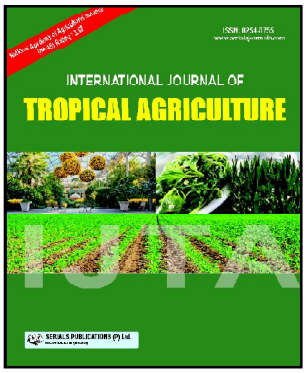

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Topological Modeling of Anti Malarial Activities of Selected Phenothiazine Derivatives

[1]Dr. Venkateshwar and [2]Dr. (Prof.) Vijay K. Agrawal

QSAR Laboratory, A.P.S. University, Rewa, M.P. (India)
Author for correspondence: [1]vktvkt3@gmail.com

Abstract: Topological parameters and connectivity indices are widely used in modeling of large variety of drugs. In the present study, Log IC_{50} values for the given set of anti malarial compounds which were phenothiazine derivatives was modeled using selective physiochemical and topological parameters along with two indicator parameters. A series of step wise regression analysis of the independent parameters with the dependent parameter was carried out with the help of statistical parameters. A tetra parametric model containing topological and connectivity indices obtained after series of regression analysis was found to be significant in modeling the activity.

Key words: topological and connectivity indices, step wise regression, phenothiazine derivatives.

INTRODUCTION

Malaria is still prevalent in developing countries. Phenothiazine derivatives have been found to posses anti malarial activity towards *P.Falciparum*. The inhibitory activity for such derivatives has been reported by Dominguez *et al.* **[1].** The general structure of these compounds is shown in fig 1.

The structural details of these phenothiazine derivatives have been reported in **Table 1**. This Table also contains Log IC_{50} values for various compounds.

A peruses of **Table 1**, gives some information regarding variation of activity with functional groups attached at different positions. The compound 10,

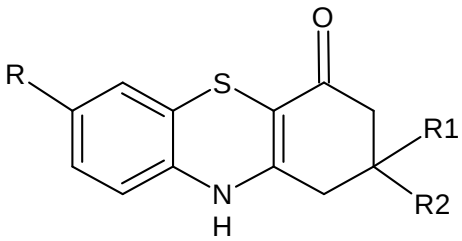

Figure 1: General structure of phenothiazine derivatives

exhibits highest inhibitory activity. This activity can be compared with compound number 2, where fluoro, group has been replaced by chloro group at R. Similarly, presence of fluoro group at R, in case of compound number 12 is comparable with compound number 4. Here, a replacement of fluoro with chloro group has no effect on the activity. On the other hand, the presence of fluoro group at R, in compound number 16, lowers the IC_{50} activity as compared to compound number 7, therefore it is very difficult to draw any conclusions while variation is observed because of functional groups present at any one position. It appears, that the presence of one functional group, changes the property of the molecule as a whole. Therefore, in the present investigation topological and physico-chemical parameters have been chosen for modeling Log IC_{50} activity. Two indicator parameters (IP) have been taken, IP_1 which accounts for the presence of halogen attached to the phenyl ring present at R2 and IP_2 which accounts for the presence of phenyl ring present at R2.

The values of indicator parameters are shown in Table 1. The values of calculated topological parameters used in the present study like Weiner index (W),**[2]** Balban index (B) **[3]** and Balban type indices are tabulated in **Table 2**, whereas **Table 3**, demonstrates the values of various order Randic **[4]** and Kier-Hall valency connectivity indices. **[5]**

AIM OF PRESENT INVESTIGATION

The present investigation highlights the importance of topological and connectivity indices of certain order in modeling the activity of selected anti malarial compounds and further using the obtained equations in designing newer anti malarial drugs and improving the existing ones.

METHODOLOGY USED

The physiochemical data for the compounds under the present study, were calculated using advanced version of Chemsketch software **[6]** and this data was subjected to the regression analysis with the activity (dependent parameter) using NCSS (software used for statistical analysis) However, after a series of regression, none of the physiochemical parameter in mono, bi, tri or tetra parameter category was found to be significant. Hence, the focus was shifted to topological parameters.

The topological parameters were calculated by making a mole file followed by exporting the data to Dragon software **[7]** used to calculate the topological parameters of various orders.

The data was again subjected to multiple regression analysis **[8]** and on the basis of R^2, R^2A, F-ratio and Pogliani Quality Factor (Q), **[9, 10]** some statistically significant correlations were obtained.

Table 1
Structural details of the compounds with their activity used in the present study along with their indicator parameter values

Compd. No.	*R*	*R1*	*R2*	*logIC_{50}*	*IP_1*	*IP_2*
1	Cl	H	H	1.6020	0	0
2	Cl	CH_3	CH_3	1.4771	0	0
3	Cl	H	C_6H_5	1.0000	0	1
4	Cl	H	3-$CH_3OC_6H_4$	1.3010	0	1
5	Cl	H	4-$CH_3OC_6H_4$	1.0000	0	1
6	Cl	H	2,3-$(CH_3O)_2C_6H_3$	1.0000	0	1
7	Cl	H	3,4-$(CH_3O)_2C_6H_3$	1.4771	0	1
8	Cl	H	4-ClC_6H_4	0.6020	1	1
9	F	H	2,4-ClC_6H_4	1.0000	1	1
10	F	CH_3	CH_3	1.7781	0	0
11	F	H	C_6H_5	1.3010	0	1
12	F	H	3-$CH_3OC_6H_4$	1.3010	0	1
13	F	H	2,3-$(CH_3O)_2C_6H_3$	1.3010	0	1
14	F	H	2,4-$Cl_2C_6H_3$	1.0000	1	1
15	F	H	4-ClC_6H_4	0.6989	1	1
16	F	H	3,4-$(CH_3O)_2C_6H_3$	1.3010	0	1

IP_1 = 1, if halogen is attached to the phenyl ring present at R2; IP_2 = 1, if phenyl ring is present at R2.

Table 2
Values of calculated topological indices for the compounds used in the present study

Compd. No.	*W*	*J*	*Jhetz*	*Jhetm*	*Jhetv*	*Jhete*	*Jhetp*	*BAC*
1	404	1.7050	2.6330	2.6360	1.9530	2.1490	2.1280	5
2	558	1.7300	2.5020	2.5030	1.9330	2.1120	2.0740	17
3	1031	1.4220	1.9380	1.9380	1.6110	1.7260	1.6860	5
4	1332	1.4070	1.8900	1.8910	1.5330	1.7130	1.5760	11
5	1364	1.3770	1.8540	1.8550	1.510	1.6830	1.5520	11
6	1617	1.4510	1.9290	1.9290	1.5240	1.7660	1.5460	21
7	1681	1.3960	1.8650	1.8650	1.4860	1.7120	1.5070	21
8	1186	1.4020	1.9110	1.9120	1.5940	1.7070	1.6670	10
9	1313	1.4260	1.9420	1.9430	1.6170	1.7330	1.6910	17
10	558	1.7300	2.4770	2.4800	1.8710	2.1180	1.9590	17
11	1031	1.4220	1.9250	1.9270	1.5750	1.7300	1.6240	5
12	1332	1.4070	1.8810	1.8820	1.5050	1.7150	1.5280	11
13	1617	1.4510	1.9200	1.9210	1.5000	1.7680	1.5060	21
14	1313	1.4260	1.9320	1.9340	1.5870	1.7350	1.6370	17
15	1186	1.4020	1.9000	1.9020	1.5620	1.7100	1.6100	10
16	1681	1.3960	1.8560	1.8570	1.4630	1.7140	1.4680	21

Table 3
Values of calculated Randic, Kier and Hall Valence Connectivity indices for the compounds used in the present study

Compd. No.	$^{0}\chi$	$^{1}\chi$	$^{2}\chi$	$^{3}\chi$	$^{0}\chi^{v}$	$^{1}\chi^{v}$	$^{2}\chi^{v}$	$^{3}\chi^{v}$
1	11.1210	7.7370	7.2420	6.1530	10.1200	6.4410	5.4410	4.2700
2	12.9140	8.4440	8.8830	6.6080	11.9130	7.1480	7.1050	4.7340
3	15.1040	10.7040	9.9410	8.5150	13.3770	8.4570	7.1030	5.5930
4	16.6810	11.6350	10.7430	9.2660	14.7080	8.9800	7.4690	5.8870
5	16.6810	11.6350	10.7320	9.3340	14.7080	8.9800	7.4650	5.9090
6	18.2590	12.6010	11.3780	10.0680	16.0390	9.5150	7.7750	6.1950
7	18.2590	12.5840	11.4520	10.0950	16.0390	9.5090	7.8070	6.2010
8	15.9740	11.0970	10.5620	8.9260	14.4340	8.9340	7.6800	5.9150
9	16.8450	11.5080	11.1020	9.3020	15.4900	9.4180	8.2020	6.2870
10	12.9140	8.4440	8.8830	6.6080	11.1570	6.7700	6.6680	4.4990
11	15.1040	10.7040	9.9410	8.5150	12.6210	8.0790	6.6660	5.3580
12	16.6810	11.6350	10.7430	9.2660	13.9520	8.6020	7.0320	5.6520
13	18.2590	12.6010	11.3780	10.0680	15.2830	9.1370	7.3390	5.9600
14	16.8450	11.5080	11.1020	9.3020	14.7340	9.0400	7.7650	6.0520
15	15.9740	11.0970	10.5620	8.9260	13.6780	8.5560	7.2440	5.6800
16	18.2590	12.5840	11.4520	10.0950	15.2830	9.1310	7.3700	5.9660

During the selection of final model, care was taken for the parameters which were highly correlated. Since, colinerarity sometimes hides the favorable information needed to design a model and may lead to wrong conclusions.

RESULTS AND DISCUSSION

The best mono-parametric model having R^2 (0.5916), contains Weiner index "W". The model is as below:

$$\text{Log } IC_{50} = -0.3286(\pm 0.0730)\ W + 2.2350 \quad (4.2.1)$$

N = 16, Se = 0.2099, R^2 = 0.5916, F-Ratio = 20.2780 , Q = 3.6641

When W and Randic connectivity index of first order "$^1\chi$" have been taken together, then R^2 comes out to be 0.6790, but on the basis of Q value, this combination has found to be inferior, to two other combinations in which R^2 value is lower than this, but their Q values are more than the previous ones. However, the best bi-parametric correlation is that, containing W and $^1\chi$ as correlating parameters. The model is as below:

$$\text{Log } IC_{50} = -0.1665(\pm 0.0392)\ W + 0.0203(\pm 0.0052)\ ^1\chi + 2.7496 \quad (4.2.2)$$

N = 16, Se = 0.1929, R^2 = 0.6790, R^2_A = 0.6296, F-Ratio = 13.7500, Q = 4.2717

A, drastic improvement in the quality of the model was obtained when IP_1, is added to bi-parametric model obtained above and R^2 shows a jump, from 0.6790 to 0.8391. For this model R^2 comes out to be 0.8391 and Q value is found to be 6.4371. The model is as reported below:

$$\text{Log } IC_{50} = -0.1014(\pm 0.0198)\ W + 7.8231(\pm 1.9211)\ IP_1 - 0.8860(\pm 0.1729)\ ^1\chi - 3.5077 \quad (4.2.3)$$

N = 16, Se = 0.1423, R^2 = 0.8391, R^2_A = 0.7989, F-Ratio = 20.8620 , Q = 6.4371

Finally, tetra-parametric models were tried, and one with W, IP_1, $^1\chi$ and $^1\chi^v$ has been found to be the best, having R^2 (0.8717) and Q value (7.0410).

$$\text{Log } IC_{50} = 0.0261(\pm 0.0074)\ W - 0.8081(\pm 0.1761)\ IP_1 - 0.0142(\pm 0.0037)\ ^1\chi - 6.8872(\pm 1.8047)\ ^1\chi^v + 13.5952 \quad (4.2.4)$$

N = 16, Se = 0.1326, R^2 = 0.8717, R^2_A = 0.8250, F-Ratio = 22.5978 , Q = 7.0410

The above model was finally choosen, since it does not have the colineraity defect hence it does not contains those parameters, which overshadows the influence of other parameters. The final model suggests that to design the new drug, the presence of halogen atom at the phenyl ring (IP_1) must be avoided which is reflected in the above model by its negative coeffcient and connectivity indices must be kept minimum while branching may be increased as depicted by the model.

The superiority of the above chosen tetra parametric model, was also established by the calculation of cross validated parameters, reported in **Table 4.** To be a reasonable, QSAR model, the ratio of PRESS / SSY must lie between 0.1 to 0.4, with values less than 0.1 indicates that the model is excellent in nature. The value for PRESS / SSY for the tetra parametric model comes close to 0.1 suggesting the better predictivity of the model.

An important feature of the QSAR models are, it must be free from any kind of colinerarity defect. However, recently it was argued that such defects can be overcome using Randic recomendations **[11]** which states that under certain circumstances, highly corelated descriptors cn be retained in the model.

Further, the activities of the compounds used in the present study were calculated / estimated using the above tetra parametric model and a comparison between the observed and the estimated activities is reported in **Table 5.** Since, the differences between the observed and calculated activities are quite close hence the estimated activities are in close agreement

Table 4
Cross Validated Parameters

Model No.	*Parameters Used*	*PRESS*	*SSY*	*PRESS/SSY*	R^2cv	S_{PRESS}	*PSE*
1	W	0.5246	0.9008	0.5823	0.4177	0.2008	0.1870
2	W, J	0.4842	1.0243	0.4727	0.5273	0.1929	0.1739
3	W, J, IP1	0.2427	1.2658	0.1917	0.8083	0.1422	0.1231
4	W, IP1, $^1\chi$, $^1\chi^v$	0.1935	1.3149	0.1471	0.8529	0.1326	0.1099

Table 5
Comparison of observed and estimated activity (Log IC_{50})

Compd. No.	*Observed Log IC_{50}*	*Estimated Log IC_{50}*	*Residual*
1	1.6020	1.6210	-0.0190
2	1.4770	1.5330	-0.0560
3	1.0000	1.0630	-0.0630
4	1.3010	1.1470	0.1540
5	1.0000	1.1470	-0.1470
6	1.0000	1.2160	-0.2160
7	1.4770	1.2160	0.2610
8	0.6020	0.5850	0.0170
9	1.0000	0.9240	0.0760
10	1.7780	1.7100	0.0680
11	1.3010	1.2140	0.0870
12	1.3010	1.2900	0.0110
13	1.3010	1.3400	-0.0390
14	1.0000	1.0620	-0.0620
15	0.6990	0.7300	-0.0310
16	1.3010	1.3400	-0.0390

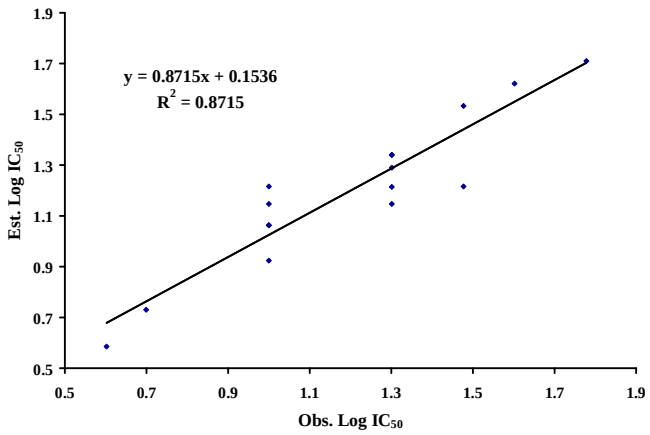

Figure 2: Correlation between observed and estimated activity (Log IC_{50})

with the observed one, also evident with the little residual values.

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