

## COMPUTER AIDED DRUG DESIGNING OF 1-ALKYL, 4-ACYL, PIPERAZINE IMIDAZOL FREE DERIVATIVE AS H<sub>3</sub> RECEPTOR ANTAGONIST

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### ABSTRACT

The histamine H<sub>3</sub> receptor subtype negatively modulates the release of various neurotransmitters such as histamine, glutamate, norepinephrine, acetylcholine and many others mainly in the CNS and H<sub>3</sub> 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<sub>3</sub> receptor consistent with binding affinity at rat brain H<sub>3</sub> 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 geometry convergence function by Argus Lab software. The most feasible position for the drug to interact with the receptor 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 H<sub>3</sub>-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 H<sub>3</sub>-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<sub>3</sub> 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<sub>3</sub>R compounds was eagerly awaited.

In search for H<sub>3</sub> blockers with greater selectivity and less side effects, the development of non-imidazole H<sub>3</sub> antagonists, no longer structurally related to the endogenous mediator histamine, has been pursued and described (Ganellin, D. Jayes, *et al.* 1991) and in recent researches the replacement of the imidazole ring of known H<sub>3</sub> receptor antagonists by alicyclic amines, such as piperidine or piperazine, succeeded in promising compounds such as UCL 2190 (pK<sub>i</sub> (rat) = 8.4, ED<sub>50</sub> (mouse) = 0.18 mg kg<sup>-1</sup> 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 characterized as potent and selective brain penetrating H<sub>3</sub> antagonists. Histamine H<sub>3</sub> 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 (geometry 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 to infer the shape of molecule from geometry optimization calculations. The 1-Alkyl-4-Acyle piperazine structure is generated by Argus Lab, and minimization was performed with the semi-empirical Austin model 1 (AM1) parameter (Dewar *et al.*, 1985)

The minimum potential energy is calculated by using geometry convergence function in Argus Lab software. In order to determine the allowed conformation the contact distance between the atoms in adjacent residues is examined using criteria for minimum Vander waal contact distance (Simons *et al.*, 1983). Surfaces created to visualize ground state properties such as orbital, electron densities, electrostatic potentials (ESP), spin densities and generated grid data used to make molecular orbital surfaces and visualized the molecular orbital and making an electrostatic potential mapped and 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 torsional 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-piperazine derivative are shown in figure 1. Figure 2 shows 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 shows regions of highest stability for a positive test charge, magenta / blue show the regions of least stability for a positive test charge. 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 represents a decrease 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 graph 1.

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).

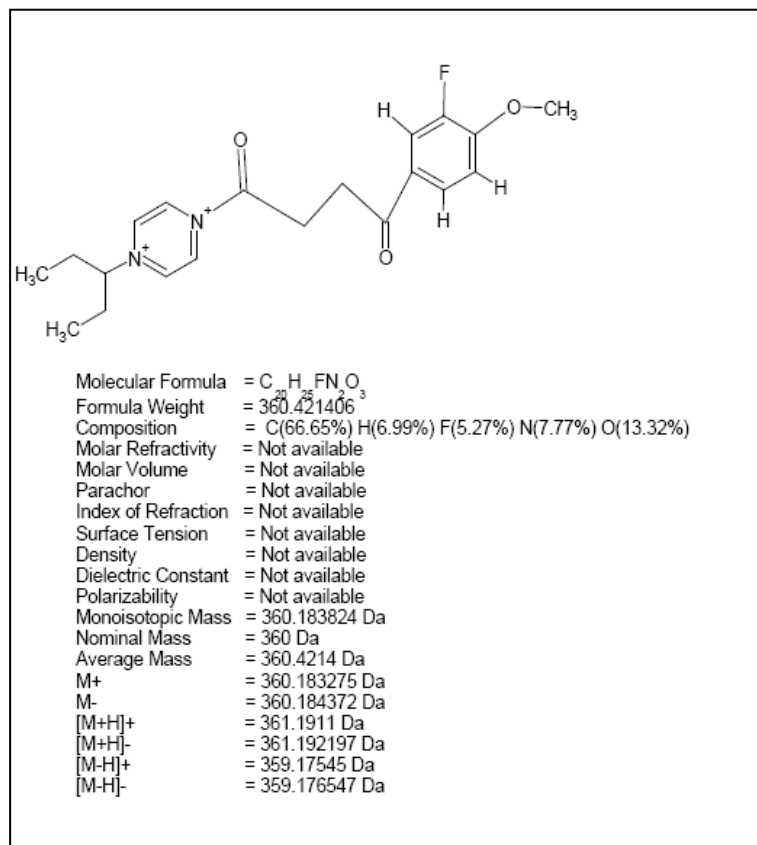


Fig. 1. prospective view and calculated properties of 1-alkyl ,4-acyl –piperazine derivative.

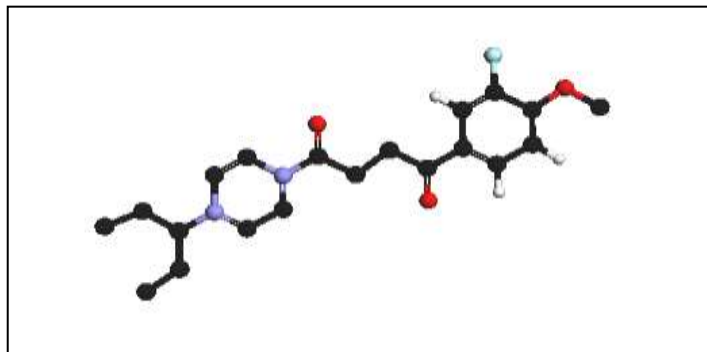


Fig. 2. Prospective view of active conformation of 1-alkyl, 4-acyl –piperazine

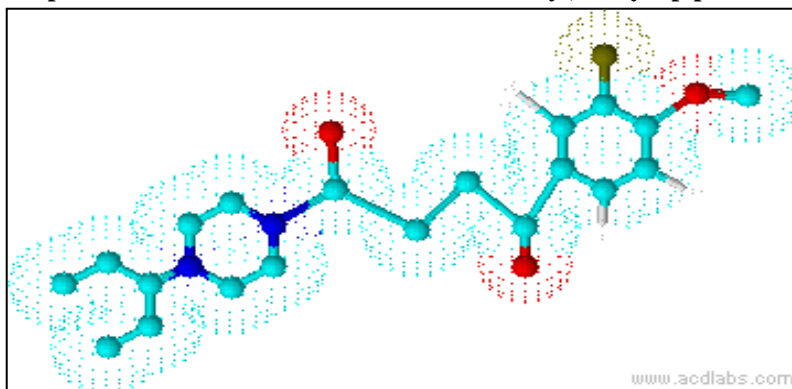


Fig. 3. Electron density cloud 1-alkyl ,4-acyl –piperazine derivative.

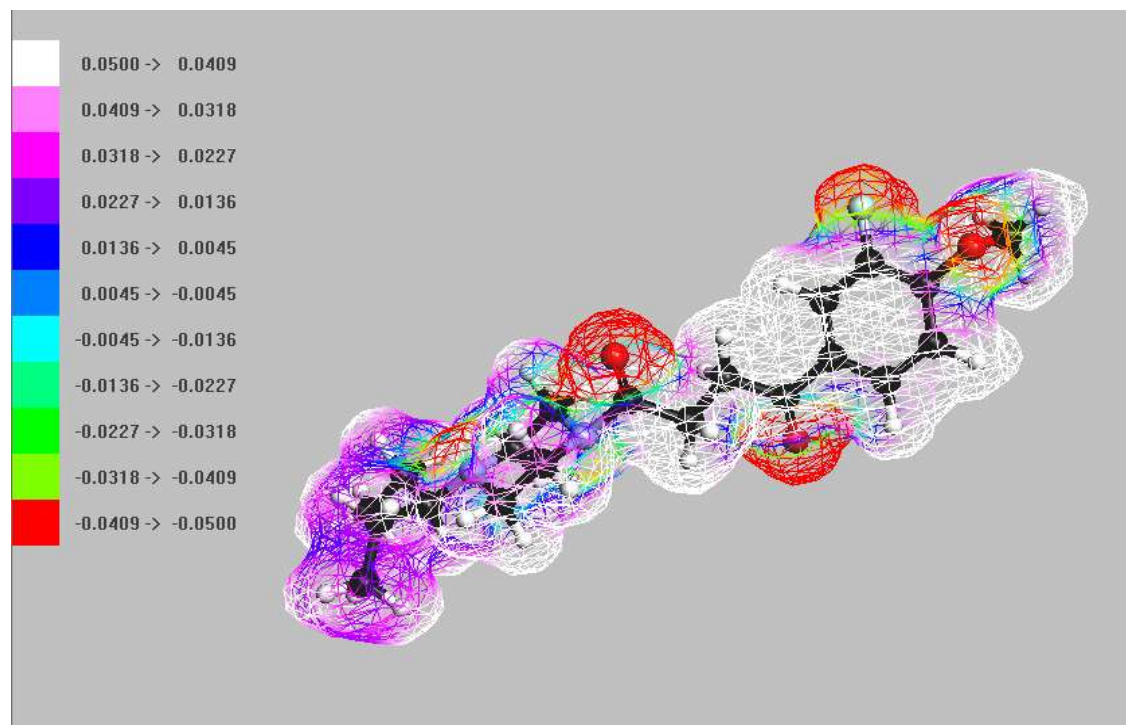


Fig. 4. Electro static potential (ESP) mapped electron density surface (mesh)

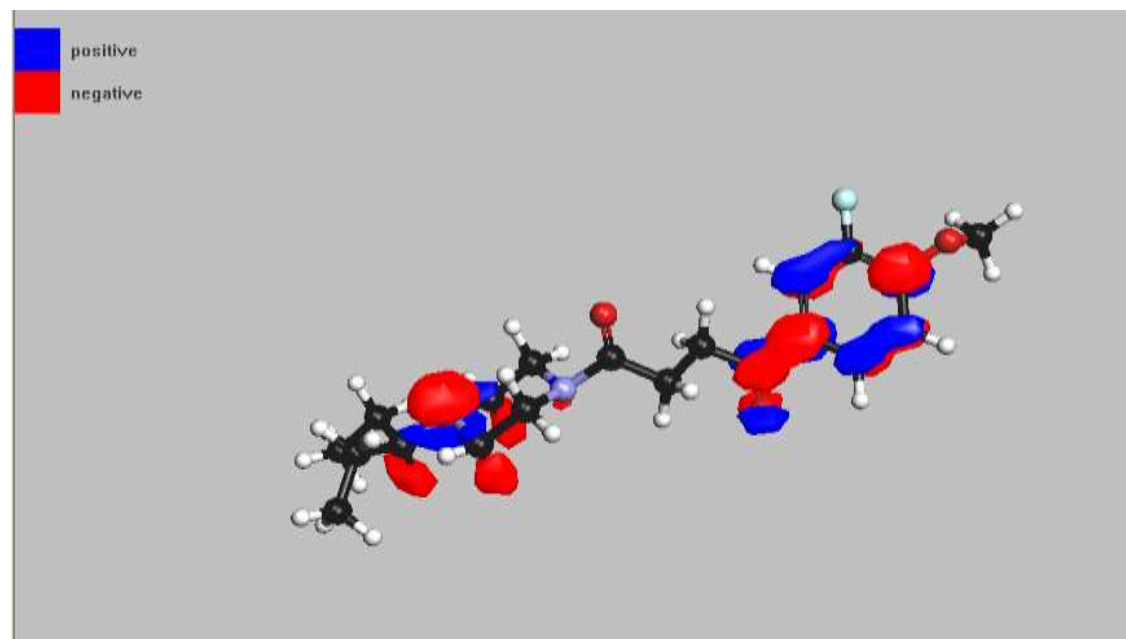


Fig. 5. (Molecular orbital ) red shows negative and blue shows positive.

## CONCLUSION

In the present potential energy of non-bonded interactive for 1-alkyl-4-acyl piperazine 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 piperazine 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-acyl –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-acyl –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  |

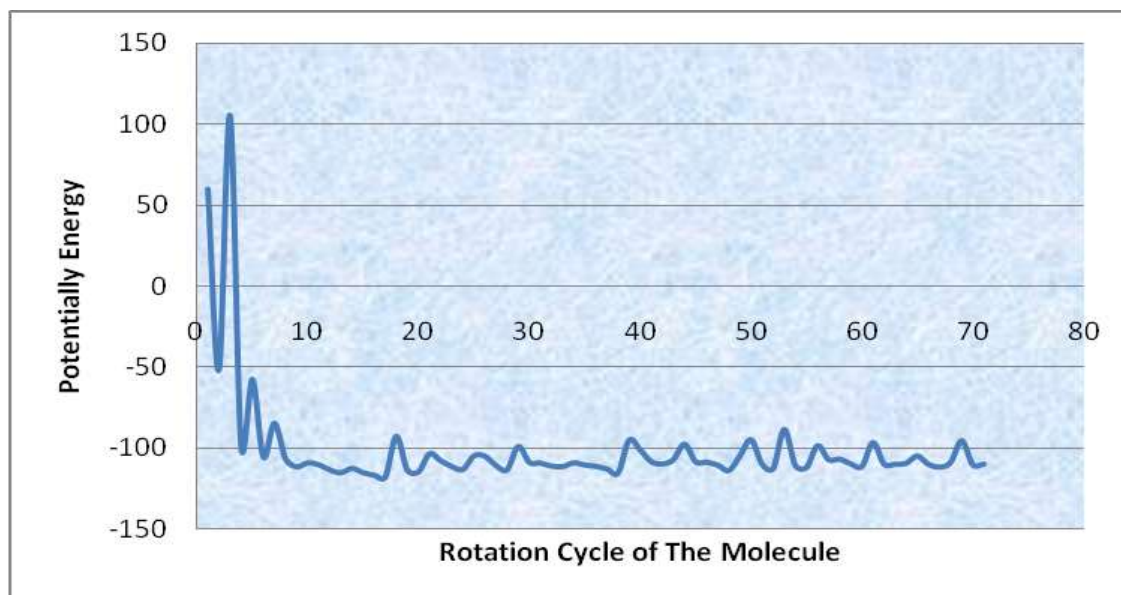


Cont'd.....Table 4

|    |                 |           |
|----|-----------------|-----------|
| 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

## REFERENCES

- Alvarez, E. O. (2009). The role of histamine on cognition. *Behavioral Brain Research*, 199(2):183-9.
- Arrang J.-M., Garbarg M. and Schwartz J.-C., Auto-inhibition of brain histamine release mediated by a novel class (H<sub>3</sub>) of histamine receptor. *Nature (London)* 302 (1983), pp. 832–837.
- Benjamin M. Lovaasen†, Jenny V. Lockard, Brian W. Cohen†, Shujiang Yang, Xiaoyi Zhang, Cheslan K. Simpson†, Lin X. Chen and Michael D. Hopkins (2012). Ground-State and Excited-State Structures of Tungsten–Benzylidyne Complexes. *Norg. Chem., Article ASAP*. DOI: 10.1021/ic202622s
- Clapham, J. and G.J. Kilpatrick (1992). Histamine H<sub>3</sub>-receptors modulate the release of [3H]-acetylcholine from slices of rat entorhinal cortex-evidence for the possible existence of H<sub>3</sub>-receptor subtypes. *Br. J. Pharmacol.*, 107: 919–923.
- Dewar, M.J.S., E.G. Zoobisch, E.F. Healy and J.J.P. Stewart (1985). AMI: A new general purpose quantum mechanical molecular model. *J. Am. Chem Soc.*, 107: 3902-3910.
- Esbenshade, T.A., G.B. Fox, K.M. Krueger, J.L. Baranowski, T.R. Miller, C.H. Kang, L.I. Denny, D.G. Witte, B.B. Yao, J.B. Pan, R. Faghih, Y.L. Bennani, M. Williams and A.A. Hancock (2004). Pharmacological and behavioral properties of A-349821, a selective and potent human histamine H<sub>3</sub> receptor antagonist. *Biochemical Pharmacology*, 68 (5): 933–45.
- Fox, G.B., T.A. Esbenshade, J.B. Pan, R.J. Radek, K.M. Krueger, B.B. Yao, K.E. Browman, M.J. Buckley, M.E. Ballard, V.A. Komater, H. Miner, M. Zhang, R. Faghih, L.E. Rueter, R.S. Bitner, K.U. Drescher, J. Wetter, K. Marsh, M. Lemaire, R.D. Porsolt, Y.L. Bennani, J.P. Sullivan, M.D. Cowart, M.W. Decker and A.A. Hancock (2005). Pharmacological properties of ABT-239 [4-(2-{2-[(2R)-2-Methylpyrrolidinyl]ethyl}-benzofuran-5-yl) benzonitrile]: II. Neurophysiological characterization and broad preclinical efficacy in cognition and schizophrenia of a potent and selective histamine H<sub>3</sub> receptor antagonist. *J. Pharmacol. Exp. Ther.*, 313 (1): 176–90.
- Gao, J. and Xinfu Xia (1993). A two-dimensional energy surface for a type II SN<sub>2</sub> reaction in aqueous solution. *J. Am. Chem. Soc.*, 115: 9667-9675.
- Le, S., J.A. Gruner, J.R. Mathiasen, M.J. Marino and H. Schaffhauser (2008). Correlation between ex vivo receptor occupancy and wake-promoting activity of selective H<sub>3</sub> receptor antagonists. *J. Pharmacol. Exp. Ther.*, 325 (3): 902–9.
- Ligneau, X., J. Lin, G. Vanni-Mercier, M. Jouvet, J.L. Muir, C.R. Ganellin, H. Stark, S. Elz, W. Schunack and J. Schwartz (1998). Neurochemical and behavioral effects of ciproxifan, a potent histamine H<sub>3</sub>-receptor antagonist. *J Pharmacol Exp Ther.*, 287(2):658-66.
- Parmentier, R., C. Anacleit, C. Guhenec, E. Brousseau, D. Bricout, T. Giboulot, D. Bozyczko-Coyne, K. Spiegel, H. Ohtsu, M. Williams and J.S. Lin (2007). The brain H<sub>3</sub>-receptor as a novel therapeutic target for vigilance and sleep-wake disorders. *Biochem. Pharmacol.*, 73 (8): 1157–71..
- Passani, M.B., P. Giannoni, C. Bucherelli, E. Baldi, and P. Blandina (2007). Histamine in the brain: beyond sleep and memory. *Biochem. Pharmacol.*, 73 (8): 1113–22.
- Passani, M.B., J.S. Lin, A. Hancock, S. Crochet and P. Blandina (2004). The histamine H<sub>3</sub> receptor as a novel therapeutic target for cognitive and sleep disorders. *Trends Pharmacol. Sci.*, 25 (12): 618–25.
- Pillot, C., J. Ortiz, A. Héron, S. Ridray, J.C. Schwartz and J.M. Arrang (2002). Ciproxifan, a histamine H<sub>3</sub>-receptor antagonist/inverse agonist, potentiates neurochemical and behavioral effects of haloperidol in the rat. *J. Neurosci.*, 22 (16): 7272–80
- Pillot, C. (2002). Ciproxifan, a histamine H<sub>3</sub> receptor antagonist/inverse agonist, potentiates neurochemical and behavioral effects of haloperidol in the rat. *J. Neurosci.*, 22: 7272–7280.
- Pomponi, S. et al. Harbor Branch Oceanographic. Method for treating airway congestion, US5352707
- Schlicker, E., K. Fink, M. Hinterthaler and M. Göthert (1989). Inhibition of noradrenaline release in the rat brain cortex via presynaptic H<sub>3</sub>-receptors. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 340: 633–638.
- Schlicker, E., M. Malinowska, M. Kathmann and <. Göthert (1994). Modulation of neurotransmitter release via histamine H<sub>3</sub>-heteroreceptors. *Fundam. Clin. Pharmacol.*, 8: 128–137
- Schlicker, E., R. Betz and <. Göthert (1988). Histamine H<sub>3</sub>-receptor-mediated inhibition of serotonin release in the rat brain cortex. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 337: 588–590.
- Simon, J., P. Jorjensen, H. Taylor and J. Ozment (1983). Walking on potential energy surfaces. *J. Phys. Chem.*, 87: 2745-2753.
- Simona Bertoni (2008). *In vitro and in vivo pharmacological analysis of imidazole-free histamine H<sub>3</sub> receptor antagonists*. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 378 (3): 335-343.

- Vande Water Beemd, H. R.E. Carter, G. Grassy, H. Kubinyi, Y. C. Martin, M.S. Tute and P. Willet (1997). Glossary of Terms used In: *Computer Drug Design*. Academic Press, San DIEGO.
- Witkin, J.M. and D.L. Nelson (2004). Selective histamine H<sub>3</sub> receptor antagonists for treatment of cognitive deficiencies and other disorders of the central nervous system. *Pharmacol. Ther.*, 103 (1): 1–20.
- Yoneyama, H., A. Shimoda, L. Araki, et al. (2008). Efficient approaches to S-alkyl-N-alkylisothioureas: syntheses of histamine H<sub>3</sub> antagonist clobenpropit and its analogues. *J. Org. Chem.*, 73 (6):
- Zaragoza, F., H. Stephensen, B. Peschke, and K. Rimvall (2005). 2-(4-alkylpiperazin-1-yl)quinolines as a new class of imidazole-free histamine H<sub>3</sub>-receptor antagonists. *J Med Chem.*, 48: 306–311.
- Zhang, M. (2005). Lack of cataleptogenic potentiation with non-imidazole H<sub>3</sub> receptor antagonist reveals potential drug-drug interactions between imidazole-based H<sub>3</sub> receptor antagonists and antipsychotics drugs. *Brain Res.*, 1045: 142–149.

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