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Atomic softness based QSAR study of triazines inhibiting dihydrofolate reductase

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ABSTRACT

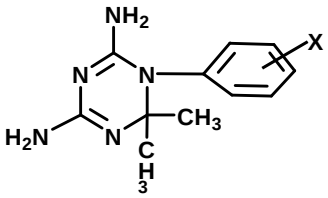
Thiry derivatives of triazine in which the substituent SO_2F is at position –3 of the phenyl ring. Values of the descriptors $1/E_n^{\ddagger}$, $1/E_m^{\ddagger}$, fukui function, density distribution function, average atomic softness, atom electron density, local softness and local hardness of these compounds have been calculated on each hetero atom of the compound. The values of descriptors of the atom having highest value of $E_m^{\ddagger}$ have been taken into account. Values of observed activities are given in the terms of log 1/C. One hundred sixty two QSAR models have been developed using four descriptors in maximum among eight descriptors. Out of these QSAR models, only five QSAR models have been found to provide good predictive power. The best QSAR model has the value 0.902456 for regression coefficient. This QSAR model contains inverse of $E_n^{\ddagger}$ as first descriptor, inverse of $E_m^{\ddagger}$ as second descriptor, Fukui Function as third descriptor and Density Distribution Function as fourth descriptor.

KEYWORDS

Atomic softness;
Density distribution function;
Fukui function;
Triazine;
Local softness;
Local hardness.

INTRODUCTION

On the basis of chemical structure activity relationship, reliable models having good predictive powers for activity or any other parameter can be developed. Techniques such as pattern recognition,[1,2] discriminate analysis,[3] cluster analysis,[2,4] and regression analysis,[5] has been developed and used outside of chemistry. These are now used by those who are working with structure activity relationship in development of QSAR models. In this paper the regression analysis have been applied for QSAR study. The relationship has been worked out between the Log 1/C values of a series of thirty compounds and certain quantum chemical descriptors. The compound chosen for study is given below.



Compound-I
[4,6-diamino-1, 2, dihydro-2, 2,dimethyl-1-1 (x-phenyl)-s-triazines]

Baker et. al.[6] synthesized 256 derivatives of compound-I, a drug now in clinical trials against cancer, and studied their inhibiting effect on dihydrofolate reductase isolated from Walker 256 and L1210 leukemia tumors. Enzyme dihydrofolate reductase isolated from Leukemia tumor forms covalatent bond with highly re-

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active derivatives of triazines. These compounds are strongly electrophilic, react through carbonium ion and form covalent bonds with amino, hydroxyl, carboxyl groups[13].

Out of 256 compounds synthesized by Baker the QSAR study of 50 compounds has recently been reported[7-9]. The remaining compounds leave a wide scope for their QSAR study. The remaining compounds have been divided into three groups as detailed below.

1- The X substituents of compound-I have SO_2F at position –3 of the phenyl ring.
2- The X substituents of compound-I have SO_2F at position –4 of the phenyl ring.
3- The X substituents of compounds-I have no -SO_2F.

The work of this paper is limited to compounds of serial–1, that is X substituents having -SO_2F at position-3 of phenyl ring. The compounds of this series are listed in TABLE 1, along with their inhibiting activity in terms of Log 1/C. Atomic properties such as effective softness values ($E_n^‡$, $E_m^‡$), Fukui function, density distribution function, average atomic softness, atom electron density, local softness and local hardness have been evaluated for the development of QSAR models to predict the Log 1/C value of any new derivative of triazine.

MATERIAL AND METHOD

30 derivatives of compound-I have been taken as study material. They are listed in TABLE 1 along with their biological activity in terms of Log 1/C, where C is molar concentration of inhibitor causing 50% reversible inhibitions of enzyme.

Quantum chemical[10] descriptors that have been used for QSAR study are the following: -

1- Effective Softness Values	$E_n^‡$, $E_m^‡$
2- Fukui Function	f(r)
3- Density Distribution Function	DDF
4- Average Atomic Softness	AAS
5- Atom Electron Density	ρ(r)
6- Local Softness	s(r)
7- Local Hardness	η(r)

For QSAR prediction, the 3D modeling and geometry optimization of all the derivatives of triazines have been done with the help of CAChe software using the semiempirical PM3 Hamiltonian. The MOPAC calculations have also been performed with same software. We have developed a computer program to calculate the values of all the descriptors with the help of the parameters viz. ionization potential, electron affinity, atom electron density, charge on atom etc. obtained by MOPAC calculations. The radius of atom has been taken from the literature. The values of atomic softnesses $E_n^‡$ and $E_m^‡$ of all the hetero atoms of traizine derivatives have been calculated. The values of all the descriptors corresponding to the atom having highest value of $E_m^‡$ have been taken in to account. The value of $E_m^‡$ is highest at S atom in all the compounds except in com-

TABLE 1 : Log1/C data for reversible inhibition of dihydrofolate reductase by 2,6-Diamino-1, 2-dihydro-2, 2-dimethyl-1- (X phenyl)-S-triazines

No.	X	Log 1/C (Observed)
1	3 -SO_2F	7.27
2	3-Cl, 4-$OCH_2C_6H_4$-6-Cl, 3'-SO_2F	7.38
3	3-Cl, 4-S $(CH_2)_2$-$CONHC_6H_4$-4'-SO_2F	7.39
4	3 -Cl, 4-$SCH_2CONHC_6H_4$-4'-SO_2F	7.42
5	3 -Cl, 4-OCH_2CONH-C_6H_4-4'-SO_2F	7.43
6	3-Cl, 4-$OCH_2C_6H_4$-2'-Cl, 3' -SO_2F	7.49
7	4 -SCH_2 $CONHC_6H_4$-4'-SO_2F	7.52
8	3-Cl, 4-$OCH_2C_6H_3$-4'-Cl, 2'-SO_2F	7.52
9	3-Cl, 4-O $(CH_2)_4$-ONC_6H_4-4' -SO_2F	7.57
10	3-Cl, 4-O $CH_2C_6H_4$-4' -SO_2F	7.58
11	3-Cl, 4-$(CH_2)_2$ $CONH$-C_6H_4-4' -SO_2F	7.62
12	3-$CH_2NHCONHC_6H_4$-3' -SO_2F	7.62
13	2-Cl, 4-$(CH_2)_2$ $CONH$-C_6H_4-4' -SO_2F	7.66
14	3-Cl, 4 -O$(CH_2)_3$NH-$CONHC_6H_4$-4' -SO_2F	7.68
15	3-$(CH_2)_4C_6H_3$-3'-Cl, 4'-SO_2F	7.70
16	3-Cl, 4-$(CH_2)_4C_6H_3$-3'-Cl, 4'-SO_2F	7.70
17	3-Cl, 4-$OCH_2C_6H_3$-6'-Cl, 2'-SO_2F	7.72
18	3-Cl, 4-$CH_2NHCONH$-C_6H_4-3'-Me, 4'- SO_2F	7.80
19	3-Cl, 4-O $(CH_2)_2$-$NHCONH$-C_6H_3-3'-Me, 4'- SO_2F	7.82
20	3-O $(CH_2)_2OC_6H_4$-4'-SO_2F	7.82
21	3-Cl, 4-$(CH_2)_4C_6H_3$-4'-Cl, 2'- SO_2F	7.82
22	3-Cl, 4 -$(CH_2)_2C_6H_4$-4'-SO_2F	7.85
23	3-Cl, 4 -$(CH_2)_2$ C_6H_3-5'-Cl, 2'- SO_2F	7.85
24	3-Cl, 4-O $(CH_2)_2$NH-$CONHC_6H_4$-3'-SO_2F	7.92
25	3-$(CH_2)_4C_6H_3$-5'-Cl, 2'- SO_2F	7.96
26	3-Cl, 4-$OCH_2C_6H_3$-4'-Cl, 3'- SO_2F	8.00
27	3-Cl, 4-$(CH_2)_4C_6H_4$-3'-SO_2F	8.03
28	3-Cl, 4-O $(CH_2)_3$NH-CONH C_6H_3-4'-Me, 3' -SO_2F	8.06
29	3-$(CH_2)_4C_6H_4$-3'-SO_2F	8.10
30	3-Br, 4-OCH_2CONH- C_6H_4-4' -SO_2F	8.14

pound number 30 where it is highest at Br atom,

The quantities of descriptors in different combination (total 162 combinations in which maximum four descriptors have been considered out of eight descriptors) have been put to MLR analysis. The result of MLR analysis provides the predicted value of Log 1/C. The quality of the regression analysis was adjudged by regression coefficient[11-13]. The descriptors or the combination of descriptors, providing the best result, was recognized, and be used for prediction purpose.

The values of quantum chemical descriptors such as effective softness values ($E_n^{\ddagger}$, $E_m^{\ddagger}$), Fukui function, density distribution function, average atomic softness, atom electron density, local softness and local hardness have been evaluated by solving the equations given below-

Effective Softness Values

The softness of an atom in a molecule was described by Klopman[14] and modified by Singh et. al.[15] The Klopman equation is given by

$$E_m^{\ddagger} = IP_m - a^2(IP_m - EA_m) - [\chi_r (C_r^m)^2/R_r] \quad (1-1/\in)[q_r + 2b^2\chi_r (C_r^m)^2] \quad (1)$$

$$E_n^{\ddagger} = IP_n - b^2(IP_n - EA_n) - [\chi_s (C_s^n)^2/R_s] \quad (1-1/\in)[q_s - 2b^2\chi_s (C_s^n)^2] \quad (2)$$

where $E_n^{\ddagger}$ is the softness of Lewis acid, $E_m^{\ddagger}$ is the softness of a Lewis base, IP is the ionization potential of atom[21,22], EA is the electron affinity[23] of atom, $\in$ is the dielectric constant of the medium in which reaction is carried out. R, q are the radius and charge of atom s & r, C is the electron density, χ is $q - (q-1)\sqrt{k}$ and k = 0.75 and a, b is the variational parameter defined as $a^2 + b^2 = 1$.

It is well established that the stability of the compound formed between nucleophile and electrophile depends upon the value of difference between softness values of $E_m^{\ddagger}$ of nucleophile, and softness values of $E_n^{\ddagger}$ of electrophile, $\Delta E^{\ddagger}_{nm}$ represent the difference. The higher is the $\Delta E^{\ddagger}_{nm}$ greater is the stability of the compound.[16-20]

$$\Delta E^{\ddagger}_{nm} = | E_n^{\ddagger} - E_m^{\ddagger} | \quad (3)$$

Local Softness

The site-selectivity of a chemical system, cannot, however, be studied using the global descriptors of reactivity. For this, appropriate local descriptors need to be defined. An appropriate definition of local softness $s(r)$ is given by[24]

$$s(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} \left(\frac{\partial N}{\partial \mu}\right)_{v(r)} = f(r)S \quad (4)$$

Such that

$$\int s(r)d(r) = S \quad (5)$$

where $f(r)$ is defined as the Fukui function.[24] It is obvious that local softness contains the same information as the Fukui function,[25] in addition, information to the softness of the whole molecule.

Fukui Function

Fukui function can be interpreted either as the change of the electron density $\rho(r)$ at each point r when the total number of electrons is changed or as the sensitivity of a system chemical potential to an external perturbation at a particular point r.

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} = \left(\frac{\partial \mu}{\partial v(r)}\right)_{N} \quad (6)$$

Atom Electron Density

Atom electron density[21] is the measure of the probability of an electron being present at a specific location. In molecules, regions of electron density are usually found around the atom, and its bonds. In de-localized or conjugated systems, such as phenol, benzene and compounds such as hemoglobin and chlorophyll, the electron density covers an entire region, i.e., in benzene they are found above and below the planar ring. The Atom Electron Density (AED) is the measure of the probability of an electron at an atom and may be defined as-

AED = Electrons in outermost shell of atom – Partial charge on that atom

Density Distribution Function

Density distribution function (DDF) is defined as

$$DDF = 4\pi r^2 (AED) \quad (7)$$

where r is the radius of atom and AED is atom electron density.

Average Atomic Softness

The Average Atomic Softness (AAS) is defined as

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$$AAS = \frac{\varepsilon LUMO/8 - Xr \cdot AED^2 \cdot (\varepsilon - 1) \cdot (2q\ Xr \cdot AED^2)/(4r \cdot AED) + f(r)/\{2(\varepsilon LUMO - \varepsilon HOMO)\}}{} \quad (8)$$

where

AED	=	Atom electron density
e	=	Dielectric constant of the medium
f(r)	=	fukui function
	=	AED/atomic no.
Xr	=	q-(q-1)√0.75
q	=	charge on atom.
εLUMO	=	Energy of LUMO
εHOMO	=	Energy of HOMO

Local Hardness

Local hardness η(r) is defined as

$$\eta(\mathbf{r}) = \left(\frac{\partial \mathbf{u(r)}}{\partial \mathbf{N}}\right)_{\sigma} \quad (9)$$

Where u(r)	=	modified potential
	=	ν(r) - μ
μ	=	Chemical potential
ν(r)	=	External potential
σ(r)	=	Shape function= ρ(r)/N
N	=	Total number of electrons

RESULT AND DISCUSSION

The values of eight descriptors of compounds listed in TABLE 1 have been calculated and are presented in the TABLE 2 alongwith their observed activity in terms of Log 1/C. We have examined QSAR models using combination of maximum four descriptors. Following five QSAR models were found to have good regression coefficient. The predicted activities of these QSAR models are given in TABLE 3.

TABLE 2 : Values of descriptors and observed activities of triazine derivatives

Comp	Atom	$1/E_n^{\ddagger}$	$1/E_m^{\ddagger}$	Fukui Function	Density Distribution Function	Average Atomic Softness	Atom Electron Density	Local Softness	Local Hardness	Log 1/C (Obsd)
1	S	0.062290063	0.048371283	0.226163	49.203035	9.839059	3.618600	0.029000	0.882623	7.27
2	S	0.062814863	0.048420253	0.226000	49.167682	9.790182	3.616000	0.030200	0.845025	7.38
3	S	0.062471291	0.048500413	0.226150	49.200315	9.828350	3.618400	0.029300	0.873361	7.39
4	S	0.062216042	0.04838442	0.226194	49.209833	9.848117	3.619100	0.028800	0.889508	7.42
5	S	0.062214521	0.048496067	0.226238	49.219351	9.853569	3.619800	0.028700	0.892629	7.43
6	S	0.063048856	0.048446946	0.225931	49.152725	9.798094	3.614900	0.029800	0.855257	7.49
7	S	0.062354045	0.04852343	0.226200	49.211193	9.832587	3.619200	0.029200	0.874973	7.52
8	S	0.061633593	0.048514004	0.226450	49.265582	9.833637	3.623200	0.029700	0.864656	7.52
9	S	0.062173593	0.056043065	0.228756	49.767321	9.648759	3.660100	0.044700	0.584715	7.57
10	S	0.062223564	0.048536786	0.226250	49.222071	9.825043	3.620000	0.029600	0.865894	7.58
11	S	0.062359998	0.048543517	0.226206	49.212553	9.849203	3.619300	0.028800	0.889886	7.62
12	S	0.062288748	0.048527569	0.226225	49.216632	9.858271	3.619600	0.028500	0.897351	7.62
13	S	0.062424486	0.04860242	0.226206	49.212553	9.838893	3.619300	0.029100	0.880493	7.66
14	S	0.062492595	0.048662653	0.226206	49.212553	9.833071	3.619300	0.029200	0.875116	7.68
15	S	0.063030194	0.048576809	0.225988	49.164962	9.817796	3.615800	0.029300	0.870964	7.70
16	S	0.062961865	0.048530749	0.225994	49.166322	9.823916	3.615900	0.029100	0.876173	7.70
17	S	0.061522969	0.048624746	0.226531	49.283259	9.836864	3.624500	0.029700	0.864123	7.72
18	S	0.061576802	0.048706103	0.226544	49.285978	9.889065	3.624700	0.028200	0.911541	7.80
19	S	0.061818291	0.048798891	0.226494	49.275100	9.858725	3.623900	0.029000	0.885918	7.82
20	S	0.062735592	0.048668728	0.226125	49.194876	9.853173	3.618000	0.028500	0.897175	7.82
21	S	0.06212858	0.048755378	0.226369	49.247906	9.833363	3.621900	0.029514	0.868100	7.82
22	S	0.062134065	0.048633283	0.226319	49.237028	9.854218	3.621100	0.028800	0.889632	7.85
23	S	0.061523105	0.048623354	0.226531	49.283259	9.836458	3.624500	0.029700	0.863666	7.85
24	S	0.062419954	0.048743379	0.226263	49.224790	9.828021	3.620200	0.029500	0.867978	7.92
25	S	0.061717236	0.048688981	0.226488	49.273740	9.831392	3.623800	0.029800	0.860999	7.96
26	S	0.063671224	0.048554487	0.225763	49.116012	9.756067	3.612200	0.030900	0.824310	8.00
27	S	0.062100253	0.048795729	0.226394	49.253345	9.855060	3.622300	0.028900	0.886990	8.03
28	S	0.061707266	0.048876679	0.226563	49.290057	9.863603	3.625000	0.028900	0.887364	8.06
29	S	0.062155097	0.048844469	0.226394	49.253345	9.851877	3.622300	0.029000	0.884004	8.10
30	Br	0.005962209	0.006189494	0.198683	113.611626	52.55269	6.953900	0.025300	0.781648	8.14

TABLE 3 : Values of predicted activities PA1-PA5 of triazine derivatives

Compound	PA1	PA2	PA3	PA4	PA5
1	7.294	7.293	7.282	7.390	7.396
2	7.418	7.418	7.420	7.524	7.527
3	7.507	7.507	7.510	7.583	7.587
4	7.315	7.315	7.310	7.359	7.366
5	7.495	7.494	7.484	7.515	7.522
6	7.530	7.531	7.540	7.658	7.667
7	7.545	7.545	7.547	7.714	7.714
8	7.574	7.574	7.576	7.458	7.445
9	7.568	7.568	7.569	7.594	7.595
10	7.543	7.543	7.545	7.558	7.556
11	7.585	7.586	7.594	7.558	7.566
12	7.567	7.567	7.569	7.637	7.644
13	7.670	7.670	7.680	7.664	7.669
14	7.778	7.778	7.788	7.899	7.900
15	7.735	7.735	7.728	7.805	7.817
16	7.662	7.662	7.660	7.793	7.804
17	7.730	7.731	7.739	7.663	7.645
18	7.865	7.865	7.862	7.624	7.623
19	7.969	7.969	7.967	7.845	7.838
20	7.833	7.833	7.838	7.822	7.836
21	7.913	7.913	7.911	7.910	7.902
22	7.701	7.701	7.698	7.723	7.724
23	7.745	7.745	7.754	7.690	7.671
24	7.910	7.910	7.903	7.905	7.902
25	7.831	7.831	7.822	7.751	7.734
26	7.921	7.921	7.916	7.640	7.653
27	7.961	7.961	7.959	7.942	7.938
28	8.090	8.090	8.083	8.067	8.054
29	8.045	8.045	8.045	8.008	8.004
30	8.140	8.140	8.140	8.141	8.141

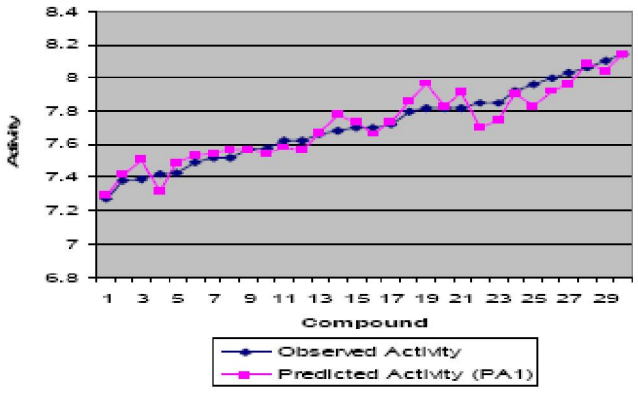
1st QSAR model

The predicted activity of compounds have been obtained by the following regression equation,

$$PA1 = 9743.7*1/E_n^{\ddagger} - 9229*1/E_m^{\ddagger} + 24987 *f(r) + 13.151* DDF - 6451.44 \quad (10)$$

$$r^2 = 0.902456$$

This regression equation contains inverse of $E_n^{\ddagger}$ as first descriptor, inverse of $E_m^{\ddagger}$ as second descriptor, Fukui Function as third descriptor and Density Distribution Function as fourth descriptor. Regression coefficient indicates that, this model has high degree of predictive power as the value of r^2 is 0.902456. The values of predicted activities (PA1) of compounds are listed in TABLE 3. Graph 1 shows the relationship between observed activity and activity predicted by this QSAR model of all the thirty compounds.



Graph 1 : Graph between observed activity and predicted activity PA1

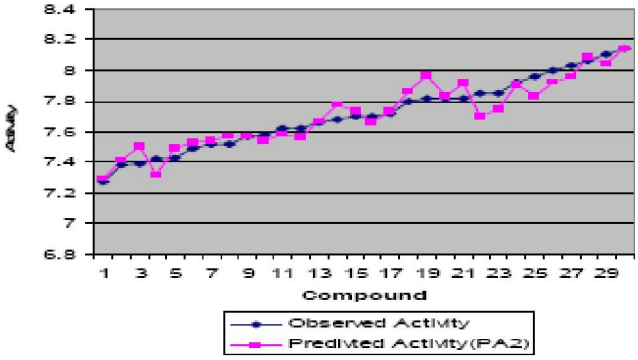
2nd QSAR model

The predicted activity of compounds have been calculated by the following regression equation,

$$PA2 = 9747.31* 1/E_n^{\ddagger} - 9232.41* 1/E_m^{\ddagger} + 23933.5 * f(r) + 245.299* AED - 6453.79 \quad (11)$$

$$r^2 = 0.902369$$

This regression equation contains inverse of $E_n^{\ddagger}$ as first descriptor, inverse of $E_m^{\ddagger}$ as second descriptor, Fukui Function as third descriptor and Atom Electron Density as fourth descriptor. Regression coefficient indicates that, this model has high degree of predictive power as the value of r^2 is 0.902369. The values of predicted activities (PA2) of compounds are listed in TABLE 3. Graph 2 shows the relationship between



Graph 2 : Graph between observed activity and predicted activity PA2

observed activity and activity predicted by this QSAR model of all the thirty compounds.

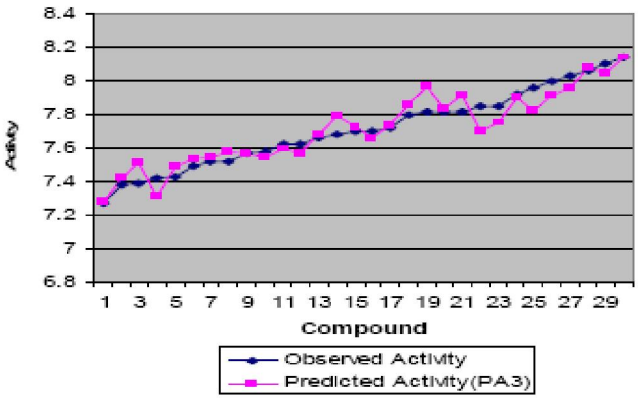
3rd QSAR model

The third predicted activity of compounds of TABLE 1 have been calculated by the following regression equation,

$$PA3 = 9820.06*1/E_n^{\ddagger} - 9301.06*1/E_m^{\ddagger} - 298.466*DDF + 5812.2*AED - 6501.11 \quad (12)$$

$$r^2 = 0.89967$$

PA3 involves inverse of $E_n^{\ddagger}$ as first descriptor, inverse of $E_m^{\ddagger}$ as second descriptor, Density Distribution Function as third descriptor and Atom Electron Density as fourth descriptor. Regression coefficient indicates that, this model has high degree of predictive power as the value of r^2 is 0.89967. The values of predicted activities (PA3) of compounds are listed in TABLE 3. Graph 3 shows the relationship between observed activity and activity predicted by this QSAR model of all the thirty compounds.



Graph 3 : Graph between observed activity and predicted activity PA3

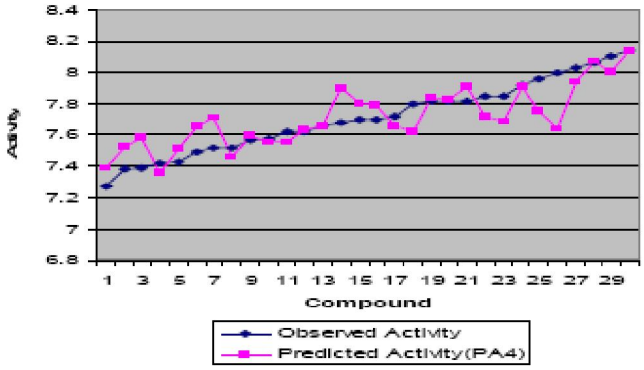
4th QSAR model

The fourth predicted activity of compounds of TABLE 1 have been calculated by the following regression equation,

$$PA4 = 1384.82*1/E_m^{\ddagger} + 13.7017*AED - 1905.51*s(r) - 63.5343*\eta(r) + 2.15963 \quad (13)$$

$$r^2 = 0.683394$$

This regression equation contains inverse of $E_m^{\ddagger}$ as first descriptor, Atom Electron Density as second descriptor, Local Softness as third descriptor and Local Hardness as fourth descriptor. Regression coefficient indicates that, this model has high degree of predictive power as the value of r^2 is 0.683394. The values of predicted activities (PA4) of compounds are listed in TABLE 3. Graph 4 shows the relationship between observed activity and activity predicted by this QSAR model of all the thirty compounds.



Graph 4 : Graph between observed activity and predicted activity PA4

5th QSAR model

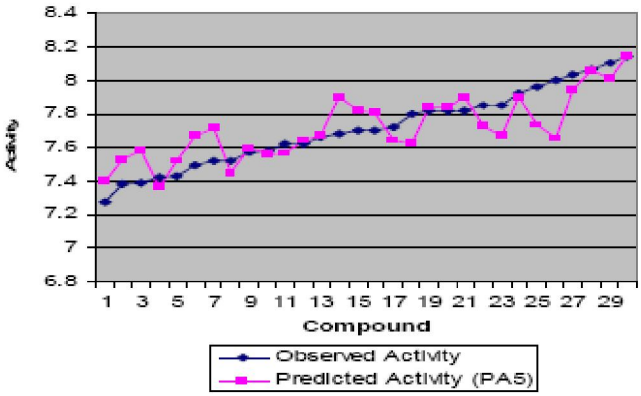
The fourth predicted activity of compounds of TABLE 1 have been obtained by the following regression equation,

$$PA5 = 1390.42*1/E_m^{\ddagger} + 0.717595*DDF - 1869*s(r) - 62.0013*\eta(r) + 13.7562 \quad (14)$$

$$r^2 = 0.670024$$

This regression equation contains inverse of $E_m^{\ddagger}$ as first descriptor, Density Distribution Function as second descriptor, Local Softness as third descriptor and Local Hardness as fourth descriptor. Regression coefficient indicates that, this model has high degree of predictive power as the value of r^2 is 0.670024. The values of predicted activities (PA5) of compounds are listed in TABLE 3. Graph 5 shows the relationship between observed activity and activity predicted by this QSAR model of all the thirty compounds.

The values of regression coefficient of all the five models are presented collectively in TABLE 4 in their decreasing order, alongwith the combination of descriptors providing the various models. The 1st QSAR model is the best model having the regression coefficient value above 0.9. The combination of descriptors providing the best model (1st QSAR model) is the inverse of $E_n^{\ddagger}$, the inverse of $E_m^{\ddagger}$, the Fukui Function and the Density Distribution Function.



Graph 5 : Graph between observed activity and predicted activity PA5

TABLE 4 : QSAR models in decreasing order of predictive powers.

S. No.	Predicted Activity	r^2	Combination of Descriptors
1	PA1	0.902456	$1/E_n^{\ddagger}$, $1/E_m^{\ddagger}$, f(r), DDF
2	PA2	0.902369	$1/E_n^{\ddagger}$, $1/E_m^{\ddagger}$, f(r), AED
3	PA3	0.89967	$1/E_n^{\ddagger}$, $1/E_m^{\ddagger}$, DDF, AED
4	PA4	0.683394	$1/E_m^{\ddagger}$, AED, s(r), η(r)
5	PA5	0.670024	$1/E_m^{\ddagger}$, DDF, s(r), η(r)

CONCLUSION

It is clear that the atomic properties especially Klopman softness values play an important role in QSAR study. The values of r^2 indicates that, on the basis of atomic properties we can construct good QSAR models

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