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Conformational analysis (geometry optimization) of 2-[4-(3-Ethoxy-2-pyridyl) butylamino]-5-(3-pyridylmethyl)-4-pyrimidone as a cimetidine derivative histamine H_2 receptor antagonist

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Abstract: This study was designed to optimize and calculate the structure of Histamine H2 receptor antagonist drug, Cimetidine derivative. The non-bonded potential energies were computed for 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone, which is the H_2 receptor antagonist and sedative psychoactive in nature. In the present calculation all the possible pairs of non –bonded interaction have been included for the energy calculation. The present work describes the conformational analysis of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone, by using Kitaigorodskii function and Arguslab 4.0.1 software. The maximum and minimum potential energy by taking upper limit K_1 found to be 121.824 kcal/mole at ω_1=20 and ω_2=160 and -.0065 kcal/mole, at this point molecule will be active as a H_2 receptor antagonist. At this point cimetidine Derivative drug will be more active as a H2 receptor Antagonist agent. It is possible that drug amlodipine besylate will interact with receptor in this conformation.

Keywords: Histamine, H_2 receptor antagonist, cimetidine derivative, Argus lab 4.0.1, conformational analysis, geometry optimization.
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INTRODUCTION

A good ligand must bind in a relatively low energy conformation .The purpose of conformational analysis is to obtain a description of the 3D structure of molecules. Such knowledge is required in order to understand the interaction between molecules[1-7.]

Cimetidine is a member of H_2 blocker (histamine blocker) family of drugs that prevents the release of gastric acid into stomach. Cimetidine is used to treat stomach and duodenal ulcers, reflux of stomach acid into the esophagus, and Zollinger–Ellison syndrome. Cimetidine is available as a prescription over the counter product for the relief of heartburn.Colin et al[8] report the crystal and molecular structure of a selection of these compounds 1 to 7 are specific H_1 antagonists and others 8 to 10 are active as both H_1 and H_2 receptor antagonists.

The present work describes the computer aided conformational analysis that is based on geometry optimization (active conformation) of drug by ArgusLab software. ArgusLab is an electronic structure program that is based on the quantum mechanics, it predicts the potential energies, molecular structures, geometry optimization of structure, vibrational frequencies of coordinates of atoms, bond length, bond angles and reaction pathway [9].Conformational analysis of molecule is based on molecular mechanics, it is method for the calculation of molecular structures, conformational energies and other molecular properties using concept form classical mechanics. A molecule is considered as a collection of atoms held together by classical forces. These forces are described by potential energy function of structural features like bond lengths, bond angles and torsional angles etc.

The energy (E) of the molecule is calculated as a sum of terms as in equation.

$$E=E_{stretching}+E_{bending}+E_{torsion}+E_{vanderwaals}+E_{electrostatic}+E_{hydrogen\ bond}+\text{cross term.}$$

These terms are of importance for the accurate calculation of geometric properties of molecules. The set of energy functions and the corresponding parameters are called a force field[10].

The molecular mechanics method calculates the energy as a function of the coordinates and energy minimization is an integral part of method. A molecular geometry is constructed by using computer graphics techniques and the atoms moved are iteratively moved (without breaking bonds) using computer graphic techniques and an energy minimization technique until the net forces on all atoms vanish and the total energy of the molecule reaches a minimum. The 3D (3 rotatable bonds) structure of molecule corresponding to this energy minimum is one of the stable conformations of molecule but not necessarily the most stable one[11].

Since the energy minimum methods cannot move the molecule across energy barriers, the minimization of a trial molecule continues until the first local energy minimum is found. Other local energy minima including the lowest energy one, the globle energy minimum, may be found by repeating the calculation with another start geometry or more efficiently .Conformation search methods random numbers are used to determine how many and which torsional angles and space to be translated[12].

MATERIALS AND METHODS

The three dimensional quantitative structure activity relationships (3D-QSAR) describe the biological activity of molecule with pharmacological

potential as a function of their structural properties[13,14].

Computational advances have generated many tools and representations of molecular structure[15,16]. All conformational analysis (geometry optimization) study was performed on a window based computer using ArgusLab and ACD Lab Chem Sketch softwares. The chemical structure of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone was refined by x-ray crystallography technique. The cimetidine derivative is utilized to determine 3D structure of molecule. Several computer programs were use to infer the shape of molecule from geometry optimization calculations[17]. The 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone structure is generated by Argus Lab, minimization was performed with semi-empirical Austin Model 1 (AM1) parameterization[6].

The minimum potential energy is calculated by using geometry convergence function in ArgusLab software. In order to determine the allowed conformation the contact distance between the atoms in adjacent residues is examined using criteria for minimum Vander waal contact distance.[18] Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP) spin densities and generated the grid data used to make molecular orbital surfaces and visualized the molecular orbital and making an electrostatic potential mapped and electron density surface[19]. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map.

RESULTS AND DICUSSION

Figure 1a describes the 100 projection of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone by statistica. This figure describes the actual co-ordinates presentation at Y-axis Vs Z-axis. Figure 1b describes the 001 projection of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone by Statistica software. This figure describes the actual co-ordinates presentation at X-axis Vs Y-axis. Prospective view and active conformation of 2- [4-(3-Ethoxy-2-pyridyl)butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone are shown in figure 2a and 2b respectively. Figure 2c shows the electron density map of 2-[4-(3-Ethoxy-2-pyridyl)butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone by ACDLABS-3D viewer software .The electrostatic potential of drug caused by charged side chains and bound ions play a role in recognition of active site of specific receptor . Fig 2d shows the electrostatic potential of 2-[4-(3-Ethoxy-2-pyridyl)butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone ground state mapped onto the electron density surface for the ground state.

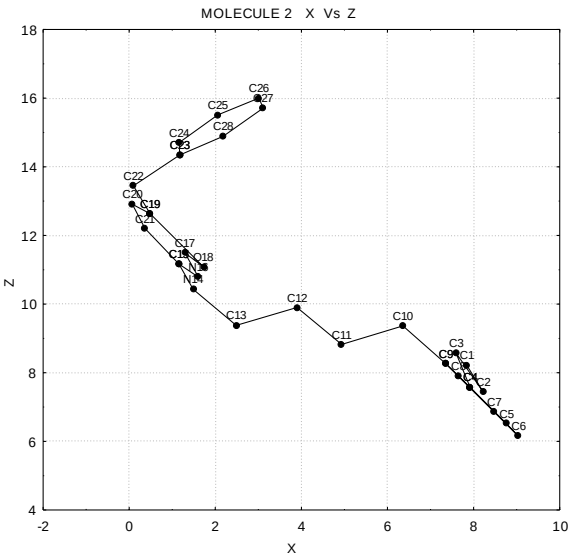

Figure 1a: 100 Projection of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone.

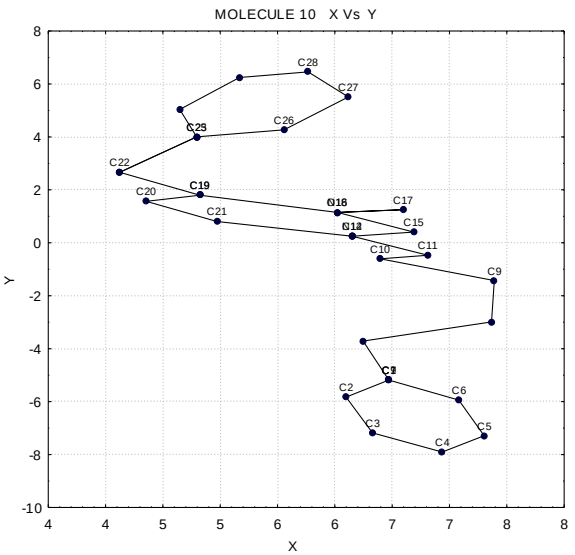

Figure 1b: 001 Projection of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone.

This is done by using a clipping plane showing a cutaway of the same surface revealing the under lying molecular structure. The color map shows the ESP energy (in hartrees) for the various colors. The red end of the spectrum shows the region of highest stability for a positive test charge, magenta/blue show the regions of least stability for a positive test charge. These images show that the carboxyl end of the

molecule is electron rich relative to amino end. Fig 2e shows the occupied л – molecular orbital of 2-[4-(3-Ethoxy-2-pyridyl)butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone calculated with the ZINDO method and rendered as mesh. The positive and negative phases of the orbital are represented by the two colors, the blue regions represent an increase in electron density and the red regions a decrease in electron density. To compute a molecular surface with an electrostatic potential, activate the "color by electrostatic potential" in the "Surface" preferences and compute the surface.

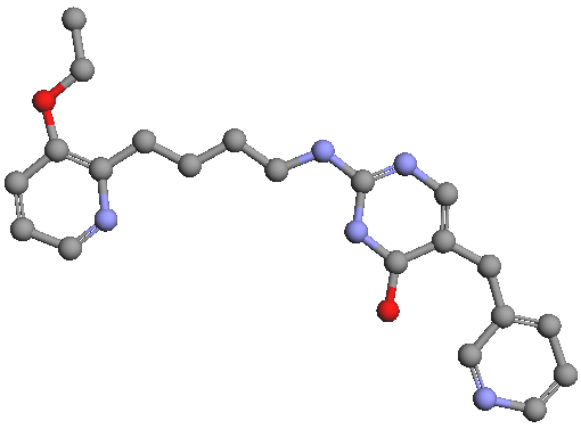

Figure 2a: Prospective view of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone.

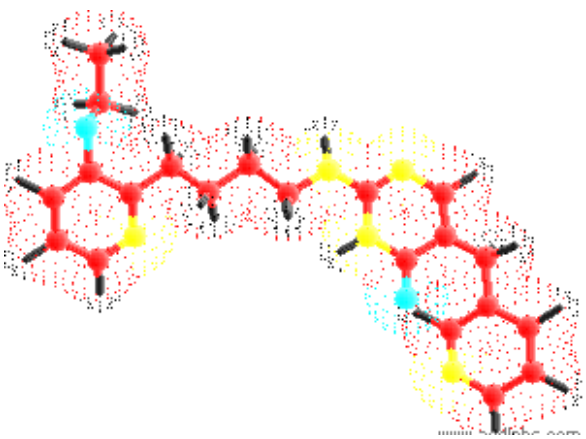

Figure 2b: Prospective view of active conformation of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone.

These types of surface representations are useful to discuss drug receptor interaction. Rectangular coordinates of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone are given in table 1. Bond angles and bond lengths are given in tables 2 and 3 respectively, which are taken after geometry optimization of 2-[4-(3-Ethoxy-2-pyridyl)butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone molecule from ArgusLab by using molecular mechanics calculation.

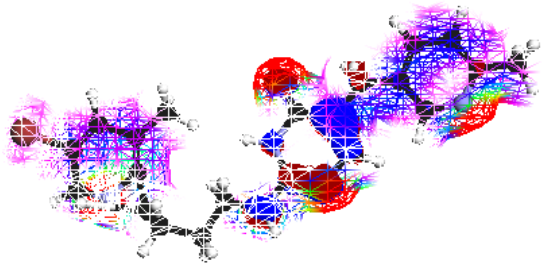

Figure 2d: Electrostatic potential (ESP).

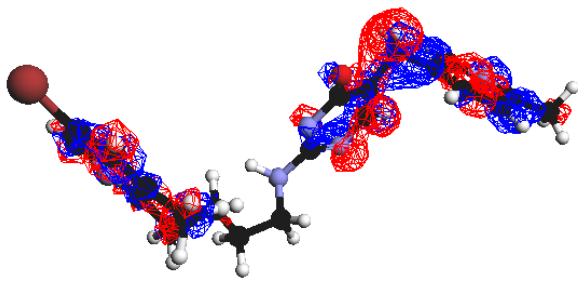

Figure 2e: Mapped electron density surface (mesh).

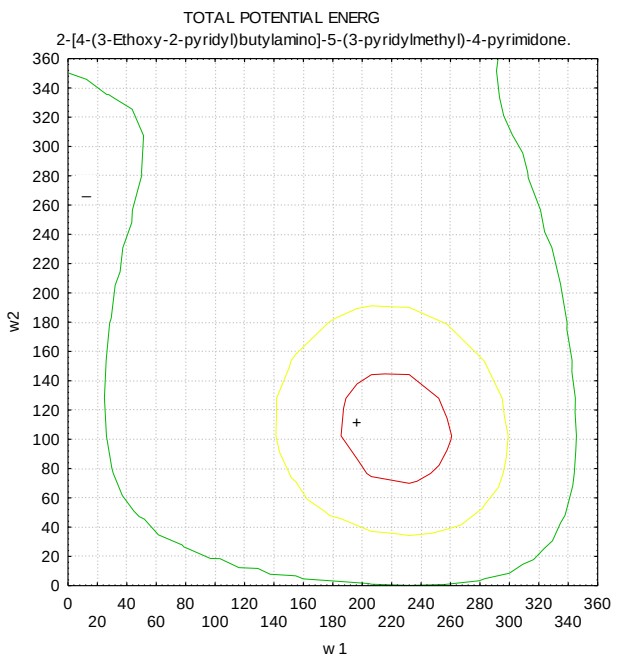

Figure 2f: Visualize the molecular orbitals, blue shows positive and red shows negative.

It is possible that the best drug in this conformation interact with receptor. The results indicates that the best conformation of the molecule is present at minimum potential energy is found to be -

0.0065 kcal/mole. At this point cimetidine derivative, 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone will be more active as histamine H_2 receptor antagonists. Electrostatic potential map, electron density maps and colored regions of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone represent active sites of drug receptor binding interaction with different charged groups.

Table 1: Rectangular coordinates of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone.

Atoms	X	Y	Z
C1	7.84399	8.221164	6.3450
C2	8.221766	7.445225	5.128015
O3	7.588781	8.063082	3.997542
C4	7.917621	7.578039	2.760036
C5	8.760152	6.522088	2.538752
C6	9.037082	6.15228	1.235101
C7	8.472116	6.861796	0.2176761
N8	7.641213	7.900195	0.4173126
C9	7.350704	8.266143	1.668048
C10	6.359203	9.365068	1.859266
C11	4.934555	8.824202	1.985542
C12	3.898731	9.90172	2.099792
C13	2.486907	9.378449	2.1948
N14	1.488247	10.4287	2.239297
C15	1.155961	11.16768	3.297612
N16	1.605878	10.78789	4.541131
C17	1.294268	11.4897	5.693251
O18	1.730136	11.07881	6.787645
C19	0.48464	12.6358	5.509249
C20	0.07333219	12.90823	4.241677
N21	0.3670179	12.20443	3.137662
C22	0.09720421	13.46447	6.702257
C23	1.17338	14.3429	7.247049
C24	1.161517	14.7064	8.5964
N25	2.055658	15.51218	9.159231
C26	3.01328	16.00284	8.391952
C27	3.112968	15.71114	7.059439
C28	2.180681	14.87021	6.51104

CONCLUSION

The present work indicates that the best conformation of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone is found to be at -0.0065kcal/mole which is the minimum potential energy by ArgusLab 4 software. At this point 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone will be more active as histamine H_2 receptor antagonist. In this work it is shown that conformational analysis with minimum potential energy is crucial when establishing SAR/QSAR models using theoretically calculated descriptors, since it can be dependent on molecular structure. Finally all geometric variables were completely optimized for each compound and the lowest energy conformations were used in molecular modeling studies.

Table 2: Bond Angles of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone.

Pairs	Bond Angles
C1-C2-O3	107.903
C2-O3-C4	116.9877
O3-C4-C5	124.5758
O3-C4-C9	115.5313
C5-C4-C9	119.9465
C4-C5-C6	118.8313
C5-C6-C7	118.802
C6-C7-N8	123.2008
C7-N8-C9	119.0457
C4-C9-N8	120.312
C4-C9-C10	121.84
N8-C9-C10	117.826
C9-C10-C11	111.6882
C10-C11-C12	113.3454
C11-C12-C13	113.7381
C12-C13-N14	113.3038
C13-N14-C15	126.7274
N14-C15-N16	118.9190
N14-C15-N21	119.4313
N16-C15-N21	121.6762
C15-N16-C17	122.609
N16-C17-O18	118.9953
N16-C17-C19	115.5602
O18-C17-C19	125.5167
C17-C19-C20	117.1774
C17-C19-C22	119.4074
C20-C19-C22	123.4716
C19-C20-N21	126.5707
C15-N21-C20	116.4866
C19-C22-C23	115.3842
C22-C23-C24	120.0018
C22-C23-C28	124.5824
C24-C23-C28	115.4594
C23-C24-N25	124.1575

Table 3: Bond Lengths of 2-[4-(3-Ethoxy-2-pyridyl) butyl amino]-5-(3-pyridylmethyl)-4-pyrimidone.

C1---C2	1.210786
C1---C6	1.469568
C2---C3	1.361243
C3---C4	1.371387
C4---C5	1.378361
C5---C6	1.391005
C6---C7	1.502819
C7---C8	1.53492
C8---C9	1.515958
N11---C12	1.324274
C12---N13	1.347043
C12---C14	1.323893
C12---N18	1.344574
N13---C14	1.030691
C16---C17	1.34676
C16---C19	1.504538
C17---N18	1.356347
C19---C20	1.512461
C20---C21	1.378244
C20---C25	1.379336
C21---C22	1.373952
N24---C25	1.323111

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