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QSAR Study Of Fluorovinyloxyacetamide And Its Derivatives With PM3 Parameterization

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ABSTRACT

QSAR study of fluorovinyloxyacetamide has been made with the help of quantum chemical parameters such as absolute hardness (η) and electronegativity (χ). These two parameters have been derived with the help of density functional theory and used to correlate the structural features to the biological activities. The 3D modeling and geometry optimization of all the derivatives have been done with the help of PCMODEL software and semiempirical PM3 calculations performed with the help of WinMOPAC-7.21 software. The absolute hardness provides valuable information due to maximum hardness principle and used in the development of QSAR models. These QSAR models may be used to predict the biological activities of hypothetical derivatives of fluorovinyloxyacetamide.

KEYWORDS

PM3;
Fluorovinyloxyacetamide;
Absolute hardness;
QSAR.

INTRODUCTION

Oxyacetamide has been developed as a herbicide, which shows good herbicidal activity for annual weeds through inhibition of cell division and amino acid biosynthesis[1]. Especially, the excellent selectivity between crop (rice) and weeds (barnyard grass), an important weed in paddy fields, is a merit of oxyacetamide herbicide[2]. To exploit a new and highly active herbicide, fluorovinyloxyacetamides, which was introduced fluorovinyl group into oxyacetamide, were synthesized and evaluated their herbicidal activities. In this research, we have described QSAR of fluorovinyloxyacetamide.

The QSAR[3-8] methods are characterized by two assumptions with respect to relation between chemical structure and biological activity. The first is that one can derive a quantitative measure from the structure of those global and local properties of significance to the biological activity of a compound and the other is that one can mathematically describe the relationship between biological activity one wishes to optimize and the molecular property calculated from the structure. The DFT based global

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phenomenon have convenient role to determine the predictive QSAR models[9-12]. For QSAR study of chemical compound various reactivity indices like energy of frontier orbitals (HOMO and LUMO), absolute hardness η[13-14], global softness S[15], electronegativity χ[16,17] and chemical potential μ[18] have been taken.

Theory DFT is based on two famous theorems by Hohenberg and Kohn[19], considered the electron density ρ as basic information for atomic and molecular system instead of wave function ψ. There are many important application of DFT in chemistry. By application of variational principle to the functional $E_{el}[\rho(r)]$[20] (where E_{el} is electronic energy of the system), taking into account that the electron density should all time integrate to the total number of electrons, one obtains the density functional analogue to the Schrodinger equation:

$$\nu(r) + \partial F_{E(r)} / \partial \rho(r) = \mu \quad (1)$$

where $\nu(r)$ is the external (i.e. due to nuclei) potential at position r, and $\rho(r)$ is the ground state electron density. $F_{E(r)}$ yields upon integration the electronic kinetic energy and the electron-electron repulsion energy and μ is the Lagrange multiplier.

The Lagrange multiplier is called the electronic chemical potential and is defined as the partial derivative of the energy of the system, E, with respect to the number of electrons N at a constant external potential $\nu(r)$.

$$\mu = (\partial E / \partial N)_{\nu(r)} \quad (2)$$

This electronic chemical potential was identified by Parr et al[21] as the opposite of electronegativity, as defined by Iczkowski and Margrave[22]

$$\chi = -(\partial E / \partial N)_{\nu(r)} = -\mu \quad (3)$$

Assuming a quadratic relationship between the energy and the number of electrons and using a finite difference approximation, one obtain from equation-3 Mullikins formula[23] for the electronegativity

$$\chi = I + A / 2 \quad (4)$$

With I and A the ionization energy and the electron affinity of the system respectively. A functional relationship is seen to exist between μ on one hand and N and $\nu(r)$ on the other hand obtain

$$d\mu = (\partial^2 E / \partial N^2)_{\nu(r)} dN + \int (\delta\mu / \delta\nu_{(r)})_N \int \nu(r)\, dr \quad (5)$$

where $(\delta\mu / \delta\nu_{(r)})_N$ is the Fukui function as defined by Parr and Yang[24] i.e.,

$$f(r) = (\delta\mu / \delta\nu_{(r)})_N = (\partial\rho_{(r)} / \partial N)_{\nu(r)} \quad (6)$$

and

$$\eta = 1/2\, (\partial^2 E / \partial N^2)_{\nu(r)} \quad (7)$$

is the hardness defined by Parr and Pearson[25-26]. Again assuming that the energy varies quadratically with the number of electrons and using a finite difference approximation we obtain

$$\eta = 1/2\, (I - A) \quad (8)$$

According to Koopman's theorem, the IP is simply the eigen value of HOMO with change of sign and EA is the eigen value of LUMO with change of sign[27]. Therefore on this basis we can write reactivity indices in terms frontier orbital energy as

$$\text{Hardness } \eta = 1/2\, (\varepsilon \text{ LUMO} - \varepsilon \text{ HOMO}) \quad (9)$$

MATERIAL AND METHOD

For the purpose a set of 28 derivatives of fluorovinyloxyacetamide with their observed biological activity[28] in terms of $-\log EC_{50}$ values have been taken and are tabulated under TABLE 1. For QSAR prediction, the 3D modeling, and geometry optimization of all the compounds has been done with the help of PCMODEL software, using PM3 hamiltonian[29]. The MOPAC calculation have been performed with WINMOPAC 7.21 software, by applying keywords PM3 Charge=0 Gnorm=0.1, Bonds, Geo-OK, Vectors Density and all the values required for the determination of the value of absolute hardness, global softness, chemical potential and electronegativity have been obtained from this software by solving the equation given in theory and the result are reported in TABLE 2.

RESULT AND DISCUSSION

The structure of fluorovinyloxyacetamide is given in TABLE 1. 28 derivatives of fluorovinyloxyaceta mide are listed with their observe herbicidal activity in same table. The activity was expressed in terms of 50%-growth-inhibition concentration (EC_{50}) of

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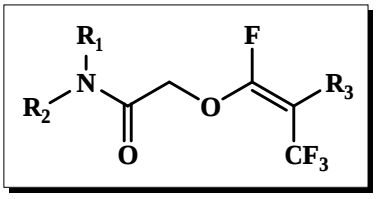
TABLE 1: Structure of 38 derivatives of fluorovinyloxyacetamide and their biological activity in terms of EC_{50} values



No	R_1	R_2	R_3	Activity
		Subgroup-1		
1	-$(CH_2)_5$-		3-CH_3-C_6H_4	2.114
2	-$(CH_2)_5$-		4-C_2H_5-C_6H_4	1.738
3	-$(CH_2)_5$-		3,5-Cl_2-C_6H_3	1.674
		Subgroup-2		
4	-$CH(C_2H_5)(CH_2)_4$-		4-CH_3-C_6H_4	1.807
5	-CH(CH)(CH2)$_3$CH(CH_3)-	3-Cl-C_6H_4	1.738	
6	-$CH(CH_3)$(CH2)$_4$-		4-CH_3-C_6H_4	1.574
		Subgroup-3		
7	-$(CH_2)_6$-		3-CH_3-C_6H_4	2.102
8	-$(CH_2)_6$-		3-CH_3O-C_6H_4	2.036
9	-$(CH_2)_6$-		3,4-$(CH_3)_2$-C_6H_3	1.992
10	-$(CH_2)_6$-		3,5-$(CH_3)_2$-C_6H_3	1.910
11	-$(CH_2)_6$-		4-C_2H_5-C_6H_4	1.867
		Subgroup-4		
12	C_6H_5	CH_3	C_6H_5	2.408
13	C_6H_5	CH_3	3-F-C_6H_4	2.387
14	C_6H_5	CH_3	3-CH_3-C_6H_4	2.366
15	C_6H_5	CH_3	3-CF_3-C_6H_4	2.046
16	C_6H_5	CH_3	4-C_2H_5O-C_6H_4	1.937
		Subgroup-5		
17	4-F-C_6H_4	CH_3	C_6H_5	2.387
18	4-F-C_6H_4	CH_3	4-CH_3-C_6H_4	1.941
19	4-F-C_6H_4	CH_3	4-CH_3O-C_6H_4	1.763
		Subgroup-6		
20	4-Cl-C_6H_4	C_2H_5	4-CH_3-C_6H_4	1.517
21	4-CH_3O-C_6H_4	n-C_3H_7	4-CH_3-C_6H_4	1.360
22	3-CF3-C6H4	C_2H_5	4-CH_3-C_6H_4	1.259
		Subgroup-7		
23	3-CH_3-C_6H_4	i-C_3H_7	C_6H_5	2.036
24	3-CH_3-C_6H_4	i-C_3H_7	3-F-C_6H_4	1.673
25	3-CH_3-C_6H_4	i-C_3H_7	3-CH_3O-C_6H_4	1.470
		Subgroup-8		
26	4-Cl-C_6H_4	CH_3	C_6H_5	1.988
27	4-Cl-C_6H_4	CH_3	3-CH_3O-C_6H_4	1.691
28	4-Cl-C_6H_4	CH_3	4-CH_3O-C_6H_4	1.670

TABLE 2: Various reactivity indices of fluorovinyloxyacetamide derivatives and their biological activity in terms of EC_{50} values

No.	εHOMO	εLUMO	χ	η	A
			Subgroup-1		
1	-9.48232	-0.61146	5.04689	4.43543	2.114
2	-9.35334	-0.58712	4.97023	4.38311	1.738
3	-9.59467	-0.9222	5.258435	4.336235	1.674
			Subgroup-2		
4	-9.45975	-0.62675	5.04325	4.4165	1.807
5	-9.53741	-0.71721	5.12731	4.4101	1.738
6	-9.37616	-0.77491	5.075535	4.300625	1.574
			Subgroup-3		
7	-9.52718	-0.69689	5.112035	4.415145	2.102
8	-9.38277	-0.83731	5.11004	4.27273	2.036
9	-9.42996	-0.59459	5.012275	4.417685	1.992
10	-9.44652	-0.62845	5.037485	4.409035	1.91
11	-9.42351	-0.61736	5.020435	4.403075	1.867
			Subgroup-4		
12	-9.74093	-0.55614	5.148535	4.592395	2.408
13	-9.78464	-0.68396	5.2343	4.55034	2.387
14	-9.56045	-0.50447	5.03246	4.52799	2.366
15	-9.79702	-0.89059	5.343805	4.453215	2.046
16	-9.17541	-0.56713	4.87127	4.30414	1.937
			Subgroup-5		
17	-9.63653	-0.71533	5.17593	4.4606	2.387
18	-9.53356	-0.68843	5.110995	4.422565	1.941
19	-9.11083	-0.69437	4.9026	4.20823	1.763
			Subgroup-6		
20	-9.52276	-0.62753	5.075145	4.447615	1.517
21	-9.39814	-0.5043	4.95122	4.44692	1.36
22	-9.54142	-0.89167	5.216545	4.324875	1.259
			Subgroup-7		
23	-9.49216	-0.2859	4.88903	4.60313	2.036
24	-9.76973	-0.68775	5.22874	4.54099	1.673
25	-9.06923	-0.33726	4.703245	4.365985	1.47
			Subgroup-8		
26	-9.56145	-0.61275	5.0871	4.47435	1.988
27	-9.3403	-0.49878	4.91954	4.42076	1.691
28	-9.30762	-0.79186	5.04974	4.25788	1.67

ε_{HOMO} and ε_{LUMO} are eigen values of highest occupied molecular orbital and lowest unoccupied molecular orbital respectively obtained from PM3 calculation (29). χ is electronegativity, η is absolute hardness and A is observed biological activity in terms of $-\log EC_{50}$ (1, 28).

barnyard grass. The EC_{50} values were estimated by fitting data to sigmoidal type function[1] because the experiments were performed in a range of concentration (1.000, 0.2500, 0.0625, 0.0156, 0.0040 kg/ha) and activities were represented by 10 percent unit. In the equation-10, the initial and final values were fixed. Activities were demonstrated to 100 percent, and other variables were changed to fit. The

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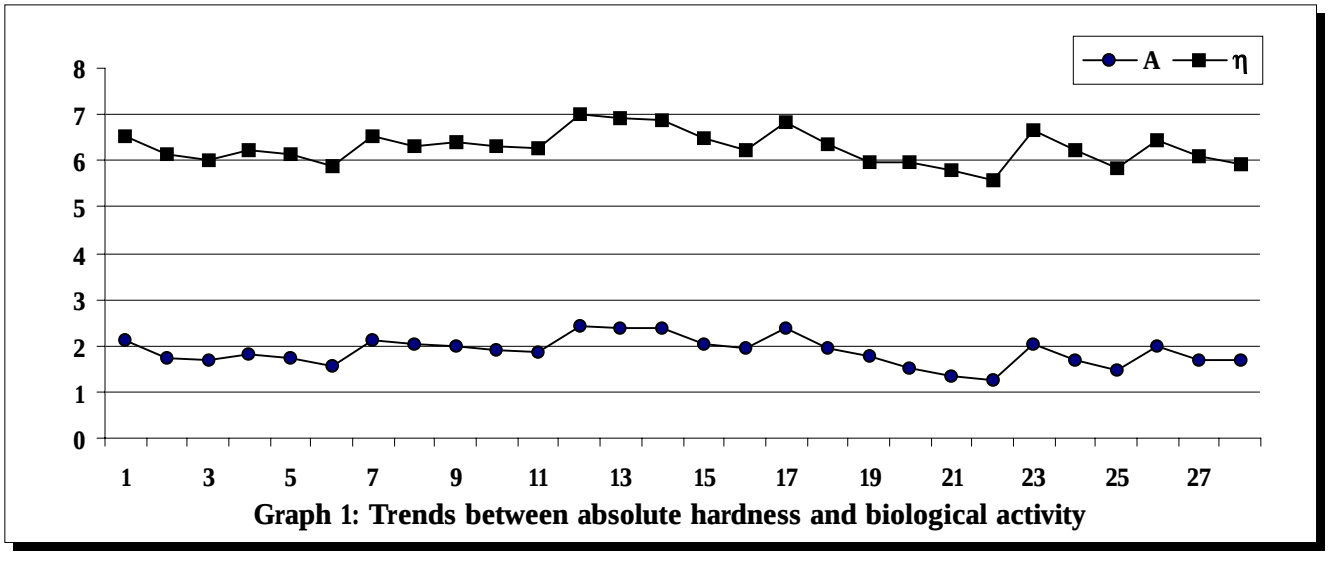
concentration and EC_{50} value were converted by -log function to fit scale.

$$Y = \frac{A_1 - A_2}{1 + e^{(\chi - \chi_0)/d\chi}} + A_2$$

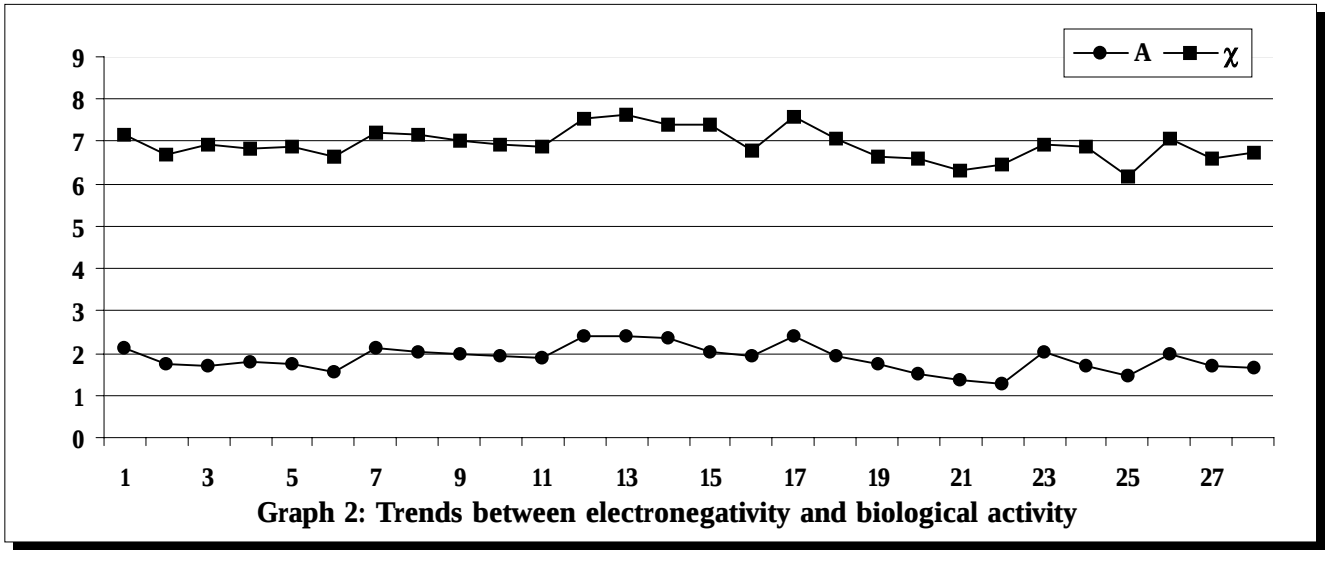
(A_1: initial value = 0, A_2: final value = 100, χ_0: center, dx: time const.)

The TABLE 2 contains eigen values of frontier orbitals (HOMO & LUMO) of derivatives, absolute hardness and electronegativity. These two reactivity indices are DFT based fundamental tool for describing the chemical properties and reactivity for chemical system as we have published for different compounds earlier[30-36]. A close look at TABLE 2 indicates a very good relationship between absolute hardness and biological activity as demonstrated in graph-1. The trends between electronegativity and activity is shown in graph-2 is not as clear as in case of absolute hardness. Hardness provides better relationship because of maximum hardness principle[37]. The direct relationship between absolute hardness and herbicidal activity provides a strong background to develop QSAR model. Although there is a direct relationship but there is no sequential rise or fall. In order to provide sequential relationship we have divided the set into subgroups on basis of their structural similarities. If the relationship is examined in these subgroups separately the relationship is exhibited sequentially.

In subgroup-1 compounds **(1)**, **(2)** and **(3)** are present in which the parent structure is same with only small variation at R_3 position. In this subgroup



Graph 1: Trends between absolute hardness and biological activity



Graph 2: Trends between electronegativity and biological activity

the highest activity is associated with compound number **(1)** and the absolute hardness of this compound is also highest, while the lowest value of activity and absolute hardness is associated with compound number **(3)**. Thus the activity has direct relationship with absolute hardness. The compounds **(4)**, **(5)** and **(6)** have almost same parent structure with small variation and are considered as second subgroup. The highest value of activity as well as absolute hardness of subgroup-2 is also along with compound number **(4)**, as the hardness decreases the biological activity also decreases. The compound number **(6)** has lowest value of hardness as well as biological activity. The subgroup-3 has five compounds on the basis of their structural similarities and follows same trends between biological activity and hardness, as the hardness decreases the biological activity also decreases. The compounds **(7)** and **(8)** are R3 substituted with an aromatic group. The aromatic group has single substitution while rest compound of series have disubstituted aromatic nucleus at R3 position. So it shows some variation however **(7)** and **(8)** itself follow the trend. The subgroup-4 contains five compounds with almost same structure and the variation takes place only at R_3 position, the compound number **(12)** have highest activity as well as highest hardness and as the hardness decreases the activity also decreases. The Subgroup–5 contains three compounds, which have same structure with only variation at R_3 position they show direct relationship with hardness. The subgroup-6 contains three compounds the structure is almost same with small variation, the relationship between absolute hardness and biological activity in this subgroup is well defined. The subgroup-7 contains three compound and have same structure with substitution only at R_3 position these compound also show direct relationship with absolute hardness. The subgroup-8 contains three compounds in these compounds the substitution at R_3 position and have good relationship with absolute hardness and herbicidal activity.

CONCLUSION

From the above structure activity relationship discussion it is clear that the absolute hardness is an important parameter for QSAR study. On the basis of this we can build up theoretical base for demonstrating relative activity of compounds. Besides absolute hardness (η), we have evaluated another DFT based reactivity indices electronegativity (χ), which is also included in TABLE 2. Hardness provides a better relationship because of maximum hardness principle[37]. The close examination of TABLE 2 shows that the trend of relationship between biological activity and electronegativity is not as clear as in case of absolute hardness. So with help of absolute hardness it is easy to asses the biological activity of any hypothetical compound by comparing previously known one even without their synthesis.

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REFERENCE

[1] H.Matsumoto; Proceedings I (A), Weed and Environmental Impact; The 17th Asian-Pacific Weed Science Society Conference, 39 **(1999)**.
[2] S.Ito, A.Kamochi, K.Sawada, T.Goto, K.Yasui; Proceedings, The 12th Asian-Pacific Weed Science Society Conference, 255 **(1989)**.
[3] C.Hansch, T.Fujita; J.Am.Chem.Soc., **86**, 1616 **(1964)**.
[4] T.Fujita; 'QSAR and Drug Design, New Developments and Applications', Elsevier, Amsterdam **(1995)**.
[5] D.L.Lee, P.A.Kollman, F.J.Marsh, M.E.Wolff; J.Med. Chem., **20**, 1139 **(1977)**.
[6] Hugo, Kubinyi; '3D QSAR in Drug Design: Theory, Methods and Applications', ESCOM: Leiden **(1993)**.
[7] Y.Zhou, L.Xu, Y.Wu, B.Liu; J.Chem.Intell.Lab.Sys., **45**, 95 **(1999)**.
[8] T.J.Hou, J.M.Wang, N.Liao, X.J.Xu; J.Chem.Inf. Comput.Sci., **39**, 775 **(1999)**.
[9] M.Randic; J.Am.Chem.Soc., **97**, 6609 **(1975)**.
[10] B.W.Clare; J.Med.Chem., **41**, 3845 **(1998)**.
[11] K.Baumann; J.Anal.Chem., **18**, 36 **(1999)**.
[12] R.M.Sweet, D.Eisenberg; J.Mol.Biol., **171**, 479 **(1983)**.
[13] R.G.Parr, Z.Zhou; Acc.Chem.Res., **26**, 256 **(1993)**.
[14] F.DeProft, P.Geerlings; J.Chem.Phys., **106**, 3270 **(1997)**.
[15] J.R.Sabin, S.B.Trickey, S.P.Apell, J.I.Oddershede; J. Quan.Chem., **77**, 358 **(2000)**.

Full Paper

[16] C.J.Umrigar, M.P.Nightingale, K.J.Runge; J.Chem. Phys., **99**, 2865 **(1993)**.
[17] A.Mushinski, M.P.Nightingale; J.Chem.Phys., **101**, 883 **(1994)**.
[18] P.K.Chattaraj, A.Cedillo, R.G.Parr; J.Chem.Phys., **103**, 7645 **(1995)**.
[19] P.Hohenberg, W.Kohn; Phys.Rev.B, **136**, 864 **(1964)**.
[20] R.G.Parr, W.Yang; 'Density Functional Theory of Atoms and Molecules', Oxford University Press, New York, **(1989)**.
[21] R.G.Parr, R.A.Donnelly, M.Levy, W.E.Palke; J.Chem. Phys., **68**, 3801 **(1978)**.
[22] R.P.Iczkowski, J.L.Margrave; J.Am.Chem.Soc., **83**, 3547 **(1961)**.
[23] R.S.Mullikins; J.Chem.Phys., **2**, 782 **(1934)**.
[24] R.G.Parr, W.Yang; J.Am.Chem.Soc., **106**, 4049 **(1984)**.
[25] R.G.Parr, R.G.Pearson; J.Am.Chem.Soc., **105**, 7512 **(1983)**.
[26] W.Yang, R.G.Parr; Pro.Natl.Acad.Sci., USA, **82**, 6723 **(1985)**.
[27] R.G.Pearson; Acc.Chem.Res., **26**, 250 **(1993)**.
[28] D.H.Cho, S.K.Lee, B.T.Kim, K.T.No; Bull.Korean Chem.Soc., **22**, 388 **(2001)**.
[29] J.J.P.Stewart; J.Comp.Chem., **10**, 209 **(1989)**.
[30] P.P.Singh, H.K.Srivastava, F.A.Pasha; Bioorg.Med. Chem., **12(1)**, 171 **(2003)**.
[31] P.P.Singh, F.A.Pasha, H.K.Srivastava; QSAR and Comb.Sci., **22(8)**, 843 **(2003)**.
[32] P.P.Singh, F.A.Pasha, H.K.Srivastava; Indian J Chem.-B, **43B**, 983-991 **(2004)**.
[33] H.K.Srivastava, F.A.Pasha, P.P.Singh; Intr.J.Quant. Chem., **103(3)**, 237-245 **(2005)**.
[34] F.A.Pasha, H.K.Srivastava, P.P.Singh; Intr.J.Quant. Chem., **104(1)**, 87-100 **(2005)**.
[35] F.A.Pasha, H.K.Srivastava, P.P.Singh; Molecular Diversity, **9(1-3)**, 215-220 **(2005)**.
[36] F.A.Pasha, H.K.Srivastava, P.P.Singh; Bioorg.Med. Chem., **13(24)**, 6823-6829 **(2005)**.
[37] R.G.Parr, P.K.Chattaraj; J.Am.Chem.Soc., **113**, 1854 **(1991)**.