Journal of Quantum Information Science, **2011, 1, 26-33**
doi:10.4236/jqis.2011.11004 Published Online June 2011 (http://www.SciRP.org/journal/jqis)

Scientific Research

Electronic Structure of some A_3 Adenosine-Receptor Antagonist

——A Structure Activity Relationship

Rifaat Hilal*, Mohamed F. Shibl, Moteaa El-Deftar
Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt
E-mail: *rhhilal@hotmail.com*
Received April 26, 2011; *revised May* 27, 2011; *accepted June* 6, 2011.

Abstract

DFT quantum chemical computations have been carried out at the B3LYP/6-31G(d) level. Full geometry optimization has been performed and equilibrium geometries for a new series of phenyl thiazoles have been located. Ground state electronic properties, charge density distributions, dipole moments and its components have been calculated and reported. Effect of substituents on the geometry and on the polarization of the studied series of compounds are analyzed and discussed. Some structural features have been pinpointed to underline the affinity and selectivity of the studied compounds as adenosine A_3-receptor antagonists. Results of the present work indicate that activity towards A_3 receptor sites is directly correlated with both of the polarity and the co-planarity of the thiazole.

Keywords: DFT/B3LYB, Thiazoles, Substituent Effect, A_3-Receptors, Adenosine-Receptor Antagonist

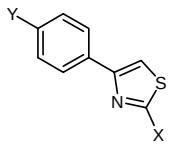
1. Introduction

Adenosine, a metabolite of adenine nucleotides, is a physiological regulator of several cellular activities and cellular metabolism. It acts as an autacoid and activates G-protein-coupled membrane receptors. These receptors are present on almost every cell. However, receptor subtype distribution and densities vary greatly. In our previous work [1] a QSAR model has been developed for 1,3-dimethylxanthines as adenosine receptor antagonists. The model is capable of predicting the affinity towards both A_1 and A_2 receptors. Furthermore, several diverse classes of heterocyclic compounds have been developed [2-4] and reported as selective antagonists for A_3 receptors. Recently, thiazole and thiadiazole analogues have been described as the possible core skeletons of A_3 receptor antagonists with moderate affinity and selectivity [5-6].

The current study aims to present the ground state electronic properties of some new thiazole derivatives with expected biological activity, namely, A_3 Adenosine-receptor antagonist. A structure-activity correlations (SAR) will be attempted.

2. Materials and Methods

4-phenylthiazole is considered as the parent to the studied series of compounds



X = Me, NHMe, NHPh

Y = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 3,4-$CH_2O_2C_6H_3$, 4-$MeOC_6H_4$, 3-thienyl

Compounds studied in the present work were prepared [7] through microwave-assisted cross- coupling reactions in water, and microwave-assisted Suzuki cross-coupling reactions. These methods have been reviewed [8,9].

Theoretical computations carried out throughout this work were performed using the Gaussian 2003 program package [10]. Full geometry optimizations were performed at the DFT (Density Functional Theory) level of theory [11]. The B3LYB method [12,13] has been adopted.

3. Results and Discussion

3.1. Electronic Structure of 4-Phenylthiazole

The choice of the appropriate basis set is of prime impor-

Copyright © 2011 SciRes.

tance. The size of the molecules studied in the present work is medium to large, hence, a cost-effective study of basis sets, is in order. Such a study revealed that the 6-31G(d) basis set provides the minimum acceptable level of accuracy. This point can be appreciated by inspection of **Table (1)**, where the optimized geometric parameters, atomic charges and dipole moments of 4-phenylthiazole are presented, at the 6-31G and the 6-31G(d) levels of theory. Inclusion of the d-polarization functions has but limited effect on the geometric parameters of 4-phenythiazole. Such effect is confined to the sulphur atom region where significant deformation is observed. Upon d-orbital inclusion, the C-S bond length shows >3% shortening whereas, the C-S-C bond angles show widening by ~1 degree. This angle widening is due to the much better extension in space of the d-orbitals. This extension ensures a better description of the molecular structure.

The effect on the charge density distribution and on the dipole moment is more pronounced. Thus, the net charge on "S" is reduced from a value of 0.4 e to a value of 0.25 e upon inclusion of "d" functions. The "d" polarization function enabled a much better description of the "S" electron-affinity. The effect in this case is not localized; it is transmitted to all atoms of the 5-membered ring. In case of the 6-31G(d) basis set, the N-atom is able to accumulate 25% more negative charge, whereas, C5 became more positive. This indicates the direction of migration of the electron charge density. The 6-membered ring, on the other hand, shows but little dependence on the d-functions. The overall redistribution of the charge density is reflected in the increase in the magnitude of the dipole moment to a value of 1.044 D.

The direction of the dipole moment shows also dramatic dependence on the "d" functions. **Figure (1)** shows the dipole moment vectors upon using the 6-31G and the 6-31G(d). The change in direction is most probably due to the fact that polarization functions are able to provide much better description of the lone pair electrons on both "S" and "N".

The above discussion indicates clearly that the 6-31G (d) basis set is much more capable of describing the molecular electronic properties of the studied molecules. Consequently, this basis set is adopted throughout the present study.

3.2. Substituted 4-Phenylthiazole

Substituted 4-phenylthiazoles studied in the present work fall into two main groups: in the first, substituent (X) is in the five-membered ring and the second represent variation of the substituent (Y) in the six-membered ring. Our discussion of the main molecular features will be along these two lines.

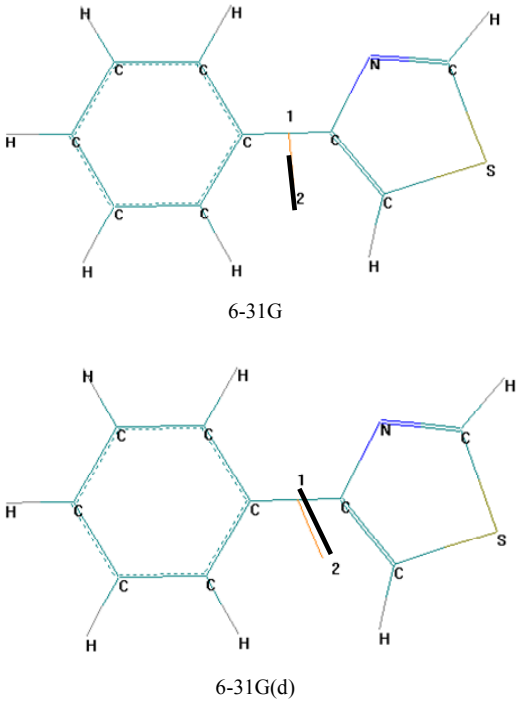


Figure 1. Perspective view of dipole moment orientation of 4-phenylthiazole using 6-31G and 6-31G (d). The origin of coordinate system used is located at the center of mass at point "1" for each molecule; the orientation of dipole moment is along the bold line from 1 to 2.

3.3. Substituted-2-Methylthiazoles

Substitution by a methyl group is not expected to cause major geometric deformation. Careful inspection (table supplementary material) of the main geometric parameters of 4-phenyl-2-methylthiazole reveals that there is no noticeable change in N_1-C_2 or C_2-S_3 bonds in the immediate vicinity of the substitution center. This is true for all bond lengths. However, there seems to be considerable deformation in bond angles. The $N_1C_2S_3$ bond angle is reduced by ~2° upon 2-methyl substitution, an effect which causes an increase in ring strain. However this effect is not transmitted to the 6-membered ring.

2-methyl substitution causes polarization of the σ-framework in a direction opposite to that of the polarization of the π framework. This increase in σ polarization is reflected in two main effects. First, the increase in the negative charge density accumulated on the N atom and the reduction of the dipole moment by ~16%. This polarization and the subsequent reduction in polarity would certainly have the effect of reducing the activity towards the A_3-receptors [1].

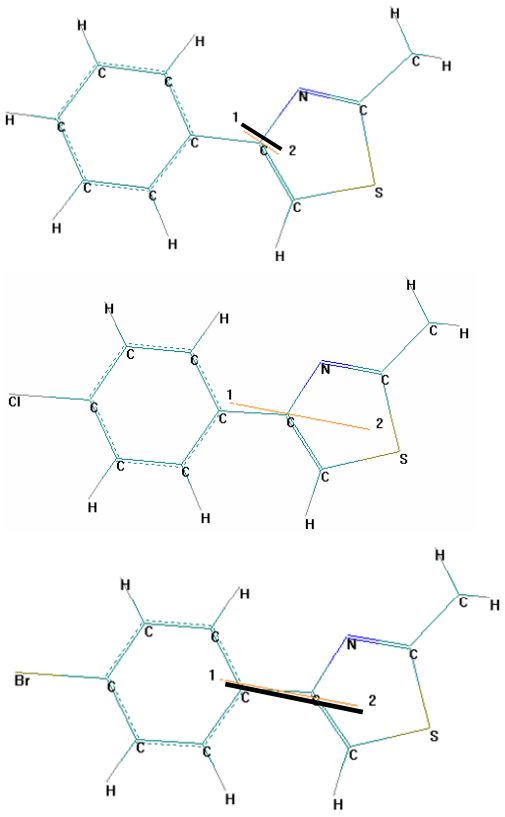
Substitution in C_9 of the six-membered ring by a halogen atom has a considerable effect on the charge redistribution. While the effect on the C-C bond length is almost negligible, the dipole moment increases dramatically

Copyright © 2011 SciRes.

from a value of 0.87 D to 2.98 and 2.88 D for the chloro- and the bromo-derivatives, respectively. The geometric and electronic features of the chloro-and the bromo- derivatives are given in tables supplementary material.

The high electronegativity of the halogen atom induces polarization in both the σ- and the π-frameworks, of the phenylthiazole moiety. Both the chloro-and the bromo-derivatives show their dipole moment vectors pointing in the same direction, towards the 5-membered ring. This indicates a net charge transfer from the 6- to the 5-membered ring. It is very important to realize that, the planarity of 4-phenylthiazole is due to the fact that the π-system extends all over the entire σ-framework. This planarity is a very important geometric feature for adenosine receptor antagonist [14]. Substitution by a chloro-, a bromo-or a methyl group lead to an increase in the tightness of binding. This has the direct consequence of keeping the two rings co-planar. **Figure (2)** presents the geometries of the studied thiazoles and the corresponding dipole moment vectors.

Substitution by an aryl group in the phenyl ring, would certainly add to the σ/π polarization. Careful inspection of the geometric and electronic features of aryl-4-phenyl-2-methylthiazoles studied in this work (tables supplementary material) reveals that, extending the π-system has the direct consequence of enhancing the polarity of the system.



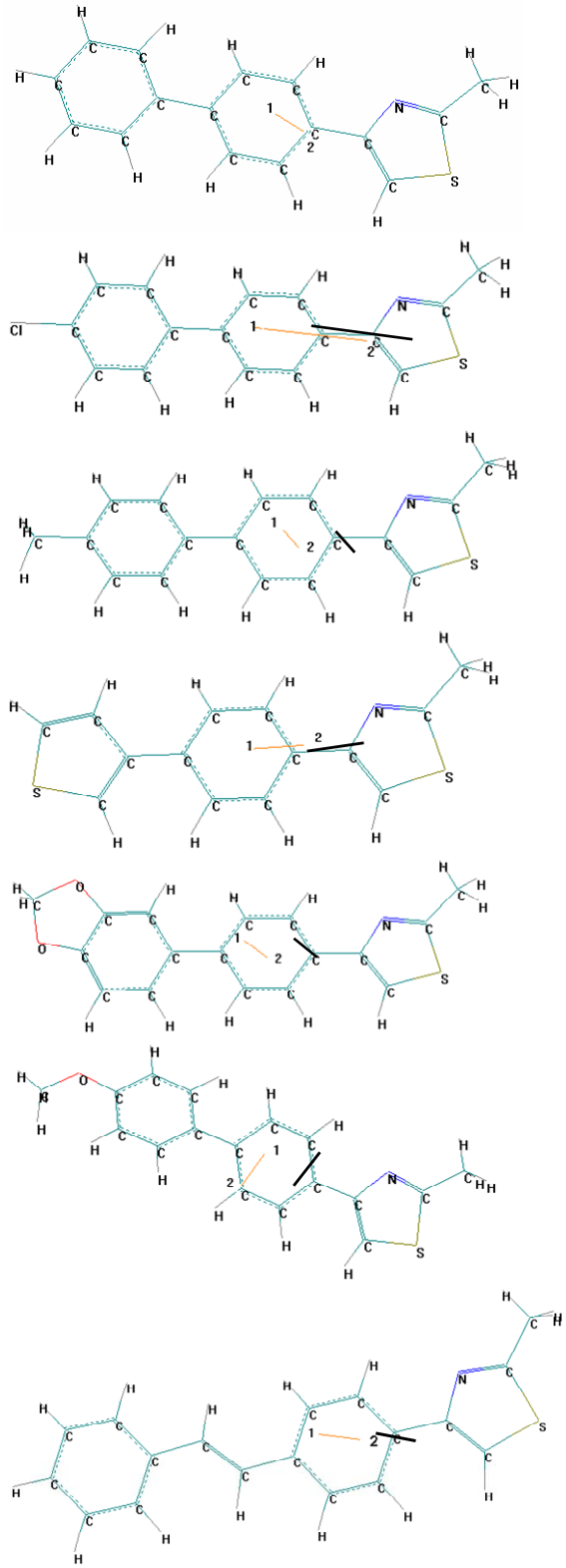


Figure 2. Perspective view of dipole moment orientation of substituted-2-methylthiazole. The origin of coordinate system used is located at the center of mass at point "1" for each molecule; the orientation of dipole moment is along the bold line from 1 to 2.

Copyright © 2011 SciRes.

It is also evident that the conjugation is much tighter on the aryl-phenyl region. This shift of π-conjugation, away from the 5-membered ring, has two main effects. First, reduction in magnitude of the dipole moment by almost 20%, and lifting of co-planarity. The thiazole ring is out of the plane of the rest of the molecule. It should be noticed that, although the dipole moment has been reduced considerably, yet its direction is not significantly affected. This is most probably due to the fact that the directional character of the lone-pair electrons on "S" and on "N" plays a dominant role in this respect. P-chlorophenyl substitution has a pronounced effect on the polarity of the molecule. Thus, the thiazole ring is forced back towards the molecular plane and the dipole moment has increased to 3.15 D. The effect of the chlorine atom substitution is to considerably polarizes the σ-framework in a direction opposite to that of the π- system. Replacement of 4-chloro by a 4-methyl group causes a reduction of the magnitude of the dipole moment to 0.462 D and forcing the thiazole ring out of the molecular plane. Thus, an electron-withdrawing substituent in the 4-phenyl moiety is essential for the A_3-adenosine antagonist receptors reactivity. This is due to the enhanced polarity and co-planarity of the molecule.

This is true for all substituted-2-methylthiazole derivatives studied in the present work. **Table (2)** summarizes the dipole moment values, its components and the dihedral angles for the studied 2-methylthiazoles.

It is also important to examine the variation of the electron-donating strength and the electron affinity values of the studied molecules. **Table (3)** presents the ionization energies (I.P) and electron affinities (E.A) of the studied molecules. Substitution in the 6-membered ring has but little effect on the donating strength. However, this substitution has considerable effect on the electron-affinity. The halogen atom substitution has pronounced effect in lowering the LUMO *i.e*. increasing the electron-affinity of the molecule. This point is of prime importance in determining the activity as A_3 receptor antagonists.

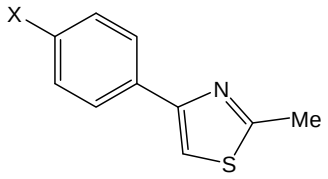
Table 1. Optimized geometry of 4-phenylthiazole.

Bond (A°)	6-31G	6-31G(d)	Angle	6-31G	6-31G(d)	Charge	6-31G	6-31G(d)
N1-C2	1.295	1.296	N1C2S3	114.363	115.138	N1	–0.323	–0.401
C2-S3	1.826	1.748	C2S3C4	86.531	88.379	C2	–0.222	–0.122
S3-C4	1.795	1.73	S3C4C5	111.728	110.883	S3	0.401	0.251
C4-C5	1.371	1.375	C4C5N1	114.089	114.057	C4	–0.498	–0.401
N1-C5	1.409	1.388	C5N1C2	113.289	111.543	C5	0.18	0.265
C5-C6	1.474	1.477	C4C5C6	127.297	126.882	C6	0.098	0.115
C6-C7	1.408	1.404	C5C6C7	119.644	119.716	C7	–0.146	–0.174
C7-C8	1.397	1.394	C6C7C8	120.562	120.644	C8	–0.134	–0.131
C8-C9	1.399	1.396	C7C8C9	120.399	120.403	C9	–0.112	–0.125
C9-C10	1.401	1.397	C8C9C10	119.470	119.423	C10	–0.140	–0.137
C10C11	1.396	1.393	C9C10C11	120.268	120.285	C11	–0.140	–0.181
C11-C6	1.408	1.405	C10C11C6	120.706	120.775	H12	0.189	0.185
C2-H12	1.079	1.084	C11C6C7	118.594	118.468	H13	0.182	0.183
C4-H13	1.077	1.08	N1C2H12	125.703	124.127	H14	0.182	0.16
C7-H14	1.083	1.084	S3C4H13	119.130	120.330	H15	0.128	0.131
C8-H15	1.086	1.087	C6C7H114	118.675	118.716	H16	0.127	0.130
C9-H16	1.085	1.087	C7C8H15	119.549	119.52	H17	0.126	0.130
C10-H17	1.085	1.087	C8C9H16	120.334	120.356	H18	0.126	0.122
C11-H18	1.085	1.086	C9C10H17	120.094	120.134			
			C10C11H18	119.139	119.071			

	6-31G	6-31G(d)
E (a.u.)	–799.968	–800.108
Dipole moment (Debye)	0.877	1.044

Copyright © 2011 SciRes.

Table 2. Dipole moment of 4-substituted-2-methyl thiazole using 6-31G(d).



Cpd No	substituent	PX (D)	PY (D)	PZ (D)	Total (D)	Dihedral angle ($N_1C_5C_6C_7$)
1	4-phenylthiazole	0.387	–0.97	–0.0002	1.044	0.013
2	H	0.749	–0.447	0.0004	0.872	0.012
3	Cl	2.921	–0.591	–0.0002	2.980	0.043
4	Br	2.833	–0.539	0.0005	2.884	0.012
5	Ph	–0.806	–0.379	–0.0505	0.893	3.097
6	4-ClC_6H_4	–3.113	–0.465	–0.0707	3.149	1.934
7	4-MeC_6H_4	–0.316	–0.336	–0.0068	0.462	2.973
8	3-thienyl	–1.262	–0.068	–0.1842	1.277	1.479
9	3,4-$CH_2O_2C_6H_4$	–0.338	–0.262	–0.3553	0.556	2.749
10	4-$MeOC_6H_4$	0.241	–1.422	0.4346	1.506	3.481
11	4-styryl	–0.884	–0.296	–0.0007	0.932	–0.108

Table 3. Ionization potential and electron affinity of 4-substituted-2-methyl thiazole.

Compound No.	I.P (eV)	E.A (eV)
2	5.79	–9.25
3	5.93	–1.17
4	5.90	–1.17
5	7.58	–1.14
6	5.71	–1.31
7	5.49	–1.09
8	5.52	–1.14
9	5.28	–1.09
10	5.33	–1.03
11	5.25	–1.55

4. 2-*N*-methylthiazole-2-amine and Its Derivatives

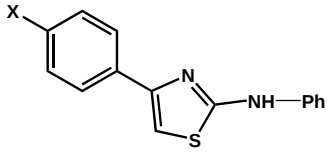
Table (4) summarizes the dipole moment data and dihedral angles of the studied compounds. The π-electron density redistribution in this series of compounds seems to be dominated by a localized conjugation in the thiazole-amine moiety. This would impose a subsequent cross-conjugation in the phenylthiazole region. This is reflected in the magnitude of the dihedral angles reported in **Table (4)**. In general, the aryl group is out of the plane of the thiazole amine moiety. Substitution in the 4-position of the phenyl ring does not change much the non-coplanarity of the studied molecules. Substitution with a Cl or with a Br atom enhances the polarity considerably; both the magnitude and direction of the dipole moments are affected.

Thiazole amines are of better electron donating and of less electron-accepting strength then the corresponding methylthiazoles. **Table (5)** presents the ionization energies and electron affinities of the studied thiazole amines.

The geometric and electronic features of aryl-4-phenyl -2-N-methylthiazoles-2-amine studied in this work are analyzed (presented in (tables, supplementary material)). This series of compounds do not show significant geometry changes upon substitution. However, thiazole amines are characterized by a pronounced increase (~20%) of the negative electron density accumulated on the thiazole nitrogen atom. The variation of the charge density upon substitution is remarkable and reflects itself in the alteration of the direction of the dipole moments (cf. **Figure 3**).

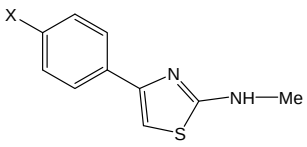
5. 4-Phenyl-2-*N*-phenylthiazole-2-amine and Its Derivatives

Table (6) presents the dipole moments, its components and dihedral angles of the studied compounds.



Copyright © 2011 SciRes.

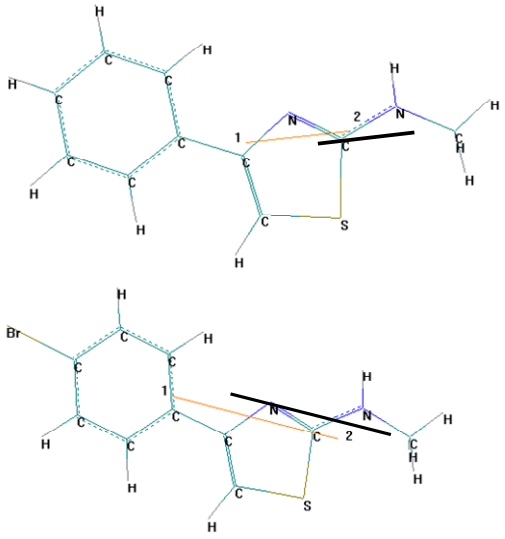
Table 4. Dipole moments of 4-substituted-2-N- methylthiazole-2-amine using 6-31G(d).



Cpd No	substituent	PX (D)	PY (D)	PZ (D)	Total (D)	Dihedral angle ($N_1C_5C_6C_7$)
12	H	–2.133	–0.433	0.582	2.253	2.506
13	Cl	–4.342	–0.307	0.546	4.387	2.072
14	Br	–4.253	–0.410	0.550	4.308	2.413
15	Ph	–2.227	–0.566	0.672	2.394	–2.675
16	4-ClC_6H_4	–4.567	–0.601	0.488	4.632	4.0978
17	4-MeC_6H_4	–1.441	0.728	–0.590	1.719	0.733
18	3-thienyl	2.404	0.859	0.518	2.605	–3.920
19	3,4-$CH_2O_2C_6H_4$	1.763	–0.900	0.917	2.182	2.598

Table 5. Ionization potential and electron affinity of 4-substituted-2-N-methylthiazole-2-amine.

Compound No.	I. P (eV)	E. A (eV)
11	5.25	–0.62
12	5.41	–0.87
13	5.41	–0.9
14	5.19	–0.03
15	5.30	–1.14
16	5.14	–0.92
17	5.17	–0.98
18	5.09	–0.898



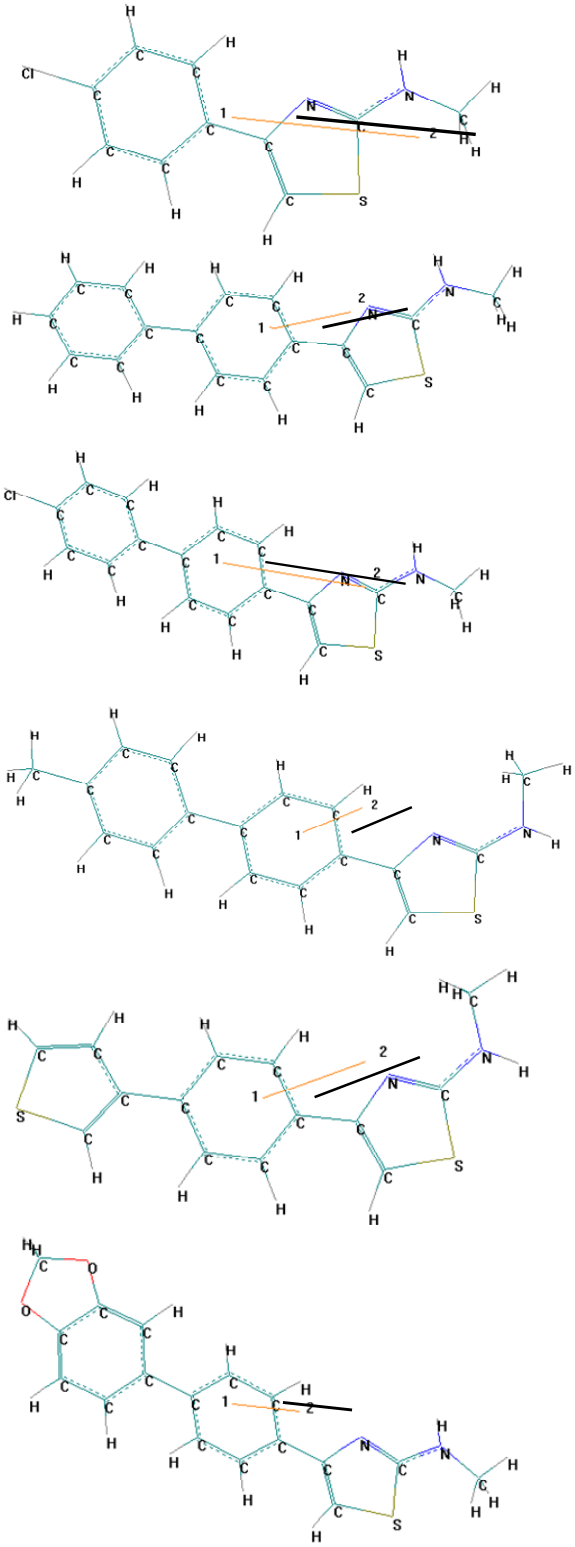
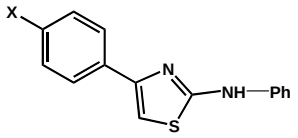


Figure 3. Perspective view of dipole moment orientation of substituted-2-N-methylthiazole-2-amine. The origin of coordinate system used is located at the center of mass at point "1" for each molecule; the orientation of dipole moment is along the bold line from 1 to 2.

Copyright © 2011 SciRes.

Table 6. Dipole moments of 4-substituted-2-N-phenyl thiazole-2-amine using 6-31G(d).

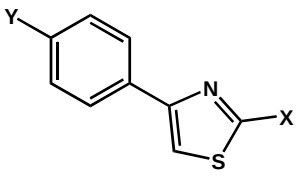


Cpd No	substituent	P_X (D)	P_Y (D)	P_Z (D)	Total (D)	Dihedral angle ($N_1C_5C_6C_7$)
20	H	1.1453	–0.11	–0.1338	1.1583	9.269
21	Cl	3.4309	0.2951	–0.2081	3.4499	4.226
22	Br	3.3616	0.17	–0.1977	3.3717	3.454
23	Ph	1.1034	–0.8256	0.0533	1.3792	–15.122
24	4-ClC_6H_4	–3.4104	–1.3513	–0.0421	3.6686	–15.758
25	4-MeC_6H_4	0.6603	–0.6164	0.0927	0.908	–15.631
26	3-thienyl	1.4437	1.196	0.1257	1.879	–15.496

Inspection of geometric data of these compounds (tables and figures, supplementary material) indicates clearly that:

- All the studied molecules show accumulation of the negative charge density on the thiazole N-atom. This negative charge facilitates hydrogen bonding which is a very important structural feature related directly to the ability to bind to the A_3 receptor sites.
- The NH-phenyl derivatives are non-coplanar. Indicating cross-conjugation between the phenyl and the thiazole moieties. It should be noted that the chlorine and bromine atom substituents have exactly the same effect as noted before. First, it reduced the dihedral angles forcing the phenyl ring towards coplanarity. Second, it enhances the polarity of the molecule as indicated by the magnitude of the dipole moments (cf. **Table 6**).
- The dipole moment vectors seem but little affected by substitution in the 6-membered ring. The dipole moments are dominated by contributions from heteroatoms especially "N" lone-pair.
- NH-phenyl derivatives have almost the same electron-donating and electron-accepting strength as that of the NH-CH_3 derivatives.

Substituted 4-phenylthiazoles studied in the present work fall into three main categories.



Y	X	groups
Cl, Br, Ph, 4-ClC_6H_4, 4-MeC_6H_4, 3,4-$CH_2O_2C_6H_3$, 4-$MeOC_6H_4$, 3-Thienyl	CH_3	I
Cl, Br, Ph, 4-ClC_6H_4, 4-MeC_6H_4, 3,4-$CH_2O_2C_6H_3$, 3-Thienyl	$NHCH_3$	II
Cl, Br, Ph, 4-ClC_6H_4, 4-MeC_6H_4	NHPh	III

Substitution in general, has but little effect on the geometric features of phenylthiazoles, the major geometric effect, however, is traced in the co-planarity of the molecules studied.

Thus, while 4-phenylthiazole itself is coplanar, substitution in the 5-membered ring lefts this co-planarity. It is very important to notice the effect of substitution by Cl- or Br-, in the phenyl ring. This substitution has the geometric effect of restoring the co-planarity back. It seems that Cl- or Br- substituents would have a marked effect on the activity of phenylthiazole as A_3-receptor antagonists.

Substitution has a remarkable effect on the dipole moments, magnitudes and directions. Analysis of dipole moments show fluctuations of their values by substitution. It has been indicated that activity towards A_3-receptor sites is directly proportional to the polarity of the thiazole. In the present work, the enhanced polarity of some phenylthiazoles has been analyzed and attributed to σ-/π-polarization. In some cases, especially for N-CH_3 and N-Ph substitutents, cross-conjugation has but a very little effect on the polarity of molecules. This elaborates upon our previous conclusion that, the contributions from the lone-pair electrons dominate the dipole moments.

Analysis of the effect of substitution, on the net electronic charge on the thiazole "N" atom, shows that the NH-CH_3 and NH-Ph derivatives accumulate more than 0.53e on the thiazole "N" atom. On the other hand, substitution in the phenyl ring has but little effect on the amount of charge on the thiazole N atom. This charge is of prime importance in H-bond formation with A_3-receptor sites. This hydrophilic interaction seems to underlie the selectivity for the human A_3-receptor. In vitro, the thiazole moiety is surrounded by many hydrophobic amino acids.

The tendency of the studied phenylthiazoles to act as electron-donors or electron-acceptors has also been in-

Copyright © 2011 SciRes.

vestigated. The energies of the HOMO's of the studied series of thiazoles are around 5 eV. This low ionization potential indicates a high tendency toward electron donation. Furthermore, aryl-2-methylthiazoles are characterized by low lying LUMO's, indicating considerable electron-affinity. This is of prime importance in enhancing the activity towards A_3-receptor sites.

The present analysis of the structure and electronic properties of phenylthiazoles focuses on four main structural features. The first feature is the co-planarity of molecules. The second is the polarity, as indicated by the dipole moments and their directions. The third feature is the net negative charge on the thiazole "N" atom. This charge enhances H-bond formation; a property of prime importance for binding to A_3-receptor sites. Finally, the fourth feature is the electron donating and accepting tendency of the studied thiazoles. A substituent that forces co-planarity increases the dipole moment and the charge accumulated on the thiazole "N" atom, and lowers the LUMO, would certainly enhance the activity as potent and selective adenosine A_3-receptor antagonists.

6. References

[1] S. El-Tahar, K. M. El-Sawy and R. Hilal, "Electronic Structure of Some Adenosine Receptor Antagonists: V. QSAR Investigation ,"*Journal of Chemical Information And Computer Science*, Vol. 42, No. 2**,** 2002, pp. 386-392. doi:10.1021/ci010307x

[2] Y.-C. Kim and K. A. Jacobson, "Derivatives of the Trizoloquinazoline Adenosine Antagonist (CGS15943) are Selective for the Human A(3) Receptor Subtype," *Journal Medicinal Chemistry*, Vol. 39, No. 21, 1996, pp. 4142-4148.doi:10.1021/jm960482i

[3] P. G. Baraldi, B. Cacciari, R. Romagonoli, G. Spalluts, K.-N. Klotz, E. Leung, S. Gessi, S. Merighi and P. A. Porea, "Pyrazolo [4,3-e]-1, 2, 4-Triazolo[1,5-c]-Pyrimidine Dervatives as Highly Potent and Selective Human A(3) Adenosine Peceptor Antagonists," *Journal Medicinal Chemistry*, Vol. 42, No. 22, 1999, pp, 4473-4478.

[4] K.-Y. Jung, S.-K. Kim, Z.-G. Gao, A. S. Gross, N. Melman, K. A. Jacobson and Y-C. Kim, "Structure-Activity Relationships of Thiazole and Thiadiazole Derivatives as Potent and Selective Human Adenosine A(3) Receptor Antagonists," *Bioorganic and Medicinal Chemistry*, Vol. 12, No. 3, 2004, pp. 613-623. doi:10.1016/j.bmc.2003.10.041

[5] J. E. V. Muijlwijk-Kooezen, H. Timmerman, R. C. Vollinga, J. F. Kunzel, M. de Goote, S. Visser and A. P. Ijzernan, "Thiazole and Thiadiazole Analogues as a Novel Class of Adenosine Receptor Antagonists," *Journal Medicinal Chemistry*, Vol. 44, No. 5, 2001, pp. 749-762.doi:10.1021/jm0003945

[6] N. J. Press, J. R. Fozard, D. Beer, R. Heng, F. Padova, P. Tranter, A. Trifilieff, C. Walker and T. H. Keller, "New Highly Potent and Selective Adenosine A3 Receptor Antagonists," *Abstracts of Papers of the American Chemical Society*, Vol. 224, 2002,1-2, MEDI 419.

[7] K. M. Dawood and M. M. El-Deftar, "Microwave-Assisted Synthesis of 2-Substituted 4-Biarylyl-1, 3-thiazoles by Carbon-Carbon Cross-Coupling in Water," *Synthesis*, Vol. 6**,** 2010, pp. 1030-1038.doi:10.1055/s-0029-1218662

[8] F. Bellina, A. Carpita and R. Rossi, "Palladium Catalysts for the Suzuki Cross-Coupling Reaction: An Overview of Recent Advances," *Synthesis*, Vol. 15, 2004, pp. 2419-2440.

[9] L. Botella and C. Nájera, "A Convenient Oxime-Carbapalladacycle-Catalyzed Suzuki Cross-Coupling of Aryl Chlorides in Water," *Angewandte Chemie International Edition*, Vol. 41, No. 1, 2002, pp. 179-181. doi:10.1002/1521-3773(20020104)41:1<179::AID-ANIE179>3.0.CO;2-O

[10] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Jr. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, "Gaussian , " Revision C.02, Gaussian, Inc., Wallingford, CT, 2004.

[11] P. Hohenberg and W. Kohn, "Inhomogenous Electron Gas," *Physical Review*, Vol. 136, No. 3, 1964, pp. 864-871. doi:10.1103/PhysRev.136.B864

[12] A. D. J. Becke, "Density-Functional Thermochemistry. 3. The Role of Exact Exchange," *The Journal of Chemical Physics*, Vol. 98, No. 7, 1993, pp. 5648-5652. doi:10.1063/1.464913

[13] W. Y. Lee and R. G. Parr, "Development of The Colle-Salvetti correlation-energy Formula Into A Functional of The Electron-Density," *Physical Review*, Vol. 37, No. 2, 1988, pp, 785-789.doi:10.1103/PhysRevB.37.785

[14] K. A. Jacobson, P. J. M. Van Galen and M. Williams, "Adenosine Receptors-pharmacology, Structure- Activity-Relationships, and Therapeutic Potential," *Journal Medicinal Chemistry*, Vol. 35, No. 3, 1992, pp. 407-422. doi:10.1021/jm00081a001

Copyright © 2011 SciRes.