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# CONFORMATIONAL ANALYSIS OF HISTAMINE $H_1$-RECEPTOR ANTAGONIST "TEMALASTINE" AS A CIMETIDINE DERIVATIVE

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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 function. The minimum potential energy was found to be -0.0089 k.cal/mol at $\omega 1 = 100^o$ and $\omega 2 = 300^o$ . Allowed region is obtained for the Temalastin, using minimum potential energy, and the results indicates that possible allowed zone by using conformation for the Temalastin is $315^o$ to $360^o$.

**Key words:** Cimetidine, Temalastine, Histaminergic receptors, $H_1$ & $H_2$ antagonists, conformational analysis

## INTRODUCTION

Neuronal histamine has been implicated in a variety of brain functions including learning and memory ( Haas *et al*., 2003). Central histaminergic neurons are located exclusively in the tuberomammillary nucleus of posterior hypothalamus, from where they project diffusely to all regions of brain (Tatsuya *et al*.,2007). 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 amygdala (Ryu *et al*., 1995). These brain regions are closely involved in cognition and emotion (Hongmei *et al*.,2006). Cimetidine, a histamine-2 ($H_2$) receptor antagonist, has been demonstrated to have anticancer effects on colorectal cancer, melanoma and renal cell carcinoma (Tatsuya *et al*., 2007) also capable of reducing gastric acid secretion with usual therapeutic dose (Jan M. *et al*., 2005). Since the identification of the 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 , tiotidine, famotidine and oximetidine (Brown *et al*., 1988) have the general form of a heterocyclic 'head' linked by a four-atom chain, often methylthioethyl, to a dipolar 'tail'. These compound 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 (Cooper *et al*., 1991). 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 histamine, $H_2$ 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 (Onoa *et al*., 2002) . In the histamine $H_2$ receptor antagonist metiamide 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 substituents into the guanidine group reduces basicity and gives potent $H_2$ receptor antagonists, the cyanoguanidine (Brown *et al*., 1986). It has been found that a predominance use of low energy conformation with distances between cromatic 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 (Bannister *et al*., 1994).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 histamine $H_2$ 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 $\alpha$ = 102.47, $\beta$=92.77 and $\gamma$=103.28, Mr = 685.09, P1, V= 1298.51 A3, Z =2, Dx =1.75 g $cm^{-3}$ , $\mu$ = 61.6 $cm^{-1}$ , F(000) = 672, R = 2.93 % for 3208 independent reflexions and behavior shown like $H_1$ antagonist activity (Bannister *et al*., 1994).In this work semiempirical conformational energy calculation were performed for the temalastin and only non-bonded interactions are considered (Haleem *et al*., 1988), similar to other drugs (Farhat *et al*., 2006, Naheed *et al*., 2004). The calculation suggests the temalastin adopts limited allowed conformation.

**METHODS OF CALCULATION**

The three dimensional Quantitative structure activity relationships (3D QSAR) provides the valuable information about the nature of the receptor (Asim *et al*., 2001 ; Benjamin *et al*., 1994 ; Michael *et al*., 1987 ; Greedide *et al*., 2001). It helps to describe new drug candidates and helps ti improve in vitro potency( Manule *et al*., 1992). 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 (Bannister *et al*., 1994). 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. The fractional coordinates by multiplying with unit cell dimensions.

a =6.314,b=11.192,c=19.441

Triclinic coordinates(xi, yi, zi) have been converted into rectangular coordinates using the following relationship.

$$x = xi + yi \cdot \cos\gamma + zi \cos\beta$$

$$y = yi \cdot \sin\gamma + zi (\cos\gamma - \cos\beta.\cos\gamma)/\sin\gamma$$

$$z = zi[1-\cos^2\alpha - \cos^2\beta - \cos^2\gamma + 2\cos\alpha.\cos\beta.\cos\gamma)]^{1/2} / \sin\gamma$$

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

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 rectangular system before and after the rotation through $\omega_1$,$\omega_2$ and $\omega_3$ 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(Clark *et al*., 1972).

$L = X_2 - X_1$ / 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 ($\omega_1$,$\omega_2$) (Pizzi *et al*., 1984)

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

Where as $z = Rij / R^o$

Rij = bond length

$R^o$ = Equlibrium distance between non bonded atoms.

Values of $R^o$ are given in article (Scott *et al*., 1966) .

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 $\omega_2$.

We calculated potential energy by the Kitaigorodskii function (Kitaigorodskii *et al*., 1961) with upper (K1) and lower (K2) limits. 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 through out this work, here we used bond angle and bond length programs (Haleem *et al*., 1988), Statistica software was used for graphics.

**Table 1. Bond length of fractional co-ordinates.**

| S.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 |

**Table 2. Bond angles of co-ordinates.**

| S.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 |

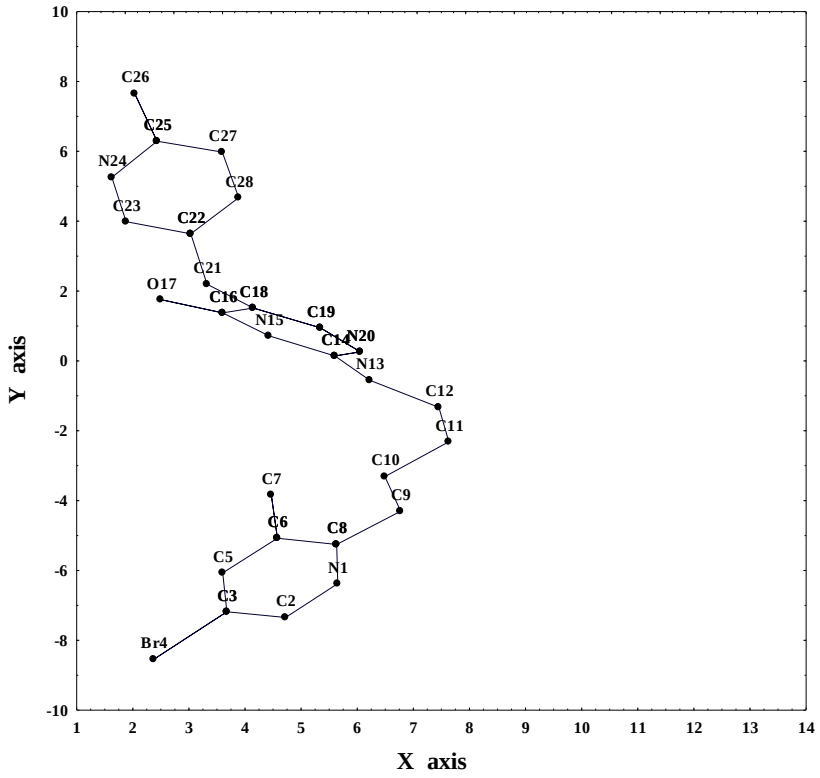


Fig 1. 010 PROJECTION OF TEMALASTIN

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 nonbonded interactions for Temalastin is calculated. 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.
**$C_{27} - C_{19}$, $N_{24} - C_{19}$, $C_{27} - C_{16}$, $N_{24} - C_{16}$, $C_{23} - N_{20}$, $C_{27} - N_{20}$, $C_{26} - N_{20}$, $N_{24} - N_{20}$**

The results give detail information about the conformation of temalastine can exist in at least two stable conformations. The stable conformation are the maximum $\omega_1$= 280 , $\omega_2$ =60 and the minimum ω1= 120 , ω2= 300($\omega_1$ and $\omega_2$ are the angle of rotation about the bonds $C_{21}$-$C_{22}$,$C_{21}$- $C_{22}$ respectively).
The maximum and minimum potential energy by taking upper limit $K_1$ found to be 121.824 k.cal/mole at $\omega_1$ = 280 and $\omega_2$ = 60 & -0.0089 k.cal/mole at $\omega_1$= 100 and $\omega_2$ =300 respectively,shown in Fig. 2.
Similarly the Maximum and Minimum Potential Energy has been calculated by taking lower limit $K_2$ found to be 65.2 k.cal/mole at $\omega_1$=280 and $\omega_2$ = 60 and –0.097 k.cal/mol at $\omega_1$ =200 and $\omega_2$ = 280 respectively shown in Fig. 3.

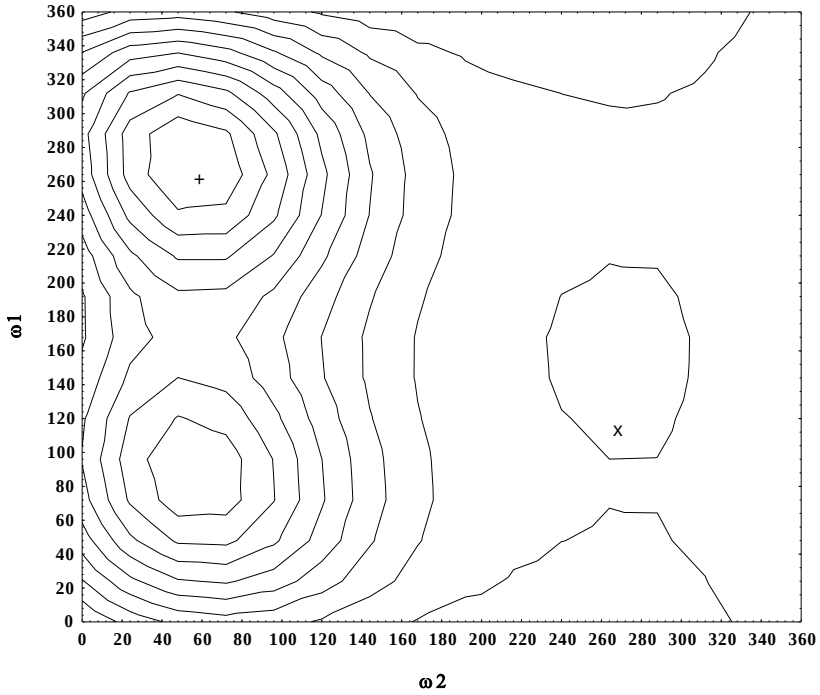


Fig. 2. Total Potential Energy Contour Graph by Kaitiagorodakii Function with upper limits(K1).
+ = The maximum potential energy is found to be 2223.77 k.cal/mol at $\omega_1 1=280$ , $\omega_1 2 = 60$.
x = The minimum potential energy is found to be -.0089k.cal/mol at $\omega_2 1=100$ , $\omega_2 2 = 300$.

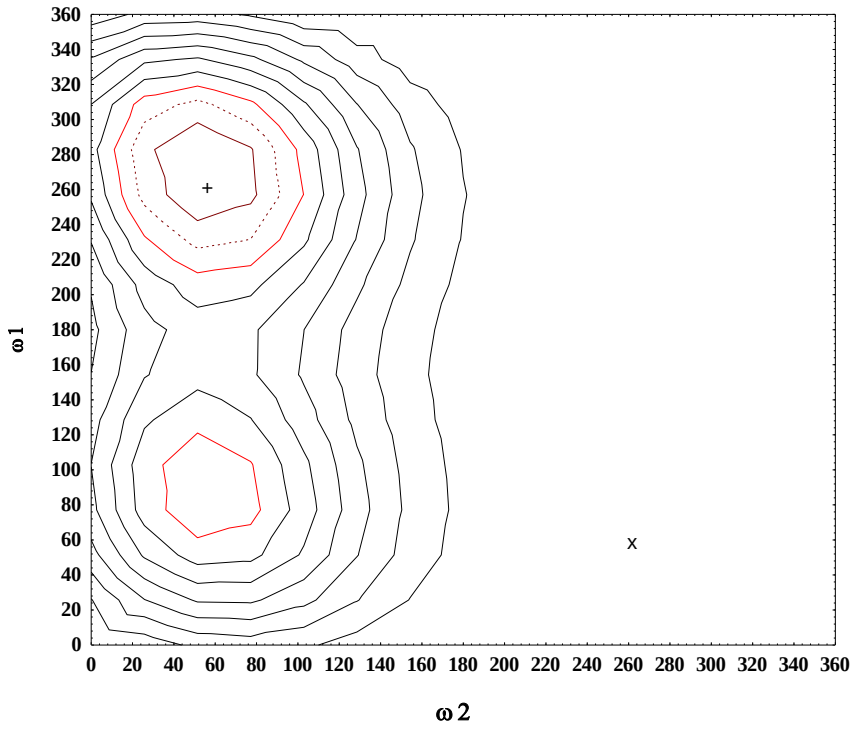


Fig 3. Total Potential Energy Contour Graph By Kataigorodskii function with lower limits ( K2).
+ = The maximum potential energy is found to be 65. 2 k.cal/mol at $\omega_1 1=280$ , $\omega_1 2 = 60$.
x = The minimum potential energy is found to be - 0. 097 k.cal/mol at $\omega_2 1=100$ , $\omega_2 2 = 300$.

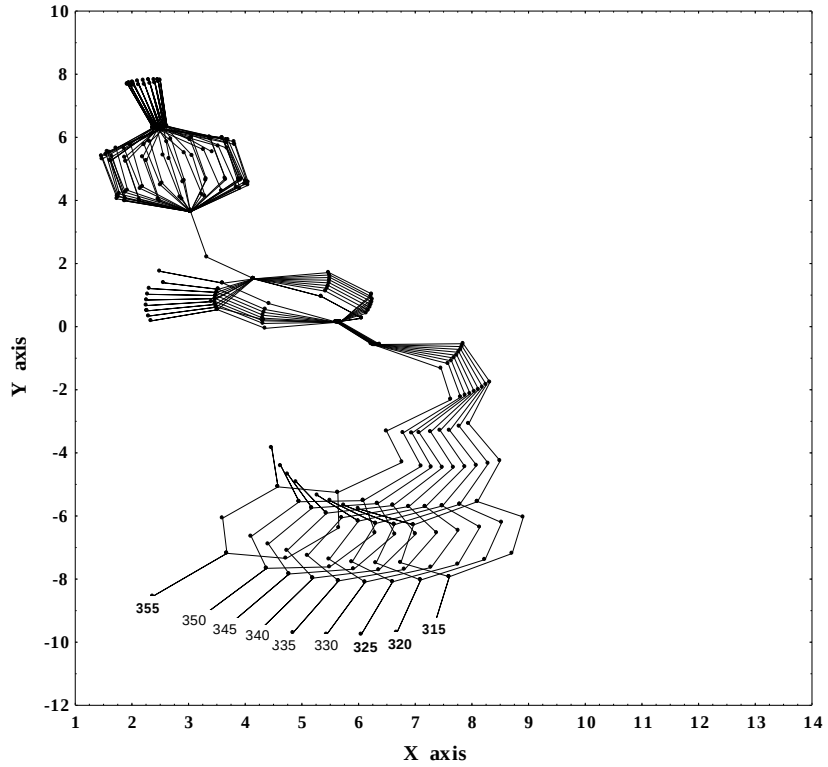


Fig. 4. Flexibility of molecule by allowed zone.

The allowed region found to be $\omega_1$= 0 to 70, $\omega_2$ = 0 to 20, $\omega_1$ = 170 to 250, $\omega_2$ = 0 to 20, $\omega_1$=0 to 20, $\omega_2$ =0 to 360, $\omega_1$ = 0 to 100 and $\omega_2$ =150 to 180, $\omega_1$ = 120 to 180 and $\omega_2$ =100 to 180, $\omega_1$ = 180 to 220, $\omega_2$ = 140 to 240 and $\omega_1$ = 240 to 360, $\omega_2$ = 100 to 200, $\omega_1$ = 0 to 360 and $\omega_2$ = 320 to 360.
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 its flexibility in Fig. 4 .

## DISCUSSION

Results of the present work indicates that flexibility for the temalastine is less as compared to the structure proposed by (Bannanster *et al*., 1994) and the ring information about non equilibrium conformation energies , electron densities as well as electrostatic maps. It is likely to provide a much more detailed picture of active receptor site and conformation of molecules for the interaction with the receptor.

The molecular pharmacologist ideally knowledge of the detailed nuclear and electronic topography of receptor binding sites, although he would probably be satisfied with crystal structure data or receptors. Until this is available, inferred from studies of agonist and antagonist molecules preferably with effects such as metabolism and distribution reduced or excluded. Comparative investigations of flexible compounds may reveal which conformations are essential for binding and are easier task is present if the active compounds are rigid. Theoretical calculation can supply non equilibrium conformational energies and electron densities well as electrostatic potential maps from such calculation it is in principle possible to provide a much more detail picture of an active receptor site the those currently to be found in the literature.

## REFERENCES

Asim, K. (2001). Quantitative Structure activity (QSAR) paradigm-hansch era to new millinium. *Mini Reviews in Medical Chemistry*. pp.187-195.

Bannister, C., K. Burns and D.J. Waykin (1994). Structures of Histamine H1- Receptor Antaginists derived from the Cimetidine group of Histamine H2 Receptor Antagonists. *Acta Cryst*., B50: 221- 243.

Benjamin, J., E.J. Dunna and A.J. Hoffer (1994). Construction of molecular shapes analysis "three dimensional quantitative structure analysis relationships for an analog series of pyridobenzo diazepinone. *J. Med. Chem*., 37: 3775-3788.

Black, J.W., W.M.A. Duncan, G.J. Durant, C.R. Ganellin and M.E. Parson (1972). Definition and antagonism of histamine H2 receptor. *Nature*., 236: 385-390.

Brimblecombe, R.W., W.A.M. Ducan, G.J. Durant, C. Emmett, C.R. Ganellin and ME. Parsons (1975). Cimetidine , A non-Thiourea H2 receptor antagonist. *J. Int. Med. Res.*, 3: 86-92.

Chikai, T., R. Oishi and K. Saeki (1994). Increase in the extracellular histamine concentration in the rat striatum by mu-opioid receptor activation. *J. Neurochem.* 62: 724-729.

Chung, Y.H., H. Miyake, C. Kamei and J. Tasaka (1984). Analgesic effect of histamine induced by intracerebral injection into mice. *Agents Actions*, 15: 137-142.

El Kadi A. O. and S.L. Sharif (1996). The role of histaminergic-noradrenergic axis in naloxone-induced withdrawal symptoms in mice. *Pharmacol. Biochem. Behav*. 55: 49-54.

Farhat, B., A. Naheed and M.A. Haleem (2006). Conformational Analysis Of Azaprophen Hydrochloride. *Intl. Chem. Pharm. Med. J.*, 3: 187-190.

Grazyna, K., C.D. Jan and P.M. Aleksander (2003). Conformation and Tautamerism of the Cimetidine molecule: a theoretical study . *J. Mol. Struc.*, 645:1) 37-43.

Greendige, P.A. (2001). A Comparison of methods for Pharmacophore generation with the catalyst software and their use for 3D QSAR . *Mini Review in Medical Chemistry*,pp. 79-87.

Haleem, M.A. and Z.S. Saify (1989). Potential Energy Calculation of Treptilaninum. *Pak. J. Sci. Ind. Res*., 32(2): 74-76.

Haleem, M.A. (1988) *A Basic program for calculating total potential energy on the basis of Potential energy calculation*. Biophysics Research Uni. Dept. of Biochem.,University of Karachi, Pakistan.

Haas, H.L. and P. Panula (2003). The role of histamine and the tuberomamillary nucleus in the nervous system. Nature reviews, *Neuroscience* 4: 121–130.

Hongmei, D., K Kenya, K. Hiroshi, F. Satoshi, J. Yuhong, X. Ajing, S. Eiko, K. Motohisa, O. Nobuyuki, K. Atsuo and Y. Kazuhiko (2006). Selective cognitive dysfunction in mice lacking histamine H1 and H2 receptors . *J. Neures (online).* www.sciencedirect.com.

Jan, M., A.O. Shaukat, T.M.J. Shafique, A. Shafiq, H. Muhammad and Q. Muhammad (2005). Comparison for their effects on volume and acidity of carbachol induced gastric secretion in fasting rabbits. *J. Ayub. Med. Coll. Abbottabad*., 17(3): 33- 41.

Kitaigorodskii, A.I. (1961). The interaction curve of non bonded carbon and hydrogen atoms and its application. *Tetrahedron*., 14: 230-236.

Kitaigorodskii, A.I. (1965). The Principle of close packing and the condition of thermodynamic stability of organic crystals. *Acta Cryst.* 18: 585-590.

Manuel, A. .N (1992). Use of Structral information in drug designing. *Current Opinion in Structural Biology*, pp.201-202.

Naheed, A., B. Farhat, N. Sadaf and M.A. Haleem (2004). Computer Aided Conformational Analysis of Sulfonated azo dyes diammonium Orange G(C16H10N2 O7S2 (NH4). 4H2O. *Pak. J. Pharma. Sci.*,18 (3): 66-70.

Onoa, G.B., V. Moreno, E. Freisinger and B. Lippert (2002). Pd (II)- and Pt (II)- cimetidine)2]Cl2.12H2O . *J. Inorg. Biochem*., 89: 237-247.

Pizzi, A and N. Eaton (1984).The structure of cellulose by conformational analysis 1. cellobios and Methyl □□ cellobioside. *MacroMol.Scl .Chem*., A21: (11 and 12).

Ramachandran G.N. and V.Sasisekharan (1968). Conformation of Polypeptide and proteins. *Adv. Protein Chem*., 23: 283-438.

Ryu, J.H., K. Yanai, E. Sakurai, C.Y. Kim and T. Watanabe (1995). Ontogenetic development of histamine receptor subtypes in rat brain demonstrated by quantitative autoradiography, *Dev. Brain Res.*, 87: 101–110.

Scott, R.A. and H.A. Scheraga (1966). Conformational Analysis of Macromolecules. II. The Rotational Isomeric States of Normal Hydrocarbons. *J. Chem. Phys*., 44: 3054.

Toshimasa, I., I. Yasuko, D. Mitsunobu and I. Masatoshi (1989). Structural Study of Histamine H2 Receptor Antagonists. Five 3-[2-(Diaminomethyleneamino)-4-thiazolymethylthio] pro- pionamidine and –amide Derivatives. *Acta Cryst*.. B(45): 505 – 512.

Tatsuya, F., S. Hidenori, N. Yutaka, T. Nobuyuki, U. Naoki, S. Mayumi and S. Yasushi (2007). Cimetidine inhibits epidermal growth factor-induced cell signaling. *J. of Gastroenterology and Hepatology,* 22 (3) : 436–443 .

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