Asian Journal of Chemistry Vol. 20, No. 8 (2008), 5941-5946

QSAR Studies of Some Pharmacological Schiff Base Compounds

KISHOR ARORA
Department of Chemistry, Government K.R.G. Autonomous Post Graduate College, Gwalior-474 001, India
E-mail: kishorarora@rediffmail.com

A set of nine Schiff base compounds containing anti-inflammatory activity were subjected to quantitative structural and activity relationship (QSAR) studies using various combinations of electronic, spatial and structural descriptors. Experimental data of these compounds are available which prompted study of their theoretical parameters using AM1 semi-empirical quantum-chemical studies and to correlate these properties with their activities according to QSAR studies. Statistical significance of the proposed models have been discussed. Among the various descriptors for the proposed models, some of the descriptors *viz.*, energy of highest occupied molecular orbital, energy of lowest unoccupied molecular orbital, bend energy, dipole moment and principal moment of inertia Y-component gave good statistical significance.

Key Words: QSAR, Schiff base, Semi-empirical methods.

INTRODUCTION

In the recent years, it has been shown that *ab initio* quantum chemical approaches which utilize the SCF approach within the Hartree-Fock Roothanian approximation are limited in their practical approach as they are restricted to very small molecules[1,2] and they require the calculations of very large number of many center integrals. Therefore, semi-empirical methods were introduced that retain the characteristics of quantum chemical approach in the calculations of wave function from which electronic and other properties can be obtained. Though semi-empirical methods are approximate but they serve the purpose of calculations of wave function, energy and other properties like ionization potentials, molecular geometry, force constants, electron density distribution, interpretation of molecular spectra[3-8].

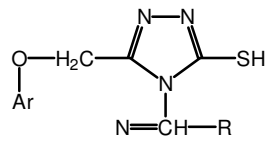
Semi-empirical quantum-chemical methods use a simpler Hamiltonian than the correct Hamiltonian and use the parameters whose values are adjusted to fit experimental data. Because of difficulties in applying *ab initio* methods to medium and large molecules many semi-empirical methods were developed to treat them.

Austin model 1 (AM1) is an improved version of MNDO semi-empirical method and it has been parameterized for various elements like H, B, Al, C, Si, Ge, Sn, N, P, O, S, Cl, I, Zn and Hg[9,10]. AM1 is re-parameterized to give PM3 method. A major limitation of the original version of these semi-empirical methods is that they use a basis set of s and p valance electrons only.

Quantitative strucutre and activity relationship (QSAR) studies for various series of compounds with different drug activities have been reported correlating the electronic parameters of those compounds calculated on the basis of semi-empirical methods widely available in many programs/software package like MOPAC, Hyperchem, *etc.*[11-15].

Antiinflammatory activities of the Schiff bases of 3-aryloxy-4-amino-5-mercapto-1,2,4-triazole with furfural, nitro furfural and 4-dimethyl amino benzaldehyde were reported[16]. It has been reported in the literature that these Schiff base compounds have moderate antiinflammatory activity (Edema inhibited % activity)[16].

This prompted to study and reported the electronic and other related molecular properties of the Schiff base compounds containing inflammatory activitites (Fig. 1) using semi-empirical methods and to study quantitative structure and activity relationship (QSAR)[11-15].



Ar = $C_{10}H_7$, $(CH_3)C_6H_4$, (Cl) $(CH_3)C_6H_3$
R = C_4H_3O, (NO_2) C_4H_2O, $N(CH_3)_2C_6H_4$

Fig. 1. Schiff base compounds

COMPUTATIONAL DETAILS

Quantum chemical calculations were carried out by semi-empirical AM1 method of MOPAC program. PC model was used to draw the structures of the compounds. The semi-empirical methods, in general do not make use of symmetry in SCF cycles in economizing the CPU time. Therefore, all the geometries were fully optimized without any symmetry constraints using AM1 method and stationary points were obtained on the potential energy surfaces. Bond lengths, bond angles, electron densities, net atomic charges, thermodynamic parameters *viz.*, heat of formation, ionization potential, total energy, electronic energy, core-core repulsion energy, *etc.* were calculated with the help of standard parameters as implemented in the software.

The following descriptors were calculated for QSAR analysis: bend energy (EB), heat of formation (HF), vander-waal's energy (VDW), total energy (TE), HOMO energy (HOMO), LUMO energy (LUMO), torsion energy (TOR), electronic energy (EE), dipole moment (DM), principal moment of inertia-X (PMI-X), principal moment of inertia-Y (PMI-Y), principal moment of inertia-Z (PMI-Z) and zero point energy (ZE). All the biological activity data have been converted into negative log values for QSAR analysis (pI).

All the computed parameters were considered as independent variables and biological activity was taken as dependent variable. Step-wise regression analysis method[17,18] was used to develop equations. Statistical parameters such as correlation coefficient (r), standard error(s) and Fischer test (F-test), *etc*. were considered to select best QSAR model.

RESULTS AND DISCUSSION

When the set of parameters/descriptors were subjected to stepwise liner regression analysis in order to develop the QSAR model, various statistical equations with different values of correlation coefficient (r), standard error (s) and F-test valus (F) were obtained. These equations are listed as under:

$$pI = (-0.015684) \times EB + 1.636147363 \quad (1)$$
$$n = 9, s = 0.18486, F \text{ test} = 2.50E\text{-}12$$
$$pI = (0.004794409) \times TOR + 1.08270186 \quad (2)$$
$$n = 9, s = 0.1840, F \text{ test} = 4.24E\text{-}11$$
$$pI = (0.18013689) \times VDW + 1.095828 \quad (3)$$
$$n = 9, s = 0.18482, F \text{ test} = 2.70E\text{-}08$$
$$pI = (0.00489509) \times HF + 0.5716116 \quad (4)$$
$$n = 9, s = 0.1769, F \text{ test} = 2.389E\text{-}16$$
$$pI = (2.1091E\text{-}05) \times TE + 1.274874923 \quad (5)$$
$$n = 9, s = 0.1850, F \text{ test} = 1.120E\text{-}32$$
$$pI = (-0.483427463) \times HOMO + 1.0514837 \quad (6)$$
$$n = 9, s = 0.1836, F \text{ test} = 0.48913$$
$$pI = (-1.0418920) \times LUMO + 1.26342057 \quad (7)$$
$$n = 9, s = 0.0.1819, F \text{ test} = 0.00685$$
$$pI = (-0.2306083) \times DM + 2.491545 \quad (8)$$
$$n = 9, s = 0.1728, F \text{ test} = 0.002217$$
$$pI = (1.79478E\text{-}05) \times PMI\text{-}X + 1.1396762 \quad (9)$$
$$n = 9, s = 0.1846, F \text{ test} = 4.498E\text{-}29$$
$$pI = (-253165E\text{-}06) \times PMI\text{-}Y + 1.21919706 \quad (10)$$
$$n = 9, s = 0.1849, F \text{ test} = 2.763E\text{-}31$$
$$pI = (1.93136E\text{-}05) \times PMI\text{-}Z + 1.0056143 \quad (11)$$
$$n = 9, s = 0.18441, F \text{ test} = 2.0719E\text{-}31$$
$$pI = (0.001495036) \times ZE + 0.89443904 \quad (12)$$
$$n = 9, s = 0.0.18456, F \text{ test} = 7.750E\text{-}17$$

TABLE-1
SEMI-EMPIRICAL QUANTUM CHEMICAL ELECTRONIC OR MOLECULAR PROPERTIES/PARAMETERS FOR THE SCHIFF BASE COMPOUNDS UNDER STUDY FOR WHICH QSAR STUDIES HAVE BEEN CARRIED OUT

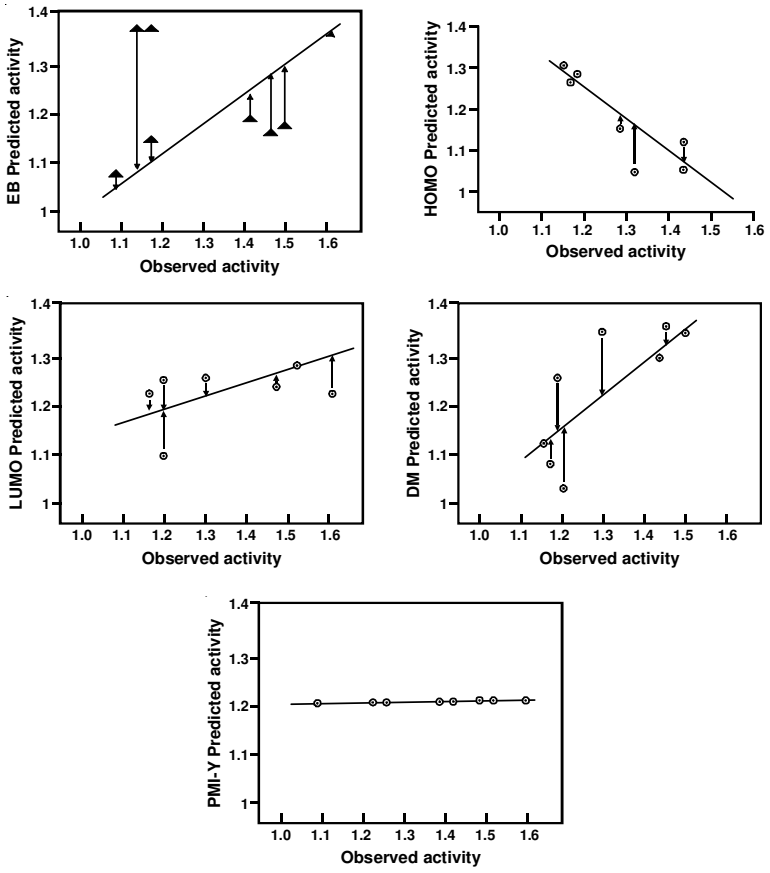
Electronic or molecular property/parameter	Compd. I	Compd. II	Compd. III	Compd. IV	Compd. V	Compd. VI	Compd. VII	Compd. VIII	Compd. IX
EB	17.345	30.232	32.072	30.180	17.095	37.852	17.434	31.755	36.336
TOR	28.747	19.860	18.434	19.861	28.983	18.067	34.956	25.949	25.239
VDW	8.296	3.726	3.980	3.135	8.028	3.090	10.312	5.572	5.882
HF	136.37	107.57	130.63	113.68	147.72	88.33	179.23	140.88	116.75
TE	-4626.71	4130.91	-4990.28	-3770.85	-4266.7	-4630.3	-4650.2	-4154.3	-5013.7
HOMO	-0.53348	-0.18446	-.0557	-0.50752	-0.4785	-0.5692	-0.3011	-0.1628	-0.0211
LUMO	0.04238	0.01249	0.16452	0.01652	0.14817	0.00082	0.04544	0.03018	0.08775
DM	6.117	5.032	5.225	5.375	6.485	5.012	6.1724	4.973	6.016
PMI-X	4467.72	1921.34	3109.30	2092.942	4296.86	3633.69	4624.10	2428.44	3649.96
PMI-Y	8778.11	9231.17	10985.5	4917.883	6084.67	5579.12	7217.82	7135.36	8494.39
PMI-Z	12154.1	10528.0	12815.7	6365.272	9290.81	8108.2	10734.5	8705.18	10471.5
ZE	233.727	169.054	185.378	174.608	239.428	191.113	253.05	188.251	204.541

TABLE-2
CORRELATION MATRIX TABLE FOR THE ELECTRONIC/MOLECULAR PROPERTIES OF THE COMPOUNDS UNDER STUDY

	EB	TOR	VDW	HF	TE	HOMO	LUMO	DM	PMI-X	PMI-Y	PMI-Z	ZE
EB	1.0000											
TOR	0.7800	1.0000										
VDW	0.8360	0.9770	1.0000									
HF	0.7680	0.8710	0.8690	1.0000								
TE	0.0859	0.2960	0.3156	0.3020	1.0000							
HOMO	0.3790	0.0990	0.1050	0.1108	0.1328	1.0000						
LUMO	0.2162	0.1131	0.2260	0.3450	0.3540	0.3970	1.0000					
DM	0.7420	0.7710	0.8210	0.6040	0.3760	0.2080	0.4350	1.0000				
PMI-X	0.5960	0.6940	0.7910	0.5210	0.5770	0.2860	0.3280	0.7930	1.000			
PMI-Y	0.0418	0.0933	0.0272	0.0935	0.2130	0.7111	0.4332	0.0751	0.051	1.000		
PMI-Z	0.2830	0.2298	0.3830	0.3388	0.0060	0.4790	0.4990	0.2600	0.398	0.903	1.000	
ZE	0.8030	0.8960	0.9490	0.7550	0.4570	0.2810	0.2840	0.8740	0.925	0.094	0.318	1.000

The computed properties for the Schiff base compounds are listed in Table-1. These computed parameters are subjected to step-wise linear regression analysis on the basis of which above equations are framed. Correlation matrix of the parameters used in the QSAR studies is given in Table-2. To ascertain the validity of the suggested models internal validation using leave-one-out cross validation process and randomization test were performed.

From the point of view of the simple QSAR studies of Schiff base compound in present study HOMO (HOMO energy), EB (bend energy), LUMO (LUMO energy), DM (dipole moment) and PMI-Y (principal moment of inertia-Y) are the descriptors, which contribute to the pI *i.e.* log of activity positively. Therefore, equations number 1, 6, 7, 8 and 10 may be selected as proposed model equations for the compounds. Computed activities for the compounds are plotted with the observed activity for these predicted five models (equations 1, 6, 7, 8 and 10) and it was inferred that equation number 7 gives the good results. The plots of observed activities for the compounds and their predicted activities as shown below:



Thus, is a good agreement between the predicted properties and observed properties.

REFERENCES

1. W.G. Richards, T.E.H. Walker and R.K. Hinkley, A Bibliography of *ab initio* Molecular Wave Function, Clerdon Press, Oxford (1971).
2. L. Rondom and J.A. Pople, in ed.: W. Byer-Brown, MTP International Reviews of Science, Physical Chemistry 1 Series, Butterworths, London, p. 71 (1972).
3. K. Arora and D. Kumar, *Asian J. Chem.*, **13**, 1325 (2001).
4. K. Arora and D. Kumar, *J. Indian Chem. Soc.*, **79**, 693 (2002).
5. K. Arora, A. Gupta and D.D. Agarwal, *Asian J. Chem.*, **14**, 1611 (2002).
6. K. Arora, *Asian J. Chem.*, **14**, 1719 (2021).
7. K. Arora and S. Agnihotri, *J. Saudi Chem. Soc.*, **6**, 445 (2002).
8. K. Arora and K. Burman, *J. Saudi Chem. Soc.*, **9**, 297 (2005).
9. M.J.S. Dewar, E.G. Zoebisch, E.F. Healy and J.J.P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
10. M.J.S. Dewar and Y.C. Yuan, *Inorg. Chem.*, **29**, 3881 (1990).
11. A.K. Gupta, L.K. Soni, P. Hanumantharao, S.V. Sambasivarao, M. Arockia Babu and S.G. Kashedikar, *Asian J. Chem.*, **16**, 67 (2004).
12. A.K. Gupta, L.K. Soni, P. Hanumantharao, S.V. Sambasivarao and S.G. Kashedikar, *Indian J. Chem.*, **44B**, 1481 (2005).
13. A.K. Srivastava, Mohd. Shakeel and A.A. Khan, *Indian J. Chem.*, **41B**, 436 (2002).
14. K. Roy, D.K. Pal, C.C. Ghosh, A.U. De and C. Sengupta, *Indian J. Chem.*, **40B**, 209 (2001).
15. G. Tripathi and J.P. Mishra, *Indian J. Chem.*, **44A**, 1398 (2005).
16. K.I. Bhatt, R.V. Kumar and K. Balakrishna, *Asian J. Chem.*, **16**, 96 (2004).
17. C. Hansch, Comprehensive Medicinal Chemistry, Pregmon Press, New York, Vol. 4, p. 579 (1990).
18. H.J. Smith and H. Williums, Introduction to the Principles of Drug Design, John Wright & Sons Ltd., Bristol, p. 216 (1983).

(*Received*: 25 September 2007; *Accepted*: 28 June 2008) AJC-6632