Computer assisted drug designing : Quantitative structure Activity Relationship studies on mono- and Bis- Thiazolium salts having Potent antimalarial activity

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Abstract :-

Quantitative structure-activity Relationship QSAR model is based on changes in molecular structure that would reflect changes in observed biological activity or physicochemical property. In the present work QSAR studies have been performed on 18 compounds of mono and Bis-Thiazolium salts and valuable correlations are obtained. Three new series of 24 novel cationic choline analogues and consisting of mono or bis (N-Or C-5 duplicated) thiazolium salts. Thiazolium salts showed potent antimalarial activity (Much Superior to monothiazoliums). Various QSAR models have been developed by using multiple linear regression analysis methodology. Randic index have been calculated for analysis. Valuable correlation equations showed the relation between physicochemical parameters (specially with Parachor and Vander Walls Volume) and antimalarial activity. This model has been validated by calculating R and R^2 Value. Various models were developed based on different combinations of descriptors to analysis which contribute best in predicting good antimalarial activity. The best model for n = 18 shows Value for R = .071. When electron donation group taken as outlier the QSAR model improved. Presence of ($-CH_2O$) group enhances the antimalarial activity.

Key words :- *Antimalarial activity : (IC_{50}) (nM), Protozoan : P. falciparum ; mono and Bis-Thiazolium; QSAR,*

INTRODUCTION

QSAR is widely used in drug designing .This method saves money, time, animal killing as well as gives less toxic and less expensive drugs which can be used for humanity. In the present work I have used QSAR for getting more potent antimalarial drug.

Malaria is found throughout the tropical and subtropical regions of the world. It causes more than 300 million deaths annually[1-2]. Due to drug-resistant parasites[3], Chloroquine (CQ) and Sulfadoxime pyrimethamine have become inefective although these are inexpensive. Artemisinin another alternative have limited use due to high cost and toxicity[4-5] so new drugs with novel mechanism of action[6] and low cast are urgently required to overcome this problem. In the present work QSAR model have been developed for three new series of 24 novel cationic choline analogous and consisting of mono-or bis (N) or (C-5 duplicated) thiazolium salts. These salts synthesized by Abdallah[7] Hamze, Eric Ruler et.al. which showed antimalarial activity (much superior to monothiazolium). The compounds mono-and bis-ammonium salts have a long lipophilic alkyl chain at the N-position. These are very active compounds against Plasmodium falciparum. These antimalarial compounds target the plasmodial phospholipid (PL) metabolim. The quantitative structure activity relationships have been performed on 18 compounds out of 24. The structure and the activity as IC_{50}(nM) on P. falciparum are used from the data reported by Abdallah Hamze et.al. Steric parameters ($^{1}\chi^{V}$) molecular connectivity index (Randic index) are calculated from these substituted compounds as described by Kier and Hall[8-11]. In the same manner Vander Walls Volume (Vw)[12] and Parachor(P)[13] is also calculated for the correlation. For the purpose of developing QSA R model the multiple linear regression analysis methodology is adopted and finally the correlation equations were developed and analysed. The analysis of these equations and the data thus obtained enables for the synthesis of some new drugs of the future.

MATERIAL AND METHODS:

(i) Antimalarial activity - (IC_{50})- The antimalarial activity (IC_{50}) (nM) of thiazolium salts against P. faliparum were adopted from the literature[7].

(ii) Physicochemical Parameters -

(a) [Molecular Connectivity Index ($^1\chi^V$)] Randic Index-

Molecular connectivity is a method of molecular structure quantitation in which weighted counts of substructure fragment are incorporated into numerical indices, structural features such as size, branching, unsaturation, heteroatom content and cyclicity are encoded.

The connectivity Index, also known as Randic Index (Milan Randic), so the randic Index, of a graph is the sum of bond contributions, $(1/d_i d_j)^{1/2}$ where d_i and d_j are the degrees of the vertices making bond i-j. This graph invariant was introduced by Milan randic in 1975.[15] It is often used in chemoinformatics for investigations of organic compounds.

The first order molecular connectivity index ($^1\chi^V$) term was calculated as given by Kier and Hall[8-11], ($^1\chi^V$) is calculated as-

$$^1\chi^V = (\delta i \, . \, \delta j)^{-1/2}$$

The first order valence molecular connectivity ($^1\chi^V$) when extended over all the connections or edges in the hydrogen suppressed graph for a molecule then the first order molecular connectivity for a molecule is expressed with the help of following summation term-

$$^1\chi^V = \sum_n (\delta_i^v \, . \, \delta_j^v)^{-1/2}$$

(b) Vander Walls Volume (Vw)

The Vander Walls volume is (Vw) also known as atomic volume or molecular volume. It is an atomic property which is directly related to the Vander Waals radius. It is a volume which is occupied by an individual atom or molecule. It can be calculated with the help of Vander Waals radii of atoms and the inter atomic distance and angles in the given molecule.

For spherical single atom, it is the volume of the sphere whose radius is the Vander Waals radius of the atoms.

$$Vw = \frac{4}{3} \pi r^3_w$$

Or

$$r_w = \sqrt{\frac{3}{4\pi}} . Vw$$

For a molecule it is the volume enclosed by Vander Waals surfaces. The Vander Waals volume of a molecule is always smaller than the sum of Vander Waals volume of constituent atoms. The reason behind this difference is due to the atoms that overlap when they form chemical bonds.

For determination of the Vander Waals volume of a single atom or molecule, it is necessary to divide by Avogadro's no. N_A.

The Vander Waals Volume is one of the most fundamental characteristic of the drug structure controlling the biological activity.

The shape and size of the molecule can be determined by the Vander Walls volume (Vw), which is important part of drug receptor interactions. Various biological activities of drug molecules can be decided with the help of Vander Waals Volume.

The Vw term was calculated as given by Moriguchi et. al.[12-13] and Bondii[14].

Parachor (P)

The parachor (P)[15] may be defined as the molar volume of a liquid at a temperature that its surface tension is unity. It is both an additive and constitutive property

according to Macleod[16-18]

$$\frac{\gamma^{1/4}}{D-d} = C \qquad \text{----------(1)}$$

Where γ is the surface tension, D its density and d the density of vapour at the same temperature, C is a constant. Sugden (1924)[19] modified this equation by multiplying both sides by M, the molecular weight of the liquid.

$$\frac{M.\gamma^{1/4}}{D-d} = MC = [P] \qquad \text{----------(2)}$$

The quantity [P], which was constant for liquid, was given the name parachor. As d is negligible compared to D the equation (2).

reduces to

$$\frac{M}{D} \cdot \gamma^{1/4} = [P]$$

or $$V_M \cdot \gamma^{1/4} = [P] \quad \text{----------(3)}$$

Where V_m is the molar volume of the liquid. If surface tension (γ) is unity, from equation (3), we may write

$$[P] = V_m$$

The parachor of an individual compound can be expressed as a sum of:

(1) Atomic parachors: They are contributions of each of the atoms present in the molecule.

(2) Structural Parachors. They are the contributions of the various bonds and rings present in the molecule.

Parachor(P) was calculated by the values of structural bond rings and atoms given by vogel.[20]

Indicator Parameter (I)

The indicator parameter (I_{-CH_2O}) has been adopted for the presence of $-CH_2O$ group as substituents and has given the value 1 for their presence

and zero for their absence.

Statistical analysis-

The Multiple linear regression analysis methodology was adopted to obtain the significant correlation, and developing best QSAR model, SPSS-13 programme is also used to obtain the degree of correlation (r), regression coefficient value of degree of freedom (F), standard error of estimate(s) and finally correlation equations are obtained.

QSAR Methodology-

QSAR[21] involves chemistry, biology and statistics fields for analysis. It has been widely accepted model for predicting association between molecular structure and its activity. Over the years many algorithms have been proposed and applied in QSAR studies, framework of model involves molecular structure (graph) representation, calculation of molecular descriptors (graph invariants) and multiple linear regression method is applied for analysis. Model has been validated though statistical parameters (R and R2) Quantitative structure activity relationship (QSAR) represents an attempt to correlate structural or property descriptors of compounds with activities. These physiochemical descriptors which include parameters to account for hydrophobicity, topology, electronic properties and steric effects are determined empirically or more recently by computational methods activities used in QSAR include chemical measurements and biological assay.

The physicochemical descriptors used in this paper are molecular connectivity index ($^{1}\chi^{V}$), Vander waals volume (Vw), and indicator parameter (I- CH_2O) and Anti malarial activity related with these parameters

review on methods involved in prediction analysis has enlightened that model with reduced molecular descriptor subset and outlier detector method shows better performance by improving quality of the dataset. Main application of QSAR analysis in drug discovery process. QSAR corrently widely used in drug designing[22-23].

Here QSAR is used for predicting better anti malarial drug.

Regression Methodology Method[24-30]

It determines the strength of the relationship between changing variable called independent variables and dependent variables. Changing variables here used are Randic Index ($^{1}\chi^{V}$) Vander walls volume (Vw) and Parachor (P) Indicator Parameter (I) dependent variable is antimalarial activity (IC_{50}) (nM) values.

Regression models involve the following variables:

- The unknown parameters denoted as β; this may be a scalar or a vector.
- The independent variables, X.
- The dependent variable, Y.

In various fields of application, different terminologies are used in place of dependent and independent variables.

A regression model relates Y to a function of X and β.

$$Y \approx f\ (X, \beta)$$

The approximation is usually formalized as $E(Y \mid X) = f\ (X, \beta)$. To carry out regression analysis, the form of the function f must be specified.

Multiple Regression

This is first used by Pearson, (1908) In this method we can use two or more variables. It can be represented as follows:-

$$Y = a + b_1X_1 + b_2X_2 + B_3X_{3.....} + B_tX_t + \mu$$

Where

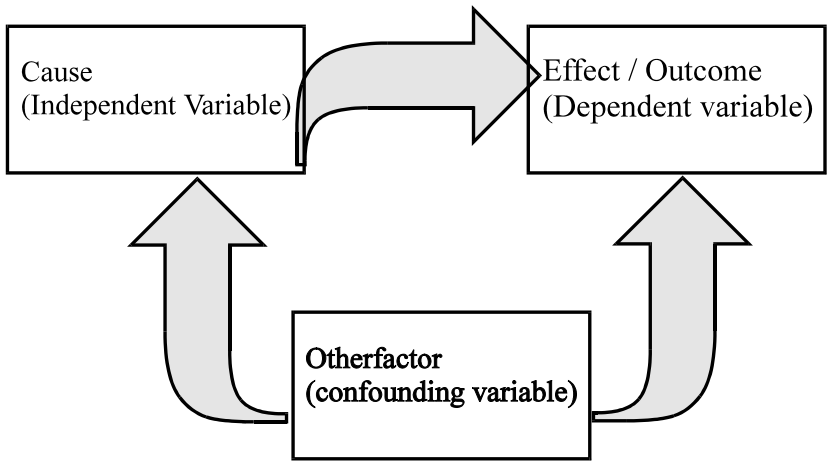
Y = the variable that we are trying to predict.

X = the variable that are using to predict Y.

a = The intercept

b = slope (regression coefficient)

μ = the regression residual.



Result and Discussion:

QSAR studies have been carried out on 18 compounds using regression analysis methodology. The structure and the activity as IC_{50}(nM) on P. falciparum are used from the data reported by Abdallah Hamze et. al.[7] Steric parameters molecular connectivity index ($^1\chi^V$), Vander Walls Volume (Vw) and Parachor (P) have been calculated. A series of correlation equations are obtained showing a moderate correlation between antimalarial activity (IC_{50}nM) and ($^1\chi^V$), Vw and Parachor (P) along with indicator parameter $I_{(-CH2O-)}$. All the compounds with different substituent Z, R_2 and R_3 are given in table I. Here (-CH2O-) group is working as indicator parameter, which is a part of substituent R_3. The presence of $I_{(-CH_2O-)}$ has value 1 and for the absence it is taken as 0.

Initially the correlation between antimalarial activity (Log IC_{50}) and molecular connectivity index ($^1\chi^V$) are obtained which yielded the equation-

Model-1

$$\text{Log } IC_{50} = -0.23\ ^1\chi^V + 1.55 \text{ ----------(1)}$$

$$n=18,\ r=.034,\ r^2=.001,\ F=.019,\ s=1.27$$

The model equation (1) show a very poor correlation.

The introduction of Indicator parameter $I_{(-CH_2O-)}$ changes the equation as follows-

Model-2

$$\text{Log } IC_{50} = -0.30\,{}^{1}\chi^{V} + .036\ I\ (-CH_2O-) + 1.618 \text{---------(2)}$$

$n=18,\ r=.036,\ r^2=.001,\ F=.010,\ S=1.31$

The value of r shows a little improvement in the correlation. Further correlation with Vw against IC_{50}(nM) gives following value-

Model-3

$$\text{Log } IC_{50} = -.083\ Vw + .914 \text{ ----------(3)}$$

$n=18,\ r=.053,\ r^2=.003,\ F=.046,\ S=1.26$

Equation (3) again show slight enhancement in the degree of correlation.

A good correlation is observed between Parachor(P) and (IC_{50}) value as follows-

Model-4

$$\text{Log } IC_{50} = -.001\ P + 1.834 \text{ ----------(4)}$$

$n=18,\ r=.071,\ r^2=.005,\ F=.082,\ S=1.26$

In all these the value of r increases but still good correlation is not obtained .On taking compund (9), (15), (16) as outlier the value of correlation improved very much and in the process following correlation equations are obtained.

Model-5

$$\text{Log } IC_{50} = -.246\ {}^{1}\chi^{V} + .405I\ (-CH_2O-) + 3.657 \text{----------(5)}$$

$n=15,\ r=.52,\ r^2=.270,\ F=2.22,\ S=.657$

Model-6

and

Log IC_{50}=-.466 Vw+2.727----------(6)

n=.5, r=.54, r^2=.54, F=5.359, S=.62

Thus correlation increases with less error. When Vw is taken with $I_{(-CH_2O-)}$

The equation (6) becomes-

Model-7

Log IC50= -.549Vw+.245 $I_{(-CH_2O-)}$+2.954 ----------(7)

n=15, r=.56, r^2=.314, F=2.75, S=.63

So the value of correlation increased (56%).

Thus indicator parameter enhanced the antimalarial activity.

Later on when $^1\chi^V$ is correlated with Vw along with $I_{(-CH_2O)}$ it gave a good correlation equation which is represented as-

Model-8

Log IC50 = -.06 $^1\chi^V$ - .443 Vw + .308 $I_{(-CH_2O)}$----------(8)

n=15, r=.564, r^2=.318, F=1.71, S=.66

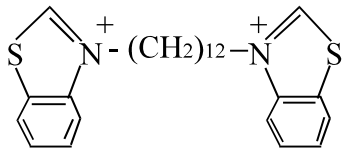
Equation (8) shows a moderate value of correlation (56%).

Thus model equation (4), (6), (7) and (8) shows a good correlation about (71%), (54%), (56%), between antimalarial activity and steric parameters along with indicator parameter $I_{.(-CH_2O-)}$

On observing all these equations it is very much clear that (eq 4,6 and 8) is much significant.

Table II represents the comparison of the calculated antimalarial activity with the respective experimental values obtained with the help of equations (4),(5), (6), (7) and (8).

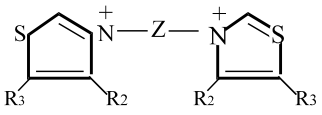
Compound no. (9), (15) and (16) are taken as outlier to improve correlation. The compound (9) have $(CH_2)_2OCH_3$ molecule as substituent R3, compound (15) has a phenyl ring as substituent R_2 and Compound (16) has



molecule as substituent, R_2 the phenyl group in compound (15) and the benzathiazolium head in compound (16) have ability of π electron donation whereas the R-O-4 group in compound (9) has some electronegative effect.

TABLE - 1

Mono-and Bis-Thiazolium Salts have Potent Antimalarial Activity.



Compound Number	Z	R_2	R_3
1	$-(CH_2)_8$	$-CH_3$	$-(CH_2)_2OH$
2	$-(CH_2)_8$	$-CH_3$	$-(CH_2)_2OCH^3$

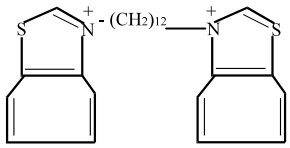
3	$-(CH_2)_{10}$	$-CH_3$	$-(CH_2)_2OH$
4	$-(CH_2)_{10}$	$-CH_3$	$-(CH_2)_2OCH_3$
5	$-(CH_2)_{12}$	$-CH_3$	-H
6	$-(CH_2)_{12}$	$-CH_3$	$-CH_3$
7	$-(CH_2)_{12}$	$-CH_3$	$-C_2H_5$
8	$-(CH_2)_{12}$	$-CH_3$	$-(CH_2)_2OH$
9	$-(CH_2)_{12}$	$-CH_3$	$-(CH_2)_2OCH_3$
10	$-(CH_2)_{12}$	$-CH_3$	$-(CH_2)_2OC_2H_5n$
11	$-(CH_2)_{12}$	$-CH_3$	$-(CH_2)_2OCH(CH_3)_2$
12	$-(CH_2)_{12}$	$-CH_3$	$-(CH_2)_2OCOCH_3$
13	$-(CH_2)_{12}$	$-CH_3$	$-(CH_2)OCH(CH_2)_2\ CO_2CH_3$
14	$-(CH_2)_{12}$	$-CH_3$	$-(CH_2)_2Cl$
15	$-(CH_2)_{12}$	$-C_6H_5$	-H-
16	-		
17	$-(CH_2)_4$-Ph | $(CH_2)_4$	$-CH_3$	$-(CH_2)_2OCH_3$
18	$-(CH_2)_{16}$	$-CH_3$	$-(CH_2)_2OCH_3$

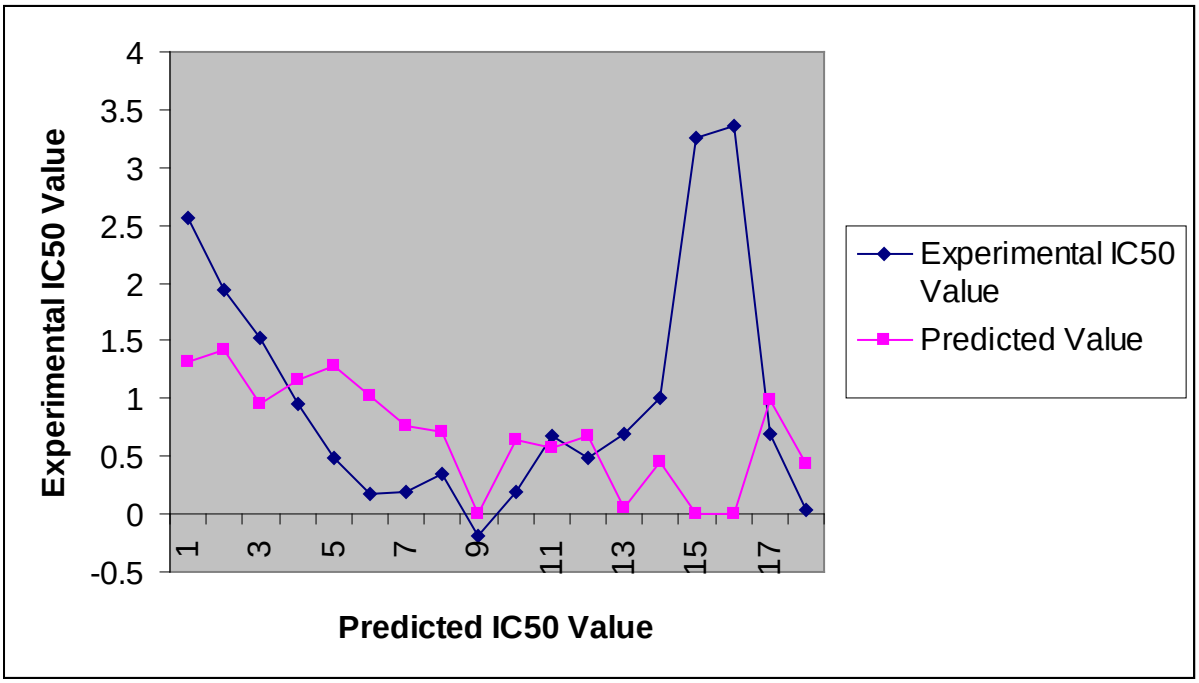
Table - II

Comp. Number	$^1\chi^V$	Vw	P	I_{CH_2O}	IC_{50} nM (P.falciparum)						
					Observed		Calculated				
					IC_{50}	log IC_{50}	eq.4	eq.5	eq.6	eq.7	eq.8
1	9.5	3.48	969	0	362	2.56	1.32	1.18	1.04	1.37	1.12
2	10.77	2.69	958.2	1	87.5	1.94	1.42	1.53	1.72	1.38	1.70

3	11.00	2.94	1047	0	34	1.53	.95	1.42	1.34	1.29	1.27
4	11.77	4.08	1104.6	1	8.9	.95	1.17	.91	.96	1.23	1.02
5	9.67	3.34	908.6	0	3.0	.48	1.28	1.24	1.12	1.43	1.17
6	10.67	3.9	986.6	0	1.5	.18	1.03	.99	.81	1.35	.86
7	11.78	3.87	1064.6	0	1.6	.20	.76	1	.82	1.27	.81
8	12.00	4.04	998	0	2.25	.35	.71	.93	.73	1.34	.72
9	11.77	4.37	1182.6	0	.65	-.19	-	-	-	-	-
10	13.93	4.68	1260.6	1	1.6	.20	.64	.64	.63	1.08	.63
11	14.22	4.97	1338.6	1	4.8	.68	.57	.51	.47	1.00	.49
12	13.76	4.5	1281	1	3.1	.49	.68	.72	.73	1.06	.72
13	16.31	5.83	1575.4	1	5.0	.70	.06	.13	0	.76	-.02
14	13.06	4.18	1087.4	0	10.0	1	.45	.87	.65	1.25	.6
15	12.55	5.15	1169.1	0	1800	3.26	-	-	-	-	-
16	11.24	4.24	949.6	0	2300	3.36	-	-	-	-	-
17	12.52	4.49	1199.5	1	5.0	.70	.99	.73	.73	1.14	.8
18	14.77	4.97	1338.2	1	1.1	.04	.44	.51	.47	1.0	.45

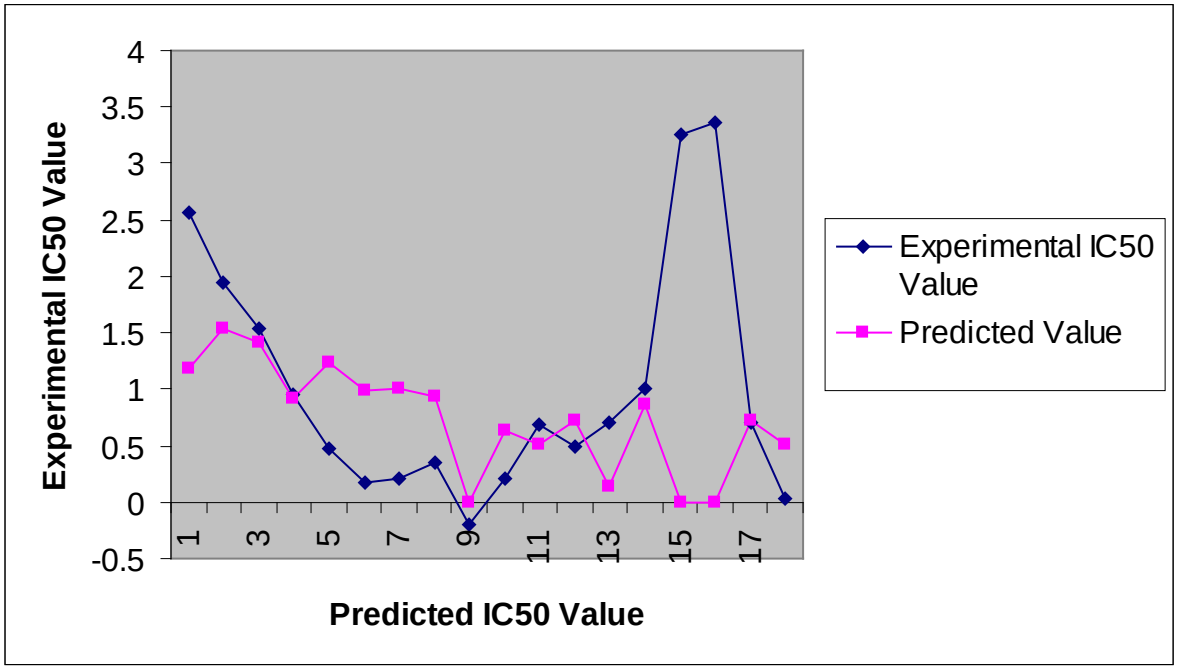
GRAPH NO.1-

REPRESENTATION SHOWS RELATION BETWEEN EXPERIMENTAL AND PREDICTED IC_{50} VALUES WITH MODEL EQUATION-4



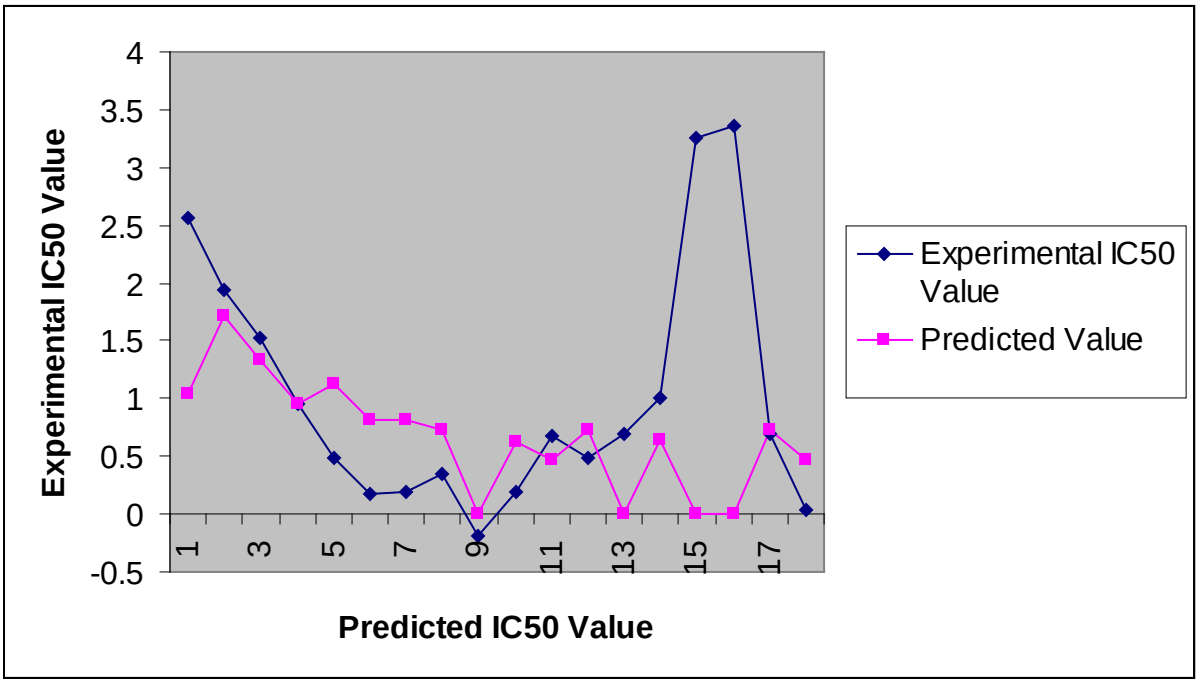
GRAPH NO.2

REPRESENTATION SHOWS RELATION BETWEEN EXPERIMENTAL AND PREDICTED IC_{50} VALUES WITH MODEL EQUATION-5



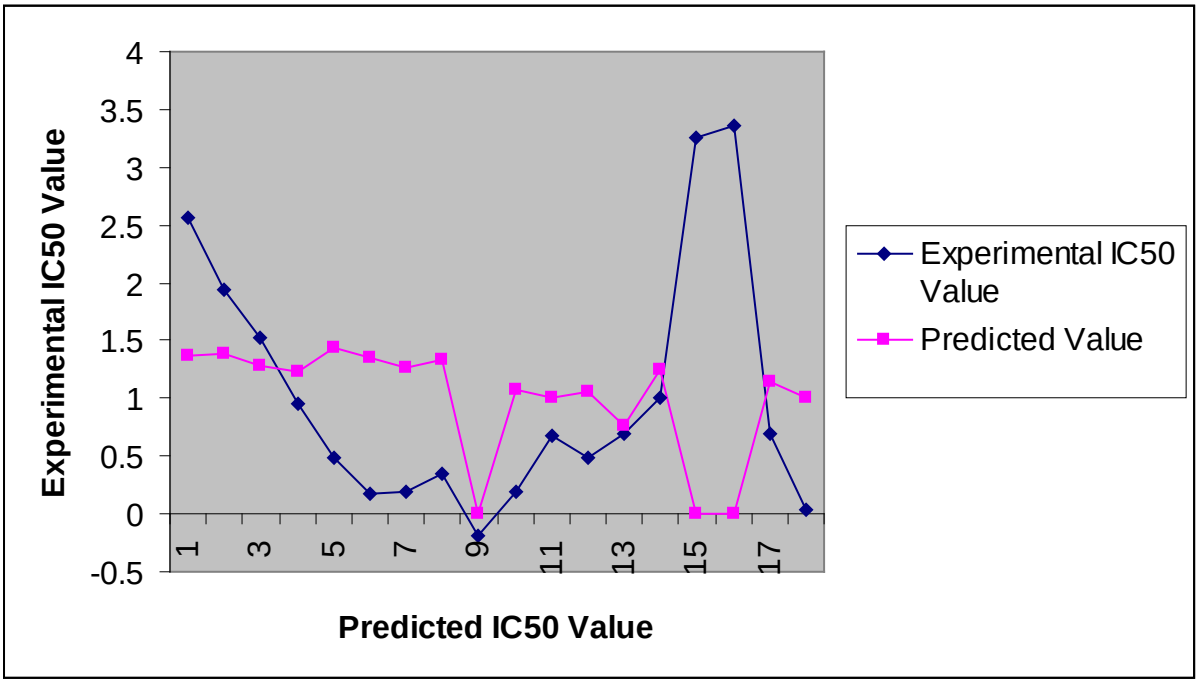
GRAPH NO.3

REPRESENTATION SHOWS RELATION BETWEEN EXPERIMENTAL AND PREDICTED IC_{50} VALUES WITH MODEL EQUATION-6



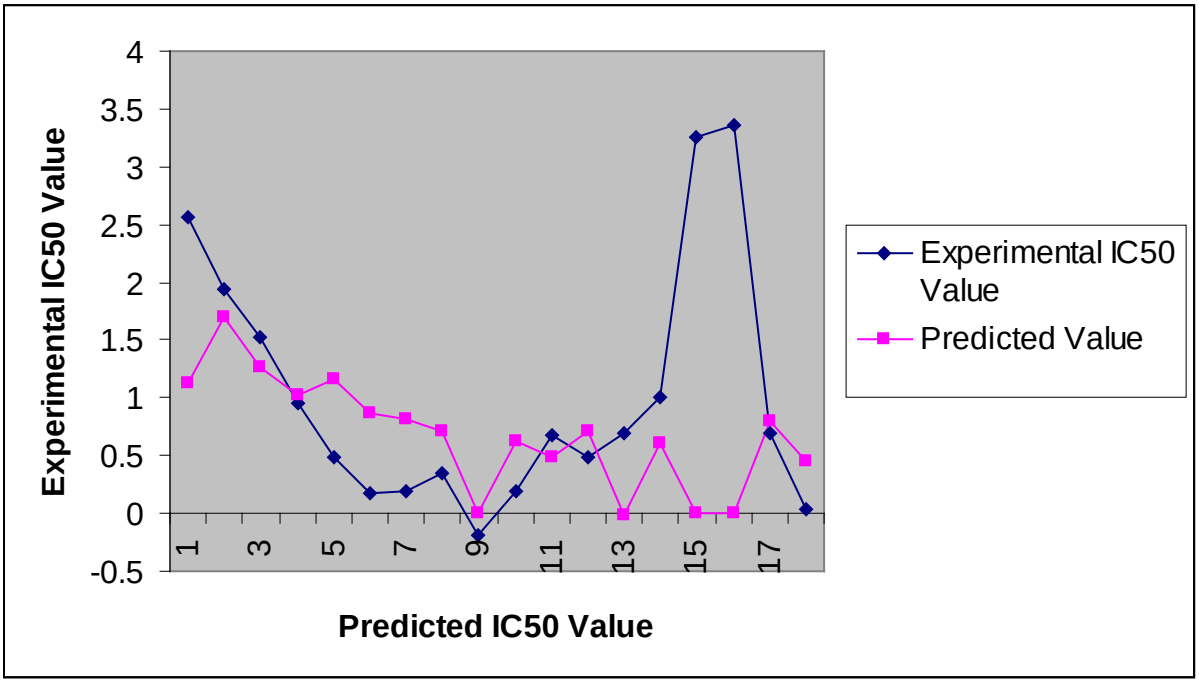
GRAPH NO.4

REPRESENTATION SHOWS RELATION BETWEEN EXPERIMENTAL AND PREDICTED IC_{50} VALUES WITH MODEL EQUATION-7



GRAPH NO.5

REPRESENTATION SHOWS RELATION BETWEEN EXPERIMENTAL AND PREDICTED IC_{50} VALUES WITH MODEL EQUATION-8



CONCLUSION-

From the above discussions and observations with the help of different regression equations it is very much clear that these equations have negative values of correlation coefficient for $^{1}\chi^{V}$ and Vw. At the same time Indicator parameter I(-CH2O-) has positive value of correlation coefficient.

Thus on increase in the value of these steric parameters will retard the antimalarial activity i.e. the molecules having smaller volume will decrease the antimalarial activity at the same time big molecules with more branching enhances the antimalarial activity whereas the presence of I(-CH_2O-) group in place of substituent (R3) groups enhances the antimalarial activity. At the same time compound (9), (15) and (16) which have π electron donation and

electronegative effect also retard the value of correlation and hence the antimalarial activity. Thus by decreasing the size of molecule and selecting substituents which provide (-CH2O-) group can synthesize a new series of Mono and Bis-Thiazolium salts with enhanced antimalarial activity which may be helpful for curing a dangerous disease and may be the drugs of future.

Supporting Information available

General materials, methods, analytical data of all compounds. The biological activity. This material is available free of charge through the internet some literature is available through CDRI INDIA.

Acknowledgement:-

My studies were supported by department of chemistry G.S.P.G. College India and CDRI India. I want to thank Dr. K.P. Dwivedi and Dr. V.K. Singh for helping in proofreading of the manuscript and Mr. Rajeev for technical support.

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