*Pak. J. Biochem. Mol. Biol. 2010; 43(3): 109-113*

# Conformational analysis of flavanoid derivative as histamine $H_1$ receptor antagonist

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**Abstract:** Conformational analysis and geometry optimization of flavanoid derivative 2-phenyl-4H-chromen-4-ones, as a histamine $H_1$ receptor antagonist, was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4 software . The result indicates that the best conformation of the molecule is present at minimum potential energy is found to be -68696.5088 kcal/mol. At this point molecule will be more active as histamine $H_1$ receptor antagonist.

**Keywords:** Histamine N–methyl transferase (HMT), histamine $H_1$ receptor antagonist, ArgusLab 4.
**Received:** March 03, 2010 **Accepted:** July 20, 2010
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## INTRODUCTION

Histamine occurs throughout the gastrointestinal tract, in enterochromaffin-like cells, restricted to the fundic mucosa of the stomach, mast cells and nerves. Histamine is actively produced and released in enterochromaffin-like (ECL) cells, rich in the synthesis enzyme; histidine decarboxylase (HDC), while it is mainly stored in mast cells. Histamine exerts its effects through $H_1$, $H_2$, $H_3$ and $H_4$ receptors. Histamine $H_1$ receptor are reported to be expressed on enterocytes, connective tissue cells, muscle layer, blood vessels, immune cells and ganglion cells of the myenteric plexus in the human intestine[1]. $H_2$ receptors appear to be located on parietal cells in the fundic mucosa[2] and have also been found in the intestinal epithelium, immune cells and myenteric ganglia in humans[1]. The presence of $H_3$ receptors in periphery remains controversial. $H_3$ receptor mRNA expression is reported to be undetectable in peripheral tissues of humans and rats[3-5] or alternatively to be restricted to liver and epithelia, including the mucosa of the gastrointestinal tract[6]. Immunostaining of human intestinal tissues have failed to reveal the presence of $H_3$ receptor1. The ganglia of enteric nervous system are negative for $H_3$ receptor mRNA expression[1]. $H_4$ receptor mRNA appears to have a moderate to low expression in human stomach, small intestine and colon[7,8]. Immunostaining revealed that enterocytes, intraepithelial neuroendocrine cells and leucocytes express the $H_4$ receptor in human intestinal tissue[1].
The term antihistamine is traditionally used to refer to drugs that block the $H_1$-receptors.

The $H_1$ receptors are found in smooth muscles, endothelium and central nervous system tissue. Abnormal release of histqamine binds $H_1$ receptors and its stimulation causes a variety of inflammatory disease, including asthama, glomerulonephritis, psoriasis, inflammatory bowel diseases, rhinitis symptoms, anaphylactic attack and acute pulmonary injury[9]. Antihistamines have a much broader use than decongestants. They are used to treat symptoms of allergic reactions such as the sneezing and runny nose of hay fever, itching swelling and other allergic rashes. HMT and diamine oxidase are two enzymes involved in the metabolism of histamine. Histamine N methyl transferase plays a significant role in degrading histamine and in regulating the airway response to histamine. It may be termed as the key enzyme involved in allergy and immune responses host defense against infection, it is mainly known for pathogenic against allergy related asthma/human allergic bronchspasm[10].

Flavanoids represent an important group of organic compounds exhibit significant biological activity, including anti-inflammatory[11,12] and pharmacological effects.

A recent study reveals that compound 2-phenyl-4H-chromen-4-ones screened for its activity as histamine N-methyltransferase[13] enzyme inhibitor to assess its potential to cure adverse effects produced by histamines and other allergic diseases. Selecting flavones for computational analysis as anti histamine focused our investigation for many more reason as their mode of action is not only confined to anti- inflammatory but also act as anti oxidants, for their affinity towards divalent ions of heavy metals, those catalyze the processes involving free redical generation.

The present work describes the computer aided conformational analysis that is based on geometry optimization (active conformation) of flavanoid derivative by Argus Lab Software, that flavones ligand showed highest binding score with HMT enzyme (PDB: 2aot) active site cavity with comparison to other ligands including well known anti histamine such as diphenhydramine, promethazine, cyproheptadine, trimeton[9]. Argus Lab is the electronic structure program that is based on the quantum mechanics, it predicts the potential energies, molecular structures; geometry

optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angle and reactions pathway[14].

Conformational analysis of molecule is based on molecular mechanics, it is a method for the calculation of molecular structures, conformational energies and other molecular properties using concept from 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 torsion 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 Vander Waals + E electrostatic + E hydrogen bond + cross term[15].

Molecular mechanics potential energy functions (MMPEFs) incorporate both 'bonded' and 'non-bonded' terms. The bonded terms apply to sets of two to four atoms that are covalently linked, and they serve to constrain bond lengths and angles near their equilibrium values. The bonded terms also include a torsional potential that models the periodic energy barriers encountered during bond rotation. The non-bonded terms consist of the Lennard–Jones (LJ) function (which includes van der Waals attraction and repulsion owing to orbital overlap) and Coulomb's law. The parameters for the bonded and non-bonded terms of an MM-PEF are derived from quantum calculations and from thermodynamic, crystallographic and spectroscopic data on a wide range of systems. MM-PEFs have been used predominately to simulate protein folding and dynamics, are also used to refine X-ray crystal structures[16,17].

## MATERIALS AND METHODS

All conformational analysis (geometry optimization) study was performed on a window based computer using Argus lab and ACD Lab chem Sketch softwares. The chemical structure of 2-phenyl -4H-chromen-4-ones[18] was refined by X-ray crystallography technique[19].

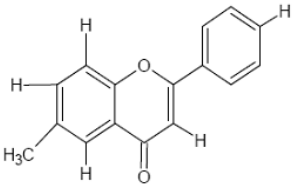
The flavanoid derivative, 2-phenyl -4H-chromen-4-ones molecule is utilized to determine 3D structure of molecule. Several computer programs were used to infer the shape of molecule from geometry optimization calculations. We take structure of flavanoid derivative[9] and generated by ACDLAB Chem sketch and Argus lab 4 softwares. ACDLAB Chem sketch is an integrated software package from advanced chemistry development for drawing chemical structures, reactions and to plot best projection with minimum energy and calculate all properties of ligand.

The minimum potential energy is calculated by using geometry convergence function by ArgusLab4 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[20].

Surfaces created to visualize ground state properties as well as excited properties such as orbital, electron densities, electrostatic potentials (esp.) spin densities and generated the grid data used to make molecular orbital surfaces and visualize the molecular orbital and making an electrostatic potential mapped and electron density surface by ArgusLab4. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map.

## RESULTS

Prospective view and calculated properties of molecule are shown in figure 1. The active conformation and electron density mapped of atoms by ACD LABS 3D Viewer software in figures 2 and 3 respectively.




| | |
|---|---|
| Molecular Formula | = $C_{18}H_{12}O_2$ |
| Formula Weight | = 236.26528 |
| Composition | = C(81.34%) H(5.12%) O(13.54%) |
| Molar Refractivity | = 69.03 ± 0.3 $cm^3$ |
| Molar Volume | = 195.5 ± 3.0 $cm^3$ |
| Parachor | = 514.0 ± 6.0 $cm^3$ |
| Index of Refraction | = 1.623 ± 0.02 |
| Surface Tension | = 47.7 ± 3.0 dyne/cm |
| Density | = 1.208 ± 0.06 $g/cm^3$ |
| Dielectric Constant | = Not available |
| Polarizability | = 27.36 ± 0.5 $10^{-24} cm^3$ |
| Monoisotopic Mass | = 236.08373 Da |
| Nominal Mass | = 236 Da |
| Average Mass | = 236.2653 Da |
| M+ | = 236.083181 Da |
| M- | = 236.084278 Da |
| [M+H]+ | = 237.091006 Da |
| [M+H]- | = 237.092103 Da |
| [M-H]+ | = 235.075356 Da |
| [M-H]- | = 235.076453 Da |

**Figure 1:** Prospective view and properties of flavanoid derivative 2 phenyl-4H-chromen-4-ones.

Figure 4 shows electrostatic potential of molecule ground state mapped on to the electron density surface for the ground state and figure 5 shows the complete surface with the color map . Figures 4 and 5 use a clipping plane showing a cutaway of the same surface revealing the underlying molecular structure.

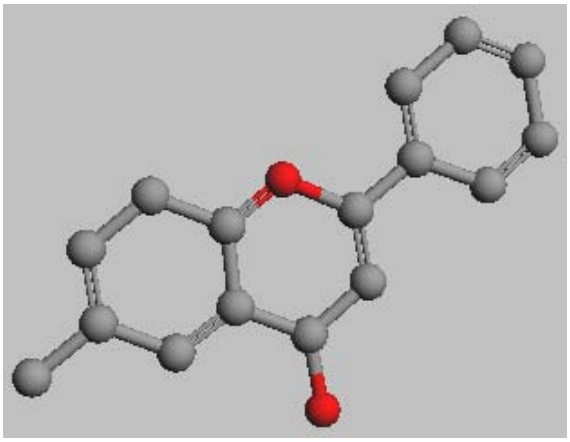


**Figure 2:** Prospective view of active conformation of flavanoid derivative 2 phenyl-4H-chromen-4-ones.

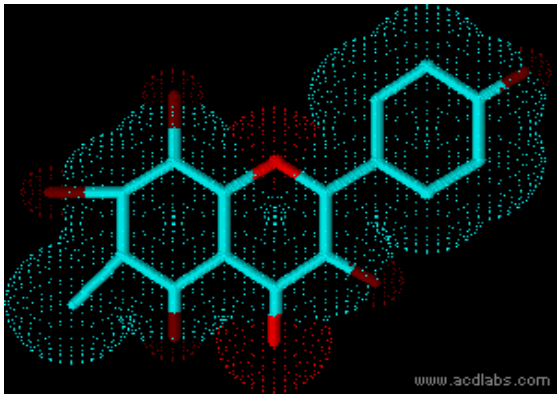



**Figure 3:** Electron density cloudes generated by ACD LABS.3D VIEWER.

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 6 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 the two colors. The blue region represents an increase in a density the red region a represent in electron density.

Fractural coordination of molecule are given in table 1 and bond length and bond angles are given in tables 2 and 3 respectively with are taken after geometry optimization of molecular from Argus lab by using molecular mechanics calculation.

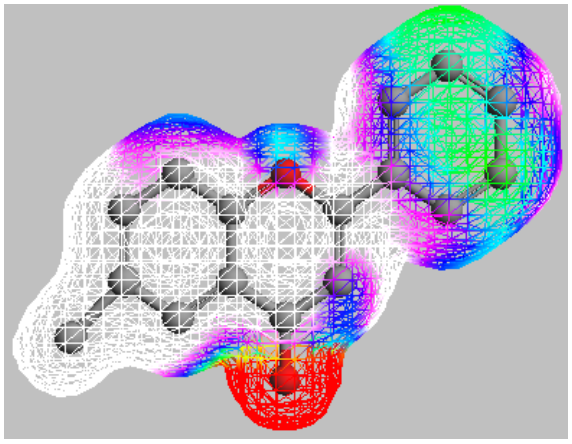


**Figure 4:** Electro static potential ESP mapped electron density.

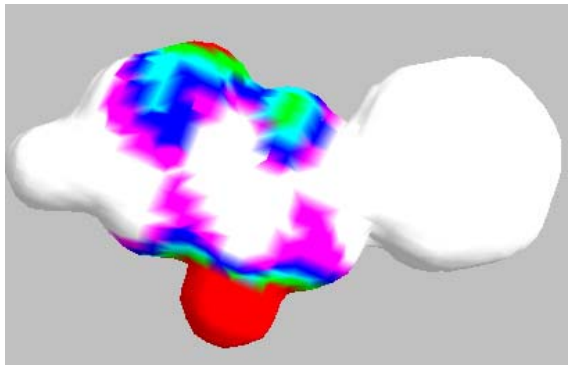


**Figure 5:** The complete surface with the color map of ESP

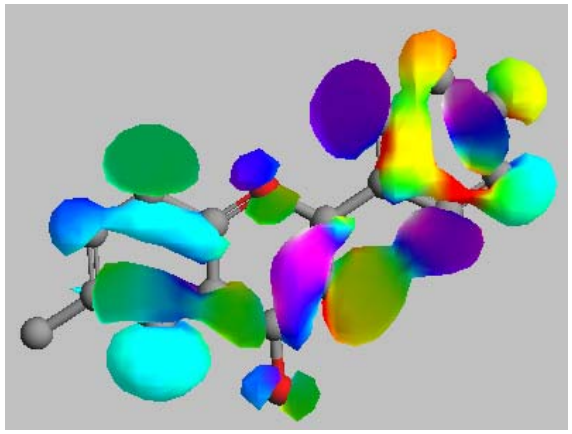


**Figure 6:** Visualize the molecular orbital.

**Table 1:** Fractional Co-ordinates of molecule ($A^o$).

| No | Atoms | X | Y | Z |
|---|---|---|---|---|
| 1 | C1 | 9.964722 | 8.87104071 | 0.07376782 |
| 2 | C2 | 9.977345 | 10.34635478 | 0.02664765 |
| 3 | C3 | 8.660826 | 8.20143070 | 0.17026786 |
| 4 | C4 | 8.831688 | 11.03987298 | 0.03035231 |
| 5 | C5 | 7.4406910 | 9.02538485 | 0.16056928 |
| 6 | C6 | 7.5215044 | 10.35812170 | 0.06607493 |
| 7 | C7 | 12.358212 | 8.82790216 | 0.01863061 |
| 8 | C8 | 12.464041 | 10.16329968 | 0.11265950 |
| 9 | O9 | 11.066587 | 8.14649856 | 0.07861821 |
| 10 | C10 | 11.273256 | 11.00473815 | 0.12239378 |
| 11 | C11 | 14.93235 | 8.62230807 | 0.11112120 |
| 12 | C12 | 13.58416 | 8.00339088 | 0.01412966 |
| 13 | C13 | 15.90948 | 6.39048454 | 0.00351892 |
| 14 | C14 | 16.03121 | 7.85874360 | 0.10600572 |
| 15 | C15 | 14.70074 | 5.82451897 | 0.08441719 |
| 16 | C16 | 13.487009 | 6.66779083 | 0.07853759 |
| 17 | C17 | 6.275568 | 11.16767454 | 0.05620709 |
| 18 | O18 | 11.386776 | 12.40614431 | 0.22300263 |

**Table 2:** Bond angles.

| Atom 1 | Atom2 | Atom 3 | Bond Angles | Alternative Angles |
|---|---|---|---|---|
| (C3) | (C1) | (O9) | 120.000000 | 266.809634 |
| (C3) | (C1) | (C2) | 120.000000 | 188.442082 |
| (C1) | (C3) | (C5) | 120.000000 | 188.442082 |
| (O9) | (C7) | (C4) | 120.000000 | 266.809634 |
| (C1) | (O9) | (C7) | 110.000000 | 287.358611 |
| (C1) | (C2) | (C4) | 120.000000 | 216.488007 |
| (C1) | (C2) | (C10) | 120.000000 | 188.442082 |
| (C4) | (C2) | (C10) | 120.000000 | 216.488007 |
| (C2) | (C4) | (C6) | 120.000000 | 216.488007 |
| (C2) | (C10) | (C8) | 120.000000 | 188.442082 |
| (C2) | (C10) | (O10) | 120.000000 | 238.736810 |
| (C3) | (C5) | (C6) | 120.000000 | 216.488007 |
| (C4) | (C6) | (C5) | 120.000000 | 216.488007 |
| (C4) | (C6) | (C17) | 120.000000 | 183.094781 |
| (C5) | (C6) | (C17) | 120.000000 | 209.804299 |
| (O9) | (C7) | (C12) | 120.000000 | 233.320318 |
| (O9) | (C7) | (C8) | 120.000000 | 268.751288 |
| (C12) | (C7) | (C8) | 120.000000 | 216.488007 |
| (C7) | (C12) | (C11) | 120.000000 | 188.442082 |
| (C7) | (C12) | (C16) | 120.000000 | 216.488007 |
| (C7) | (C8) | (C10) | 120.000000 | 216.488007 |
| (C8) | (C10) | (O18) | 120.000000 | 238.736810 |
| (C14) | (C11) | (C12) | 120.000000 | 216.488007 |
| (C11) | (C14) | (C13) | 120.000000 | 216.488007 |
| (C11) | (C12) | (C16) | 120.000000 | 216.488007 |
| (C12) | (C16) | (C15) | 120.000000 | 216.488007 |
| (C14) | (C13) | (C15) | 120.000000 | 216.488007 |
| (C13) | (C15) | (C16) | 120.000000 | 216.488007 |

It is possible that drug in this conformation interact with receptor. The result indicates that the best confirmation of the molecule is present at minimum potential energy is found to be –68695.5088 kcal/mol. At this point molecule will be more active as histamine $H_1$ antagonist.

**Table 3:** Bond length

| Atoms | Bond Length | Alternative Bond Length |
|---|---|---|
| (C1)- (C3) | 1.458000 | 391.674090 |
| (C1) -(O9) | 1.299873 | 664.866073 |
| (C1)-(C2) | 1.458000 | 391.674090 |
| (C2)-(C4) | 1.323387 | 523.765496 |
| (C2)-(C10) | 1.458000 | 391.674090 |
| (C3)-(C5) | 1.458000 | 391.674090 |
| (C4)-(C6) | 1.458000 | 391.674090 |
| (C5)-(C6) | 1.323387 | 523.765496 |
| (C6)-(C17) | 1.486000 | 369.948258 |
| (C7)-(O9) | 1.429962 | 499.417161 |
| (C7)-(C12) | 1.458000 | 391.674090 |
| (C7)-(C8) | 1.323387 | 523.765496 |
| (C8)- (C10) | 1.458000 | 391.674090 |
| (C10)- (O18) | 1.407689 | 523.501065 |
| (C11)-(C14) | 1.323387 | 523.765496 |
| (C11)-(C12) | 1.458000 | 391.674090 |
| (C12)-(C16) | 1.323387 | 523.765496 |
| (C13)-(C14) | 1.458000 | 391.674090 |
| (C13)-(C15) | 1.323387 | 523.765496 |
| (C15)-(C16) | 1.458000 | 391.674090 |

**Table 4:** Dihedral angles.

| Atoms | Torsional Angles | Angles | Plain of Angles |
|---|---|---|---|
| (C5 )-(C3)-(C1)-(O9) | 5.000000 | 2 | 180.0 |
| (C3)-(C1)-(O9)-(C7) | 19.486776 | 2 | 180.0 |
| (C5)-(C3)-(C1)-(C2) | 5.000000 | 2 | 180.0 |
| (C3)-(C1)-(C2)-(C4) | 2.500000 | 2 | 180.0 |
| (C3)-(C1)-(C2)-(C10) | 2.500000 | 2 | 180.0 |
| (C1)-(C3)-(C5)-(C6) | 10.000000 | 2 | 180.0 |
| (C7)-(O9)-(C1)-(C2) | 19.486776 | 2 | 180.0 |
| (O9)-(C1)-(C2)-(C4) | 2.500000 | 2 | 180.0 |
| (O9)-(C1)-(C2)-(C10) | 2.500000 | 2 | 180.0 |
| (C1)-(O9)-(C7)-(C12) | 5.000000 | 2 | 180.0 |
| (C1)-(O9)-(C7)-(C8) | 5.000000 | 2 | 180.0 |
| (C1)-(C2)-(C4)-(C6) | 19.486776 | 2 | 180.0 |
| (C1)-(C2) (C10)-(C8) | 2.500000 | 2 | 180.0 |
| (C1)-(C2)-(C10)-(O18) | 2.500000 | 2 | 180.0 |
| (C6)-(C4)-(C2)-(C10) | 19.486776 | 2 | 180.0 |
| (C4)-(C2)-(C10)-(C8) | 2.500000 | 2 | 180.0 |
| (C4)-(C2)-(C10)-(O18) | 2.500000 | 2 | 180.0 |
| (C2)-(C4)-(C6)-(C5) | 5.000000 | 2 | 180.0 |
| (C3)-(C6)-(C6)-(C4) | 19.486776 | 2 | 180.0 |
| (C3)- (C5)-(C6)-(C17) | 19.486776 | 2 | 180.0 |
| (O9)- (C7)-(C12)-(C11) | 2.500000 | 2 | 180.0 |
| (O9)-(C7)-(C12)-(C16) | 2.500000 | 2 | 180.0 |
| (O9)-(C7)-(C8)-(C10) | 19.486776 | 2 | 180.0 |
| (C11)-(C12)-(C7)-(C8) | 2.500000 | 2 | 180.0 |
| (C16)-(C12)-(C7)-(C8) | 2.500000 | 2 | 180.0 |
| (C12)-(C7)-(C8)-(C10) | 19.486776 | 2 | 180.0 |
| (C7)-(C12)-(C11)-(C14) | 5.000000 | 2 | 180.0 |
| (C7)-(C12)-(C16)-(C15) | 19.486776 | 2 | 180.0 |
| (C13)-(C14)-(C11)-(C12) | 38.973552 | 2 | 180.0 |
| (C14)-(C11)-(C12)-(C16) | 5.000000 | 2 | 180.0 |
| (C11)-(C14)-(C13)-(C15) | 10.000000 | 2 | 180.0 |
| (C11)-(C12)-(C16)-(C15) | 19.486776 | 2 | 180.0 |
| (C12)-(C16)-(C15)-(C13) | 10.000000 | 2 | 180.0 |
| (C14)-(C13)-(C15)(C16) | 38.973552 | 2 | 180.0 |

## CONCLUSION

In the present study, potential energy of non-bonded interaction for flavanoid derivative is calculated. Total potential energies were calculated by summation of all individual pairs. The result indicates that the best confirmation of flavanoid derivative is found to be at -68695.5088 kcal/mol which is minimum potential energy. At this point molecule will be more active as $H_1$ receptor antagonist and inhibit the acid secretion in stomach more effectively.

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