323
12	(C16)-(C17)	1.458
13	(C17)-(C18)	1.323
14	(C18)-(C19)	1.458
15	(C19)-(C20)	1.323
16	(C15)-(C20)	1.458
17	(C18)-(C21)	1.461
18	(C21)-(C22)	1.489
19	(C22)-(C23)	1.514
20	(C23)-(C24)	1.514
21	(C22)-(C24)	1.514
22	(C21)-(O25)	1.260
23	(C2)-(H7)	1.084
24	(N3)-(H8)	1.063
25	(C4)-(H9)	1.084
26	(C6)-(H10)	1.112
27	(C6)-(H11)	1.112
28	(C12)-(H26)	1.112
29	(C12)-(H27)	1.112
30	(C13)-(H28)	1.112
31	(C13)-(H29)	1.112
32	(C16)-(H30)	1.084
33	(C7)-(H31)	1.084
34	(C19)-(H32)	1.084
35	(C20)-(H33)	1.084
36	(C22)-(H34)	1.112
37	(C23)-(H35)	1.112
38	(C23)-(H35)	1.112
39	(C24)-(H37)	1.112
40	(C24)-(H38)	1.112

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