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QSAR Studies of Some Novel Triazines Inhibiting Dihydrofolate Reductase

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Abstract: ***In this paper the Multi-linear regression analysis has been applied for QSAR study. The relationship has been worked out between the Log 1/C values of a series of compounds and certain quantum chemical and energy descriptors. The QSAR studies of Triazines inhibiting dihydrofolate reductase based on quantum chemical and energy descriptors shows that among all the 28 QSAR models PA51 to PA 78, the number of good QSAR models is 08 whose regression coefficient is greater than 0.7. In all the best 08 QSAR models, heat of formation is common. It means the best descriptor to predict the activities are the heat of formation. Also, the predicted activity obtained by taking heat of formation as single descriptor possesses the good value of regression coefficient which is 0.738250.***

Keywords: QSAR**,** descriptors, triazines, dihydrofolate reductase, steric energy, heat of formation**.**

1. Introduction

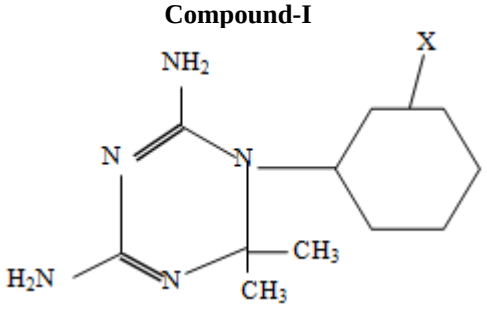
The chemical structure-activity relationship, especially in bio- and medicinal chemistry, so little solid theory is at hand on which to build that all kinds of purely empirical ideas need to be of great help in sorting out important structure-activity features which can then be used to form more firmly based theory. Techniques such as pattern recognition, [1,2] discriminate analysis, [3] cluster analysis, [2,4] and regression analysis, [5] which has been developed and used heavily out side of chemistry are now beginning to be used by those working with structure- activity relationship.

Baker and few graduate students [6] synthesized variations of I to achieve II, a drug now in clinical trials against cancer. Baker's group synthesized 256 variations of I and studied their inhibiting effect on dihydrofolate reductase isolated from Walker 256 and L1210 leukemia tumors. He did demonstrate vividly that starting at the enzyme level rather than with whole animals constitutes a powerful technique for drug development. This approach has also been brilliantly exploited by Hitching and his group [7,8] in the development of allopurinol for gout and the new antibacterial agent, trimethoprim. Out of 256 compounds synthesized by Baker the QSAR study of 50 compounds has recently been reported [9]. The remaining compounds leave a wide scope for their QSAR study. It is proposed to make their structural relationship with quantum chemical and energy parameters. The remaining compounds have been divided into three groups as detailed below.

(i) The X substituents of compound-1 have SO_2F at position –3 of the phenyl ring.
(ii)The X substituents of compounds –1 have SO_2F at position –4 of the phenyl rings.
(iii)The X substituents of compounds –1 have no -SO_2F.

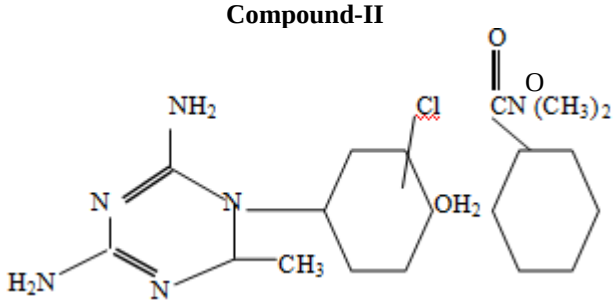
The work of the paper has been limited to compounds of serial –1, that is X substituents having - SO_2F at position-3 of phenyl ring. The compounds of this series are listed in table-1, along with their inhibiting activity in terms of Log 1/C.

Compound-I



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

Compound-II



[Dimethyl acetyl benzamide derivative of 1]

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

Comp	*I. X*	*Log 1/C (Observed)*
C51	3-Cl, 4 -$(CH_2)_4C_6H_4$-2'-SO_2F	7.77
C52	3-Cl, 4 -$(CH_2)_4C_6H_3$-2'-Cl, 4'- SO_2F	7.77
C53	3-Cl, 4 -$CH_2NHCONH$-C_6H_4-3'-Me, 4'-	7.80
C54	3-Cl, 4 -O $(CH_2)_2$- $NHCONH$-C_6H_3-3'-	7.82
C55	3 -O $(CH_2)_2OC_6H_4$-4'-SO_2F	7.82
C56	3-Cl, 4 -$(CH_2)_4C_6H_3$-4'-Cl, 2'- SO_2F	7.82
C57	3-Cl, 4 -$(CH_2)_2C_6H_4$-4'-SO_2F	7.85
C58	3-Cl, 4 -$(CH_2)_2$ C_6H_3-5'-Cl, 2'- SO_2F	7.85
C59	3-Cl, 4 -$(CH_2)_2$ C_6H_3-3'-Cl, 4'- SO_2F	7.85
C60	3-Cl, 4 -$CH_2NHCONH$-C_6H_4-4'-SO_2F	7.92
C61	3-Cl, 4 -O $(CH_2)_2NH$-$CONHC_6H_4$-3'-	7.92
C62	3 -$(CH_2)_4C_6H_3$-5'-Cl, 2'- SO_2F	7.96
C63	3-Cl, 4 -$OCH_2C_6H_3$-4'-Cl, 3'- SO_2F	8.00
C64	3 -$(CH_2)_4C_6H_3$-2'-Cl, 4'- SO_2F	8.00
C65	3-Cl, 4 -$(CH_2)_4C_6H_4$-3'-SO_2F	8.03
C66	3-Cl, 4 -$(CH_2)_2$ C_6H_3-4'-Cl, 2'- SO_2F	8.05
C67	3-Cl, 4 -O $(CH_2)_3NH$-$CONH$ C_6H_3-4'-	8.06
C68	3 -$(CH_2)_4C_6H_4$-4'-SO_2F	8.10
C69	3 -$(CH_2)_4C_6H_4$-3'-SO_2F	8.10
C70	3 -$(CH_2)_2C_6H_4$-4'-SO_2F	8.10
C71	3-Cl, 4 -$(CH_2)_4$ C_6H_3-4'-Cl, 3'-SO_2F	8.11
C72	3-Cl, 4 -$(CH_2)_4$ C_6H_4-4'-SO_2F	8.14
C73	3-Br, 4-OCH_2CONH- C_6H_4-4' -SO_2F	8.14
C74	3-Cl, 4 -$(CH_2)_4C_6H_3$-3'-Cl, 2' -SO_2F	8.20
C75	3-Cl, 4 -$(CH_2)_2$ C_6H_3-4'-Cl, 3' -SO_2F	8.27
C76	3-Cl, 4 -$(CH_2)_2$ C_6H_3-3'-Cl, 2' -SO_2F	8.30
C77	3-Cl, 4 -$(CH_2)_2$ C_6H_3-2'-Cl, 4' -SO_2F	8.33
C78	3-$(CH_2)_4$ C_6H_3-4'-Cl, 3' -SO_2F	8.37

Quantum chemical [10] and energy descriptors [11, 12] have been prominently used in the last decade for QSAR studies. Following are the descriptors:

Heat of Formation	(ΔHf)
Steric Energy	(SE)
Total Energy	(TE)
HOMO Energy	(ϵHOMO)
LUMO Energy	(ϵLUMO)
Absolute Hardness	(η)
Electronegativity	(χ)

The geometries of all the derivatives mentioned in table-1, have been first optimized, and then the values of the descriptors have been evaluated with the help of software, described in materials and method. MLR analyze the above descriptors to predict value of Log 1/C. The quality of the regression analysis has been adjudged by correlation coefficient [12]. The descriptors or the combination of descriptors, providing the best result, has been recognized. This helps is predicting the Log 1/C value of any new derivative of triazine.

2. Materials and Method

Twenty five 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.

Enzyme dihydrofolate reductase isolated from Leukemia tumor forms covalent bond with highly reactive derivatives of triazines. The compounds are strongly electrophilic, react through carbonium ion intermediate and form covalent bonds with amino, hydroxyl, carboxyl groups [13]. Consequences are

(i) bifunctional agents
(ii) DNA-DNA strand and DNA protein cross links.

The values of quantum chemical descriptors such as HOMO energy [14], LUMO energy [15], absolute hardness [16-19], electronegativity [20], total and steric energy [23-25], heat of formation [26] have been evaluated with the help of CAChe software using PM3 hamiltonian.

Parr et. al., [21] define the electronegativity as the negative of chemical potential

$$\chi = -\mu = -(\partial E/\partial N)_v \quad \text{.....(i)}$$

The absolute hardness η is defined as[22]

$$\eta = 1/2(\delta\mu/\delta N)v_{(r)}$$
$$= 1/2\,(\delta^2E/\delta^2N)v_{(r)} \quad \text{.....(ii)}$$

where E is the total Energy, N the number of electrons of the chemical species and $v_{(r)}$ the external potential

The corresponding global softness S, which bears an inverse relationship with the global hardness is defined as

$$S = 1/2\eta = (\partial N/\partial\mu)v_{(r)} \quad \text{.....(iii)}$$

The operational definition of absolute hardness, global softness and electronegativity is defined as:

$$\eta = 1/2\,(IP-EA) \quad \text{.....(iv)}$$
$$S = 1/(IP-EA) \quad \text{.....(v)}$$
$$\chi = -\mu = 1/2(IP+EA) \quad \text{.....(vi)}$$

where IP and EA are the Ionization Potential and Electron Affinity respectively, of the chemical species. According to the 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. [22]; hence, Eqs. (iv) – (vi) can be written as

$$\eta = 1/2\,(\varepsilon\,LUMO - \varepsilon\,HOMO) \quad \text{.....(vii)}$$
$$S = 1/(\varepsilon\,LUMO - \varepsilon\,HOMO) \quad \text{.....(viii)}$$
$$\chi = 1/2\,(\varepsilon\,LUMO + \varepsilon\,HOMO) \quad \text{.....(ix)}$$

The energy descriptors [23-26] are useful parameters for describing QSAR of a chemical system. A more useful quantity is the heat of formation of the compound from its elements in their standard state. This is equal to the energy required to ionize the valence electrons of the atoms involved. The heat of formation is defined as

$$\Delta H_f = E_{elect} + E_{nuc} - E_{isol} + E_{atom} \quad \text{.....(x)}$$

where E_{elect} is the electronic energy, E_{nuc} is the nuclear-nuclear repulsion energy, E_{isol} is the energy required to strip all the valence electrons of all the atoms in the system and E_{atom} is the total heat of atomization of all the atoms in the system.

Total energy of a molecular system is the sum of the total electronic energy, E_{ee} and the energy of internuclear repulsion, E_{nr}. The total electronic energy of the system is given by:

$E = ½.P(H + F)$ ……..(xi)

where P is the density matrix and H is the one electron matrix. These parameters and the charges on atoms has been obtained from PM3 [27] calculations. Multilinear regression (MLR) analysis has been performed by using Project Leader program associated with CAChe Pro software of Fujitsu.

3. Results and Discussion

The values of the descriptors; Heat of Formation (ΔHf), Steric Energy (SE), Total Energy (TE), HOMO Energy (∈HOMO), LUMO Energy (∈LUMO), Absolute Hardness (η) and Electronegativity (χ) of 28 derivatives of triazine have been evaluated and given in the table-2.

Table 2: Values of the quantum chemical and energy descriptors of the derivatives of triazine

Comp	Heat of Formation	Steric Energy	Total Energy	HOMO Energy	LUMO Energy	Absolute Hardness	Electroneg ativity	Activity
C51	117.506	-31.468	-241.778	-8.759	-0.917	3.921	4.838	7.770
C52	117.506	-33.262	-253.545	-8.797	-1.133	3.832	4.965	7.770
C53	117.959	-87.105	-263.760	-8.948	-0.891	4.028	4.919	7.800
C54	118.262	-72.989	-283.082	-8.736	-0.926	3.905	4.831	7.820
C55	118.262	-28.539	-240.040	-8.811	-0.981	3.915	4.896	7.820
C56	118.262	-32.520	-253.540	-8.695	-1.022	3.837	4.859	7.820
C57	118.716	-34.308	-227.464	-8.825	-0.984	3.920	4.904	7.850
C58	118.716	-30.750	-239.214	-8.792	-1.114	3.839	4.953	7.850
C59	118.716	-30.519	-239.234	-8.832	-1.099	3.866	4.965	7.850
C60	119.774	-87.926	-256.567	-8.957	-0.942	4.008	4.950	7.920
C61	119.774	-77.420	-275.900	-8.702	-0.923	3.890	4.813	7.920
C62	120.379	-29.734	-241.773	-8.710	-1.120	3.795	4.915	7.960
C63	120.984	-28.176	-244.238	-8.559	-1.256	3.652	4.908	8.000
C64	120.984	-32.200	-241.785	-8.734	-1.133	3.801	4.934	8.000
C65	121.438	-31.477	-241.778	-8.759	-0.917	3.921	4.838	8.030
C66	121.740	-35.350	-239.221	-8.760	-1.028	3.866	4.894	8.050
C67	121.891	-80.764	-290.235	-8.738	-0.825	3.957	4.781	8.060
C68	122.496	-31.817	-230.023	-8.734	-0.965	3.885	4.849	8.100
C69	122.496	-31.270	-230.018	-8.712	-0.931	3.891	4.822	8.100
C70	122.496	-33.101	-215.698	-8.772	-1.014	3.879	4.893	8.100
C71	122.648	-29.588	-253.554	-8.735	-1.027	3.854	4.881	8.110
C72	123.101	-33.118	-241.784	-8.782	-0.933	3.924	4.857	8.140
C73	123.101	-44.949	-257.479	-8.958	-0.975	3.992	4.967	8.140
C74	124.009	-24.091	-253.524	-8.690	-1.045	3.823	4.867	8.200
C75	125.067	-30.789	-239.234	-8.775	-1.067	3.854	4.921	8.270
C76	125.521	-25.488	-239.202	-8.699	-1.100	3.799	4.900	8.300
C77	125.975	-35.438	-239.228	-8.817	-1.179	3.819	4.998	8.330
C78	126.580	-28.336	-241.788	-8.714	-1.028	3.843	4.871	8.370

Outlier Compounds are C51, C52, C57, C58, C59, C60, C77 and C78. Outlier compounds are those compounds which are excluded in multi-linear regression (MLR) analysis. Values of regression coefficients (r^2) and cross-validation coefficients (rCV^2) have been calculated for each MLR equation. QSAR model is characterized by the values of regression coefficients (r^2) and cross-validation coefficients (rCV^2). If the value of regression coefficient is greater than 0.5 then the QSAR model is said to have good predictive power besides the value of cross-validation coefficient is greater than 0.2. As the value of regression coefficient increases, the predictive power increases. The maximum value of regression coefficient may be unity. Combination of quantum chemical and energy descriptors in the predicted activities PA51 to PA 78 are shown in the table-3.

Table 3: Combination of quantum chemical and energy descriptors in the predicted activities PA51 to PA78

Predicted Activity	*First descriptor*	*Second descriptor*	*Third descriptor*	*Fourth descriptors*
PA51	Heat of Formation	Homo Energy	Absolute Hardness	
PA52	Heat of Formation	Total Energy	Homo Energy	Electronegativity
PA53	Heat of Formation	Lumo Energy	Absolute Hardness	
PA54	Heat of Formation	Lumo Energy	Electronegativity	
PA55	Heat of Formation	Absolute	Electronegativity	
PA56	HOMO Energy	Absolute	Electronegativity	
PA57	Heat of Formation	Steric Energy	Total Energy	Homo Energy
PA58	Heat of Formation	Steric Energy	Total Energy	Lumo Energy
PA59	Heat of Formation	Steric Energy	Total Energy	Absolute Hardness
PA60	Heat of Formation	Steric Energy	Total Energy	Electronegativity
PA61	Heat of Formation	Steric Energy	Homo Energy	Lumo Energy
PA62	Heat of Formation	Steric Energy	Homo Energy	Absolute Hardness
PA63	Heat of Formation	Steric Energy	Homo Energy	Electronegativity
PA64	Heat of Formation	Steric Energy	Lumo Energy	Absolute Hardness
PA65	Heat of Formation	Steric Energy	Lumo Energy	Electronegativity
PA66	Heat of Formation	Steric Energy	Absolute Hardness	Electronegativity
PA67	Steric Energy	Total Energy	Homo Energy	Lumo Energy
PA68	Steric Energy	Total Energy	Homo Energy	Absolute Hardness
PA69	Steric Energy	Total Energy	Homo Energy	Electronegativity
PA70	Steric Energy	Total Energy	Lumo Energy	Absolute Hardness
PA71	Steric Energy	Total Energy	Lumo Energy	Electronegativity
PA72	Steric Energy	Total Energy	Absolute Hardness	Electronegativity
PA73	Steric Energy	Total Energy	Lumo Energy	Absolute Hardness
PA74	Steric Energy	Total Energy	Lumo Energy	Electronegativity
PA75	Total Energy	Homo Energy	Absolute Hardness	Electronegativity
PA76	HOMO Energy	Lumo Energy	Absolute Hardness	Electronegativity
PA77	Heat of Formation	Total Energy	Homo Energy	Lumo Energy
PA78	Heat of Formation	Total Energy	Homo Energy	Absolute Hardness

QSAR models PA51 to PA78 are developed and given by the following MLR equations:

1. PA51=0.0579006*ΔHf-0.0461471**∈HOMO-0.225465**η+1.3656
   rCV^2=0.684133
   r^2=0.723763
2. PA52=0.0550476*ΔHf+0.00219062*TE+0.0591818**∈HOMO+0.0518939**χ+2.05275
   rCV^2=0.688245
   r^2=0.735007
3. PA53=0.0579006*ΔHf-0.0461471**∈LUMO-0.133171**η+1.3656
   rCV^2=0.684133
   r^2=0.723763
4. PA54=0.0579006*ΔHf-0.179318**∈LUMO-0.133171**χ+1.3656
   rCV^2=0.684133
   r^2=0.723763

5. PA55=0.0579006*ΔHf-0.179318*η+0.0461471*χ+1.3656
   rCV^2=0.684133
   r^2=0.723763
6. PA56=-0.610321*∈HOMO-0.876175*η-0.524277*χ+8.25412
   rCV^2=-1.69257
   r^2=0.00478459
7. PA57=0.0538542*ΔHf-0.0015478*SE+0.00309132*TE+0.0716091 *∈HOMO +2.72259
   rCV^2=0.688095
   r^2=0.73825
8. PA58=0.0543591*ΔHf-0.000702575*SE+0.00274536*TE+0.0683107 *∈LUMO +2.0525
   rCV^2=0.652423
   r^2=0.735534
9. PA59=0.0542458*ΔHf-0.00138576*SE+0.00272779*TE-0.224381*η+2.83126
   rCV^2=0.713887
   r^2=0.737968
10. PA60=0.0539666*ΔHf-0.00128319*SE+0.00302903*TE-0.0815652*χ+2.4761
    rCV^2=0.697817
    r^2=0.737363
11. PA61=0.0579076*ΔHf+0.000186971*SE+0.0574968*∈HOMO-0.105622 *∈LUMO +1.29988
    rCV^2=0.683743
    r^2=0.723831
12. PA62=0.0579076*ΔHf+0.000186971*SE-0.0481254*∈HOMO-0.211245*η +1.29988
    rCV^2=0.683743
    r^2=0.723831
13. PA63=0.0579076*ΔHf+0.000186971*SE+0.163119*∈HOMO+0.211245*χ +1.29988
    rCV^2=0.683743
    r^2=0.723831
14. PA64=0.0579076*ΔHf+0.000186971*SE-0.0481254*∈LUMO-0.114994*η +1.29988
    rCV^2=0.683743
    r^2=0.723831
15. PA65=0.0579076*ΔHf+0.000186971*SE-0.163119*∈LUMO-0.114994*χ +1.29988
    rCV^2=0.683743
    r^2=0.723831
16. PA66=0.0579076*ΔHf+0.000186971*SE-0.163119*η+0.0481254*χ+1.29988
    rCV^2=0.683743
    r^2=0.723831
17. PA67=-0.00646756*SE+0.0106602*TE+0.236955*∈HOMO+0.0146516 *∈LUMO +12.1951
    rCV^2=-1.50371
    r^2=0.232571
18. PA68=-0.00646756*SE+0.0106602*TE+0.251606*∈HOMO+0.0293032*η +12.1951
    rCV^2=-1.50371
    r^2=0.232571
19. PA69=-0.00646756*SE+0.0106602*TE+0.222303*∈HOMO-0.0293032*χ +12.1951
    rCV^2=-1.50371
    r^2=0.232571
20. PA70=-0.00646756*SE+0.0106602*TE+0.251606*∈LUMO-0.473909*η +12.1951
    rCV^2=-1.50371
    r^2=0.232571
21. PA71=-0.00646756*SE+0.0106602*TE-0.222303*∈LUMO-0.473909*χ +12.1951
    rCV^2=-1.50371
    r^2=0.232571
22. PA72=-0.00646756*SE+0.0106602*TE-0.222303*η-0.251606*χ+12.1951
    rCV^2=-1.50371
    r^2=0.232571
23. PA73=0.00787113*TE+0.175781*∈HOMO-0.0625*∈LUMO+0.421875*η +9.49528
    rCV^2=-2.20801
    r^2=0.172476
24. PA74=0.00787113*TE-0.355316*∈HOMO-0.176361*∈LUMO-0.643433*χ +9.50575
    rCV^2=-1.63833
    r^2=0.172477
25. PA75=0.00787113*TE+0.162964*∈HOMO+0.346558*η+0.0535736*χ+9.4763
    rCV^2=-1.38304
    r^2=0.172448
26. PA76=-0.566559*∈HOMO-0.141571*∈LUMO-0.692917*η-0.612244*χ +8.21422
    rCV^2=-0.39848
    r^2=0.0046652
27. PA77=0.0550476*ΔHf+0.00219062*TE+0.0332348*∈HOMO-0.025947 *∈LUMO +2.05275
    rCV^2=0.688245
    r^2=0.735007
28. PA78=0.0550476*ΔHf+0.00219062*TE+0.00728785*∈HOMO-0.0518939*η +2.05275
    rCV^2=0.688245
    r^2=0.735007

Among all the 28 QSAR models PA 51 to PA 78, the number of good QSAR models is 07 whose regression coefficient is greater than 0.7. Good QSAR models in the decreasing order of predictive power are shown in the table-4 along with the descriptors used in them.

Table 4: Good QSAR models in the decreasing order of predictive power

S. No.	Predicted Activity	rCV^2	r^2	Descriptors used in QSAR model
1	PA57	0.688095	0.738250	Heat of Formation, Steric Energy, Total Energy, HOMO Energy
2	PA59	0.713887	0.737968	Heat of Formation, Steric Energy, Total Energy, Absolute Hardness
3	PA60	0.697817	0.737363	Heat of Formation, Steric Energy, Total Energy, Electronegativity
4	PA58	0.652423	0.735534	Heat of Formation, Steric Energy, Total Energy, LUMO Energy
5	PA52	0.688245	0.735007	Heat of Formation, Total Energy, HOMO Energy, Electronegativity
6	PA77	0.688245	0.735007	Heat of Formation, Total Energy, HOMO Energy, LUMO Energy
7	PA78	0.688245	0.735007	Heat of Formation, Total Energy, HOMO Energy, Absolute Hardness

Out of these 28 good QSAR models, best 07 QSAR models are described below:

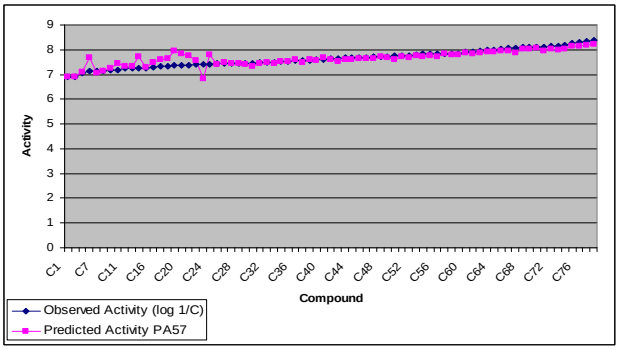
QSAR Model 1 (PA57)

This QSAR model contains the descriptors heat of formation, steric energy, total energy and HOMO energy. Predicted activity is given by the equation:

PA57=0.0538542*ΔHf-0.0015478*SE+0.00309132*TE+0.0716091 ***∈**HOMO +2.72259
rCV^2=0.688095
r^2=0.73825

Value of regression coefficient is 0.73825, which indicates that the predictive power of QSAR model given by PA57 is very good and it can be used to predict the activity of any compound of triazine series. Graph between predicted and observed activities is shown in Graph-1.

Graph 1: Graph between predicted activity PA57 and observed activity in terms of log 1/C



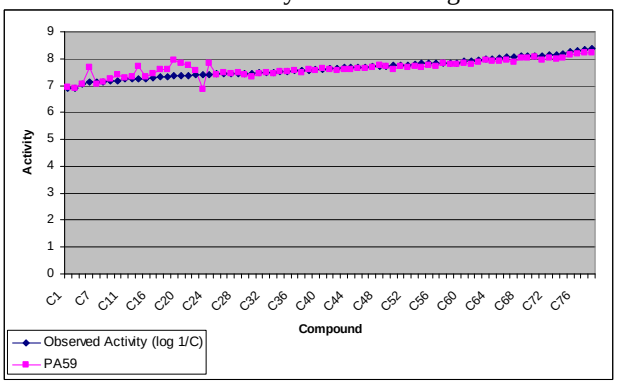
QSAR Model 2 (PA59)

This QSAR model contains the descriptors heat of formation, steric energy, total energy and absolute hardness. Predicted activity is given by the equation:

PA59=0.0542458*ΔHf-0.00138576*SE+0.00272779*TE-0.224381***η**+2.83126
rCV^2=0.713887
r^2=0.737968

Value of regression coefficient is 0.737968, which indicates that the predictive power of QSAR model given by PA59 is very good and it can be used to predict the activity of any compound of triazine series. Graph between predicted and observed activities is shown in Graph-2.

Graph 2: Graph between predicted activity PA59 and observed activity in terms of log 1/C



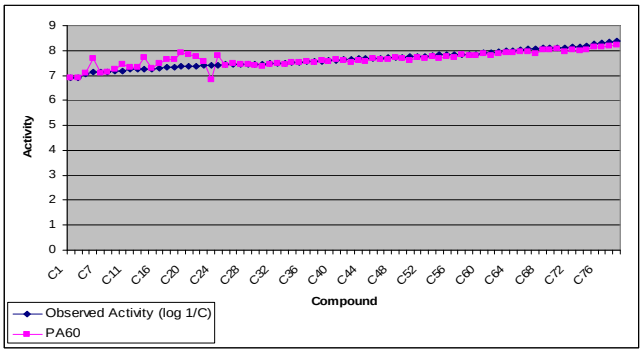
QSAR Model 3 (PA60)

This QSAR model contains the descriptors heat of formation, steric energy, total energy and electronegativity. Predicted activity is given by the equation:

PA60=0.0539666*ΔHf-0.00128319*SE+0.00302903*TE-0.0815652***χ**+2.4761
rCV^2=0.697817
r^2=0.737363

Value of regression coefficient is 0.737363, which indicates that the predictive power of QSAR model given by PA60 is very good and it can be used to predict the activity of any compound of triazine series. Graph between predicted and observed activities is shown in Graph-3.

Graph 3: Graph between predicted activity PA60 and observed activity in terms of log 1/C



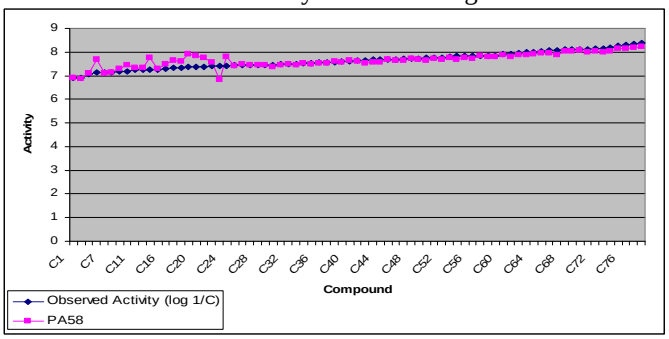
QSAR Model 4 (PA58)

This QSAR model contains the descriptors heat of formation, steric energy, total energy and LUMO energy. Predicted activity is given by the equation:

PA58=0.0543591*ΔHf-0.000702575*SE+0.00274536*TE+0.0683107 ***∈**LUMO +2.0525
rCV^2=0.652423
r^2=0.735534

Value of regression coefficient is 0.735534, which indicates that the predictive power of QSAR model given by PA58 is very good and it can be used to predict the activity of any compound of triazine series. Graph between predicted and observed activities is shown in Graph-4.

Graph 4: Graph between predicted activity PA58 and observed activity in terms of log 1/C



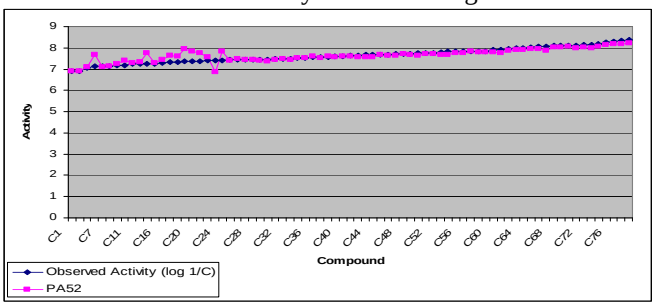
QSAR Model 5 (PA52)

This QSAR model contains the descriptors heat of formation, total energy, HOMO energy and electronegativity. Predicted activity is given by the equation:

PA52=0.0550476*ΔHf+0.00219062*TE+0.0591818**∈HO MO+0.0518939**χ+2.0527
rCV^2=0.688245
r^2=0.735007

Value of regression coefficient is 0.735007, which indicates that the predictive power of QSAR model given by PA52 is very good and it can be used to predict the activity of any compound of triazine series. Graph between predicted and observed activities is shown in Graph-5.

Graph-5: Graph between predicted activity PA52 and observed activity in terms of log 1/C



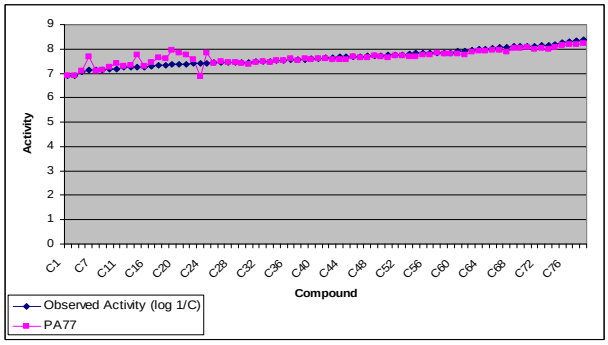
QSAR Model 6 (PA77)

This QSAR model contains the descriptors heat of formation, total energy, HOMO energy and LUMO energy. Predicted activity is given by the equation-

PA77=0.0550476*ΔHf+0.00219062*TE+0.0332348**∈HO MO-0.025947 **∈**LUMO +2.05275
rCV^2=0.688245
r^2=0.735007

Value of regression coefficient is 0.735007, which indicates that the predictive power of QSAR model given by PA77 is very good and it can be used to predict the activity of any compound of triazine series. Graph between predicted and observed activities is shown in Graph-6.

Graph-6: Graph between predicted activity PA77 and observed activity in terms of log 1/C



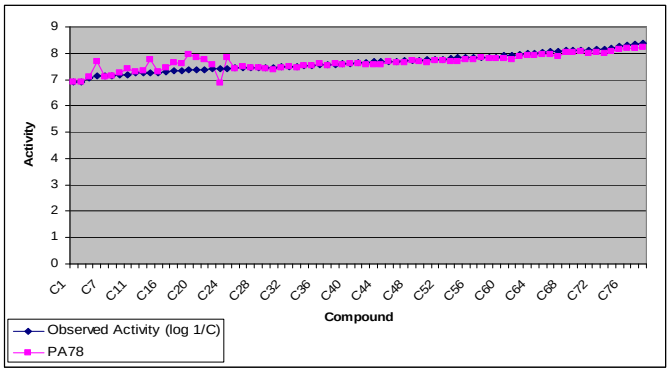
QSAR Model 7 (PA78)

This QSAR model contains the descriptors heat of formation, total energy, HOMO energy and absolute hardness. Predicted activity is given by the equation-

PA78=0.0550476*ΔHf+0.00219062*TE+0.00728785**∈HO MO-0.0518939**η +2.05275
rCV^2=0.688245
r^2=0.735007

Value of regression coefficient is 0.735007, which indicates that the predictive power of QSAR model given by PA78 is very good and it can be used to predict the activity of any compound of triazine series. Graph between predicted and observed activities is shown in Graph-7.

Graph 7: Graph between predicted activity PA78 and observed activity in terms of log 1/C



4. Conclusion

Best QSAR model PA 57 contains the descriptors heat of formation, steric energy, total energy and HOMO energy. Value of regression coefficient is 0.73825, which is too greater than 0.5 and hence indicates that the predictive power of QSAR model given by PA 57 is very good.

In all the best 07 QSAR models, heat of formation is common. It means the best descriptor to predict the activities are the heat of formation. Also, the predicted activity obtained by taking heat of formation as single descriptor possesses the good value of regression coefficient which is

0.73825. Predicted activity using heat of formation as descriptor is given by:
PA57=0.0538542*ΔHf-
0.0015478*SE+0.00309132*TE+0.0716091 *∈HOMO
+2.72259
rCV^2=0.688095
r^2=0.73825

All the combinations of the descriptors give good QSAR model in which the descriptor heat of formation is present.

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