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COMPUTER AIDED DRUG DESIGNING OF 1-ALKYL, 4-ACYL, PIPERAZINE IMIDAZOL FREE DERIVATIVE AS H3 RECPTOR ANTAGONIST

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ABSTRACT

The histamine H_3 receptor subtype negatively modulates the release of various neurotransmitters such as histamine, glutamate, norepinephrine, acetylcholine and many others mainly in the CNS and H_3 antagonists have been developed to treat central diseases characterized by neurotransmission disturbance such as schizophrenia, memory/learning and sleep disorders. The imidazole-free derivatives possessed moderate to pronounced antagonistic potency at guinea-pig ileal H_3 receptor consistent with binding affinity at rat brain H_3 receptors and showed a favourable receptor selectivity profile .Computer aided drug designing of 1 – alkyl -4 acyl piperazine derivative was performed by Argus Lab software .The minimum potential energy is calculated by grometery convergence function by Argus Lab software .The most feasible postion for the drug to interact with the recptor was found to be 38.2539624 kcal /mol

Key-words: computer aided drug, piperazine imidazol, histamine

INTRODUCTION

More recently, in addition to these two postsynaptic receptor subtypes, presynaptic H3-receptors have been identified (Arrang *et al.*, 1983) in the brain. These receptors were described to be located presynaptically on histaminergic nerve endings, regulating the release and synthesis of histamine by a negative feedback (autoreceptor). The histamine H3-receptor play an important regulatory role in the release of other neurotransmitters (e.g. serotonin, acetylcholine, noradrenaline) in the CNS (Schlicker *et al.*, 1988; Clapham and Kilpatrick , 1992; Schlicker.1994] and in the periphery as well heteroreceptor.

The H_3 blockage in the CNS has been proposed as a therapeutic strategy in the treatment of diseases affecting the CNS and related to disturbances of the neurotransmission such as schizophrenia, memory/learning and sleep disorders (Witkin and Nelson.,2004).

Imidazole-containing ligands are associated with inhibition of cytochrome P450 enzymes. Via this mechanism, imidazole-containing compounds can compromise the clearance of co-administrated drugs, thereby causing severe drug–drug interactions (Boxenbaum *et al.*, 1999; Lin *et al.*, 1998) and extrapyramidal symptoms (Zhang *et al.*, 2005; Pillot *et al*., 2006) . As a result, the development of potent non-imidazole H_3R compounds was eagerly awaited.

In search for H_3 blockers with greater selectivity and less side effects, the development of non-imidazole H_3 antagonists, no longer structurally related to the endogenous mediator histamine, has been pursued and described Ganellin, D. Jayes, .,et all 1991) and in recent researches the replacement of the imidazole ring of known H_3 receptor antagonists by alicyclic amines, such as piperidine or piperazine, succeeded in promising compounds such as UCL 2190 (pK_i (rat) = 8.4, ED_{50} (mouse) = 0.18 mg kg^{-1} p.o.), a potent non-imidazole analogue of ciproxifan (Meier and Apelt., 2001)

Recently, new classes of imidazole-free molecules with 2-(1-piperazinyl)quinoline skeleton (Zaragoza *et al.*, 2005) or 2-aminoethylbenzofurans [M. Cowart *et al.*, 2005] have been characterize as potent and selective brain penetrating H_3 antagonists histamine H_3 ligands, devoid of the imidazole ring and thiourea moiety, which are strong hydrogen bond donors and good acceptors, can easily penetrate into the brain, a useful feature for their potential therapeutic applications in CNS disorders.

MATERIAL AND METHODS

All conformational analysis (geomtery optimization) study was performed on window based computer using Argus and ACD Lab chem. Sketch softwares. The chemical structure of 1-Alkyl -4-Acyle piperazines was refined by X-ray crystallography technique.The molecule is utilized to determine the 3D structure of molecule. Several computer programs are used infer the shap of molecule from geometry optimization calculations. The 1-Alkyle-4 Acyle pieperazin structure is generated by argues Lab, and minimization was performed with the semi-emperical Austin model 1(AMI) parameter (Dewar *et al* ., 1985)

The minimum potential energy is calculated by using geometery convergence function in Argus Lab soft ware .Iorder to determine the allowed conformation the contac distance between the atoms in adjacent residues is examined using criteria for minimum Vander waal contact distance (Simons *et al.*, 1983Surfaces created to visualize ground state properties such as orbital , electron densties ,electrostatic potentials (ESP)spin densties and generated grid data used to make molecular oribtal surfaces and visualized the molecular orbital and making an electroststic potential mapped amd electron density surface .The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map .

We use ACDC LAB 12 software to draw the structure of molecule and calculate its properties by using ACDS CHEM SKETCH. By using ACDS LAB 12 (IN 3D viewer) to create electron clouds on molecule then by using Argus lab software for clean geometry optimization , to get figure , calculation and table of bond angle ,bond length ,and tensional angle and energy minimization. Now the next step is Electrostatic potential (Esp) from which we get figure and calculation then we use surface Esp. to get figures. In last step we plot orbitals.

RESULT

Prospective view and calculated properties by Acd Lab Chemsketch software, of molecule 1-alkyl-4-piperizine derivative are shows in figure 1.Figure 2 shown clean geometry view. The electron density mapped of atoms by ACD LABS 3D Viewer software in figure 3.Figure 4 shows electrostatic potential of molecule ground state mapped on to the electron density surface for the ground state and figure 5 shows the complete surface with the color map . Figure 4 and 5 use a clipping plane showing a cutaway of the same surface revealing the underlying molecular structure. The color map shows Esp. energy (in hartess) for the various colors. The red end of the spectrum show regions of highest stability for a positive test charge, magenta / blue show the regions of least stability for a positive test charges. Figure 6 shows the occupied molecular orbital of molecule calculated with the ZINDO method and rendered a mesh the positive and negative phases of the orbital are represented by the two colors. The blue region represents an increase in a density the red region a represent in electron density.

Fractural coordination of mol are given in table 1 and bond length and bond angles are given in table 2 and 3 respectively with are taken after geometry optimization of molecular from Argus lab by using molecular mechanics calculation. Table 4 and 5 show Torsional angles and improper torsion values respectively. The minimum potential energy shows for drug receptor interactive via the geometry convergence map in graph1.

It is possible that drug in this confirmation interact with receptor. The result indicates that the best confirmation of the molecule is present at minimum potential energy is found to be -38.25396246 -kcal/mol. At this point molecule will be more active as imidazol free histamine H3 antagonist.

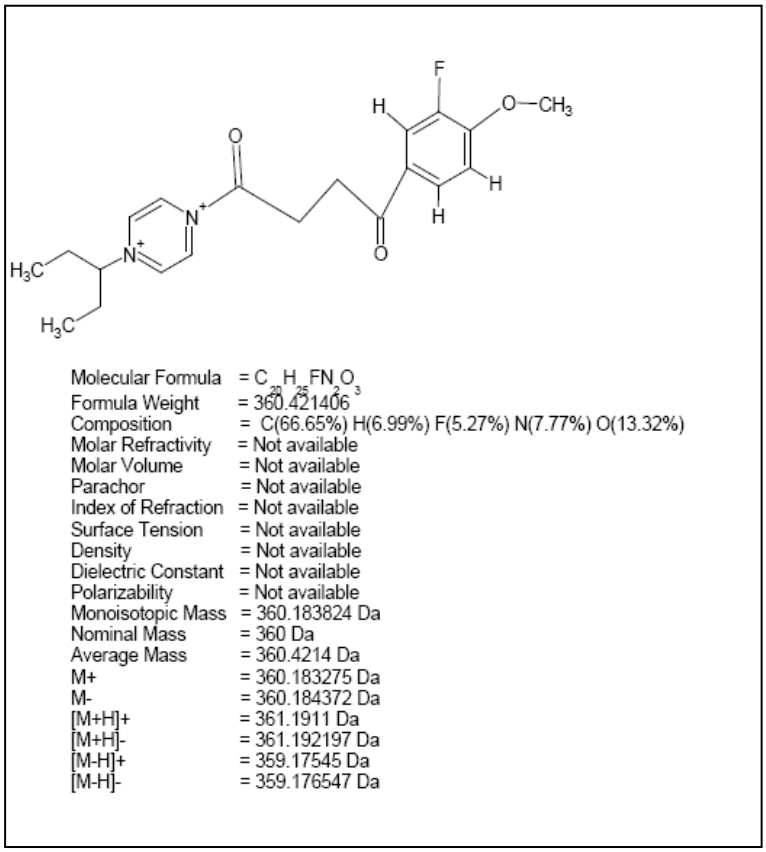
DISCUSSION

ArgusLab uses the grid files to generate contours for displaying surfaces of the relevant properties. There are many different kinds of surfaces you can visualize in ArgusLab. We generate the grid data used to make molecular orbital surfaces. The colors indicate the phase of the orbital in space.

Argus Lab can generate Mapped surfaces. These are surfaces where one property is mapped onto a surface created by another property. The most popular example of this is to map the electrostatic potential (ESP) onto a surface of the electron density. In an ESP-mapped density surface, the electron density surface gives the shape of the surface while the value of the ESP on that surface gives the colors.

The electrostatic potential is the potential energy felt by a positive "test" charge at a particular point in space. If the ESP is negative, this is a region of stability for the positive test charge. Conversely, if the ESP is positive, this is a region of relative instability for the positive test charge. Thus, an ESP-mapped density surface can be used to show regions of a molecule that might be more favorable to nucleophilic or electrophilic attack, making these types of surfaces useful for qualitative interpretations of chemical reactivity. Another way to think of ESP-mapped density surfaces is that they show "where" the frontier electron density for the molecule is greatest (or least) relative to the nuclei.

The colors are the value of the ESP at the points on the electron density surface. Always the color map is given on the left. Note the large red region around the oxygen-end of the molecule. There is enhanced electron density here. The red color indicates the most negative regions of the electrostatic potential where a positive test charge would have a favorable interaction energy. The hydrogen-end of the molecule, with the magenta color, shows regions of relatively unfavorable energy for the ESP. The N-C and C-F bond lengths for the structures were taken from (Gao and Xia, 1993). The structures were optimized using the AM1 semi-empirical Hamiltonian with the positions of the N, C, and Cl fixed (i.e. only the hydrogens were optimized in each frame).



Molecular Formula	= $C_{25}H_{25}FN_2O_3$
Formula Weight	= 360.421406
Composition	= C(66.65%) H(6.99%) F(5.27%) N(7.77%) O(13.32%)
Molar Refractivity	= Not available
Molar Volume	= Not available
Parachor	= Not available
Index of Refraction	= Not available
Surface Tension	= Not available
Density	= Not available
Dielectric Constant	= Not available
Polarizability	= Not available
Monoisotopic Mass	= 360.183824 Da
Nominal Mass	= 360 Da
Average Mass	= 360.4214 Da
M+	= 360.183275 Da
M-	= 360.184372 Da
[M+H]+	= 361.1911 Da
[M+H]-	= 361.192197 Da
[M-H]+	= 359.17545 Da
[M-H]-	= 359.176547 Da

Fig. 1. prospective view and calculated properties of 1-alkyl ,4-acyle –piperazine derivative.

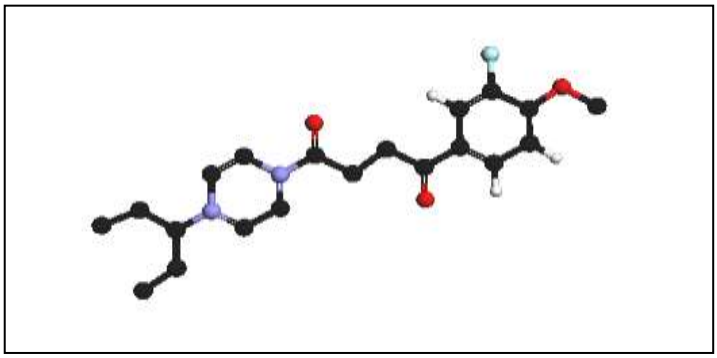


Fig. 2. Prospective view of active conformation of 1-alkyl, 4-acyl –piperazine

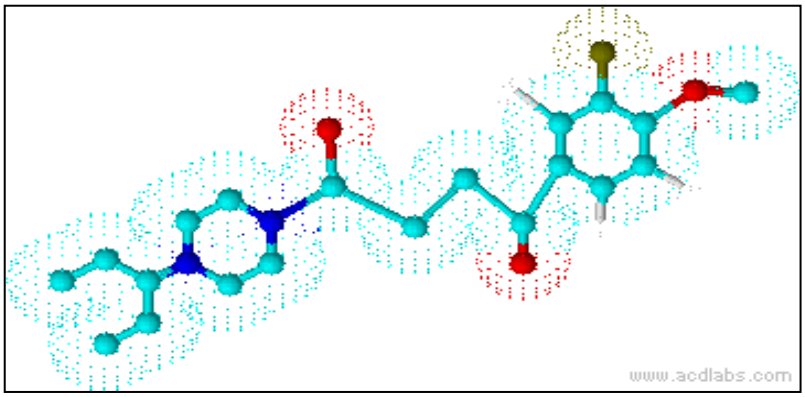


Fig. 3. Electron density cloud 1-alkyl ,4-acyle –piperazine derivative.

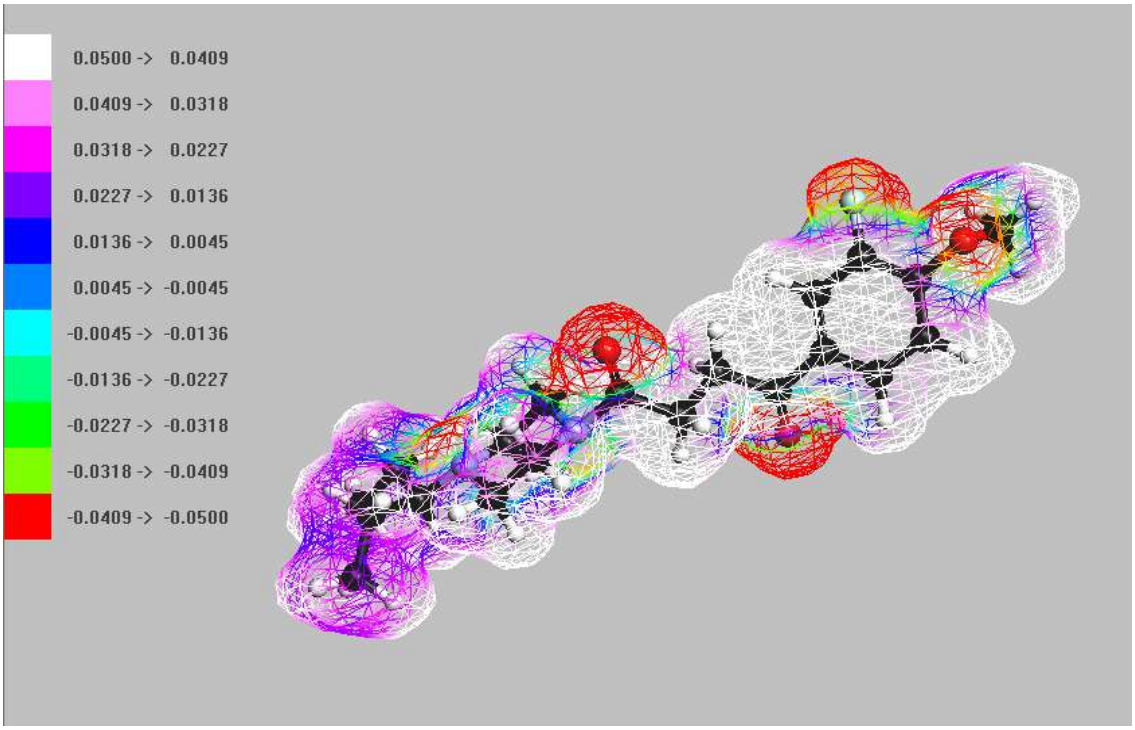


Fig. 4. Electro static potential (ESP) mapped electron density surface (mesh

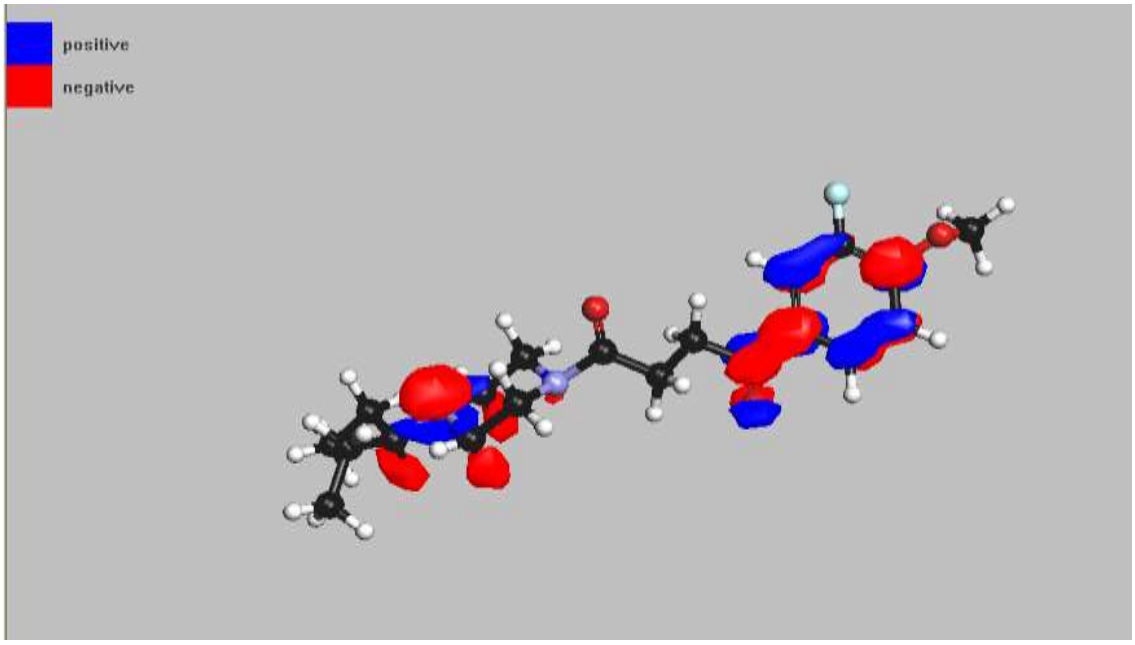


Fig. 5. (Molecular orbital) red shows negative and blue shows positive.

CONCLUSION

In the present potential energy of non-bonded interactive for 1-alkyl-4-acyl piperizine derivative is calculated. Total potential energies were calculated by Summation of all individual pairs. Contours are plotted for visual understanding. The result indicates that the best confirmation of 1-alkyl-4- acyl piperizine derivative is found to be at 38.25396246 -kcal/mol which is minimum potential energy. At this point molecule will be more active as imidazol free Histamine H3 antagonist.

Table 1. Co-ordinates of 1-alkyl ,4-acyle –piperazine derivative.

S.NO	atoms	X	Y	Z
1	C	-2.44473989	1.60215063	1.24997550
2	N	-2.41512986	1.80446369	-0.02071681
3	C	-3.50852236	1.55406897	-0.97209781
4	C	-2.59306074	-0.4362768	0.98221318
5	N	-3.70790110	-0.6586337	0.05952462
6	C	-3.65883360	0.05138748	-1.22266082
7	C	-4.84571602	-1.5183993	0.43158531
8	C	-1.51288774	2.91838661	-0.23520853
9	H	-3.30813882	1.41683867	1.85993595
10	H	-1.52357079	1.21041790	1.85068221
11	H	-4.45995572	1.95743197	0.55463121
12	H	-3.31900750	2.05290106	-1.95045454
13	H	-1.65539106	-0.8275376	0.52316105
14	H	-2.74402733	-0.9657774	1.95039538
15	H	-2.78458907	-0.3153482	-1.80940674
16	H	-4.57353610	-0.1362971	-1.83009954
17	H	-4.63998254	-0.9729840	1.43028020
18	C	-6.11577239	-0.6501519	0.58459101
19	C	-5.01356923	-2.6595392	-0.60742683
20	C	-7.29645100	-1.4081829	1.18920816
21	C	-5.28625545	-4.0163062	0.04394123
22	C	-0.18601164	3.02539767	0.47701825
23	C	0.73761716	1.87160899	0.06894729
24	C	1.94222703	1.78815370	0.95497665
26	O	1.81199624	1.56314083	2.18929808
27	O	-1.80827471	3.81213019	-1.07830908
28	H	-5.87842643	0.21007789	1.25364666
29	H	-6.42670045	-0.2328287	-0.40015960
30	H	-4.08012298	-2.7683668	-1.20803471
31	H	-5.83364408	-2.4246765	-1.32508826
32	H	-8.11714492	-6.6906522	1.41645998
33	H	-6.99788766	-1.9158311	2.13474557
34	H	-7.68837987	-2.1581078	0.46635983
35	H	-6.20032058	-30983797	0.67572941
36	H	-4.41941220	-4.3196989	0.67474472
37	H	-5.43197535	-4.7848794	-0.74849503
38	H	0.30677270	3.99043989	0.21148041
39	H	-0.34747154	3.05200200	1.57736622
40	H	0.20086727	0.89807697	0.12016813
41	H	1.07071427	2.01996337	-0.98322746
42	H	0.20086727	1.00016060	-0.06851997
43	H	1.07071427	2.73483366	0.46147972
44	H	8.22008442	2.22844660	-1.01012339
45	H	8.2345662	2.40917105	-1.49696121
46	C	9.17524329	2.17599500	-0.69641688
47	C	4.72242962	1.80901527	0.64453181
48	C	5.84717565	2.26926024	-0.95688905
49	C	3.43965836	1.91424561	0.38484363
50	C	3.28040389	1.68224520	1.18579630
51	F	4.40265389	2.78770872	-2.87788847
52	O	4.88111601	2.31010567	-1.22760500
53	H	7.11871156	1.62608443	1.26776962
54	H	6.55516149	2.43888541	-1.57569752
55	H	2.56583394	1.40076597	2.22653085

Table 2. Bond Angles of 1-alkyl ,4-acyle –piperazine derivative.

S.NO	ATOMS	ATOMS	ATOMS	BOND ANGLE
1	C8	N2	C1	120.000000
2	C8	N2	C3	120.000000
3	N2	C8	C22	120.000000
4	N2	C8	O27	120.000000
5	N2	C1	C4	109.470000
6	C1	N2	C3	120.000000
7	N2	C1	H9	109.470000
8	N2	C1	H10	109.470000
9	C1	C4	N5	109.470000
10	C4	C1	H9	109.470000
11	C4	C1	H10	109.470000
12	C1	C4	H13	109.470000
13	C1	C4	H14	109.470000
14	C4	N5	C7	120.000000
15	C4	N5	C6	120.000000
16	N5	C4	H13	109.470000
17	N5	C4	H14	109.470000
18	C7	N5	C6	120.000000
19	N5	C7	C18	109.470000
20	N5	C7	C19	109.470000
21	N5	C7	H17	109.470000
22	N5	C6	C3	109.470000
23	N5	C6	H15	109.470000
24	N5	C6	H16	109.470000
25	C6	C3	N2	109.470000
26	C6	C3	H11	109.470000
27	C6	C3	H12	109.470000
28	C3	C6	H15	109.470000
29	C3	C6	H16	109.470000
30	N2	C3	H11	109.470000
31	N2	C3	H12	109.470000
32	C18	C7	7C19	109.470000
33	C7	C18	C20	109.470000
34	C18	C7	H17	109.470000
35	C7	C18	H28	109.470000
36	C7	C18	H29	109.470000
37	C7	C19	C21	109.470000
38	C19	C7	H17	109.470000
39	C7	C19	H30	109.470000
40	C7	C19	H31	109.470000
41	C20	C18	H28	109.470000
42	C20	C18	H29	109.470000
43	C18	C20	H32	109.470000
44	C18	C20	H33	109.470000
45	C18	C20	H34	109.470000
46	C21	C19	H30	109.470000
47	C21	C19	H31	109.470000
48	C19	C21	H35	109.470000
49	C19	C21	H36	109.470000
50	C19	C21	H37	109.470000
51	C24	C23	C22	109.470000

52	C23	C24	C49	120.000000
53	C23	C24	O26	120.000000
54	C24	C23	H40	109.470000
55	C24	C23	H41	109.470000
56	C23	C22	C8	109.470000
57	C23	C22	H38	109.470000
58	C23	C22	H39	109.470000
59	C22	C23	H40	109.470000
60	C22	C23	H41	109.470000
61	C22	C8	O27	120.000000
62	C8	C22	H38	109.470000
63	C8	C22	H39	109.470000
64	F51	C45	C46	120.000000
65	F51	C45	C48	120.000000
66	C47	C46	O52	120.000000
67	C47	C46	C45	120.000000
68	C46	C47	C50	120.000000
69	C46	C47	H53	120.000000
70	O52	C46	C45	120.000000
71	C46	O52	C25	120.000000
72	C46	C45	C48	120.000000
73	C45	C48	C49	120.000000
74	C45	C48	H54	120.000000
75	C48	C49	C50	120.000000
76	C48	C49	C24	120.000000
77	C49	C48	H54	120.000000
78	C49	C50	C47	120.000000
79	C50	C49	C24	120.000000
80	C49	C50	H55	120.000000
81	C50	C47	H53	120.000000
82	C47	C50	H55	120.000000
83	C49	C24	O26	120.000000
84	O52	C25	H42	120.000000
85	O52	C25	H43	109.470000
86	H52	C25	H44	109.470000
87	H9	C1	H10	109.470000
88	H11	C3	H12	109.470000
89	H13	C4	H14	109.470000
90	H15	C6	H16	109.470000
91	H28	C18	H29	109.470000
92	H30	C19	H31	109.470000
93	H32	C20	H33	109.470000
94	H32	C20	H34	109.470000
95	H33	C20	H34	109.470000
96	H35	C21	H36	109.470000
97	H35	C21	H37	109.470000
98	H36	C21	H37	109.470000
99	H38	C22	H39	109.470000
100	H40	C23	H41	109.470000
101	H42	C25	H43	109.470000
102	H42	C25	H44	109.470000
103	H43	C25	H44	109.470000

Table 3. Bond length of 1-alkyl ,4-acyle –piperazine derivative.

S.NO	ATOMS	BOND LENGTH
1	N2---C8	1.422764
2	C1---N2	1.447870
3	C1---C4	1.514000
4	C4---N5	1.447870
5	N5----C7	1.447870
6	N5-----C6	1.447870
7	C3---C6	1.514000
8	N2----C3	1.447870
9	C7----C18	1.514000
10	C-7---C19	1.514000
11	C18----C20	1.514000
12	C19----C21	1.514000
13	C23---C24	1.489000
14	C22----C23	1.514000
15	C-8---C22	1.489000
16	C45---F51	1.439434
17	C46----C47	1.379256
18	C46----O52	1.383377
19	C45----C46	1.379256
20	C45----C48	1.379256
21	C48----C49	1.379256
22	C49----C50	1.379256
23	C47----C50	1.379256
24	C24----C49	1.461000
25	C25----O52	1.411830
26	C24----O26	1.260307
27	C8---- O27	1.260307
28	C-1--- H9	1.112599
29	C1--- H10	1.112599
30	C3---- H11	1.112599
31	C3---- H12	1.112599
32	C4--- H13	1.112599
33	C4--- H14	1.112599
34	C6---- H15	1.112599
35	C6-----H16	1.112599
36	C7---- H17	1.112599
37	C18----H28	1.112599
38	C18----H29	1.112599
39	C19----H30	1.112599
40	C19----H31	1.112599
41	C20----H32	1.112599
42	C20----H33	1.112599
43	C20----H34	1.112599
44	C21----H35	1.112599
45	C21----H36	1.112599
46	C21----H37	1.112599
47	C22----H38	1.112599
48	C22----H39	1.112599
49	C23----H40	1.112599
50	C23----H41	1.112599
51	C47----H53	1.084582
52	C48----H54	1.084582
53	C50----H55	1.084582
54	C25----H42	1.112599
55	C25----H43	1.112599
56	C25----H44	

Table 4. Torsional angles of 1-alkyl ,4-acyle –piperazine derivative.

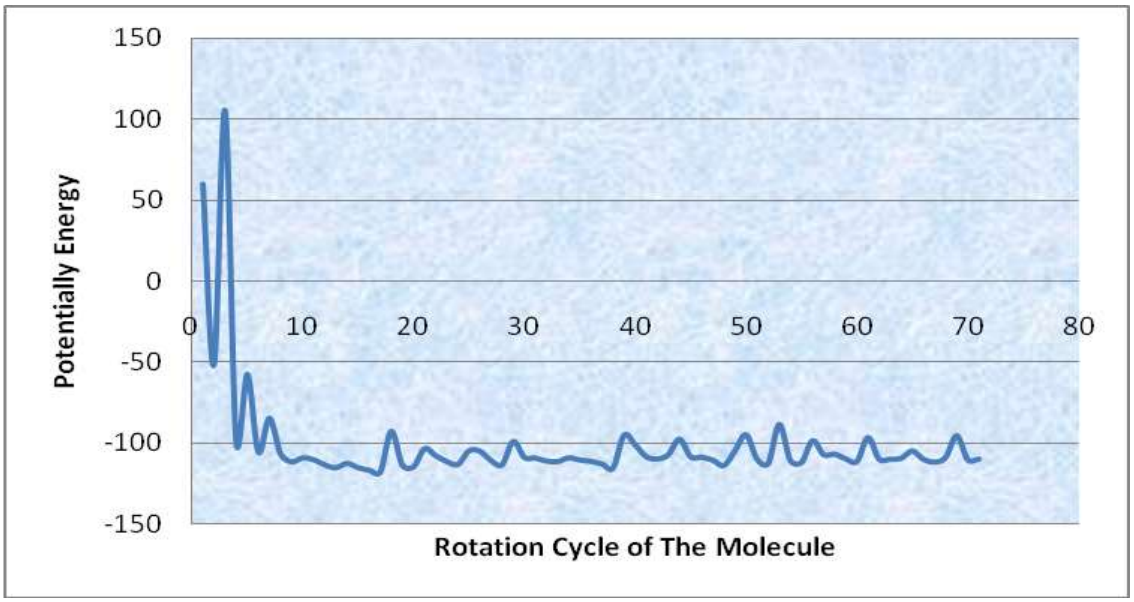
S.NO	ATOMS	ANGLE
1	O1--C2—N14—C15	6.737110
2	O1—C20—N14—C16	6.737110
3	O1—C20—C21—C22	1.000000
4	F2—C5—C3—C4	2.500000
5	F2—C5—C3—O24	2.500000
6	F2—C5—C7—C8	9.743388
7	F2—C5—C7—C29	9.743388
8	C6—C4—C3—C5	9.743388
9	H27—C4—C3—C5	9.743388
10	C4—C3—C5—C7	2.500000
11	C6—C4—C3—O24	9.743388
12	H27—C4—C3—O24	9.743388
13	C4—C3—O24—C25	5.000000
14	C3—C4—C6—C8	2.500000
15	C3—C4—C6—H28	2.500000
16	C7—C5—C3—O24	2.500000
17	C5—C3—O24—C25	5.000000
18	C3—C5—C7—C8	9.743388
19	C3—C5—C7—H29	9.743388
20	C8—C6—C4—H27	2.500000
21	H28—C6—C4—H27	2.500000
22	C4—C6—C8—C7	9.743388
23	C4—C6—C8—C23	9.743388
24	C5—C7—C8—C6	2.500000
25	C5—C7—C8—C23	2.500000
26	C7—C8—C6—H28	9.743388
27	C23—C8—C6—H28	9.743388
28	C6—C8—C7—H29	2.500000
29	C6—C8—C23—C22	2.500000
30	C6—C8—C23—O26	2.500000
31	C23—C8—C7—H29	2.500000
32	C7—C8—C23—C22	2.500000
33	C7—C8—C23—O26	2.500000
34	C8—C23—C22—C21	1.000000
35	C12—C10—C9—C11	5.000000
36	C10—C9—C11—13	5.000000
37	C12—C10—C9—N19	5.000000
38	C10—C9—N19—C17	2.5000000
39	C10—C9—N19—C18	2.500000
40	C13—C11—C9—N19	5000000
41	C11—C9—N19—C17	2.500000
42	C11—C9—N19—C18	2.500000
43	C9—N19—C17—C15	19.486776
44	C9—N19—C18—C16	5.000000
45	C17—C15—N14—C16	19.486776
46	C15—N14—C16—C18	5.000000
47	C17—C15—N14—C20	19.486776
48	C15—N14—C20—C21	6.737110
49	N14—C15—C17—N19	1.000000
50	C18—C16—N14—C20	5.000000

Cont'd…….Table 4

51	C16—N14—C20—C21	6.737110
52	N14—C16—C18—N19	38.973552
53	N14—C20—C21—C22	1.000000
54	C15—C17—N19—C18	19.486776
55	C16—C18—N19—C17	5.000000
56	C20—C21—C22—C23	2.119000
57	C21—C22—C23—O26	1.000000

Table 5. Improper torision of 1-alkyl ,4-acyle –piperazine derivative.

S.NO	ATOMS	TORSION ANGLE
1	N14—C21—C20—O1	16.666667
2	C3—C7—C5—F2	2.000000
3	C5—O24—C3—C4	2.000000
4	C6—H27—C4—C3	2.000000
5	C8—H28—C6—C4	2.000000
6	C8—H29—C7—C5	2.000000
7	C7—C23—C8—C6	2.000000
8	C22—O26—C23—C8	16.666667
9	C11—N19—C9—C10	2.000000
10	C17—C18—N14—C9	2.000000
11	C16—C20—N14—C15	2.000000



Graph 1: Potential energy convergence graph of-alkyl ,4-acyle –piperazine derivative

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