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COMPUTER AIDED CONFORMATIONAL ANALYSIS OF DIAZEPAM (7-CHLORO-1, 3-DIHYDRO-1-METHYL –5-PHENYL-2H-4-BENZODIZAPINE-2-ONE)

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ABSTARACT

Structure based drug design is based on a firm understanding of molecular recognition between active site group and interacting molecules and is a strategy that has become as integral part of modern drug discovery. Potential energy has been calculated to refine the structure of diazepam by using kaitagorodsky function. The most feasible position for the drug to interact with receptor would be at □1=220° and □2= 260°.Where the potential energy was found to be -0.957744 K.cal/mol.

Key-words: Potential energy, kaitaigorodsky, anticonvulsant

INTRODUCTION

Diazepam (7-chloro-1, 3-dihydro-1-methyl –5-phenyl-2H-4-benzo dizapine-2-one) is use as tranquillisers, sedatives and hypnotic (www.diazepam.com). In diazepam structure the two phenyl rings are planar and the obtuse angle between the normal to the two planes is 125° in diazepam structure. There are conformational features very similar to certain features found in another anticonvulsant drug diphenyl hydantion (Carmearan *et al*., 1972). The present work describe the computer aided conformational analysis.

MATERIALS AND METHODS

The three dimensional quantitative structure activity relation ships (3D.QSAR) provided 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). Its help to describe new drug candidates and help to improve in vitro potency (Manule *et al*., 1992). The crystallographic data is utilized to determine the three dimensional structure of molecule. Several computer programs were used to infer the shape of molecule from potential energy contour maps.

The potential energy calculated by using Kaitaigorodsy function (Kaitaigorodsky, 1964). 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 vander Waal,s contact distances. If X_{90} ,Y_{90} ,Z_{90} are the coordinates of an atom before rotation, then coordinated X`,Y`, Z after rotation can be given by the following relationship.

$X` = (a^2+b^2-c^2-d^2)\, X_{90} + 2(bc – ad)\, Y_{90} + 2(bd + ac)\, Z_{90}$
$Y` = 2\,(bc + ad)\, X_{90} + (a^2-b^2+c^2-d^2)\, Y_{90} + 2(cd – ab)\, Z_{90}$
$Z` = 2\,(bd – ac)\, X_{90} + 2(cd + ab)\, Y_{90} + (a^2-b^2-c^2+d^2)\, Z_{90}$
$a= \cos\ \square/2$
$b= L1\ \sin\ \square/2$
$c= M \sin\ \square/2$
$d= N \sin\ \square/2$
□= angle of rotation about the bond of first and second chain and L,M,N are the direction of cosines.
L = X1 - X_2 / bond length of the i^{th} and j^{th} atom.
M= Y1 - Y2 / bond length of the i^{th} and j^{th} atom.
N= Z1 - Z2 / bond length of the i^{th} and j^{th} atom.
Where X_1, Y_1, Z_1 and X_2, Y_2, Z_2 are the coordinates of 1st and 2nd atoms, which are non-bonded atoms.

Kitaigorodsky equction:
$U_{ij} =3.5 \{8600\exp(-13Z_{ij}) - 0.04/z^6_{i\,j}\}$
Where the value of z is calculated from the formula:

$$Z = \frac{r_{ij}}{r^o}$$

r^o =equilibrium distance
r_{ij}=distance between non-bonded interaction and can be calculated by using
r_{ij} $[(x2-x1)^2+(y2-y1)^2+(z2-z1)^2]^{1/2}$

Total potential energies were calculated by summation of all individual pairs by using kaitaigorodsky potential energy function. Contours are polluted for visual understanding.

RESULTS

The prospective view of diagram is shown in (**Fig.1**). The potential energies were calculated for lower limit (K2). The energy estimates for the following pairs. The minimum potential energies are shown by negative mark. Monoclinic coordinates of drug are given in Table 1. Bonds length and bond angle are given in Table 1, 2) respectively.

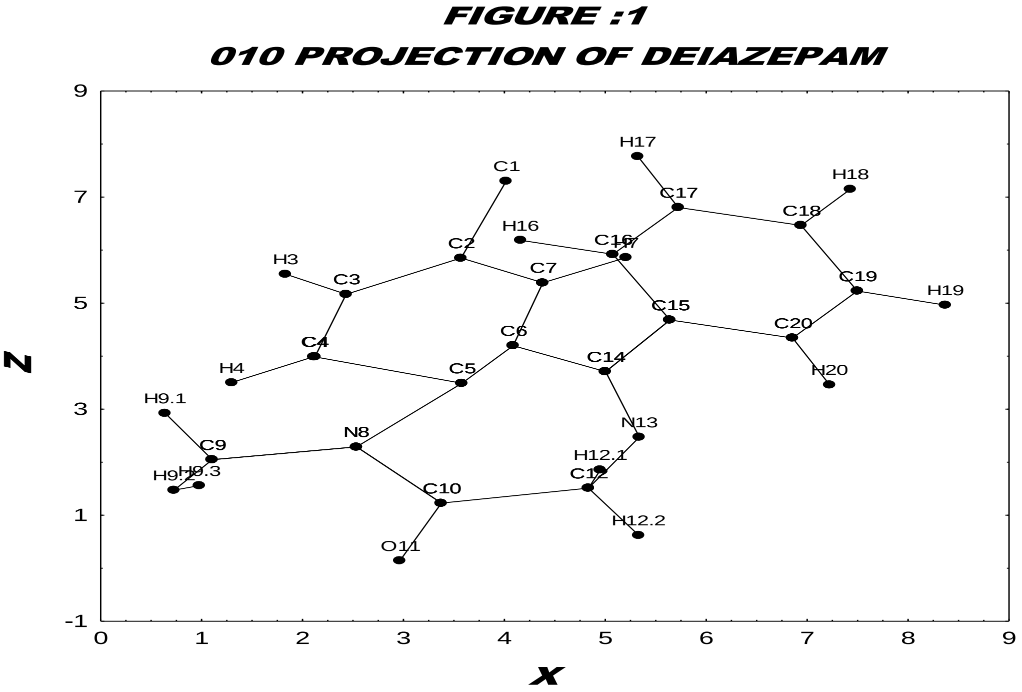

Fig.1. 010 Projection of Diazepam.

PAIR H16----H7:
The potential energy has been calculated for the pair H16…. H7 after rotating the H16 atom about the bond C14…C15 (ω1) and H7 atom about the bond C15…. C14 (ω2). The minimum potential energy was found to be –0.008313844 K.cal / mol at ω (**Fig. 2**); 1=240° and ω2=320°.

PAIR H16----C7:
The potential energy has been calculated for the pair H16…. C7 after rotating the H16 atom about the bond C14…C15 (ω) and C7 atom about the bond C15….C14 ((ω2).The same minimum potential energy were found to be –0.009565599 K.cal/ mol at ω1=40° and ω2=40° and at ω1=80° and ω2=0° (**Fig. 3**).

Total potential energy:
Total potential energy calculated for the pairs H16…H7, H16…C7 after rotating the H16 atom about the bond C14…. C15 (ω1) and H7 and C7 atom about the bound C15…. C14 (ω2).The minimum potential energy was found to be -0.00957744k.cal/mol at ω1=220° and   ω2=260°.(**Fig. 4**).

Table 1. Monoclinic coordinates of diazepam.

	ATOMS	X	Y	Z
1	C1	0.312	0.665	0.915
2	C2	0 .277	0.664	0.734
3	C3	0.189	0.629	0.648
4	C4	0 .165	0.581	0.500
5	C5	0 .277	0.504	0.437
6	C6	0 .316	0.475	0.526
7	C7	0.340	0.526	0.675
8	N8	0.197	0.456	0.287
9	C9	0 .086	0.438	0.257
10	C10	0 .262	0.442	0.154
11	O11	0.230	0.414	0.018
12	C12	0.743	0.460	0.189
13	N13	0.413	0.387	0.310
14	C14	0.388	0.397	0.465
15	C15	0.437	0.327	0.587
16	C16	0.393	0.305	0.742
17	C17	0 .443	0.241	0.853
18	C18	0 .537	0.199	0.811
19	C19	0.580	0.220	0.656
20	C20	0 .531	0.283	0.543
21	H3	0.143	0.683	0.695
22	H4	0.101	0.602	0.439
23	H7	0.404	0.508	0.735
24	H9.1	0.050	0.434	0.367
25	H9.2	0.057	0.491	0.185
26	H9.3	0.076	0.374	0.195
27	H12.1	0.384	0.534	0.233
28	H12.2	0.413	0.452	0.078
29	H16	0.322	0.339	0.775
30	H17	0 .412	0.230	0.973
31	H18	0 .575	0.155	0.896
32	H19	0 .648	0.193	0.622
33	H20	0.559	0.299	0.434

Table 2. Bonds length of diazepam.

	ATOMS	BONDS LENGTH
1	C2--------C3	1.371
2	C2---------C7	1.398
3	C3---------C4	1.378
4	C3---------H3	1.012
5	C4---------H4	0.998
6	C5---------C6	0.951
7	C6---------C7	1.394
8	C6---------C14	1.480
9	C7---------H7	0 .984
10	N8--------C9	1.469
11	N8--------C10	1.366
12	C9--------H9.1	0 .994
13	C9--------H9.2	0 .992
14	C10------H9.3	0.991
15	C10------O11	1.217
16	C10------C12	1.504
17	C12------N13	1.460
18	C12------H12.1	1.058
19	C12------H12.2	1.023
20	N13-----C14	1.286
21	C14-----C15	1.493
22	C15-----C16	1.392
23	C15-----C20	1.392
24	C16-----C17	1.389
25	C16-----H16	1.027
26	C17-----C18	1.385
27	C17-----H17	1.050
28	C18-----C19	1.384
29	C18-----H18	1.028
30	C19-----C20	1.383
31	C19-----H19	0 .978
32	C20-----H20	0 .977
33	H9.2---H9.3	1.590

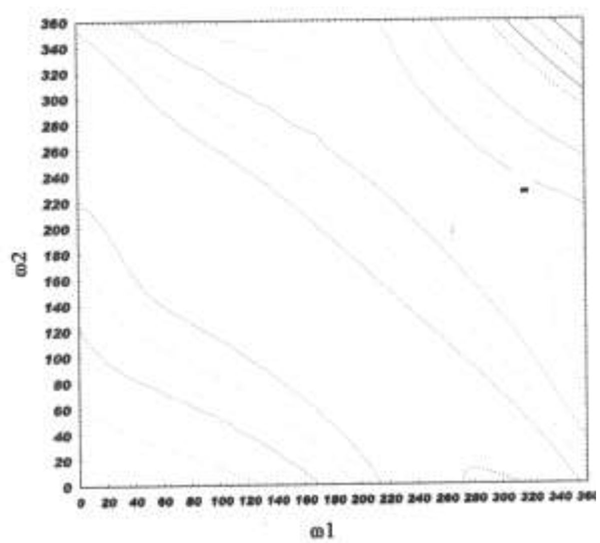

Fig.2. Potential energy contour map pair for H16-C7.

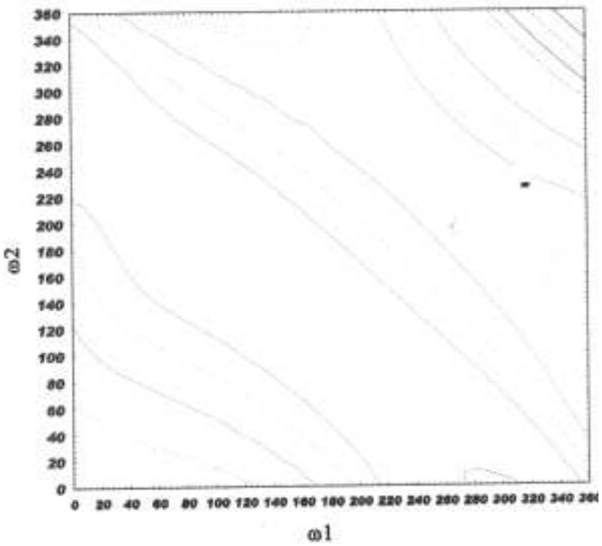

Fig.3. Potential energy contour map pair fir H16-H7.

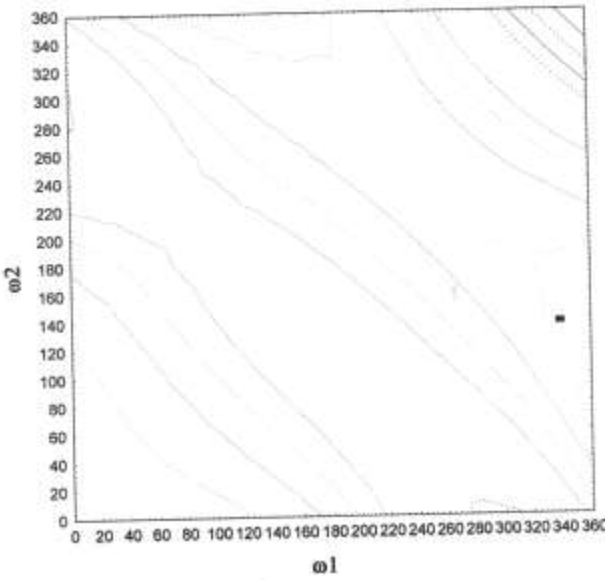

Fig.4. Potential energy contour map for sum of all pairs.

Table 3. Bonds angles of diazepam.

	ATOMS	BOND ANGLES
1	C3…...C2…...C7	119.850
2	C2…....C3…..C4	119.760
3	C2……C3…..H3	118.750
4	C4……C3…..H3	121.540
5	C3…....C4…..H4	118.000
6	C5……C6…..C7	123.660
7	C5…. .C6… .C14	111.650
8	C7….. .C6… .C14	119.610
9	C2……C7…..C6	121.320
10	C2……C7…..H7	120.480
11	C6……C7…..H7	118.150
12	C9……N8….C10	116.670
13	N8….. C9… .H9	108.660
14	N8……C9…..H9.2	110.520
15	N8……C9…..H9	110.280
16	H9.1….C9…..H9.2	111.350
17	H9.2….C9…..H9.3	109.610
18	N8……C10…O11	121.750
19	N8……C10…C1	111.928
20	O11…..C10…C12	122.900
21	C10…..C12….N13	110.510
22	C10…..C12….H12.1	108.750
23	C10…..C12….H12.2	106.920
24	N13…..C12….H12.1	112.030
25	N13…..C12….H12.2	109.46
26	H12.1...C12….H12.2	109.190
27	C12…...N13…C14	118.080
28	C6…....C14…..N13	123.700
29	C6……C14…..C15	119.570
30	N13…..C14….C15	116.720
31	C14…..C15….C16	122.620
32	C14…..C15….C20	118.570
33	C16…..C15….C20	118.870
34	C15…..C16….C17	120.410
35	C15…..C16….H16	120.830
36	C17…..C16….C16	118.780
37	C16…..C17….C18	120.340
38	C16…..C17….H17	119.430
39	C18…..C17….H17	120.050
40	C17….C18…..C19	119.390
41	C17….C18…..H18	119.360
42	C19 ..C18…..H18	121.280
43	C18…..C19….C20	120.640
44	C18… .C19.. ..H19	122.100
45	C20…..C19….H19	117.240
46	C15…..C20….C19	120.450
47	C15…..C20….H20	117.220
48	C19…..C20….H20	122.380
49	C9…….H9.2...H9.3	216.700
50	C9…….H9.3...H9.2	216.740
51	H9.2…..C9…..H9.3	106.550

DISCUSSION

The allowed region i-e the region in which the drug can bind with receptor is shown in (**Fig. 4**). The area out side the zero line is allowed region. It is possible that drug in this conformation interact with receptor. The result indicate that it can only exist at one stable conformation and stable conformation exist at minimum potential energy.

The minimum potential energy is found to be –-0.9577 K.cal/mol. at ω1 = 220° and ω2=260° (**Fig. 4**). So this conformation of diazepam will more active as anticonvulsant .It will bind its receptor readily. Drug molecules have several three-dimensional shapes (conformation) but only one or few these conformations the shape of the receptor. Among various other physical properties of molecule is its potential energy, which effect its inter action of drug molecule with receptor. These properties can be use full in designing new drug molecule with enhanced pharmacological and therapeutic properties as reported by Naheed *et al.* (2004) and Farhat *et al.* (2003).

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