

THREE DIMENSIONAL QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS OF 3-[3-(N-4-FLUROBENZYL-N-2 PYRIDYLAMINO) PROPYLAMINO]-4-ETHYLAMINO-1, 2, 5- THIAZOLE-1-OXIDE (HISTAMINE H₁ RECEPTOR ANTAGONIST) AS AN ANTI-ULCER AND ANTI-ALLERGY

Atia Masood Ahmed Chaudhary^{1, 2} and Naheed Akhtar¹

¹*Biophysics Research Unit, Department of Biochemistry, University of Karachi, Karachi-75270, Pakistan*

²*Bioassays and Plant Screening Section, H. E. J. Research Institute of Chemistry, International Center of Chemical and Biological Sciences (ICCBS), University of Karachi, Karachi-75270, Pakistan
atiamasoodahmedchaudhry@gmail.com*

ABSTRACT

This computer aided drug design based conformational and potential energy quantitative structure activity relationship established to find out best fit conformations with minimum potential energy, active structural and molecular sites for strong binding of 3-[3-(N-4-Flurobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5- thiazole-1-oxide (C₁₉H₂₃FN₆OS) as Histamine H₁ receptor antagonist which is previously derived from Cimetidine and extracted by leaves of *Espinheria santa*. Potential energy calculated for lower limit by Kitagorodasky potential energy function and in-silico approaches. This compound crystalline in monoclinic system, with unit cell dimensions a = 6.686 Å, b = 14.717 Å and c = 20.850 Å, β = 97.83°. Present work find out new bond pair (N₂₁-C₁₅) with strong bonding site and suggests that 3-[3-(N-4-Flurobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5- thiazole-1-oxide has shown minimum potential energy -0.00000983 Kcal/mole as Histamine H₁ receptor antagonist at ω₁ = 280° and ω₂ = 340° (Figure-9). It would supports stable and strong binding of antihistaminic compound to their receptors in allowed active region. The compound (C₁₉H₂₃FN₆OS) in this active conformation would be helpful for the treatment of allergy and different kind of ulcers such as stomach and duodenum ulcers.

Key words: (C₁₉H₂₃FN₆OS), Histamine H₁ receptor antagonist, Allergy, Ulcer, Coordinate, Monoclinic and rectangular unit cell system, Receptor, Conformational and quantitative analysis.

INTRODUCTION

Drug discovery leads to the concept of computer aided drug design (Florence *et al.*, 2002; James *et al.*, 2004; Michael Williams, 2004 and Tommy Liljeforl, 2004). It is use to identify drugs, drug-like compounds and assist clinical testing (Weerasak Samee *et al.*, 2004). It is dependent on the flexibility, lowest energy conformers of the most rigid compounds and superimpose. This may use to develop new compounds of minimum energy conformer, desired positions functional groups and most favorable binding mode within active sites of receptor (Munikumar Reddy Doddareddy *et al.*, 2004 and Gupta, 1989).

Histamine (2, 4-imidazolyl ethylamine) (Fig. 1) is a natural, dibasic, vasoactive amine; neuromodulator and neurotransmitter that stimulate stomach cells to produce acid (Abbas *et al.*, 1994 and Bannister *et al.*, 1994). It is located in most of body tissues and gastrointestinal tract (Abbas *et al.*, 1994; Bach, Jean-Francois, 1982; Froese, 1980 and Gallin, *et al.*, 1980). This single polypeptide chain produced by histamine decarboxylation and stored in effectors cell (Goldie, 1990; Jawetz Melnick *et al.*, 2002; Metcalfe *et al.*, 1997 and Monroe *et al.*, 1997). Release of histamine causes hay fever, bronchial infection, initial phase of asthma, (Bach, Jean-Francois, 1982 and Paul, William, 1984), urticaria (Rang *et al.*, 1995), gastrointestinal tract, suffocation and massive degranulation of mast cells (Abbas *et al.*, 1994, Bach, 1982, Sompayrac, Lauran, 1999, Spiegelberg, 1989). Its deficiency leads to lower levels of melatonin and decreased fat metabolism in the brain that can cause stress (Sompayrac, Lauran, 1999). It is used to treat different kinds of ulcers and allergies (Abbas *et al.*, 1994 and Bach, Jean-Francois, 1982).

This paper describes computer aided drug design based conformational and potential energy quantitative structure activity relationship analysis of 3-[3-(N-4-Flurobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5- thiazole-1-oxide, C₁₉H₂₃FN₆OS (Bannister *et al.*, 1994). It is histamine H₁ receptor antagonist, (Fig. 2), previously derived from cimetidine (histamine H₂ receptor, Fig. 3) (Bannister *et al.*, 1994 and Patricia Maria Ferreira *et al.*, 2004), extracted by *Maytenus aquifolium* and *Maytenus ilicifolia* (*Espinheria santa*) leaves (Fig. 4) (Patricia Maria Ferreira *et al.*, 2004). The data has been taken from literature (Bannister *et al.*, 1994). This current research also correlates and compares with previous study (Bannister *et al.*, 1994) for determination of minimum potential energy, bond lengths, bond angles, new molecular and structural sites by using potential energy function and *in-silico* approaches. The C₁₉H₂₃FN₆OS contains a heterocyclic head linked by a four-atom chain to a dipolar tail (Bannister *et al.*, 1994), (Fig. 3). It has anti-allergy and anti-ulcer properties (Abbas *et al.*, 1994; Bach,

Jean-Francois., 1982; Bannister *et al.*, 1994; Froese, 1980; Gallin *et al.*, 1980; Sompayrac, Laurant, 1999 and Spiegelberg, 1989). It can suppresses the histamines-induced wheal (swelling), flare (vasodilatation) (Abbas *et al.*, 1994; Bach, Jean-Francois., 1982; Sompayrac, Laurant, 1999 and Spiegelberg, 1989), motion sickness (Abbas, *et al.*, 1994; Goldie, 1990; Jawetz Melnick *et al.*, 2002, and Metcalfe *et al.*, 1997), certain types of headaches, Cohn's disease, acute multiple sclerosis and some stomach secretory conditions (Abbas *et al.*, 1994; Bach, Jean-Francois., 1982 and Sompayrac, Laurant, 1999), response by blocking the binding of histamine to its receptors. It is available as over-the-counter drugs, such as, Azatadine (Optimine), carbinoxamine/pseudoephedrine (cardec), cetirizine (zyrtec), ciproheptadine (peractin), fexofenadine (allegra) and loratadine (Bach, Jean-Francois, 1982; Monroe *et al.*, 1997 and Paul William, 1984). The search for histamine receptor antagonists by structural modification has lead to discovery of several new antihistaminic for clinical use (Abbas *et al.*, 1994; Bach, Jean-Francois, 1982; Gallin *et al.*, 1980; Jawetz Melnick *et al.*, 2002; Sompayrac, Laurant, 1999 and Spiegelberg, 1989).

METHODS

This work is not only describes the conformational analysis, (Lingling Shen., 2003 and Manuel *et al.*, 1992) potential energies determination and optimization of (3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5- thiazole-1-oxide) but also helpful to design potent candidate for medicinal use. It's based on quantitative predictions and action mechanism of a drugs (Munikumar *et al.*, 2004; Gupta, 1989; Tommy Liljeforl., 2004 and; Weerasak Samee *et al.*, 2004).

The structure of (3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5- thiazole-1-oxide) was constructed on gaussian-98 (Gaussian 98, Gaussian, Inc., Pittsburgh PA, 2003 USA). Structural modification, minimization and charges were calculated by sybyl 6.9 (SYBYL 6.9. Tripose Inc., 1699). Molden and Kitaigorodskii potential energy function (Kitaigorodskii, 1961 and Ramakrishan *et al.*, 1965) were used to optimizations and calculate potential energy respectively. The bond lengths, bond angles, rotation of coordinates and potential energy were calculated by in-silico approaches GW-Basic 3.0, Statistica 0.5. Gaussian 98 and Molden. In order to determine allowed conformation, the contact distances between the atoms in adjacent residues have to be examined by using the criteria for the minimum Vander Waals contact distance. X, Y, Z Cartesian coordinates on X, Y, Z-axis collected from literature (Bannister *et al.*, 1994). The fractional coordinates X_f , Y_f , Z_f were multiplied by Unit Cell dimensions $a = 6.686 \text{ \AA}$, $b = 14.717 \text{ \AA}$ and $c = 20.850 \text{ \AA}$, converted into monoclinic and rectangular system by formula such as,

$$X_r = Y_m + Z_m \cos \beta \quad (97.83^\circ)$$

$$Y_r = Y_m$$

$$Z_r = Z_m \sin \beta \quad (97.83^\circ)$$

Where,

X_m , Y_m and Z_m (mono-clinic coordinates) on X, Y and Z axis.

X_r , Y_r , and Z_r (rectangular coordinates) on X, Y and Z axis,

Contact distance between atoms can be 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 of first atom in molecule)

X_2 , Y_2 , Z_2 (coordinates of second atom in molecule)

r_{ij} = distance between non-bonded interaction

Bond angles can be calculated by given below formula,

$$\cos \theta = \frac{L_3 \cdot L_1 \cdot L_2}{2 L_1 \cdot L_2}$$

L = Bond length

Coordinates after rotation:

$$L = X_1 - X_2 / l$$

$$M = Y_1 - Y_2 / l$$

$$N = Z_1 - Z_2 / l$$

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

$$\begin{aligned}a &= \cos \omega/2 \\b &= L \sin \omega/2 \\c &= M \sin \omega/2 \\d &= N \sin \omega/2\end{aligned}$$

Where,

ω (Angle of rotation 0° to 360°)

a, b, c, d (Variables)

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

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

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

(X', Y' Z' are the coordinates after rotation)

Potential energies can be calculated by potential energy function (Kitaigorodskii, 1961 and Ramakrishan *et al.*, 1965),

$$V = 3.5 [8600 e^{-13z} - .04 / z^6]$$

$$Z = r_{ij}/r^*$$

r^* = equilibrium distance

r_{ij} = distance between non-bonded interaction

Z = variable

RESULTS AND DISCUSSION

In present work, atomic coordinates were converted into fractional, monoclinic and rectangular coordinate systems by gaussian-98, Molden and GW-Basic (Tables 1, 2 and 3). The bond lengths (Table 4) and bond angles (Table 6) were calculated newly by gaussian-98 and molden and correlated with previously calculated study bond lengths (Table 5) and bond angles (Table 7) where no above-mentioned computational approaches were used. The C₁₈, N₁₉, C₈, - C₉, N₂₁-C₁₅, S₂₂-C₁₄, O₂₃-C₁₅, C₂₀-C₁₀, N₂₄-C₁₂, N₂₆-C₁₂, C₂₇-F₁₃, C₂₈-F₁₃, N₂₁-C₁₅, S₂₂-C₁₄, and O₂₃-C₁₅ were selected as active bio-conformers in pairs for structural minimization, optimization (figures-5, 6), charges and energy calculation (Fig. 13, 14, 15). But during charges and optimization stage these pairs C₂₀-C₁₀, N₂₄-C₁₂, N₂₆-C₁₂, C₂₇-F₁₃, C₂₈-F₁₃ were found no active atomic interaction with their base pairs The C₁₈, N₁₉, C₈, - C₉. So the C₁₈, N₁₉, C₈, - C₉ and N₂₁-C₁₅, S₂₂-C₁₄, O₂₃-C₁₅, were selected as base and interacting pairs respectively for study and energy calculations. The potential energies and rotation of coordinates (Fig. 7, 8, 9, 10, 11, 12) were calculated by using gaussian-98, molden, Statistica and Kitagorodasky potential energy function.

At first stage, potential energy was calculated for pair N₂₁-C₁₅ after rotating N₂₁ atom about the bond C₁₈-N₁₉ (ω_1) and C₁₅ atom about the bond C₈-C₉ (ω_2). The minimum potential energy (-0.00000938 Kcal/mole at $\omega_1 = 280^\circ$ and $\omega_2 = 340^\circ$) and maximum potential energy (10.1 Kcal/mole at $\omega_1 = 60^\circ$ and $\omega_2 = 140^\circ$) were found respectively (Figure-16). In second stage, S₂₂-C₁₄ were selected for energy calculation after rotating S₂₂ atom about the bond C₁₈-----N₁₉ (ω_1) and C₁₄ atom about the C₈-----C₉ (ω_2) bond (Fig. 17). The minimum potential energy (-0.0001009 Kcal /mole at $\omega_1 = 360^\circ$ and $\omega_2 = 340^\circ$) and maximum potential energy (87.3 Kcal /mole at $\omega_1 = 60^\circ$ and $\omega_2 = 140^\circ$) were found respectively (Fig. 17). At third stage of energy calculation O₂₃-C₁₅ were selected after rotating O₂₃ about the bond C₁₈...N₁₉ (ω_1) and C₁₅ about C₈-C₉ (ω_2) bond. The minimum potential energy (-0.00001773 Kcal/mole at $\omega_1 = 300^\circ$ and $\omega_2 = 300^\circ$) and maximum potential energy (408.3 Kcal/mole at $\omega_1 = 60^\circ$ and $\omega_2 = 160^\circ$) were found respectively (Fig. 18). Finally, total potential energy calculated by taking sum of potential energies of all individual pairs. The minimum total potential energy (-0.000108 Kcal/ mole at $\omega_1 = 0^\circ$ and $\omega_2 = 140^\circ$) and maximum total potential energy (417.6 Kcal/mole at $\omega_1 = 60^\circ$ and $\omega_2 = 160^\circ$) were found (Fig. 18).

These results shown that 3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5-thiazole-1-oxide (Histamine H₁ receptor antagonist) has shown maximum potential energy (10.1 Kcal/mole at $\omega_1 = 60^\circ$ and $\omega_2 = 140^\circ$) and minimum potential energy (-0.00000983 Kcal/mole at $\omega_1 = 280^\circ$ and $\omega_2 = 340^\circ$) for pair N₂₁-C₁₅ (Fig. 16). The positive marked area shows non-allowed or disfavored region where C₁₉H₂₃FN₆OS would not interact with its receptor because of rigidity, short contacts and claps between atoms. While negative marked area shows allowed or favored region (no short contacts and claps found) where C₁₉H₂₃FN₆OS would show its anti-allergy and anti-ulcer properties by interact or bind strongly with its specific receptors. These kinds of analysis are beneficial for discovery of new antihistamines and would helpful for the treatment of allergy, different kind of ulcer such as stomach and duodenum ulcers and medicinal search.

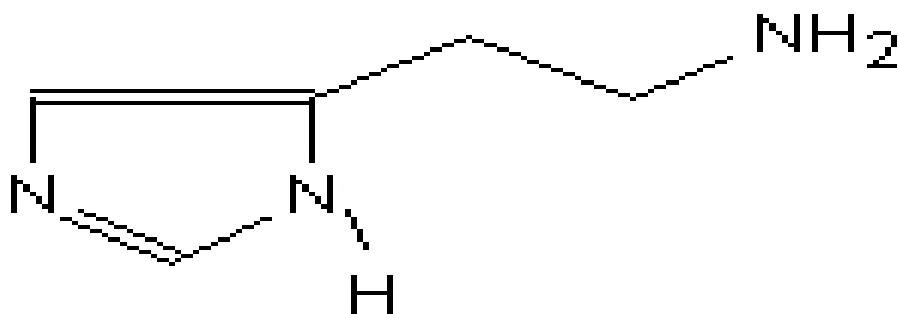


Fig.1. Histamine (2, 4-imidazolyl ethylamine).

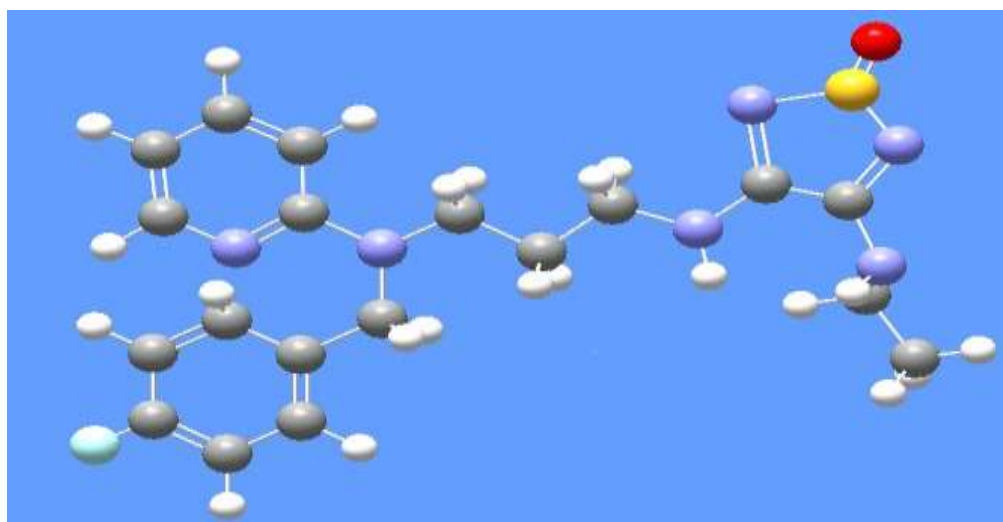


Fig.2. Structure of 3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5- thiazole-1-oxide ($C_{19}H_{23}FN_6OS$) by Gaussian.

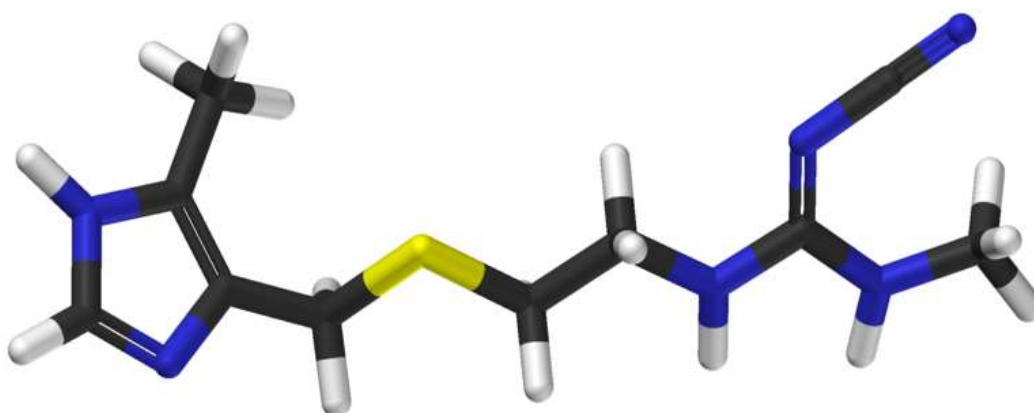


Fig.3. Structure of Cimetine (Histamine H_2 receptor).



F
Fig.4. *Espinheria santa* leaves.

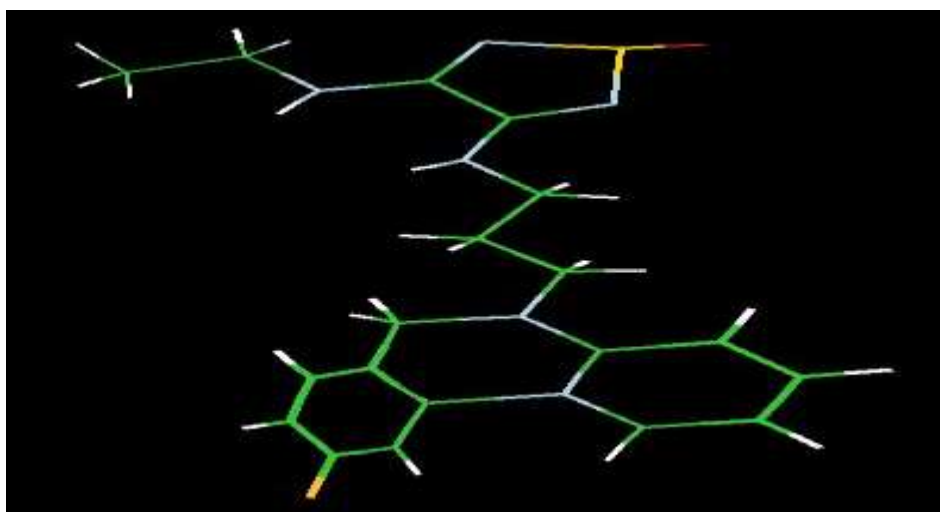


Fig.5. stereo view of $C_{19}H_{23}FN_6OS$ (before optimization) through Molden.

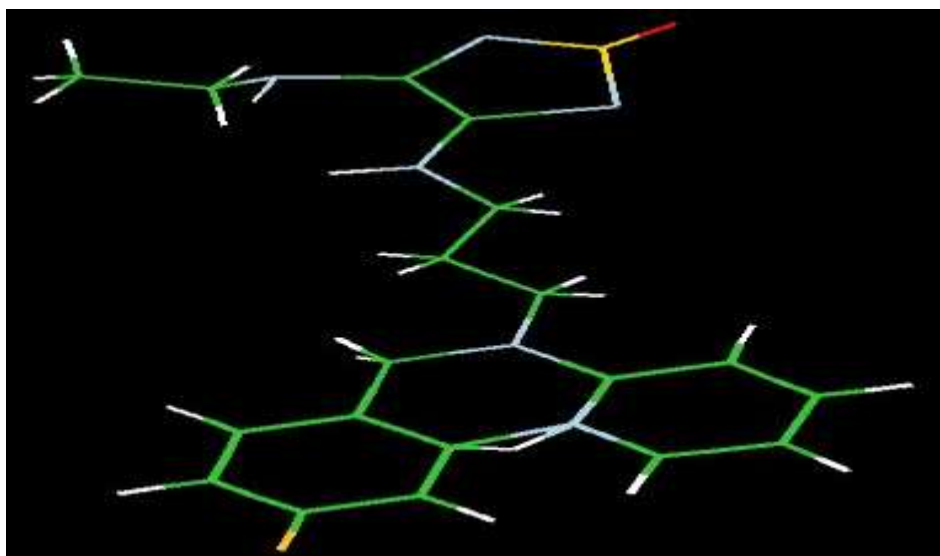


Fig.6. stereo view of $C_{19}H_{23}FN_6OS$ (after optimization) through Molden.

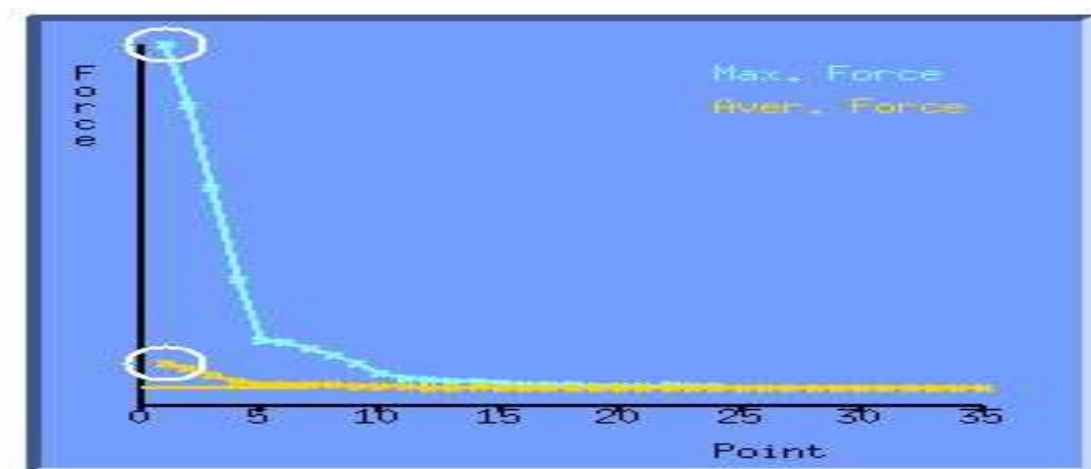


Fig.7. Compound $C_{19}H_{23}FN_6OS$ shown Maximum force (cyne) and average force (yellow) at initial stage.

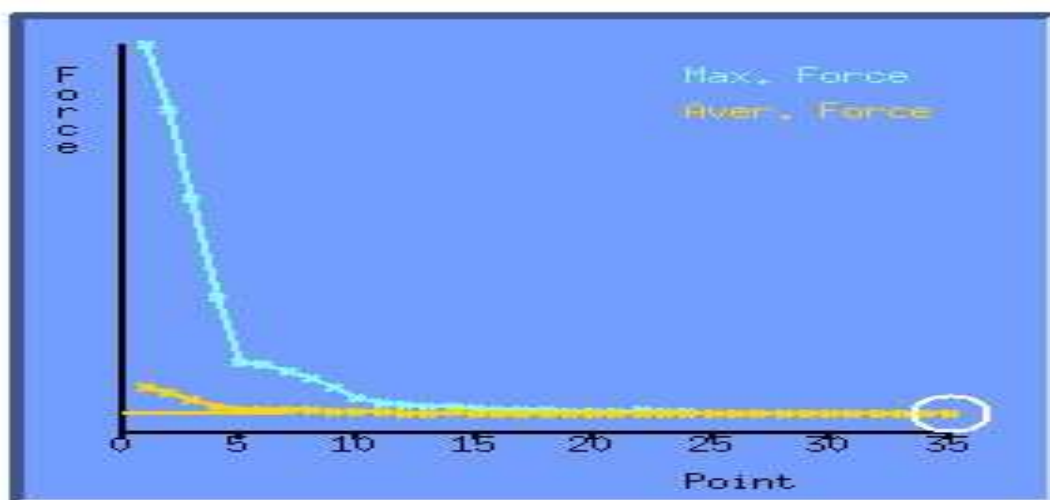


Fig.8. Compound $C_{19}H_{23}FN_6OS$ shown maximum force (cyne) and average force (yellow) at end stage.

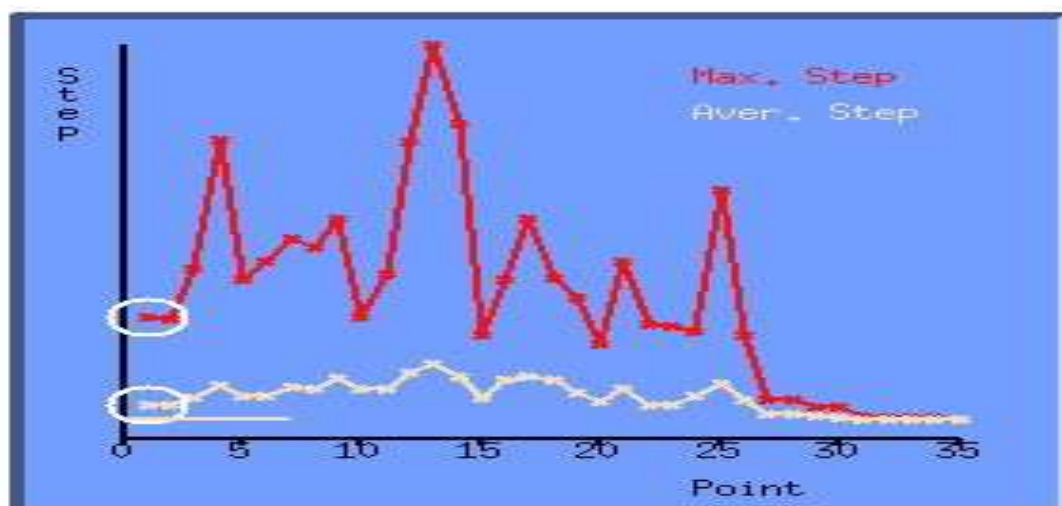


Fig.9. Compound $C_{19}H_{23}FN_6OS$ shown maximum steps (red) and average steps (yellow) involved in energy minimization at initial stage.

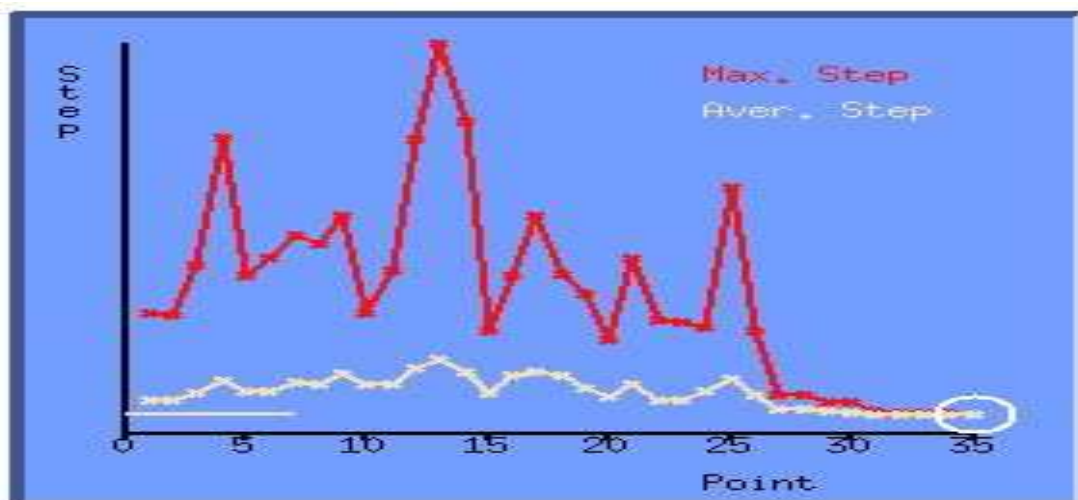


Fig.10. Compound C₁₉H₂₃FN₆OS shown maximum steps (red) and average steps (yellow) involved in energy minimization at end stage.

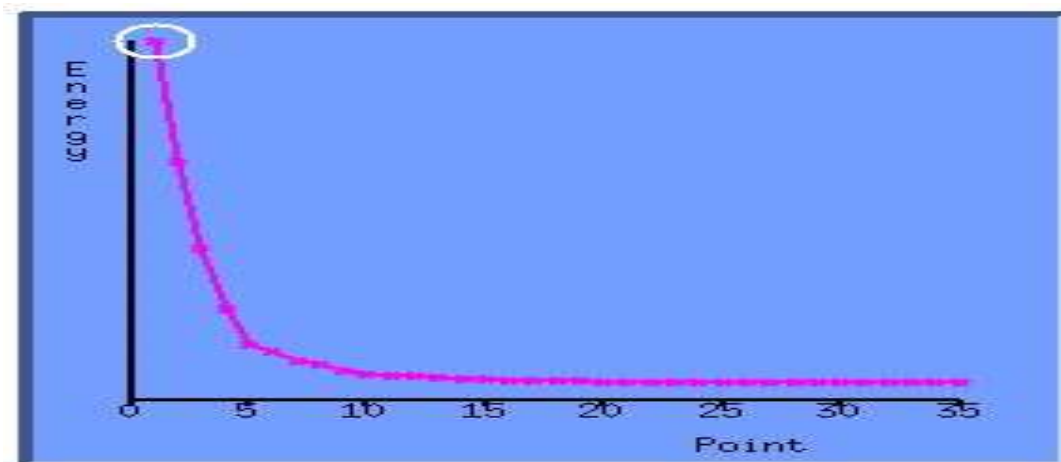


Fig.11. Compound C₁₉H₂₃FN₆OS shown maximum energy (purple) at initial stage.

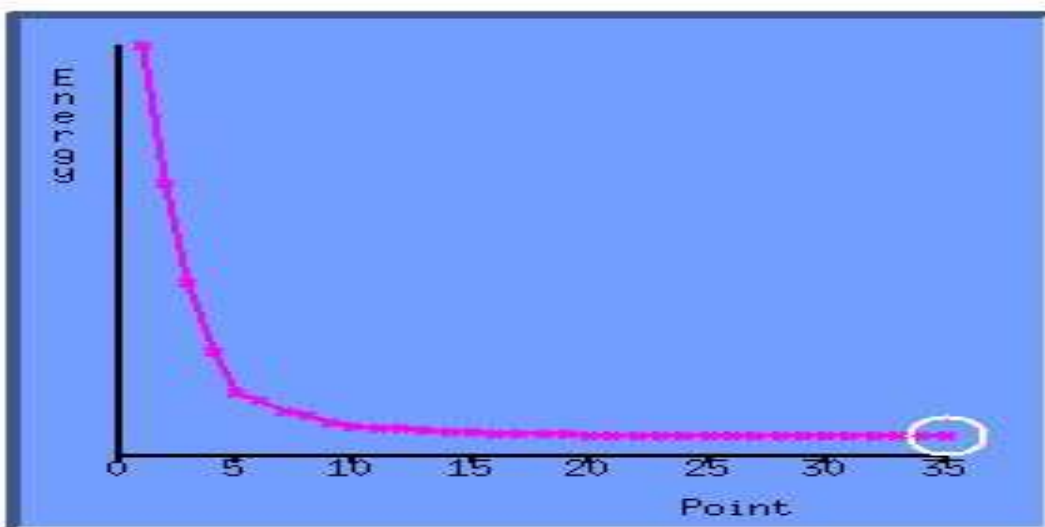


Fig.12. Compound C₁₉H₂₃FN₆OS shown minimum energy (purple) at end stage.

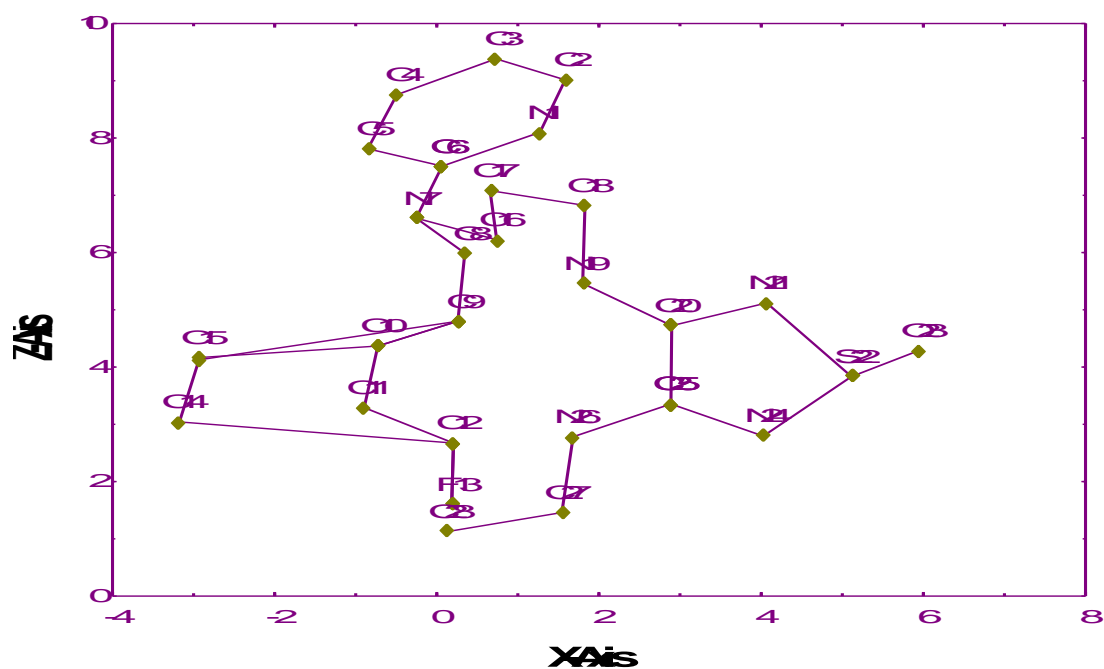


Fig-13. 010 projection of Histamine H1 receptor antagonist (3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5-thiazole-1-oxide) on ZX- axis.

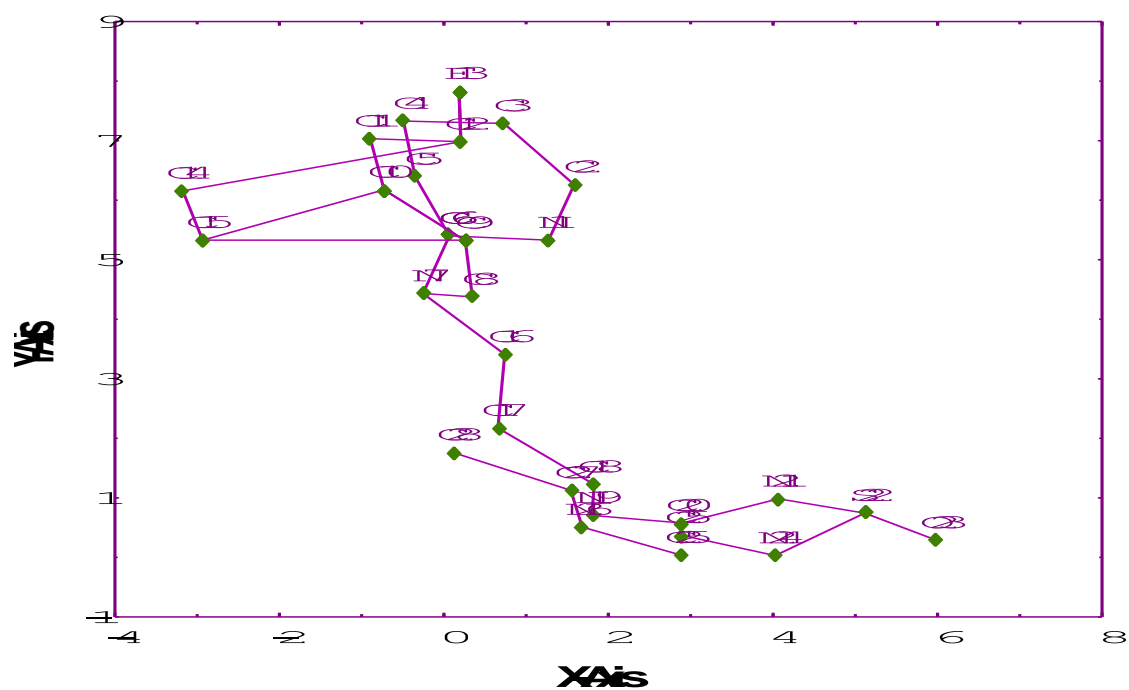


Fig-14. 001 projection of Histamine H1 receptor antagonist (3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5-thiazole-1-oxide) on YX- axis.

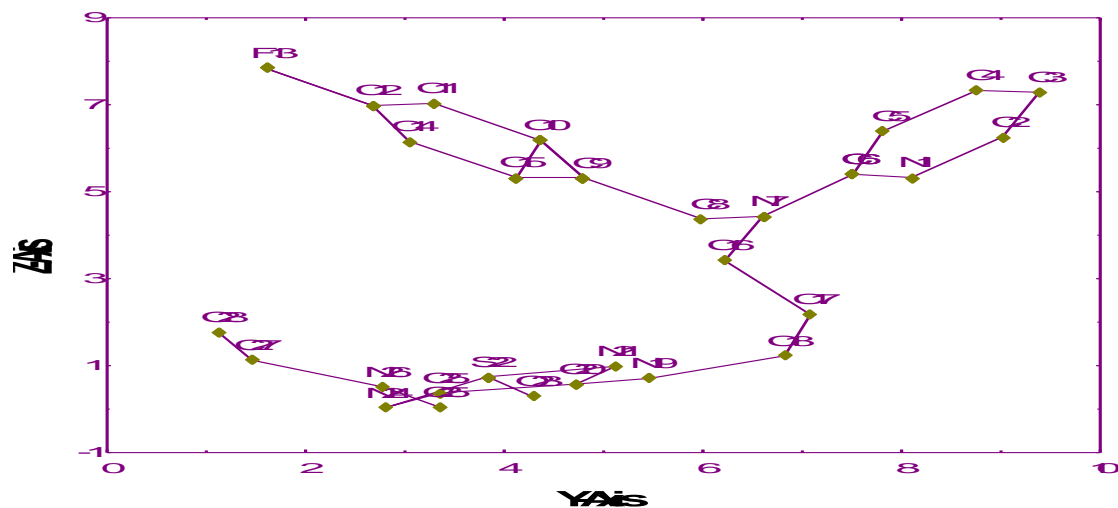


Fig-15. 100 projection of Histamine H₁ receptor antagonist (3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino]-4-ethylamino-1, 2, 5-thiazole-1-oxide) on ZY- axis.

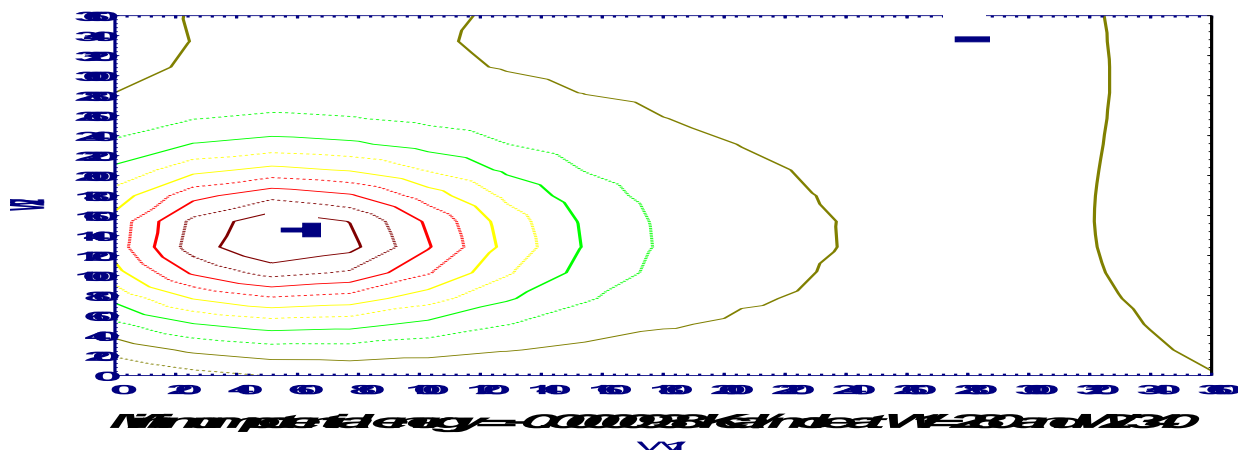


Fig-16. Potential energy calculated for pair N₂₁-C₁₅; minimum potential energy (-0.00000938 Kcal/mole at $\omega_1 = 280^\circ$ and $\omega_2 = 340^\circ$) and maximum potential energy (10.1 Kcal/mole at $\omega_1 = 60^\circ$ and $\omega_2 = 140^\circ$) were found.

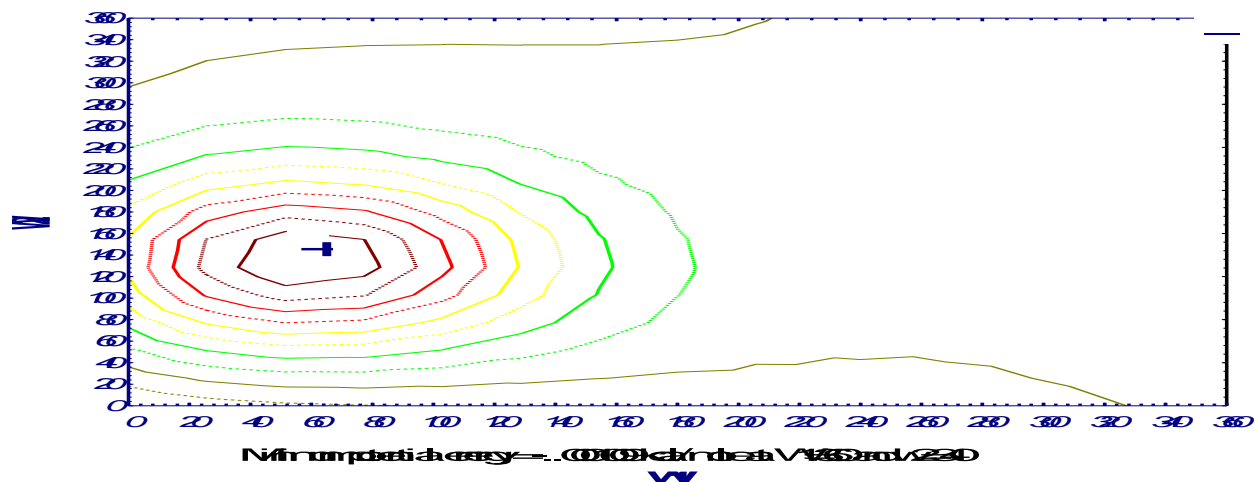


Fig-17. Potential energy calculated for pair S₂₂-C₁₄; minimum potential energy (-0.0001009 Kcal /mole at $\omega_1 = 360^\circ$ and $\omega_2 = 340^\circ$) and maximum potential energy (87.3 Kcal /mole at $\omega_1 = 60^\circ$ and $\omega_2 = 140^\circ$) were found respectively.

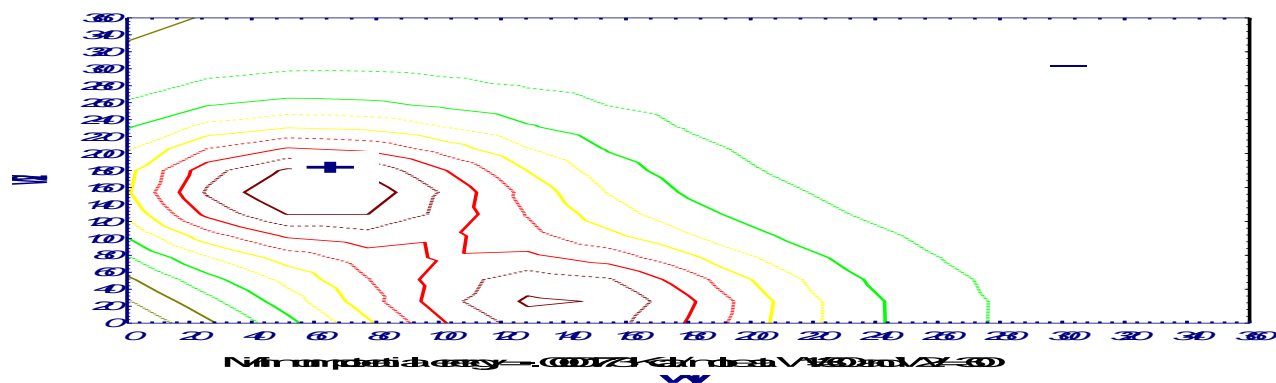


Fig-18. Potential energy calculated for pair $O_{23}-C_{15}$; minimum potential energy (-0.00001773 Kcal/mole at $\omega_1 = 300^\circ$ and $\omega_2 = 300^\circ$) and maximum potential energy (408.3 Kcal/mole at $\omega_1 = 60^\circ$ and $\omega_2 = 160^\circ$) were found respectively.

Table1. Fractional coordinates of 3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino] 4-ethylamino-1, 2, 5- thiazole-1-oxide, $C_{19}H_{23}FN_6OS$.

Serial	Atoms	Fractional Coordinates On X-axis	Fractional Coordinates On Y-axis	Fractional Coordinates On Z-axis
1	N_1	0.3001	0.5504	0.2580
2	C_2	0.3655	0.6127	0.3032
3	C_3	0.2592	0.6376	0.3528
4	C_4	0.0770	0.5951	0.3548
5	C_5	0.0042	0.5309	0.3095
6	C_6	0.1210	0.5103	0.2615
7	N_7	0.0530	0.4486	0.2146
8	C_8	0.1419	0.4070	0.2118
9	C_9	0.1484	0.3263	0.2576
10	C_{10}	0.0184	0.2969	0.2990
11	C_{11}	0.0109	0.2237	0.3405
12	C_{12}	0.1746	0.1816	0.3380
13	F_{13}	-0.1884	0.1091	0.3792
14	C_{14}	-0.3481	0.2067	0.2981
15	C_{15}	-0.3290	0.2804	0.2580
16	C_{16}	0.1805	0.4229	0.1653
17	C_{17}	0.1431	0.4812	0.1052
18	C_{18}	0.2986	0.4636	0.0593
19	N_{19}	0.2836	0.3711	0.0342
20	C_{20}	0.4453	0.3210	0.0279
21	N_{21}	0.6288	0.3479	0.0477
22	S_{22}	0.7803	0.2604	0.0366
23	O_{23}	0.9024	0.2913	0.0138
24	N_{24}	0.6087	0.1899	0.0015
25	C_{25}	0.4325	0.2280	0.0018
26	N_{26}	0.2622	0.1891	0.0247
27	C_{27}	0.3540	0.0992	0.0545
28	C_{28}	0.053	0.0763	0.0853

Table 2. Monoclinic coordinates of 3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino] 4-ethylamino-1, 2, 5- thiazole-1-oxide, C₁₉H₂₃FN₆OS.

Serial	Atoms	Monoclinic Coordinates On X-axis	Monoclinic Coordinates On Y-axis	Monoclinic Coordinates On Z-axis
1	N ₁	2.600	8.100	5.379
2	C ₂	2.443	9.017	6.321
3	C ₃	1.733	9.383	7.355
4	C ₄	0.514	8.758	7.397
5	C ₅	0.028	7.813	6.453
6	C ₆	0.809	7.510	5.452
7	N ₇	0.354	6.602	4.474
8	C ₈	0.948	5.989	4.416
9	C ₉	0.992	4.802	5.370
10	C ₁₀	0.123	4.369	6.234
11	C ₁₁	0.072	3.292	7.099
12	C ₁₂	1.167	2.672	7.047
13	F ₁₃	-1.259	1.605	7.906
14	C ₁₄	-2.327	3.042	6.215
15	C ₁₅	-2.199	4.126	5.379
16	C ₁₆	1.206	6.223	3.446
17	C ₁₇	0.956	5.461	2.193
18	C ₁₈	1.996	7.081	1.236
19	N ₁₉	1.896	5.461	0.713
20	C ₂₀	2.977	4.724	0.581
21	N ₂₁	4.204	5.120	0.994
22	S ₂₂	5.217	3.832	0.763
23	O ₂₃	6.033	4.287	0.287
24	N ₂₄	4.06	2.794	0.031
25	C ₂₅	2.89	3.355	0.037
26	N ₂₆	1.753	2.782	0.514
27	C ₂₇	1.698	1.459	1.136
28	C ₂₈	0.354	1.122	1.778

Table 3. Rectangular coordinates of 3-[3-(N-4-Fluorobenzyl-N-2 pyridylamino) propylamino] 4-ethylamino-1, 2, 5- thiazole-1-oxide, C₁₉H₂₃FN₆OS.

Serial	Atoms	Rectangular Coordinates On X-axis	Rectangular Coordinates On Y-axis	Rectangular Coordinates On Z-axis
1	N ₁	1.273	8.1	5.329
2	C ₂	1.582	9.017	6.262
3	C ₃	0.73	9.383	7.287
4	C ₄	-0.492	8.758	7.328
5	C ₅	-0.851	7.813	6.392
6	C ₆	0.066	7.51	5.401
7	N ₇	-0.255	6.602	4.432
8	C ₈	0.347	5.989	4.374
9	C ₉	0.26	4.802	5.32
10	C ₁₀	-0.072	4.369	6.176
				Cont'd.....

11	C_{11}	-0.894	3.292	7.033
12	C_{12}	0.207	2.672	6.981
13	F_{13}	0.182	1.605	7.632
14	C_{14}	-3.174	3.042	6.157
15	C_{15}	-2.932	4.126	5.329
16	C_{16}	0.737	6.223	3.414
17	C_{17}	0.657	7.081	2.172
18	C_{18}	1.827	6.822	1.224
19	N_{19}	1.799	5.461	0.706
20	C_{20}	2.898	4.724	0.576
21	N_{21}	4.068	5.12	5.114
22	S_{22}	5.114	3.832	0.743
23	O_{23}	5.994	4.287	0.285
24	N_{24}	4.065	2.782	0.03
25	C_{25}	2.886	3.355	0.037
26	N_{26}	1.683	2.782	0.51
27	C_{27}	1.543	1.459	1.125
28	C_{28}	0.112	1.122	1.761

Tables 4-5. Calculated bonds length.

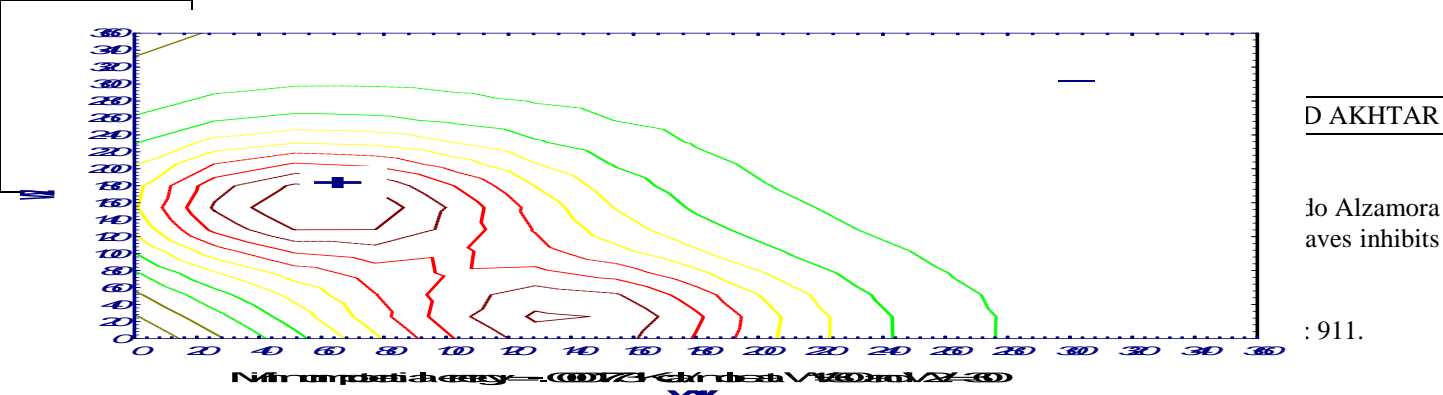
Tables 6-7. Calculation for bond angles.

Present work		Previous work		Present work		Previous work	
Atomic Pairs	Calculated Bonds Length (Å)	Atomic Pairs	Calculated Bonds Length (Å)	Atomic Bonds Angles	Calculated Bonds Angles (°)	Atomic Bonds Angles	Calculated Bonds Angles (°)
$N_1 \cdots C_2$	1.343	$N_1 \cdots C_2$	1.345	$C_2 - N_1, C_6$	117.8	$C_8 - N_7, C_6$	121.7
$N_1 \cdots C_6$	1.345	$N_1 \cdots C_6$	1.346	$N_1 - C_2, C_3$	123.6	$C_{16} - N_7, C_6$	120.2
$C_2 \cdots C_3$	1.382	$C_2 \cdots C_3$	1.381	$C_2 - C_3, C_4$	116.8	$C_{16} - N_7, C_8$	118.1
$C_3 \cdots C_4$	1.374	$C_3 \cdots C_4$	1.375	$C_3 - C_4, C_5$	121.5	$C_9 - C_8, N_7$	114.2
$C_4 \cdots C_5$	1.382	$C_4 \cdots C_5$	1.377	$C_4 - C_5, C_6$	117.4	$C_{17} - C_{16}, N_7$	112.8
$C_5 \cdots C_6$	1.382	$C_5 \cdots C_6$	1.385	$N_1 - C_6, C_5$	122.7	$C_{18} - C_{17}, C_{16}$	111.9
$C_6 \cdots N_7$	1.365	$C_6 \cdots N_7$	1.367	$N_1 - C_6, N_7$	117.6	$C_{17} - C_{18}, N_{19}$	111.3
$N_7 \cdots C_8$	0.861	$N_7 \cdots C_8$	1.434	$C_5 - C_6, N_7$	119.6	$S_{22} - N_{21}, C_{20}$	106.5
$N_7 \cdots C_{16}$	1.471	$N_7 \cdots C_{16}$	1.472	$C_6 - N_7, C_8$	110.8	$N_{21} - S_{22}, O_{23}$	105.3
$C_8 \cdots C_9$	1.521	$C_8 \cdots C_9$	1.528	$C_6 - N_7, C_{16}$	120.2	$N_{21} - S_{22}, N_{24}$	98.90
$C_8 \cdots C_{16}$	1.063	$C_8 \cdots C_{16}$	1.384	$C_8 - N_7, C_{16}$	225.4	$N_{24} - S_{22}, O_{23}$	105.2
$C_9 \cdots C_{10}$	1.375	$C_9 \cdots C_{10}$	1.385	$C_8 - N_7, C_{16}$	225.4	$S_{22} - N_{24}, C_{25}$	107.3
$C_{10} \cdots C_{11}$	1.387	$C_9 \cdots C_{15}$	1.388	$N_7 - C_8, N_9$	118.3	$N_{26} - C_{25}, N_{24}$	123.8
$C_{11} \cdots C_{12}$	1.265	$C_{10} \cdots C_{11}$	1.381	$N_7 - C_8, C_{16}$	99.29	$C_{20} - C_{25}, C_{24}$	112.9
$C_{14} \cdots C_{15}$	1.386	$C_{12} \cdots C_{14}$	1.382	$C_9 - C_8, C_{16}$	139.0	$C_{18} - N_{19}, C_{20}$	122.4
$C_{16} \cdots C_{17}$	1.511	$C_{14} \cdots C_{15}$	1.386	$C_8 - C_9, C_{10}$	132.3	$N_{19} - C_{20}, N_{21}$	122.9
$C_{17} \cdots C_{18}$	1.528	$C_{16} \cdots C_{17}$	1.509	$C_9 - C_{10}, C_{11}$	135.6	$C_{25} - C_{20}, N_{21}$	114.0
				$C_{10} - C_{11}, C_{12}$	104.4	$C_{25} - C_{20}, N_{19}$	123.0

C ₁₈N ₁₉	1.456	C ₁₇C ₁₈	1.529	N ₇ - C ₁₆ .C ₈	215.2	C ₂₀ - C ₂₅ .N ₂₆	123.3
N ₁₉C ₂₀	1.330	C ₁₈N ₁₉	1.458	N ₇ - C ₁₆ .C ₁₇	112.8	C ₂₇ - N ₂₆ .C ₂₅	122.2
C ₂₀N ₂₁	1.301	N ₁₉C ₂₀	1.330	C ₈ - C ₁₆ .C ₁₇	148.0	N ₂₆ - C ₂₇ .C ₂₈	112.2
C ₂₀C ₂₅	1.470	C ₂₀N ₂₁	1.301	C ₁₆ - C ₁₇ .C ₁₈	111.9		
S ₂₂O ₂₃	1.097	C ₂₀C ₂₅	1.500	C ₁₇ - C ₁₈ .N ₁₉	111.3		
N ₂₄C ₂₅	1.305	S ₂₂O ₂₃	1.487	C ₁₈ . N ₁₉ .C ₂₀	122.4		
C ₂₅N ₂₆	1.414	N ₂₄C ₂₅	1.304	N ₁₉ - C ₂₀ .N ₂₁	122.9		
N ₂₆C ₂₇	1.466	C ₂₅N ₂₆	1.306	N ₁₉ - C ₂₀ .C ₂₅	123.0		
		N ₂₆C ₂₇	1.459	N ₂₁ - C ₂₀ .C ₂₅	113.8		
				C ₂₀ - C ₂₅ .N ₂₄	113.2		
				C ₂₀ - C ₂₅ .N ₂₆	105.1		
				N ₂₄ - C ₂₅ .C ₂₆	126.6		
				C ₂₅ - C ₂₆ .C ₂₇	125.9		

REFERENCES

- Abbas, A., A. Lichtman, and J. Pober (1994). *Cellular and Molecular Immunology*, p. 287.
- Bach, Jean-Francois (1982). *Immunology*, pages 354-359.
- Bannister, C., K. Burns, K. Prout, D.J. Watkin, D.G. Cooper, G.J. Duránt, C.R.Ganellin, R.J. Ife and G.S. Sach (1994). Structures of Histamine H₁ receptor antagonists derived from the cimetidine group of Histamine H₂ receptors antagonists. *Acta Crystallographia*, 50: 221-2113.
- Florence, L. S., Ling Xue, W. G. Jeffrey and Jergen Bajorath (2002). Methods for compound selection focused on hits and application in drug discovery. *J. Molecular Graphic and Modeling*, 20: 439-436.
- Froese, A. (1980). Structure and function of the receptor for IgE. *Critical Reviews in Immunology*, 1(2): 79-132.
- Gallin, J., A. Weinstein, E. Cramer and A. Kaplan (1980). Histamine modulation of human eosinophil locomotion *in vitro* and *in vivo*. *The Eosinophil in Health and Disease*, 185-206PP.
- Gaussian (2003). Gaussian 98, Inc., Pittsburgh PA, USA.
- Goldie, R. (1990). Receptors in asthmatic airways. *The American Review of Respiratory Disease*, 141(3): S151-6.
- Gupta, S. P. (1989), QSAR studies on drug acting at the central nervous system. *Chemical Review*, 89: 1765-1800.
- James, L. M. and D. H. Jonathan (2004). On the stability of CoMFA models. *J. Chemical Information and Computer Sciences*, 44: 1294-1300.
- Jawetz Melnick and Adelberg (2002). *Medical Microbiology* 21st edition.
- Kitaigorodskii, A. I. (1961). The interaction curve of non-bonded carbon and hydrogen atoms and its application. *Tetrahedron*, 14: 230-236.
- Lingling Shen (2003). Steered molecular dynamics simulation on the binding of NNRTI to HIV-1 RT. *Biophysica Journal*, 84: 3547-3563.
- Manuel, A. N. (1992). Methods of conformational analysis. *Structural Biology*, 2: 202 210.
- Metcalfe, D., D. Baram, D., and Y. Mekori (1997). *Physiological Reviews*, 77(4): 1033-79.
- Michael Williams (2004). Computer aided drug Design and development. 2nd Edition.
- Monroe, E., A. Daly and R. Shalhoub (1997). Appraisal of the validity of histamine-induced wheal and flare to predict the clinical efficacy of antihistamines. *The Journal of Allergy and Clinical Immunology*, 99(2): S789-806.
- Munikumar Reddy Doddareddy, Hee Kyung Jung Hwan Cha, Yong Seo Cho, Hun Yeong KOH, Moon Ho Chang and Ae Nim Pae (2004). 3D-QSAR studies on T-type calcium channel blockers using CoMFA and CoMSIA. *Bioorganic and Medicinal Chemistry*, 12: 1613-1621.



- Spiegelberg, H. (1989). Biological role of different antibody classes. *The International Archives of Allergy and Applied Immunology*, 90(1): 22-7.
- SYBYL 6.9. Tripose Inc., 1699 Hanley Road, St. Louis, MO63144.
- Tommy Liljeforl (2004). *Computer Aided Drug Development*. 2nd Edition.
- Weerasak Samee, Jiraporn Ungwitayatorn, Chutima Matayatsuk, and Jutarat Pimthon (2004). 3D-QSAR studies on Phthalamide derivatives as HIV-1 Reverse Transcriptase Inhibitors. *Science Asia*, 30: 81-88.

(Accepted for publication October 2008)