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COMPUTER AIDED DRUG DESIGNING OF HISTAMINE H_2 RECEPTOR ANTAGONIST CIMETIDINE DERIVATIVE FOR THE TREATMENT OF DUODENAL ULCER

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ABSTRACT

Conformational analysis and geometry optimization of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone is performed according to old approach GW BASIC programming and new approaches ACD Chemsketch and Argus lab 4 Softwares. The conformational changes and potential energy calculated and predicted. Results of GW BASIC programming and ArgusLab 4.0.1 software shown that the minimum total potential energy is -0.0056 kcal/mole at ω_1 = 270° and ω_2= 340° and from all pairs and Final SCF Energy - 80741.3979 kcal/mol respectively.

Key words: ArgusLab 4.0.1, H_2 receptor antagonist, Conformational Analysis, Cimetidine.

INTRODUCTION

Computer aided drug design (CADD) has become a competitive methodology to identify new, novel drugs, drug like compounds (for medicinal purpose) and optimize lead models for specific targets as well as assists experimental programs in bringing potential drugs to preclinical trials (Munikumar *et al*., 2004; Gupta *et al*., 1989; Tommy 2004; Gohda *et al*., 2008; David *et al*., 2008; Chen *et al* ., 2008; Fumiaki, 2008). It can have a number of beneficial effects, such as; structure can serve as an organizing principles , facilitating the coherent interpretations, integration of inconsistent and disparate findings from different areas (Florence *et al*., 2002; Kitaigorodski., 1961; Michael *et al*., 2004). It is a rapidly growing , less time consuming, cost effective and important component of medicinal research for the treatment of diseases such as duodenal ulcer and related conditions. (Bercellos *et al*., 2008; Beroza and Suto, 2000; Beroza *et al*., 2002; Brown 1998; Clancy and Duncan, 2009).

The H_2-receptor antagonists are a class of drugs used to block the action of histamine on parietal cells in the stomach, decreasing the production of acid by these cells. (Rossi, 2005) Cimetidine, a histamine H_2 receptor antagonists , has been demonstrated to have anticancer effects on colorectal cancer melanoma (Tatsuya *et al.*, 2007) and renal cell carcinoma also capable of reducing gastric acid secretion with usual therapeutic dose (Jan *et al.*, 2005).Since the identification of histamine H_2 receptor (Black *et al*., 1972) a variety of compound have been shown to be specific histamine H_2 receptor antagonists. Of these compounds significant number, cimetidine (Brimblecombe *et al*., 1975), ranitidine, toitidine, famotidine and oximetidine have the general form of a heterocyclic head linked by a four atom chain, often methylthioethyl, to a dipolar tail. These compounds are both potent and highly selective in their action. Cimetidine is the histamine H_2 receptor antagonists led to the development of other derivatives, which are widely used as an effective inhibitor of gastric acid secretion in the treatment of duodenal ulcer and related conditions. (Onoa *et al*., 2002). In the histamine H_2 receptor antagonists mediate isosteric replacement of thione sulfur (=S) by carbonyl oxygen (=O) or imino nitrogen (=NH) affords the urea and guanidine which are antagonists of decreased potency.The guanidine is very basic and at physiological pH is completely protonated. However, introduction of strongly electromagnetic constituents into the guanidine group reduces basicity and gives potent H_2 receptor antagonist, the cyanoguanidine (Haleem *et al*., 1988; Khalida *et al*., 2008)

Paper describes CADD as well as conformational analysis and potential energy calculation by old approach such as GW BASIC and new approaches such as ACD Chemsketch and ArgusLab Software . It also gives correlation in work and comparison between old and new approaches. The ultimate goal is designing of a good model with potent inhibition activity and strong binding regions for cure of a given disease. ArgusLab is the electronic structure program that is based on quantum mechanics, it predicts potential energies, molecular structure, geometry optimization of structure, vibrational frequencies of coordinates of atoms, bond length, and bond angle and reaction pathway. (Peng *et al*., 1995).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 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 angles, bond lengths, torsional angles etc. The energy (E) of the molecule is calculated as a sum of terms in equation.

$E=E_{stretching}+E_{bending}+E_{torsion}+E_{vanderwaals}+E_{electrostatic}+E_{hydrogen\ bond}$ + 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 (Cramer *et al*., 1992).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 graphic technique and the atoms moved are iteratively moved (without breaking bonds) using 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. (Merz *et al* ., 1989).Since the energy minimization methods cannot move the molecule across energy barriers, the minimization of a trial molecule continues with the first local energy minimum is found .Other local energy minimum including the lowest energy one, the globle energy minimum , may be found by repeating the calculation with another start geometry or more efficiently. In conformational search methods random numbers are used to determine how many and which torsional angles and space to be incremented and which directions of x, y, z coordinates of each atoms are to be translated. (Still *et al*., 1990). ACD Chemsketch was used to generate macroscopic properties of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone .

MATERIALS AND METHODS

The structure of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone and raw coordinates were taken (step 1) and processed for molecular structure determination by converting coordinates system (step 2). The contact distance between the atoms in adjacent residues examined using criteria for minimum Vander waals contact distance, the various contact distances have done for various values of ω_1 and ω_2 (step 3) (Manuel, 1992). Bond angles and rotation in coordinates calculated (step 4 and step 5). The prediction of potential energies and conformations analyzed with the help of Kitaigorodskii function (Kitaigorodskii , 1961; Ramakrishan *et al*., 1965; Gupta., 1989).Potential energy functions for different non-bonded interaction and allowed conformations (step 6), (Kitaigorodskii, 1961; Ramakrishan *et al*., 1965).

Step-1: Data Collection:

2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone (data with X, Y, Z Coordinates) (Banneister *et al.*, 1994).

Step-2: Data conversion

Conversion of fractional co-ordinates into monoclinic co-ordinates:

The Fractional co-ordinates on X, Y, Z have been multiplied by unit cell dimensions (a=8.040A°, b=21.279A° and c=11.404A°) to obtain monoclinic coordinates:

$X_r=Y_m+\cos\beta$

$Y_r=Y_m$

$Z_r=Z_m\sin\beta$

X, Y, Z (coordinates before rotation).

X_m, Y_m, Z_m (Monoclinic coordinates).

X_r, Y_r, Z_r (Rectangular coordinates) on X, Y, Z axis.

Step-3:

Contact distance between atoms calculated by the following relationship,

$R_{ij}= (X_2-X_1)^2 + (Y_2-Y_1)^2 + (Z_2-Z_1)^2$.

X_1, Y_1, Z_1 (Coordinates for atom 1 on X, Y, Z axis).

X_2, Y_2, Z_2 (Coordinates for atom 2 on X, Y, Z axis).

R_{ij} = distance between non bonded interaction.

Step-4:

Bond angles can be calculated by given below formula,

$\text{Cos}\ \theta = - (L_3-L_1-L_2)/2L_1L_2$

L= Bond length.

Step-5:

Calculation for coordinates after rotation:

(I): $L = X_1\text{-}X_2$/ Bond length X_1 --- X_2

$M = Y_1\text{-}Y_2$/ Bond length Y_1 --- Y_2

$N = Z_1\text{-}Z_2$/ Bond length Z_1 --- Z_2

L, M, N is the direction of cosines on the axis of rotation with respect to the chosen system of coordinates.

(II): $a = \cos(\omega/2)$

$b = L \sin(\omega/2)$

$c = M \sin(\omega/2)$

$d = N \sin(\omega/2)$

Where,

ω = Angle of rotation 0 to 360.

a, b, c, d = variables.

(III): $X' = (a^2 + b^2 - c^2 - d^2) X + 2(bc - ad) Y + 2(bd - ac) Z.$

$Y' = 2(bc + ad) X + (a^2 - b^2 + c^2 - d^2) Y + 2(cd - ab) Z.$

$Z' = 2(bd - ac) X + 2(cd - ad) Y + (a^2 - b^2 - c^2 + d^2) Z.$

Where X', Y', Z', are the coordinates after rotation

Step-6:

Potential energies can be calculated with the help of following relationship, (Kitaigorodskii, 1961; Ramakrishan *et al*., 1965).

$$\mathbf{V = 3.5\ (8600\ e^{-13\,z}\ -0.04\ /z^6\ )}$$

$Z = r_{ij}/r$

r = equilibrium distance.

r_{ij} = distance between non-bonded interaction.

Z = Variable.

Then all conformational analysis (Geometry optimization) study was performed on a window based computer using ArgusLab and ACD Chemsketch softwares . Several computer programs were use to infer the shape of molecule from geometry optimization calculations. The cimetidine derivatives's structure is generated by ArgusLab, and minimization was performed with the semiemperical Austin Model 1(AM 1) parameterization (Dewar *et al*., 1985).

Step-7:

The minimum potential energy is calculated by using geometry convergence function by ArgusLab software. In order to determine the allowed conformation, the contact distance between atoms in adjacent residues is examined using criteria for minimum Vander Waal distance (Simon *et al*., 1983).

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. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map.

RESULTS AND DISCUSSION

This research made for determination of bond lengths , bond angles , rotation of coordinates ,potential energies , active conformation and possible drug binding mode of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone with receptors on target cells. The atomic coordinates (Table 1 and 2), bond length, bond angle (Table 3 and 4) potential energies and rotation of coordinates were calculated by using in silico computational approaches Gw basic 3.0 and statistica 5.0. Figure 1 describes the 010 projection of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone by Statistica. This figure describes the actual coordinate present at X- axis Vs Y-axis. The sets of pair C_6----C_{10}, C_5----N_{11} ,C_4----C_{12}, C_3----N_{13}, C_2----C_{14}, C_1----O_{15}, C_6----C_{16}, C_6----C_{17}, C_6----N_{18}, C_6----C_{19}. Selected for calculation but C_6----C_{10}, C_5----N_{11}, C_4----C_{12}, C_3----N_{13}, C_2----C_{14}, C_6----C_{16} have found interactions.

Figure 2 describes the total potential energy calculated by taking sum of potential energies of all individual pairs The minimum potential energy was found to be -0.0056 kcal/mole at $\omega_1 = 270^o$ and $\omega_2 = 340^o$. The maximum total potential energy was found to be 556.09 kcal/mole at ω_1= 160 and ω_2 = 120.

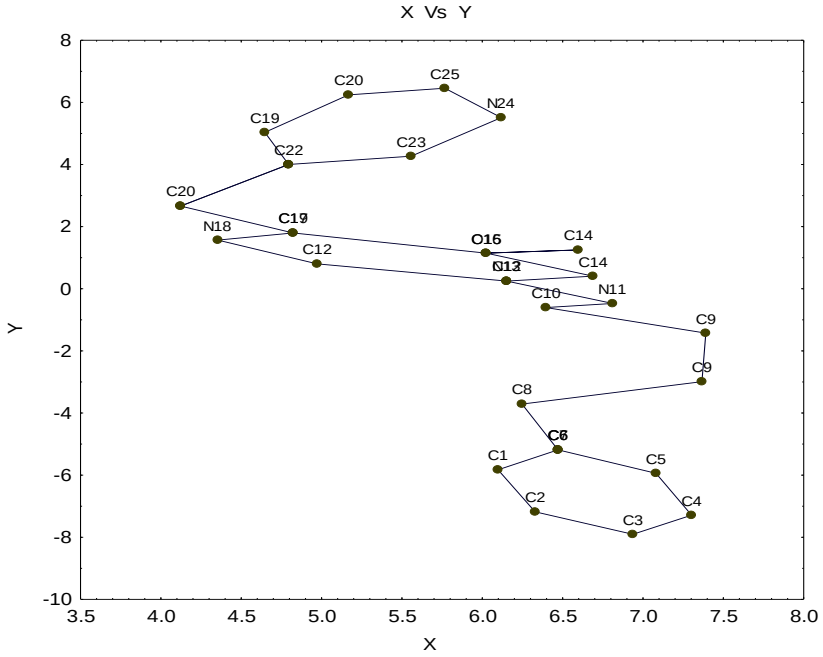
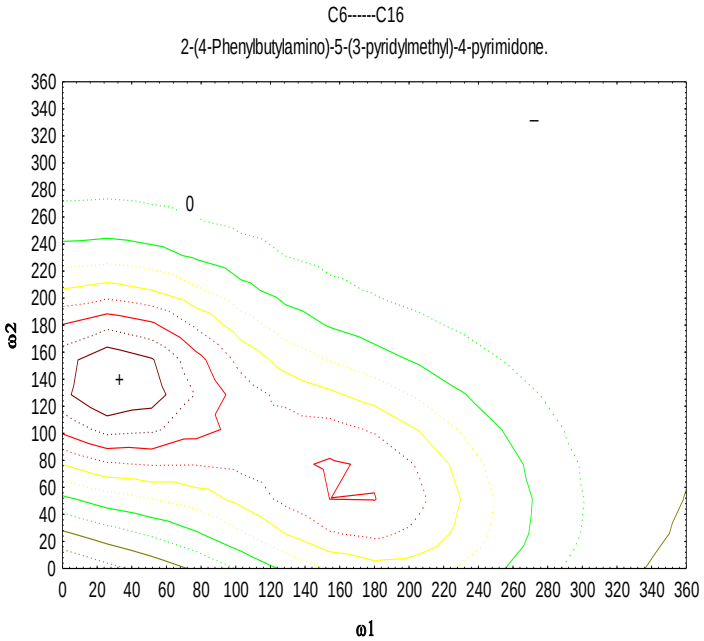
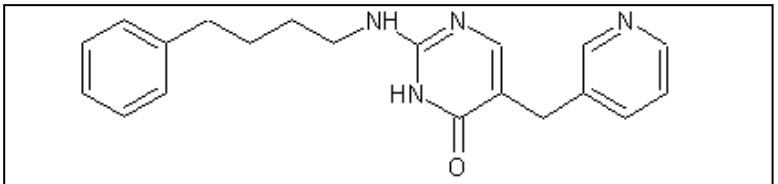


Fig. 1. 010 Projection of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone by Statistica software .



+ = The maximum potential energy is found to be121.842 k.cal/mol at □1=20 ,□2 = 140.
x = The minimum potential energy is found to be - 0. 0927 k.cal/mol at □1=340 ,□2 = 280.

Fig. 2. Contour Map of Total Potential Energy of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone



2-[(4-phenylbutyl)amino]-5-(pyridin-3-ylmethyl)pyrimidin-4(3*H*)-one

Molecular Formula	= $C_{20}H_{22}N_4O$
Formula Weight	= 334.41488
Composition	= C(71.83%) H(6.63%) N(16.75%) O(4.78%)
Molar Refractivity	= 100.14 ± 0.5 cm^3
Molar Volume	= 285.0 ± 7.0 cm^3
Parachor	= 746.8 ± 8.0 cm^3
Index of Refraction	= 1.620 ± 0.05
Surface Tension	= 47.1 ± 7.0 dyne/cm
Density	= 1.17 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 39.69 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 334.179361 Da
Nominal Mass	= 334 Da
Average Mass	= 334.4149 Da

Fig.3. Properties calculated by ACD chemskatch.

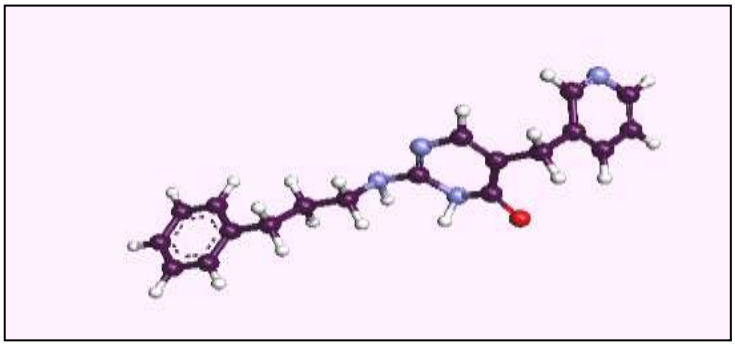


Fig. 4. Prospective view and active conformation of Prizidilol.

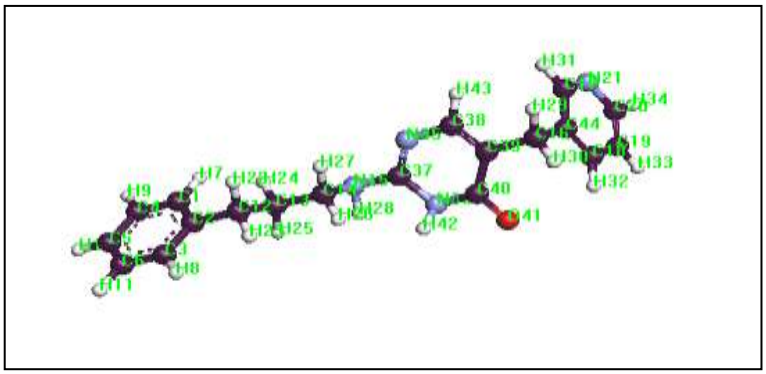


Fig. 5. Prospective and label view of molecule .

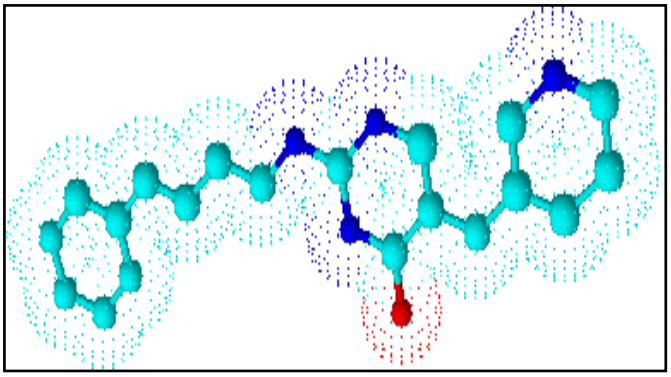


Fig. 6. Electron density mapped of atoms .

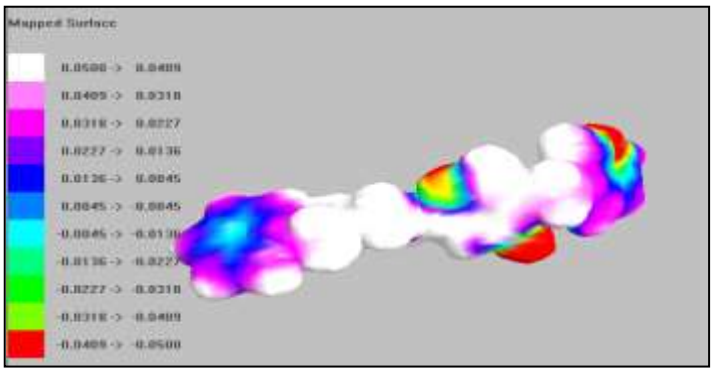


Fig. 7. The electrostatic potential of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone.

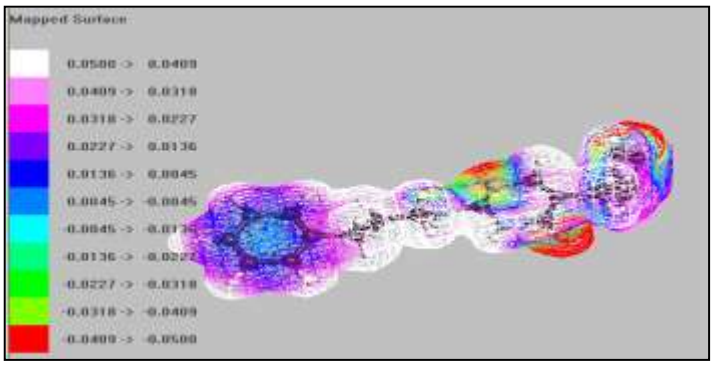


Fig. 8. The electrostatic potential of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone (mesh).

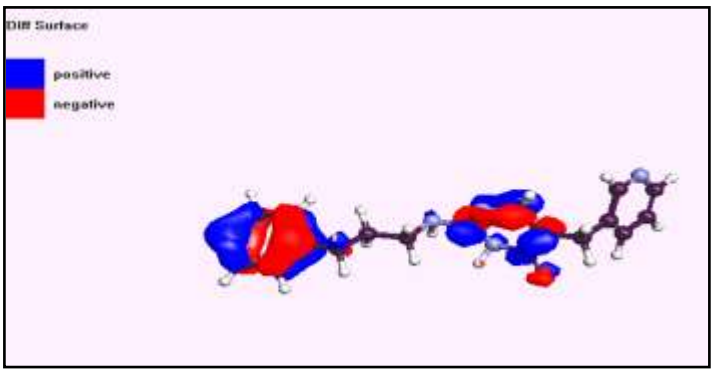


Fig. 9. The occupied π-molecular orbital of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone .

Table 1. The crystal data and structure detail for 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone is given as:

Chemical formula	C20H26N4O3
Formula Weight	13.5, 16.2, 2.4
Crystal System	Monoclinic
Dimension a, b, c (A)	8.040(4), 21.279(4), and 11.404(2)
Angles α, β, γ (°)	90, 92.08(5), and 90.
Mr	353.4
V (A^3)	1949.68
Space Group	$P2_1/C$
μ (cm^{-1})	0.93
Z	4
Dx ($gmcm^{-3}$)	1.26
F (000)	792
R	4.05%
Number of independent reflexions	3208
Number of Parameters	293
Number of Restraints	7

Table 2. Fractional coordinates of 2-(4-Phenylbutylamino)-5-(3pyridylmethyl)-4-pyrimidone.

ATOMS	X	Y	Z
C1	.7729(4)	-.2738(2)	.2821(3)
C2	.8007(4)	-.3374(2)	.2673(3)
C3	.8807(4)	-.3713(2)	.3534(3)
C4	.9316(4)	-.3424(2)	.4561(3)
C5	.9050(4)	-.2790(2)	.4716(3)
C6	.8246(4)	-.2436(1)	.3841(3)
C7	.7977(4)	-.1743(2)	.4003(4)
C8	.9357(4)	-.1357(1)	.3751(3)
C9	.9407(4)	-.0670(2)	.4088(3)
C10	.8132(4)	-.0283(1)	.3393(3)
N11	.8587(3)	-.0221(1)	.2171(2)
C12	.7724(3)	.0117(1)	.1387(3)
N13	.8336(3)	.0191(1)	.0312(2)
C14	.7522(3)	.0540(1)	.0543(3)
O15	.8125(2)	.0587(1)	-.1530(2)
C16	.5989(3)	.0845(1)	-.0232(3)
C17	.5462(4)	.0737(1)	.0850(3)
N18	.6273(3)	.0378(1)	.1677(2)
C19	.5072(3)	.1252(1)	-.1119(3)
C20	.5898(3)	.1880(1)	-.1316(3)
C21	.6795(4)	.2005(2)	-.2296(3)
C22	.7486(4)	.2589(2)	-.2444(3)
C23	.7263(5)	.3035(2)	-.1610(3)
N24	.6399(4)	.2934(1)	-.0645(3)
C25	.5757(4)	.2366(2)	-.0525(3)
O26	.3803(4)	.0150(2)	.3328(3)
O27	.5619(4)	.0852(1)	.5196(3)

Table 3. Rectangular coordinates of 2-(4-Phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone.

ATOMS	X	Y	Z
C1	6.099068	-6.004914	3.214872
C2	6.32956	-7.181531	3.046209
C3	6.936943	-7.903533	4.027423
C4	7.302525	-7.289338	5.197814
C5	7.081279	-5.940366	5.374456
C6	6.471248	-5.186435	4.377286
C7	6.247215	-3.711922	4.561905
C8	7.511552	-2.890364	4.27472
C9	7.39191	-1.428749	4.658773
C10	6.394807	0.5996584	3.866736
N11	6.812786	-.4718891	2.474118
C12	6.151508	.2479271	1.580655
N13	6.688743	.4061955	.3555619
C14	6.024086	1.14866	.6188145
O15	6.596166	1.250221	-1.743621
C16	4.823793	1.798248	-.2643922
C17	4.354353	1.567621	.9766557
N18	4.972335	.803092	1.911145
C19	4.123345	2.664967	-1.275237
C20	4.794903	4.001434	-1.499742
C21	5.557208	4.268155	-2.616571
C22	6.118221	5.510958	-2.785235
C23	5.767542	6.45697	-1.834791
N24	5.168021	6.243738	-.7350559
C25	4.647562	5.035002	-.5983013
O26	2.917208	.3166964	3.792661
O27	4.297633	1.809085	5.921473

Results by ACD Chemsketch and ArgusLab 4 can be shown as prospective view and label atoms active conformation of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone are shown in figures 3 and 4 respectively.

Figure 5 shows calculated properties of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone by ACDLab Chemsketch, and figure 4 shows prospective view of active conformation of 2-(4-phenylbutylamino)-5-(3-pyridylmethyl)-4-pyrimidone. Figure 6 shows the electron density map of cimetidine derivative by ACD Lab-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.

Figure 7 shows the electrostatic potential of cimetidine derivative ground state mapped onto the electron density surface for the ground state. Figure 8 Electrostatic potential (ESP) mapped electron density surface (mesh).

Figures 7 and 8 use 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 region of highest stability for a positive test charge, magenta/blue shows the regions of least stability for a test positive charge. These images show that the carboxyl end of the molecule is electro rich relative to the amino end . figure 9 shows the occupied π-molecular orbital of cimetidine derivative calculated with the ZINDO method and rendered as a 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. These types of surface representations are useful to discuss drug receptor interaction.

Table 4. Bond Angle of 2-(4-Phenylbutylamino)-(3-pyridylmethyl)-4-pyrimidone.

1st Atom	2nd Atom	3rd Atom	Bond Angle
C2	C1	C6	127.1214
C1	C2	C3	120.0215
C2	C3	C4	119.7979
C3	C4	C5	120.3485
C4	C5	C6	120.6193
C1	C6	C5	112.1279
C1	C6	C7	127.3133
C5	C6	C7	120.6282
C6	C7	C8	112.3227
C7	C8	C9	113.8331
N11	C12	N13	118.5999
N11	C12	C14	155.2474
N11	C12	N13	119.7943
N13	C12	C14	225.3696
N13	C12	N18	121.678
C14	C12	N18	259.205
C12	N13	C14	246.0921
C12	C14	N13	248.4658
C17	C16	C19	123.7676
C16	C17	N18	124.9542
C12	N18	C17	117.6035
C16	C19	C20	113.7331
C19	C20	C21	122.4941
C19	C20	C25	121.2012
C21	C20	C25	116.3624
C20	C21	C22	120.0483
C20	C25	N24	125.1204

Table 4. Bond Lengths of 2-(4-Phenylbutylamino)-5-5-(3-pyridylmethyl)-4-pyrimidone.

1st Atom	2nd Atom	Bond length
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

CONCLUSION

Results of GW BASIC programming and ArgusLab 4.0.1 software shown that the minimum total potential energy is -0.0056 kcal/mole at $\omega_1 = 270°$ and $\omega_2 = 340°$ from all pairs and Final SCF energy - 80741.3979 kcal/mol respectively.

The present work indicates that the best conformation of cimetidine derivative by Gw basic programming and by ArgusLab software is found to be -.0065 Kcal/mole . At this point cimetidine derivative will be more active as histamine H_2 receptor antagonists.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 use in molecular modeling studies.

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