Pak. J. Biochem. Mol. Biol., 2012; 45(3): 154-158

Computer aided drug designing of imidazole free acyl piperazine derivative as a histamine H_3 receptor antagonist

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Abstract: 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 51.19358580 kcal/mol.

Keywords: Imidazole, drug designing, acyl piperazine derivatives, histamine H_3 receptor.
Received: February 12, 2012 **Accepted:** May 10, 2012
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INTRODUCTION

The H_3 receptor is localized primarily to the central nervous system (CNS), with highest expression, in rodents, in the cerebral cortex, hippocampus formations, striatum, and hypothalamus. Centrally administered histamine H_3 antagonists lead to increased central histamine levels and may therefore be useful for the treatment of a variety of CNS disorders, such as attention deficit and hyperactivity disorders, cognitive disorders, schizophrenia or obesity[1-4]. In search for non-imidazole histamine H_3 receptor antagonists, currently indicated as a promising class of H_3 blockers, a series of simple alkyl piperazine derivatives has been studied to attain a preliminary pharmacological profile. The compounds were characterized in vitro in terms of binding affinity, antagonistic potency and selectivity at rodent H_3 receptors. Amides with two atoms between carboxyl and aryl group showed lower potency at the human H_3 receptor than those amides with a three atom spacer[5-9].

The histamine H_3 receptor subtype negatively modulates the release of various neurotransmitters such as histamine, glutamate, nor epinephrine, 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. In search for non-imidazole histamine H_3 receptor antagonists, currently indicated as a promising class of H_3 blockers, a series of simple alkyl piperazine derivatives has been studied to attain a preliminary pharmacological profile[10]. The compounds were characterized in vitro in terms of binding affinity, antagonistic potency and selectivity at rodent H3 receptors[11] Non-imidazole H_3 antagonists such as A-304121, A-317920, A-349821[12,13] as well as ABT-239 and several analogs, also work in this model of ADHD[14].

Imidazole-containing compounds have been reported to have less efficient CNS penetration and may thus fail ultimately to reach their target. Because of such well recognized challenges, almost all recent research directed toward development of H_3 antagonist ligands has been directed toward the so-called "non-imidazoles"[15].

The field of non-imidazole H_3 antagonist ligands is today characterized by an extremely broad diversity of structural classes, with structural diversity increasing over time, rather than converging toward any common group of pharmacophores. This trend reflects the ingenuity of investigators and the large number of teams working toward finding H_3 antagonists, but may also indicate an inherent ability of the receptor to accommodate a wide variety of pharmacophores. The initial disclosures and explorations of non-imidazole H_3 antagonists were from a variety of institutions. Isopropylpiperidinyl benzothiazoles were reported as early non-imidazole H3 antagonists[16]. Non alkylated piperazine or 1-alky; piperazine with aryl-, or hydroxyl-, or alkoxy - substituted alkyl groups gave inactive or significantly less potent amides[17].

The highly localized CNS distribution of the H_3 receptor[18] suggests that limited peripheral side-effects will be seen after treatment with an H_3 receptor antagonist. Furthermore, peripheral histamine-mediated tone is normally minimal, and the H_3 receptor thus is mainly quiescent under normal physiological conditions. Indeed, no cardiovascular[19] or neuroendocrine effects[20] have been reported after treatment with H_3 receptor antagonists.

MATERIALS AND METHODS

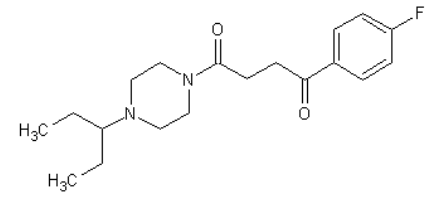
The three dimensional quantitative structure activity relationship (3D QSAR) describe the biological activity of molecule with pharmacological potential as a function of their structural properties[21,22]. Computational advances have generated many tools which are widely used to construct models, minimization and representation of molecular structure[23,24]. All conformational analysis (geometry optimization) study was performed on window based computer using Argus and ACD Lab chem. Sketch softwares. ACDS/CHEMSKETCH is an integrated software package from advanced chemistry development for drawing chemical structures, reactions and to plot best projection with minimum energy. The chemical structure of 1-Alkyl-4-Acylpiperazine was refined by X-ray crystallography technique.

The 1-alkyl-4-acylpierazine derivative molecule is utilized to determine the 3D structure of molecule .several computer programs are used infer the shape of molecule from geometry optimization calculations. The 1-Alkyl-4-Acylpieperazine derivative structure is generated by argues Lab, and minimization was performed with the semi-empirical Austin model 1(AMI) parameter, Argus is an electronic structure program that is based on the quantum mechanics it predicts the potential energies ,molecular structure, geometry optimization of structure , vibration frequencies of coordinates of atoms , bond angle , bond length , and reaction pathways . The set of energy function and the corresponding parameters are called as force field.

The molecular mechanics method calculates the energy as the function of the coordinates and energy minimization is an integral part of the method. Confirmation search method random numbers are used to determine how many and which torsion angle to be incremented and how much (torsion space) or how much and in which direction x, y, z, coordinates of each atom are to be translated. The minimum potential energy is calculated by using geometry convergence function in Argus Lab soft ware .In Order to determine the allowed confirmation the contact distance between the atoms in adjacent residues is examined using criteria for minimum Vander waal contact distance[27]. 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.

RESULTS AND DISCUSSION

Prospective view of molecule 1-alkyl-4-acylpiperazine derivative with properties is shown in figure 1. Figure 2 shows prospective view of active confirmation of 1-alkyl-4-acyl piperazine derivative. 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.



Molecular Formula	= $C_{19}H_{27}FN_2O_2$
Formula Weight	= 334.4282832
Composition	= C(68.24%) H(8.14%) F(5.68%) N(8.38%) O(9.57%)
Molar Refractivity	= 92.14 ± 0.3 cm^3
Molar Volume	= 301.5 ± 3.0 cm^3
Parachor	= 763.3 ± 6.0 cm^3
Index of Refraction	= 1.523 ± 0.02
Surface Tension	= 41.0 ± 3.0 dyne/cm
Density	= 1.108 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 36.52 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 334.205656 Da
Nominal Mass	= 334 Da
Average Mass	= 334.4283 Da

Figure 1: Prospective view of molecule by ACDC Chem. Sketch.

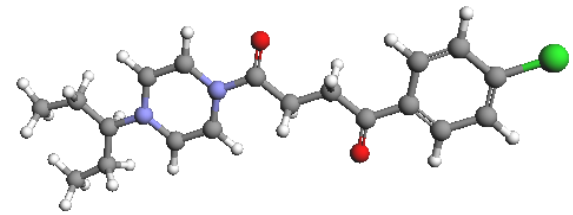


Figure 2: Prospective view of molecule by Argus lab.

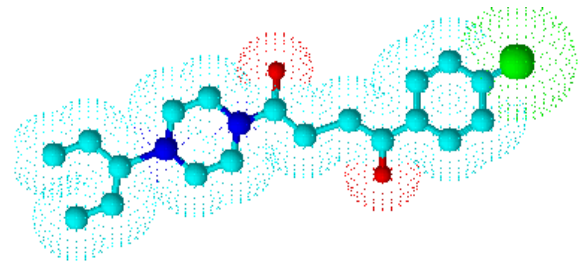


Figure 3: Electron density clouds of molecule4: labeled 1-alkyl-4-acylpiperazine derivative molecule.

Figure 5 shows the complete surface with the color map. Figure 6 show 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 represent a decrease in electron density. The minimum potential energy shows for drug receptor interactive via the geometry convergence map in fig 6 and labeled molecule shown in fig 7. Fractional coordinates of molecule is given in table 1 and bond length and bond angles are given in table 2 and 3 respectively. The result indicates that the Best confirmation of the molecule is present at minimum potential energy is found to be 51.19358580 kcal/mol.

Table 1: Fractional coordinates of molecule.

N1	11.46071015	10.43446056	0.88621856	7
C2	11.47118990	11.81125161	0.31009586	6
C3	10.33063476	10.12963470	1.80492498	6
C4	10.10550248	12.49112904	0.44003102	6
C5	8.97210968	10.41383632	1.14341618	6
N6	9.04299234	11.49824062	0.12163506	7
C7	12.69550264	9.73081666	0.99202128	6
C8	13.81353370	10.11386942	0.03375701	6
C9	14.96615466	9.12045997	0.06259786	6
C10	16.02839466	9.39619253	0.98886820	6
C11	17.36869499	8.75662048	0.79103654	6
C12	19.87911076	7.61752070	0.43988722	6
C13	19.75363671	8.77099890	1.22360985	6
C14	18.76131265	7.02073370	0.16004045	6
C15	18.49288558	9.33163310	1.39382314	6
C16	17.51086557	7.59603298	0.02345054	6
F17	21.09380882	7.06975466	0.25919244	9
C18	7.73367169	12.12067685	0.27792999	6
C17	7.12639272	11.26472049	1.40779636	6
C19	6.74567719	12.32428939	0.88931565	6
C20	6.05898902	12.02714495	2.16780207	6
C21	5.90602618	13.57419740	0.71672310	6
O22	15.81375464	10.10758763	1.95388576	8
O23	12.77076312	8.81530880	1.80122208	8
H24	11.75698169	11.71239075	0.75748791	1
H25	12.25071955	12.43853018	0.79410977	1
H26	10.37637134	9.06114113	2.09935930	1
H27	10.44365407	10.71938455	2.73947426	1
H28	9.97567336	12.92773886	1.45364962	1
H29	10.02845756	13.33381110	0.27654623	1
H30	8.59063532	9.52480891	0.60606040	1
H31	8.22903305	10.64750162	1.94158789	1
H32	13.40353382	10.18604644	0.99568334	1
H33	14.17944756	11.13101198	0.28545906	1
H34	15.42978980	9.11731460	1.06911104	1
H35	14.58235953	8.09015074	0.09272600	1
H36	20.63447750	9.22073456	1.69627536	1
H37	18.87674924	6.11523734	0.76617481	1
H38	18.38346046	10.23244904	2.01390693	1
H39	16.63355927	7.12543450	0.44229126	1
H40	8.00092931	13.12144662	0.70533360	1
H41	7.92384349	10.95368896	2.11282297	1
H42	6.71173954	10.32340727	0.99551696	1
H43	6.08011396	11.44219661	0.97927957	1
H44	7.29720149	12.36991142	1.85346742	1
H45	5.61071550	11.41729185	2.96061924	1
H46	5.24376919	12.35145435	1.49986683	1
H47	6.47220350	12.93120294	2.63517206	1
H48	5.34247392	13.54708496	0.23110338	1
H49	5.17189619	13.67643579	1.52488433	1
H50	6.52109270	14.48262669	0.70820157	1

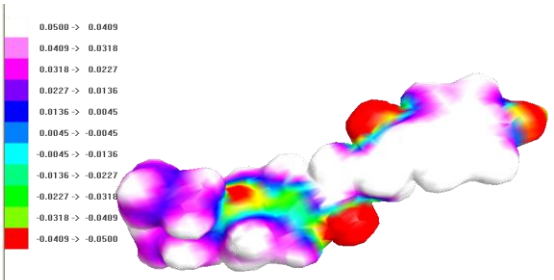


Figure 4: Shows the complete surface with the color map of ESP.

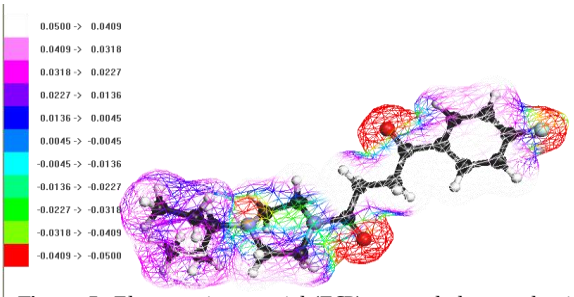


Figure 5: Electrostatic potential (ESP) mapped electron density surface (mesh).

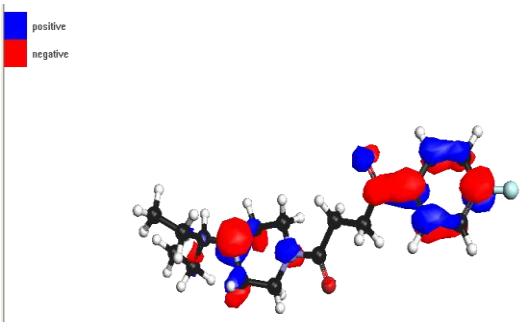


Figure 6: Visualize molecular orbital of molecule, blue shows positive and red shows negative.

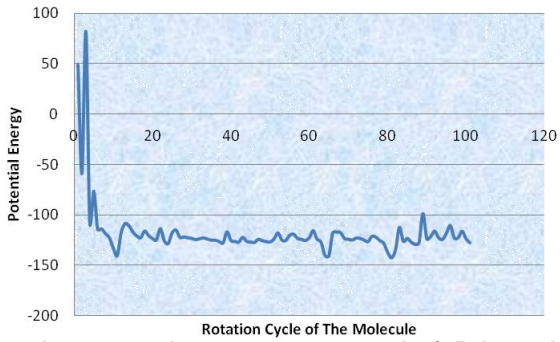
CONCLUSION

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. The result indicates that the best confirmation of 1-alkyl-4-acylpiperazine derivative is found to be at

51.19358580 kcal/mol which is minimum potential energy. At this point molecule will be more active as imidazole- free Histamine H_3 antagonist. We have identified a new class of highly potent and selective antagonists of the human Histamine H_3 receptor by interactive screening of arrays of monoacyldiamines.

Table 2: Bond length of molecule.

1 2 (N)	(C)	1.461925	516.953249
1 3 (N)	(C)	1.461925	516.953249
1 7 (N)	(C)	1.436817	544.530508
2 4 (C)	(C)	1.514000	349.799987
3 5 (C)	(C)	1.514000	349.799987
4 6 (C)	(N)	1.461925	516.953249
5 6 (C)	(N)	1.461925	516.953249
6 18 (N)	(C)	1.461925	516.953249
7 8 (C)	(C)	1.489000	367.716672
7 24 (C)	(O)	1.260307	729.470867
8 9 (C)	(C)	1.514000	349.799987
9 10 (C)	(C)	1.489000	367.716672
10 11 (C)	(C)	1.461000	389.266264
10 23 (C)	(O)	1.260307	729.470867
11 15 (C)	(C)	1.458000	391.674090
11 16 (C)	(C)	1.323387	523.765496
12 13 (C)	(C)	1.458000	391.674090
12 14 (C)	(C)	1.323387	523.765496
12 17 (C)	(F)	1.439434	369.346633
13 15 (C)	(C)	1.323387	523.765496
14 16 (C)	(C)	1.458000	391.674090
18 19 (C)	(C)	1.514000	349.799987
18 20 (C)	(C)	1.514000	349.799987
19 21 (C)	(C)	1.514000	349.799987
20 22 (C)	(C)	1.514000	349.799987
2 25 (C)	(H)	1.112599	328.226230
2 26 (C)	(H)	1.112599	328.226230
3 27 (C)	(H)	1.112599	328.226230
3 28 (C)	(H)	1.112599	328.226230
4 29 (C)	(H)	1.112599	328.226230
4 30 (C)	(H)	1.112599	328.226230
5 31 (C)	(H)	1.112599	328.226230
5 32 (C)	(H)	1.112599	328.226230
8 33 (C)	(H)	1.112599	328.226230
8 34 (C)	(H)	1.112599	328.226230
9 35 (C)	(H)	1.112599	328.226230
9 36 (C)	(H)	1.112599	328.226230
13 37 (C)	(H)	1.084582	354.325486
14 38 (C)	(H)	1.084582	354.325486
15 39 (C)	(H)	1.084582	354.325486
16 40 (C)	(H)	1.084582	354.325486
18 41 (C)	(H)	1.112599	328.226230
19 42 (C)	(H)	1.112599	328.226230
19 43 (C)	(H)	1.112599	328.226230
20 44 (C)	(H)	1.112599	328.226230
20 45 (C)	(H)	1.112599	328.226230
21 46 (C)	(H)	1.112599	328.226230
21 47 (C)	(H)	1.112599	328.226230
21 48 (C)	(H)	1.112599	328.226230
22 49 (C)	(H)	1.112599	328.226230
22 50 (C)	(H)	1.112599	328.226230
22 51 (C)	(H)	1.112599	328.226230



Graph 1: Potentitial energy convergence graph of-alkyl, 4-acyle –piperazine derivative.
Final Geom Energy = -147.7449000268 au, Final Geom Energy = -92711.4081 kcal/mol

Because unsophisticated chemistry was chosen at the outset of the project, the initial hits could be optimized quickly, and the preparation of larger amounts of selected compounds could be accomplished easily. In depth evaluation of the biological properties of these amides is in progress.

Finally all geometric variables were completely optimized for each compound and the lowest energy confirmations were used in molecular modeling studies

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