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QSAR Study on Triazine Derivatives as DHFR Inhibitors Using Electrotopological State

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Abstract: In present study efforts have been made to investigate the quantitative structure activity relationship study for a set of 33 triazine derivatives. Electrotopological state is used as a structural descriptor for prediction of inhibitory action of dihydrofolate reductase. The regression analysis resulted into multi parameter model using electrotopological state and indicator parameters. The results are discussed critically on the basis of regression parameters.

Key words: QSAR, triazine derivatives, topological indices, dihydrofolate reductase

Introduction

Recognition of the triazines as a class of diuretic agents stemmed from the research of (Klenke *et al*., 2001) who tested a group of compounds of this type. The triazine to achieve any degree of clinical use is chlorazanin. It has a more pronounced effect on the water excretion than on Na^+ and Cl^- and has a little effect on K^+ excretion, which is probably linked to lack of the marked enhancement of Na^+ excretion (Burger, 1969). Previously QSAR study was performed over the set of Baker triazines, with the activity described as dihydrofolate reductase (DHFR) inhibitors by Fradera *et al*. (1997). The biological activity is represented as log1/C, being C the concentration necessary to produce a 50% inhibition of the DHFR enzyme in an *in vitro* assay with a certain kind of cells (Michal *et al*., 1993). The ampliphication in DHFR gene causes an increase in intracellular DHFR enzyme activity (Sirawaraporn *et al*., 1993).

There is a considerable interest in the set up of Quantitative Structure Activity Relationships (QSAR) of triazine derivatives. These methods are widely accepted to be useful for the explanation of structural requirements of biologically active compounds (Hansch and Leo, 1995). In particular, QSAR provides a possibility to gain more insight into drugs (Trujillo *et al*., 1996; Basak *et al*., 1997).

During the past two decades, an increasing number of the Quantitative Structure Activity Relationship (QSAR) models have been using the theoretical molecular descriptors for predicting biomedical, toxicological and technological properties of chemicals (Basak *et al*., 1999; Thakur *et al*., 2003). However, we have shown that topological indices can be successfully used for this purpose, with interesting results being obtained and reported earlier (Thakur *et al*., 2003, 2004a; Agrawal *et al*., 2003; Thakur and Thakur, 2003a,b; Thakur, 2005).

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Table1: Substituents, Indicator parameters, Observed and Calculated biological activity of Triazine derivatives used in present study

S.No.	Substituents	I_1	I_2	Obs.log1/C	Calc.log1/C[a]
1	3,4-Cl	0	1	8.54	7.35[c]
2	3-$(CH_2)_2$-Ph	0	0	8.19	8.21
3	4-CH_2-Ph	0	0	8.05	7.58
4	3-CH_2-Ph	0	0	8.00	7.58
5	4-$(CH_2)_2$-Ph	0	0	7.89	7.00[c]
6	3-CF_3	0	1	7.76	8.14
7	3-Cl	0	1	7.76	7.08
8	3-Cl,4-OCH_2-Ph	0	1	7.52	8.10
9	3-SO_2F	0	1	7.27	6.84
10	3-Ph,4-OH	0	0	7.14	7.03
11	3-NO_2	0	1	7.07	6.68
12	4-CH_2CN	0	0	6.92	6.72
13	H	0	0	6.92	6.50
14	3-Ph	0	0	6.85	7.48
15	3-$COCH_3$	0	1	6.79	6.61
16	2,3-Cl	1	1	6.52	4.58[c]
17	4-$COCH_2Cl$	0	0	6.45	6.28
18	3-$COCH_2Cl$	0	1	6.21	6.57
19	3-OCH_3	0	1	6.17	6.71
20	4-CN	0	0	5.14	6.24
21	2-F	1	0	4.74	3.98
22	4-Ph	0	0	4.70	7.48[c]
23	2-Br	1	0	4.25	4.51
24	2-Cl	1	0	4.15	4.38
25	2-OCH_3	1	0	3.68	3.87
26	2,5-Cl	1	0	3.43	4.73[c]
27	2-CH_3	1	0	4.00	4.07
28	3-SO_2-NH_2	0	1	5.32	6.20
29	3-CO-NH_2	0	1	5.70	6.23
30	3-OH	0	1	6.38	6.47
31	3-F	0	1	7.45	6.90
32	3-$C(CH_3)_3$	0	0	7.50	7.53
33	3-CN	0	1	7.69	6.54

*I_1 = 1 if substituent at R_3 position, 0 otherwise, I_2 = 1 if substituent at R_3 position are electron attracting in nature, 0 otherwise, c = Data points not included in calculation , a = Calculated from Eq. (10)

Literature data shows that even for the Triazine as DHFR inhibitors no QSAR study using topological indices have been reported. In view of this and in continuation to our earlier work (Thakur *et al*., 2004b; Thakur, 2003b, 2005; Agrawal *et al*., 2003) the present study deals with topological investigation on this class of DHFR inhibitors, in which we have used the electrotopological state (Si) (Kier and Hall, 1976).

A detailed information of these topological indices is reported in the literature (Balaban, 1976; Davellier and Balaban, 1999; Todeschini and Consonni, 2002; Diudea and Khadikar, 2003; Diudea, 2001). Out of these topological indices: Wiener (W) (Wiener, 1947), connectivity (χ) indices (Randic 1975, 2001), Balaban index (J) (Balaban, 1982) and Szeged index (Sz) (Khadikar *et al*., 1995) have been used extensively but in the present study the electrotopological state is used for modeling. Parent structure of the Triazine is shown in Fig. 1 and the substituents, indicator parameter, experimental and estimated biological activities are presented in Table 1.

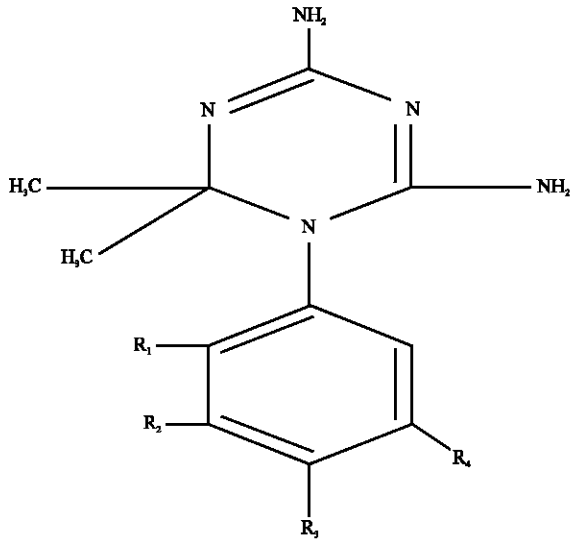

Fig. 1: Parent structure of triazine derivetive

Materials and Methods

DHFR Inhibition Activity

The DHFR inhibitory activity expressed as log1/C, was taken from the literature (Fradera *et al*., 1997).

Topological Indices

All the topological indices used were calculated from the hydrogen suppressed molecular graphs. Though their calculations are exclusively discussed in the literature, we give undermentioned expressions used for their calculations.

Wiener Index (W)

Wiener index W = W(G) of G is defined as the half sum of the elements of the distance matrix.

$$W = W(G) = \tfrac{1}{2}\sum_{i=1}, \sum_{j=1} (D)_{ij} \quad (1)$$

Where, $(D)_{ij}$ is the ijth element of the distance matrix which denotes the shortest graph- theoretical distance between sites i and j of G.

The Connectivity Index (χ)

The connectivity index $\chi = \chi(G)$ of G is defined by Randic as:

$$\chi = \chi(G) = \sum_{i,j} [d(i).\, d(j)]^{-0.5} \quad (2)$$

Balaban Index (J)

The Balaban index J = J(G) of G is defined as

$$J = M/\mu + 1 \sum_{\text{bonds}} (d_i.d_j)^{-0.5} \quad (3)$$

Where, M is the number of bonds in G, μ is the cyclomatic number of G and d_i (i = 1,2,3,….N; N is the number of vertices in G) is the distance sum.

The cyclomatic number $\mu = \mu$ (G) of a cyclic graph G is equal to the minimum number of edges necessary to be erased from G in order to transform it into the related acyclic graph. In case of monocyclic graph $\mu = 1$ otherwise it is calculated by means of the following expression

$$M = M\text{-}N+1 \quad (4)$$

Szeged index (Sz)

The Szeged index, Sz = Sz (G), is calculated according to the following expression:

$$Sz = Sz(G) = \sum_{\text{edges}} n_u . n_v \quad (5)$$

Where, n_u is the number of vertices lying closer to one end of the edge e = uv; the meaning of $n_v$is analogous. Edges equidistance from both the ends of an edges, e = uv are not taken into account.

Electrotopological State (Si)

The Electrotopological index was developed by Kier and L.H Hall (Kier, 1976). It can be calculated by the use of Intrinsic value of each group. The Intrinsic state of an atom in a chemical graph reflects its electronic and topological attributes in the absence of interaction with the rest of the molecule. The state of each atom in a chemical graph due to the intrinsic state of that atom and the molecular field may be called the electrotopological state, S. It is calculated by the sum of these two terms

$$Si = I_i + \Delta i_j \quad (6)$$

Where I_i is the column and ΔI_j is the row sum.

Indicator Parameters

These are the dummy parameters sometimes used for accounting those structural feature not covered in any molecular descriptor used. They assumed only two values 1 or 0. If the assumed structural feature (I_1 = 1 if substituent at R_2 position, 0 otherwise.I_2 = 1 if substituent at R_3 position are electron attracting in nature, 0 otherwise) is present; then the indicator parameters is 1 otherwise it is 0. The details of such parameters, used in the present study are already given in the result and discussion section (Table 1).

Regression Analysis

All the regressions are carried out using maximum r^2 method.

Step-wise regression has been performed for obtaining the best model. The predictive- potentials of these models are initially discussed on the basis of quality factor (Q) and finally using the cross-validation parameters.

Results and Discussion

The topological indices are used to model the DHFR inhibition activity of triazine derivatives. From that large pool of topological indices presented in Table 2. Electro topological index (S_i) is found suitable along the indicator parameters for the QSAR study of B. Triazine derivatives.

The inter-correlation between the indices and their correlation with biological activity log1/C are presented in the form of correlation matrix in Table 3.

From the perusal of correlation matrix, the mono parametric correlation from topological indices gave very low correlation coefficients, but correlation coefficient from indicator I_1 is better (R = -0.7376).

As shown by the correlation matrix, very low mutual correlation exists between the parameters [S_i and I_1 (0.0195) similarly between S_i and I_2 (-0.3649) and I_1 and I_2 (-0.3248)] used for the mathematical modeling of dihydrofolate reductase inhibition activity of triazine derivatives.

Results from bi parametric combination of S_i and I_1 (R = 0.7968; Se = 0.9063; Q = 0.88) is little bit improved but their statistics are not best to explain structure-activity relationship quantitatively. The addition of indicator parameter I_2 to the above combination resulted in to tri parametric combination. The results from triparameteric model is encouraging and the model obtained is as below:

$$\log 1/C = 0.0408 \times S_i(\pm 0.0117) - 2.3151 \times I_1(\pm 0.3876) + 0.7388 \times I_2(\pm 0.3417) + 5.2262 \quad (7)$$

$$N = 33;\ R = 0.828\ ;\ r^2 = 0.682\ ;\ Se = 0.8554\ ;\ Q = 0.987$$

The statistics of our model is far superior than the statistics given by the Xavier Fradera and co-workers (Fradera *et al*., 1997) (N = 33, R = 0.801 ; Q = 0.494).

The comparison can be made more précised by calculating the quality factor Q (Pogliani 1992, 1994). The quality Q is defined as the ratio of correlation coefficient to the standard error of estimation i.e., Q = R/Se. The value of Q for the model proposed by the Fradera *et al*. (1997) is 0.494 just half then that of our model 0.987. Thus our model is not only of better quality but has much more improved predictive potential.

Statistics obtained from Eq. 7 exhibits the direct relationship between electro topological state and biological activity log1/C. The positive regression coefficient of the indicator parameter I_2 express the enhancement in DHFR inhibitory action (biological activity log1/C) of triazine derivatives with the presence of electron attracting group at R_3 position and the negative coefficient of the indicator parameter I_1 show a decrease in DHFR inhibition activity of the triazine derivatives (log1/C) with the presence of substituents at R_2 position in the quantitative manner.

To improve the predictability of model outlier concept is introduced and the five compounds are (1, 5, 16, 22 and 26) expelled from the calculations in the following three different steps.

In the first step of deletion, three compounds (1, 16, 26) were deleted. After the deletion of these compounds, mathematical model is obtained as follows.

$$\log 1/C = 0.0371 \times Si(\pm 0.011) - 2.4998 \times I_1(\pm 0.4225) + 0.3753 \times I_2(\pm 0.34360) + 5.4965 \quad (8)$$

$$N = 30\ ;\ R = 0.8436\ ;\ r^2 = 0.7116\ ;\ Se = 0.7741;\ Q = 1.09$$

Improvement in the statistics of Eq. 8 exhibits the exceptional behavior of di-Chloride substituents of triazine from their Structure Activity Relationship.

Equation 8 also conforms the relationship (as model 1 Eq. 7) between descriptors and biological activity.

Table 2: Topological indices used in the present study

Comp. No.	W	χ	J	Sz	MTI	Si
1	961	10.13074	2.22391	1528	3892	38.1800
2	2380	13.77569	1.58015	3586	9999	65.3995
3	1984	12.77569	1.60406	3080	8079	50.5236
4	1816	12.77569	1.69208	2884	8079	50.5236
5	1972	13.29253	1.73435	2997	8272	36.1080
6	1225	10.93138	2.24469	1897	4920	57.0025
7	838	9.720053	2.22653	1330	3414	31.8999
8	2348	13.68638	1.60602	3674	9849	55.9803
9	1225	10.93138	2.24469	1897	4920	26.2041
10	1896	13.24122	1.80508	3073	7898	37.5033
11	1094	10.63074	2.22361	1706	4410	22.3445
12	993	10.25806	2.15738	1573	4024	30.1401
13	732	9.326205	2.21079	1164	3004	25.0100
14	1575	12.29253	1.75371	2574	6638	48.0942
15	1094	10.63074	2.22361	1706	4410	20.6388
16	933	10.14757	2.29193	1472	3776	34.3865
17	1302	11.16874	2.11737	2030	5236	19.8381
18	1246	11.16874	2.21067	1918	5004	19.8381
19	965	10.25806	2.21649	1517	3784	23.1264
20	993	10.25806	2.15738	1573	4024	19.0008
21	824	9.73689	2.26576	1302	3356	27.2588
22	1659	12.29253	1.66330	2742	7014	48.0942
23	824	9.73689	2.26576	1302	3356	39.6018
24	824	9.73689	2.26576	1302	3356	36.6509
25	937	10.27489	2.28472	1461	3792	24.4827
26	935	10.13074	2.28807	1476	3784	44.9034
27	824	9.73689	2.26576	1302	3356	29.3764
28	1537	11.87475	2.25637	2329	6136	10.9826
29	1400	11.54142	2.21314	2132	5606	11.8267
30	965	10.25806	2.21649	1517	3784	17.5561
31	838	9.720053	2.22653	1330	3414	27.5520
32	1225	10.93138	2.24469	1897	4920	49.4771
33	965	10.25806	2.21649	1517	3784	19.0008

* W =Wienerindex, ÷ =Connectivityindex, J =Balabanindex, Sz = Szegedindex, MTI = Molecular Topological Index, Si = Electrotopological state

Table 3: Correlation matrix between the topological indices, indicator parameters and biological activity (log1/C)

	log1/C	W	χ	J	Sz	MTI	Si	I_1	I_2
log1/C	1.00000								
W	0.42364	1.00000							
χ	0.40206	0.99035	1.00000						
J	-0.39643	-0.89680	-0.88571	1.00000					
Sz	0.41517	0.99738	0.99176	-0.91457	1.00000				
MTI	0.42066	0.99783	0.98925	-0.91255	0.99736	1.00000			
Si	0.28701	0.54351	0.50244	-0.63010	0.55704	0.56585	1.00000		
I_1	-0.73761	-0.43524	-0.44142	0.38360	-0.43568	-0.42068	0.01956	1.00000	
I_2	0.32843	-0.15441	-0.16134	0.34980	-0.17158	-0.18138	-0.36496	-0.32480	1.00000

In the second step, compound No. (5, 22) were deleted and the model obtained after the deletion is as follows.

$$\log 1/C = 0.458\times Si(\pm 0.0097) - 2.4026\times I_1(\pm 0.3261) + 0.679\times I_2(\pm 0.2902) + 5.1522 \quad (9)$$

$$N = 31 \; ; \; R = 0.8868 \; ; \; r^2 = 0.7864 \; ; \; Se = 0.7024 \; ; \; Q = 1.26$$

After the deletion of compounds (5, 22) improvement in the correlation coefficient suggests the exceptional behavior of compounds containing phenyl ring at R_4 position or $-CH_2-CH_2-Ph$ at R_4

Table 4: Cross validation parameters for the proposed models

S.No.	(Eq.)	Parameters	PRESS	SSY	PRESS/SSY	R^2_A
1	7	Si, I_1, I_2	21.2189	46.2793	0.46	0.653
2	8	Si, I_1, I_2	15.5792	38.4396	0.40	0.678
3	9	Si, I_1, I_2	13.3208	49.0512	0.27	0.763
4	10	Si, I_1, I_2	07.4422	41.4334	0.18	0.829

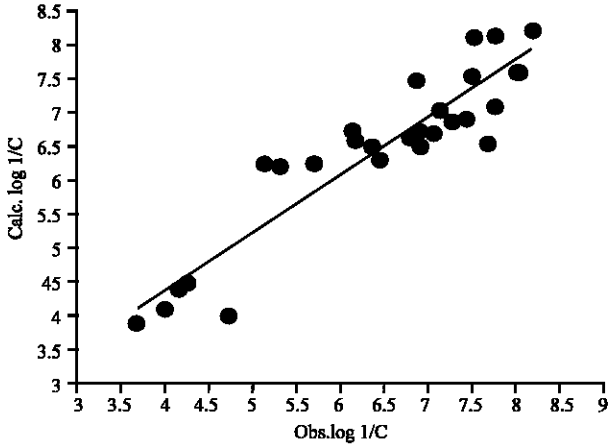

Fig. 2: Results between observed and calculated log 1/C from Eq. 10

position. The comparison of statistics of Eq. 8 and 9 expresses the more exceptional behavior of phenyl substitution and $-CH_2$-CH_2-Ph at R_4 position than the di-chloride substitution on the parent moiety.

In the third step of deletion, all these five compounds were deleted. After the deletion of all five compounds the mathematical model is obtained as follow;

$$\log 1/C = 0.0423 \times Si(\pm 0.008) - 2.61 \times I_1(\pm 0.3117) + 0.2914 \times I_2(\pm 0.2564) + 5.4414 \quad (10)$$

$$N = 28;\ R = 0.92;\ r^2 = 0.848;\ Se = 0.557;\ Q = 1.65$$

The excellent improvement in the statistics of the equation suggests that the all the five compounds mentioned earlier having well exceptional behavior than the parent series of Triazine derivatives. It also shows that the electro topological state having positive impact on modeling of DHFR inhibition and it has a direct relationship with the biological activity log1/C, hence, increase in the electro topological state of the molecule, increases the inhibitory action of Triazine derivatives on the dihydro folate reductase. The model also expresses the direct relationship between presence of electron attracting group at R_3 position and biological activity i.e., the presence of electronegative group at R_3 position favors the inhibitory action of triazine derivatives on dihydrofolate reductase. The negative coefficient of indicator parameter I_1 shows that the presence of substituents at R_2 position reduces the inhibitory action of triazine derivatives as dihydrofolate reductase inhibitor.

In order to confirm our results, we have calculate predictive correlation coefficient (R_{pre}^2) by correlate estimated DHFR inhibition activity with the experimental activity.

The obtained predictive correlation coefficients R_{pre}^2 confirm our findings. Such correlations are graphically presented in Fig. 2.

We have undergone a cross-validation methodology for deciding the predictive power of the proposed models. This is needed because a model with good statistics may not have good predictivity. The various cross-validation parameters, calculated for the proposed models, are presented in Table 4.

PRESS (predicted residual sum of squares) appears to be the most important cross-validation parameter accounting for a good estimate of the real predictive error of the models. Its value less than SSY (sum of the squares of response value) indicate that the model predicts better than chance and can be considered statistically significant. In our case (Table 4) PRESS << SSY indicating that all the models obtained are statistically significant and are better than chance.

To be a reasonable QSAR model, PRESS/SSY should be smaller than 0.4 and the data presented in Table 4 indicates that all the models proposed are significant except model 1 (Eq. 7) which is very close to line of significance.

Conclusions

On the basis of the results and discussion made above the conclusion can be drawn that the study succeed to understand the Structure Activity Relationship of triazine derivatives as dihydrofolate reductase inhibitor. The Electro topological state has shown good correlation potential with biological activity. It shows that electronic environment of molecules play significant role in inhibition of dihydrofolate reductase.

The results suggest that presence of electron attracting group at R_3-position will help to increase inhibition of dihydrofolate reductase, while the presence of substituents at R_2-position bear quantitatively negative impact on inhibition of dihydrofolate reductase.

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