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Comparative studies of cimetidine derivative "temalastine" for potential energy calculation by Kitaigorodskii and Lennard-Jones functions

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Abstract: The non-bonded potential energies were computed for 2-[4-(5-Bromo-3-methyl-2-pyridyl) butylamino]-5-(6- methyl -3 - pyridyl - methyl) - 4 – pyrimidone, trihydrobromide , (Temalastine), which is the H_1 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 temalastine by using kitaigorodsky and lennard jones functions. The minimum potential energy was found to be -0.0089 k.cal/mol at $\omega1 = 120^o$ and $\omega2 = 260^o$ by katiagorodskii function and -0.0067 k.cal/mol at $\omega1 = 120^o$ and $\omega2 = 260^o$ by leneared jones function . The comparison between results obtained from kitaigorodskii function and lennard jones function give suggestion that both function give same results.

Keywords: Kitaigorodskii function, Lennard Jones function, cimetidine, temalastine, H_1 and H_2 antagonists.
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INTRODUCTION

Neuronal histamine has been implicated in a variety of brain functions including learning and memory[1]. Central histaminergic neurons are located exclusively in the tuberomammillary nucleus of posterior hypothalamus, from where they project diffusely to all regions of brain[2]. Although histamine receptors distribution in the brain has been shown to considerably differ among species, high density of both postsynaptically located histamine H_1 and H_2 receptors has been found in the cortex, hypothalamus and other limbic regions including hippocampus and amygdale[3] , these brain regions are closely involved in cognition and emotion [4]. Cimetidine, a H_2 receptor antagonist, has been demonstrated to have anticancer effects on colorectal cancer, melanoma and renal cell carcinoma [5] also capable of reducing gastric acid secretion with usual therapeutic dose[6]. Since the identification of the H_2 receptor[7] a variety of compound have been shown to be specific H_2 receptor antagonists. Of these compounds significant number, cimetidine [8] , ranitidine , tiotidine, famotidine and oximetidine [9] 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. Certain closely related compounds in which the heterocyclic 'head' pyridine, the dipolar group is an isocytosine, as in oximetidine, and the four atom chain butyl, are active as both H_1 and H_2 antagonists[10].

Exploitation of QSAR (quantitative structure activity relationships) studies on these compounds has lead to the generation of a series of compounds which have the same general characteristics, but are specific and potent H_1 antagonists. Cimetidine is the H_2 receptor antagonists led to the development of other derivatives, which is widely used an affective inhibitor of gastric acid secretion in the treatment of duodenal ulcer and related conditions [11]. It has been found that a predominance use of low energy conformation with distances between aromatic N atoms and those in the isocytosine or thiodiazole-1-oxide groups in the region 5.2 6.0 A^o tend to correlate with H_1 activity in agreement with work by other on established H_1 antagonists [12] .The crystal and molecular structure of 2-[4-(5-Bromo-3-methyl-2-pyridyl)butylamino]-5-(6-methyl-3-pyridyl-methyl)-4-pyrimidone trihydrobromide, (temalastine) with strong structural resemblances to the cimetidine group of H_2 receptor antagonist, but exhibits selective H_1 receptor antagonist activity. This compound has molecular formula $C_{21}H_{27}BrN_5O^3.3Br$ and have triclinic structure with a = 6.314, b =11.192 and c =19.441 and bond angles are α=102.47, β=92.77 and γ=103.28, Mr=685.09, P1, V=1298.51 A3, Z=2, Dx =1.75 g cm^{-3} , μ= 61.6 cm^{-1} , F(000)=672, R=2.93 % for 3208 independent reflexions and behavior shown like H_1 antagonist activity[12]. In this work semiempirical conformational energy calculation were performed for the temalastin by two different functions.

Methods of calculation

The three dimensional Quantitative structure activity relationships (3D QSAR) provides the valuable information about the nature of the receptor[13-16]. It helps to describe new drug candidates and improve in vitro potency[17]. The crystallographic parameters were utilized in determining the three dimensional structure of the molecule , in this conformation of temalastin is analyzed based on the triclinic coordinates reported[12].

The potential energy can be calculated from these two relationships

1: Kitaigorodskii function[18,19]
2: Lennard Jones function[20]

In order to determine the allowed conformation the contact distance between the atoms in the adjacent residues have to be examined using criteria for minimum value of vander Waals contact distance [21]. The fractional coordinates by multiplying with unit cell dimensions.

a =6.314,b=11.192,c=19.441

Triclinic coordinates have been converted into rectangular coordinates using the following relationship.

$$X=xi+yi.\cos\gamma+zi\cos\beta$$
$$Y=yi.\sin\gamma+zi(\cos\gamma-\cos\beta.\cos\gamma)/\sin\gamma$$
$$Z=zi[1-\cos^2\alpha-\cos^2\beta-\cos^2\gamma)+2\cos\alpha.\cos\beta.\cos\gamma)]^{1/2}/\sin\gamma$$

Where as $\gamma = 102.47$, $\beta = 92.77$, $\gamma = 103.28$

The bond length and bond angles have also been calculated using the following relationship.

$$\text{Bond length} = L = \exp (x_2-x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2$$

$$\text{Bond angle} = Q = \cos -1\ (-L3)2 - (L1)^2 - (L2)^2 \ /\ 2 \times L1 \times L2$$

If x, y, z and X`,Y` Z` are the coordinates of atoms in triclinic system before and after the rotation through ω_1,ω_2 and ω_3 so the relationship use to evaluate these coordinates are as

$X` = (a^2+b^2-c^2-d^2)\ x + 2(bc - ad)\ y + 2(bd + ac)\ z$
$Y` = z\ (bc + ad)\ x + (a^2-b^2+c^2-d^2)\ y + 2(cd - ab)\ z$
$Z` = z(bd - ac)\ x + 2(cd + ab)\ y + (a^2-b^2-c^2+d^2)z$

Where,

$a = \text{Cos}\ (\omega/2)$
$b = L \times \sin\ (\omega/2)$
$c = M \times \sin\ (\omega/2)$
$d = N \times \sin\ (\omega/2)$

"ω" being the angle of rotation. L, M, N are the direction cosines of the axis of rotation with respect to chosen system of coordinates and determined by given relationship.

$L= X_2 - X_1$ / Bond length X_1 --- X_2
$M=Y_2 - Y_1$ / Bond length Y_2 ----- Y_1
$N=Z_2 - Z_1$ / Bond length Z_2 ----- Z_1

Kitaigorodskii function used to calculate the potential energy "V" after parameter variations (ω_1, ω_2)[21].

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

Where as $z = Rij\ /\ R^o$

Rij = bond length

R^o = Equlibrium distance between non bonded atoms.

The potential energy is also calculated by the lennard jones function.

$$V = A\ /R^6 - B\ /\ R^{12}$$

Value of R^o, A and B are given in article [22].

The atom O_{17},C_{19},C_{16} and N_{20} at which the two residues [$C_{21} - C_{18} - O_{17}$, C_{19},C_{16},N_{20}] and [C_{21}-C_{22}-C_{28} ,C_{23},C_{27},N_{24}] linked together is taken to be the origin of coordinates of a system. The coordinates of atom C_{21} are rotated at intervals of 20^o angle of ω1 and the coordinates of atoms C_{28} ,C_{23},C_{27} and N_{24} are rotated at intervals of 20^o Angle for ω_2.

We calculated potential energy by both functions. No interaction was found for some pairs and some shows interaction. We calculated the total potential energies of active pairs, for all purpose we use several computer programs which were written in Basic language and IBM compatible computer was used throughout this work, here we used bond angle , bond length , potential energy calculation and total potential energy calculation programs[23,24],and for graphics we used Statistica (SSPS) software.

Following pairs were selected for potential energy calculations:

$C_{28} - O_{17}$, $C_{23} - O_{17}$, $C_{27} - O_{17}$, $N_{24} - O_{17}$, $C_{23} - C_{19}$, $C_{28} - C_{19}$, $C_{27} - C_{19}$, $N_{24} - C_{19}$, $C_{28} - C_{16}$, $C_{23} - C_{16}$, $C_{27} - C_{16}$, $N_{24} - C_{16}$, $C_{23} - N_{20}$, $C_{27} - N_{20}$, $C_{20} - N_{20}$, $N_{24} - N_{20}$.

In the present work potential energy of non-bonded interactions for temalastin is calculated by two different functions. Total potential energies were calculated by summation of all individual pairs. Contours are plotted for visual understanding.

RESULTS

The prospective view of temalastin is shown in figure 1. Calculated value of bond angle and bond length shown in table 1 and 2 respectively. The results indicate serious type of interaction for the following pairs:

$C_{28} - O_{17}$, $C_{23} - O_{17}$, $N_{24} - O_{17}$, $C_{27} - O_{17}$, $C_{23} - C_{19}$, $C_{28} - C_{19}$, $C_{23} - C_{16}$, $C_{28} - C_{16}$

Results for these pairs indicate little interaction.

C_{27} – C_{19}, N_{24} – C_{19}, C_{27} – C_{16}, N_{24} – C_{16}, C_{23} – N_{20}, C_{27} – N_{20}, C_{26} – N_{20}, N_{24} – N_{20}

Table 1: Bond length of fractional co-ordinates.

No	Pairs	Bond length
1	N1----------C2	1.343119
2	N1----------C8	1.354302
3	C2----------C3	1.374234
4	C3----------C5	1.370825
5	C5----------C6	1.391214
6	C6----------C7	1.50633
7	C6----------C8	1.393787
8	C8----------C9	1.493925
9	C9----------C10	1.516434
10	C10--------C11	1.519984
11	C11--------C12	1.496912
12	C12--------N13	1.473045
13	N13--------C14	1.312016
14	C14--------N15	1.349114
15	C14--------N20	1.38115
16	N15--------C16	1.386858
17	C16--------O17	1.225323
18	C16--------C18	1.447999
19	C18--------C19	1.350921
20	C18--------C21	1.501098
21	C19--------N20	1.371728
22	C21--------C22	1.509971
23	C22--------C23	1.385326
24	C22--------C28	1.380211
25	C23--------N24	1.3333322
26	N24--------C25	1.343581
27	C25--------C26	1.488217
28	C25--------C27	1.385933
29	C27--------C28	1.38109

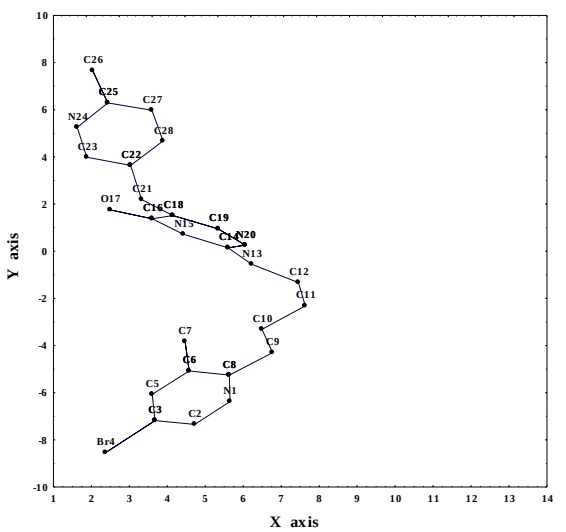

Figure 1: 010 projection of Temalastin.

The results give detail information about the conformation of temalastine can exist in at least two stable conformations. The stable conformation are the maximum at $\omega1 = 260^o$, $\omega2 = 60^o$ and the minimum at $\omega1 = 120^o$, $\omega2 = 260^o$ by both functions ($\omega1$ and $\omega2$ are the angle of rotation about the bonds C_{21}-C_{18},C_{21}-C_{22} respectively). The minimum potential energy was found to be -0.0089 k.cal/mol at $\omega1 = 120^o$ and $\omega2 = 260^o$ by katiagorodskii function and -0.0081 k.cal/mol at $\omega1 = 120^o$ and $\omega2 = 260^o$ by leneared jones function . The potential energy contour for temalastin by both functions is shown in figures 2 and 3.

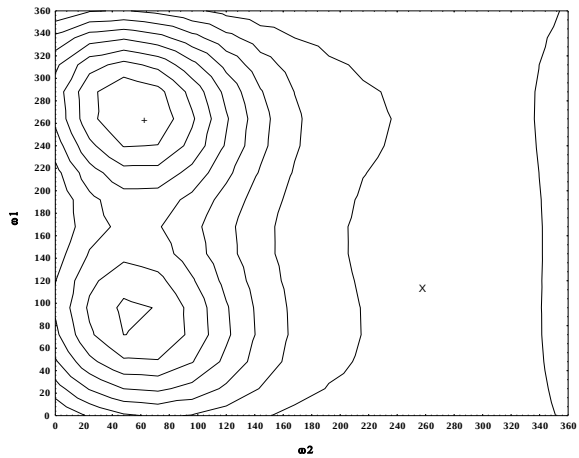

Figure 2: Total potential energy contour graph by Kitaigorodskii function.

+ =The maximum potential energy is found to be 2223.77 k.cal/mol at $\omega1 = 260^o$, $\omega2 = 60^o$.

x=The minimum potential energy is found to be -.0089k.cal/mol at $\omega1 = 120^o$,
$\omega2 = 260^o$.

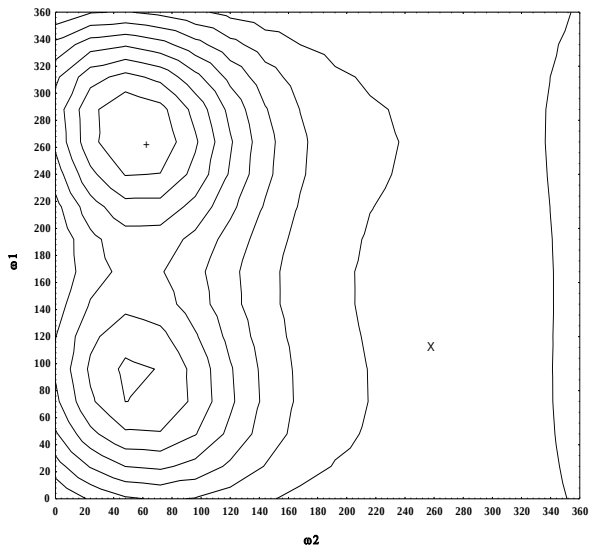

Figure 3: Total potential energy contour graph by Lennard Jones function.

+ = The maximum potential energy is found to be 1672. 02 k.cal/mol at $\omega1 = 260^o$, $\omega2 = 60^o$.

x =The minimum potential energy is found to be -. 0067k.cal/mol at $\omega1 = 120^o$,$\omega2 = 260^o$.

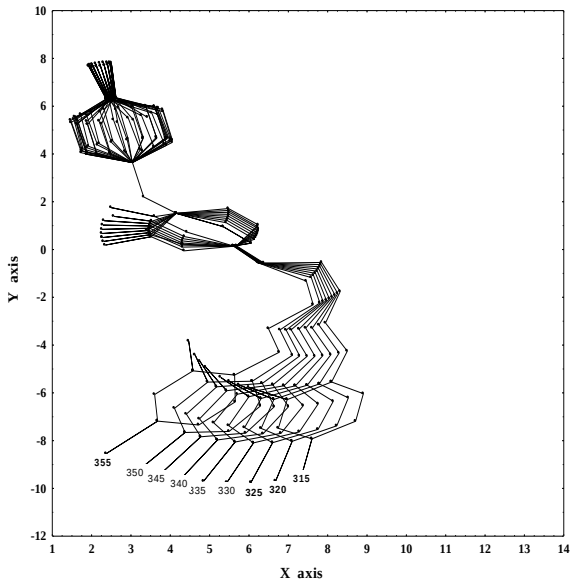

Figure 4: Allowed zone 315° to 355° by Kitaigorodskii results.

Table 2: Bond angles of co-ordinates.

No	Pairs	Bond angles
1	C2----N1----C8	125.0263
2	N1----C2----C3	117.2309
3	C2----C3----C5	120.547
4	C3----C5----C6	121.2098
5	C5----C6----C7	121.1544
6	C5----C6----C8	117.7702
7	C7----C6----C8	121.1105
8	N1----C8----C6	118.3606
9	N1----C8----C9	117.1848
10	C6----C8----C9	124.5179
11	C8----C9----C10	110.8601
12	C9----C10---C11	111.1761
13	C10---C11---C12	114.553
14	C11---C12---N13	109.9165
15	C12---N13---C14	125.0276
16	N13---C14---N15	118.3723
17	N13---C14---N20	123.1131
18	N15---C14---N20	118.5438
19	C14---N15---C16	124.6285
20	N15---C16---O17	118.9762
21	N15---C16---C18	115.0337
22	O17---C16---C18	126.0426
23	C16---C18---C19	118.6337
24	C16---C18---C21	118.9258
25	C19---C18---C21	122.3762
26	C18---C19---N20	122.0367
27	C14---N20---C19	121.0851
28	C18---C21---C22	112.7268
29	C21---C22---C23	120.5148
30	C21---C22---C28	123.2774
31	C23---C22---C28	116.2633
32	C22---C23---N24	121.1873
33	C23---N24---C25	124.4439
34	N24---C25---C26	118.797
35	N24---C25---C27	115.9613
36	C26---C25---C27	125.3081
37	C25---C27---C28	121.1321
38	C22---C28---C27	121.1569

This molecule has very fix allowed region this shows that its flexibility is very fix and very low, the allowed region for the molecule shown in figures 4 and 5 by Kitaigorodskii and Lennard Jones respectively.

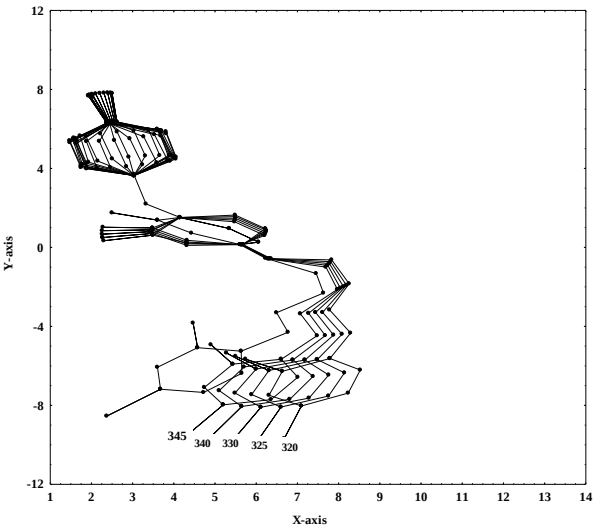

Figure 5: Allowed zone 320 to 345° by Lennard Jones results.

CONCLUSION

The comparison between results obtained from Kitaigorodskii function[18] and Lennard Jones[19] interaction give suggestion that both function give same results and difference between both allowed zone is very rear which is negligible.

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