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QSAR STUDY OF TRIOXANE DERIVATIVES AS ANTIMALARIALS AGENTS

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Abstract

Quantitative Structure-Activity Relationship (QSAR) study plays an important role in rational design of drugs in early drug discovery programme. In search of novel antimalarial drug molecules for the treatment of resistant malaria, a 2D-QSAR study was performed on a novel series of 1,2,4-trioxane analogues previously synthesized and evaluated for antimalarial activity. The classical Hansch's extra-thermodynamic (Linear Free Energy Relationship Model) method based on Linear Regression Analysis was used for the QSAR study. The QSAR analysis was carried out on 21 structural analogues of trioxane taking their log of antimalarial activity (pIC_{50}) data as dependant variable and different structural and/or physicochemical descriptors as independent variable. A tri-parametric MLR-based multitarget-QSAR model was developed for predicting activity of trioxane derivatives as antimalarial agents. The best model was developed with a combination of three parameters such as RotB, HF and Et pertaining to constitutional, thermodynamic and steric properties of molecules, respectively. The developed QSAR model was found statistically significant in terms of high correlation coefficient, high F value and low SEE. The results of cross validation study indicate that the model is a valid one with low PRESS value and high q^2 value. A close agreement between observed and predicted pIC_{50} is observed (the residual values are small) which indicates good predictability of the selected model. The statistical significance and good predictive power of the QSAR model implies its usefulness for the prediction of antimalarial activity of newer 1,2,4-trioxane derivatives against resistant P. falciparum.

Keywords: *mt*-QSAR, MLR, Trioxane, Analogues, Antimalarial.

Introduction

Over the last few decades, the burden of malaria disease has increasingly become a serious threat to public health across the world. The disease continues to be one of the

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lethal infectious diseases of human with around 200-300 million clinical cases and about 0.44 million deaths every year globally (WHO 2015). Emergence of multi-drug resistant strains of *Plasmodium falciparum* has limited the use of existing antimalarial drugs in the treatment of malaria worldwide (Gogoi et al 2016). Artemisinin (ART)-based combination therapies (ACTs) (for example, artesunate+mefloquine+piperaquine) has been recommended by WHO for the treatment of multi-drug resistant *P. falciparum* malaria, but it has several limitations such as tissue toxicities, unsatisfactory pharmacokinetics, high treatment cost and limited availability of ART-derived drugs (Kashyap et al 2016, Rudrapal et al 2016a). Because of above reasons, it becomes necessary to develop novel antimalarial agents as alternative to existing ART-based drugs/therapies to treat resistant malaria with good clinical outcomes. In view of unique antimalarial efficacy of endoperoxide structural scaffold (pharmacophore) of ART (Rudrapal et al 2016), the development of trioxane based antimalarial agents may therefore be an attractive approach in search of potent antimalarial drug molecules with ready availability at affordable cost.

Quantitative Structure–Activity Relationship (QSAR) is an important chemometric tool in rational design of drugs in drug discovery programme. QSAR study provides information relating structural features and/or physicochemical properties of structurally similar drug molecules to biological activities. It attempts to establish the correlation between the experimental activity of a set of compounds and their chemical structures as defined by various molecular descriptors using various regression-based statistical methods such as Multiple Linear Regressions (MLR), and Partial Least Squares (PLS). QSAR methods are based upon two basic assumptions, first is to derive a quantitative measure from the structural properties significant to the biological activity of a compound, and the other assumption is to mathematically describe the relationship/correlation between biological activity to be optimized and the molecular property calculated from the structure (Rudrapal et al 2016b, Roy et al).

The main objectives of the QSAR study are development of predictive and robust QSAR model (regression equations), with a specified chemical domain, for prediction of activity of untested molecules, and it acts as an informative tool by extracting significant patterns in descriptors related to the measured biological activity leading to understanding of mechanisms (drug-receptor interactions) of given biological activity. The QSAR studies help to design of novel molecules with improved activity

profile and optimization of molecule in lead development in early drug discovery process. The steps involved in QSAR analysis are data set preparation, structural optimization, calculation and selection of molecular descriptor, correlation model development, and finally model evaluation and validation (Rudrapal et al 2016b). The success of a QSAR study relies deeply on how each of these steps is performed. However, good QSAR modeling depends on the correct analysis and selection of computed descriptors as independent variables used against biological activity as dependant variable in QSAR equations. Molecular descriptors are numerical representations of chemical information encoded within a molecular structure via mathematical procedure. They include constitutional, hydrophobic, electronic, steric, geometrical, topological and quantum chemical (semi-empirical) properties of molecules. Descriptors are used to study the quantitative effects of the molecular structure of bioactive compounds on their biological including inhibitory activities. In our study, two dimensional (2D)-QSAR study was performed by MLR analysis and an attempt was made to relate the chemical structure/structural properties of a series of 1,2,4-trioxane derivatives with their antimalarial activities. The two-dimensional quantitative structure-activity relationships (2D-QSAR) involve the analysis of the quantitative relationship between the biological activity of a set of compounds and their two-dimensional properties (2D molecular descriptors) using MLR method (Taxak et al 2013). After its development, a QSAR model is usually verified by employing multiple statistical validation tools giving an estimation of its statistical quality and predictivity. According to the OECD guidelines, the development of a QSAR model should comply with unambiguous algorithm strategies and the model should pass various tests model fitness, robustness and predictivity (Jain et al 2012). A reliable QSAR model once established and validated can be useful to predict the activities of molecules, and know which structural features play an important role in biological processes. The objective of our present study was to investigate the usefulness of QSAR in the prediction of antimalarial activity of 1,2,4-trioxane derivatives against *P. falciparum*.

Materials and Methods

For the QSAR study, *in-vitro* antimalarial activity data determined as IC_{50} (μgml^{-1}) were transformed to corresponding pIC_{50} (-log IC_{50}) values and used as dependent variable, while different molecular descriptor values were used as independent

variables. The 2D-QSAR analysis was carried out by multi-parametric linear regression (MLR) method using MS Excel 2007, ChemOffice 10.0 and SPSS 19.0 software run on a HP w 1907 PC with Intel Core 2 (2.00 GHz) processor and Windows 7 ultimate OS (32-bit) with 2.00 GB memory.

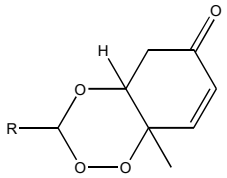
Data Set

A data set of 21 structural analogues of 1,2,4-trioxane previously synthesized and evaluated for multi-target *in-vitro* antimalarial activities was used for the QSAR study. The average values of antimalarial activities against CQ-sensitive (*3D7*) and CQ-resistant (*RKL9*) strains of *Plasmodium falciparum* (*Pf*) were calculated to carry out multi-target (*mt*)-QSAR study by MLR analysis. The data set of compounds used for the QSAR analysis is presented in Table 1.

Molecular Modeling and Descriptor Calculation

All molecular modelling studies were performed in ChemOffice 10.0 software package. The 2D structures of 21 molecules were sketched in ChemDraw Ultra 10.0 and transferred to Chem3D Ultra 10.0 to convert them into 3D structures. The Molecular Mechanics (MM2) force field included in Chem3D Ultra 10.0 was applied for preliminary geometry optimization of all the structures, and the resulting geometries were further refined by semi-empirical PM3 (Parametric Method 3) method available in MOPAC (Molecular Orbital PACkage) program of Chem3D Ultra. The geometry optimization was carried out with the root mean square (RMS) gradient value set to 0.01 kcal/mol Å and the iteration limit to 10,000. The energy minimized structure (most stable conformer with lowest energy) was used to calculate various structural and/or physicochemical properties for each molecule.

Table 1: Details of compound (1,2,4-trioxane analogues) dataset used for the QSAR analysis.



3-Substituted-8a-methyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one

Comp.	R	MF	Avg. IC_{50} (μgml^{-1})*
1	ethyl	$C_{10}H_{14}O_4$	0.027
2	propyl	$C_{11}H_{16}O_4$	0.021
3	butyl	$C_{12}H_{18}O_4$	0.14
4	but-1-formyl	$C_{12}H_{16}O_5$	3.525
5	phenyl	$C_{14}H_{14}O_4$	0.067
6	2-hydroxyphenyl	$C_{14}H_{14}O_5$	0.0055
7	3-methoxyphenyl	$C_{15}H_{16}O_4$	0.0076
8	4-chlorophenyl	$C_{14}H_{13}O_4Cl$	0.032
9	4-nitrophenyl	$C_{14}H_{13}O_6N$	0.038
10	4-tolyl	$C_{15}H_{16}O_4$	0.053
11	4-bromophenyl	$C_{14}H_{13}O_4Br$	0.058
12	4-fluorophenyl	$C_{14}H_{13}O_4F$	0.038
13	1-naphthyl	$C_{16}H_{16}O_4$	0.076
14	4-dimenthylaminophenyl	$C_{16}H_{19}O_4N$	0.016
15	1-cinnamyl	$C_{16}H_{16}O_4$	1.34
16	4-hydroxy-3-methoxyphenyl	$C_{15}H_{16}O_6$	0.0011
17	3,4-dimethoxyphenyl	$C_{16}H_{18}O_6$	0.06
18	isophthalyl	$C_{15}H_{14}O_5$	0.0465
19	furan-2-yl	$C_{12}H_{12}O_5$	2.545
20	thiophen-2-yl	$C_{12}H_{12}O_4S$	3.555
21	pyridin-4-yl	$C_{13}H_{13}NO_4$	0.00685

*Average value of activities against *Pf 3D* and *Pf RKL9* strains

Initially, 22 different molecular descriptors were selected covering a wide range of constitutional, thermodynamic, electronic, spatial, topological and semi-empirical (quantum chemical) properties of molecules. The descriptors pertaining to above structural parameters were calculated individually for all energy minimized structures. The details of descriptors calculated for the QSAR study is enlisted in Table 2.

Table 2: Details of molecular descriptors (2D) calculated for the QSAR study.

Descriptor type	**Descriptors calculated**
Constitutional	Molecular Weight (*MW*), Rotational Bonds (*RotB*), Hydrogen Bond Acceptors (*HBA*) and Hydrogen Bond Donors (*HBD*)
Thermodynamic	Heat of Formation (*HF*), Log of Partition Coefficient (*LogP*), Standard Gibbs Free Energy (*G*), Stretch Energy (*Es*), Torsional Energy (*Et*) and Total Energy (*E*)
Electronic	Dipole (*DPL*), Electronic Energy (*ElecE*) and Molecular Polar Surface Area (*MPSA*)
Steric and/or Spatial	Molar Refractivity (*MR*) and Molar Volume (*MV*)
Topological	Balaban Index (*BIndx*), Cluster Count (*ClsC*), Shape Coefficient (*ShpC*), Total Connectivity (*TCon*), Molecular Topological Index (*TIndx*) and Wiener Index (*WIndx*)
Semi-empirical (Quantum chemical)	Energy of Highest Occupied Molecular Orbital (*HOMOEnergy*) and Energy of Lowest Unoccupied Molecular Orbital (*LUMOEnergy*)

Descriptor Selection

The descriptors having the same value or almost same value or that are highly correlated with other descriptors were removed, because they do not contribute to the QSAR. Since in MLR analysis descriptors used in QSAR models must be independent, the correlation coefficient for each pair of descriptors as well as between a descriptor and the pIC_{50} value was calculated by using SPSS 19.0 software. The predictor variables with lower inter-correlation descriptors ($|r| \leq 0.50$, where r is the simple linear coefficient) were only considered (Dai et al 2010). The analysis of the Pearson's correlation matrix revealed six significant descriptors for the development of a reliable QSAR model. The calculated values of six significant descriptors and their correlation matrix are presented in Table 3 and Table 4, respectively. The

reduced set of descriptors was then treated by Forward Stepwise (FS) Variable Selection method for further reduction of non-significant descriptors. The forward selection method adds descriptors to the regression equation one at a time. The first descriptor included in the linear regression is the one that gives the highest fitness function (the highest correlation with the pIC_{50} value or minimum residual sum of squares). The descriptor selected first is forced into all further regression equations. New descriptors are progressively added to the regression, each descriptor being selected because it gives the highest fitness function when added to those already chosen (Shahlaei et al 2013). Regression equations (mono-/multi-parametric) were evaluated by performing statistical calculations to judge descriptors that contribute significantly to the antimalarial activity.

MLR Analysis and Building QSAR Model

After descriptor selection, an optimum 2D-QSAR model was constructed with three significant descriptors (*HF*, *Et* and *RotB*) by tri-parametric MLR analysis for the entire dataset of compounds (n=21), and no outliers were identified. The descriptors selected for QSAR modeling are described in Table 5.

The MLR analysis was performed using the SPSS software package. For getting reliable results, parameters were set such that the regression equation should generate number of independent variables (descriptors) 5/6 times less than that of compounds or molecules (Wei et al 2006). The tri-parametric QSAR model was built in the following form as mentioned in Equation (1)

$$y = b_1x_1 + b_2x_2 + b_3x_3 + b_o \qquad (1)$$

where, y is calculated dependent variable (antimalarial activity, pIC_{50}), the b_1 to b_3 are regression coefficients (contribution of respective descriptors, i.e., x_1 to x_3), x_1 to x_3 are independent variables (descriptors) and b_o is a regression constant or intercept).

Further, statistical calculations (using SPSS) were performed to test the significance of the developed QSAR model with the following statistical parameters: high correlation coefficient (r), high squared correlation coefficient (r^2), high adjusted squared correlation coefficient high (r^2_{adj}), high Fischer's value (F-test) and low standard error of estimate (s). Equation (1) was then used to calculate the antimalarial

activity (predicted activity) for all the compounds. The observed and predicted activity data along with residual values is given in Table 6.

Validation of QSAR model

For testing validity of the predictive power of the developed QSAR model cross-validation was performed using Leave-One-Out (*LOO*) method (Liton et al. 2014). The results of cross validation are the sum of squared prediction errors, called the predicted residual sum of squares (*PRESS*). To calculate *PRESS*, each observation (N^{th} compound) was individually eliminated from the original data set and remaining *N*-1 observations were used to develop a regression model. This model is used to predict the antimalarial activity of the compound which was not included in the model. The cross-validation cycle is repeated until each compound has been excluded and predicted exactly once. The difference between the observed y value, y_{obs}, and the predicted y, y_{calc}, is called the prediction error. The sum of the squared prediction errors is the *PRESS* value. The smaller *PRESS* is the better the predictability of the model.

For evaluation of the overall analysis, the *PRESS* is commonly expressed as a cross-validation correlation coefficient, r^2_{cv} (q^2) which is defined as follows [Equation (2)]:

$$q^2 = 1-\sum(Y_{pred}-Y_{obs})^2/\sum(Y_{obs}-Y_{mean})^2 \qquad (2)$$

where, Y_{pred}, Y_{obs} and Y_{mean} are predicted, observed and mean values of the target activity (pIC_{50}), respectively and $\sum(Y_{pred}-Y_{obs})^2$ is the predictive residual error sum of squares.

The overall *PRESS* value was calculated. It is possible to have a high r^2 and a very low r^2_{cv}. When this occurs, it implies that the fitted model is data dependent. The r^2_{cv} ranges from below zero to above one. Moreover, in many cases high values (>0.5) of r^2_{cv} and r^2_{adj} are taken as proof of the high predictive ability of QSAR models. Adjusted *r*-squared (r^2_{adj}) is an adjusted version of r^2. The adjustment seeks to remove the distortion due to a small sample size (Podunavac et al 2009).

Table 3: Calculated values of six significant descriptors.

Comp.	***MW***	***HF***	***G***	***Et***	***LUMOEnergy***	***ShpC***	***RotB***
1	198.220	-609.79	-257.77	1.6353	-0.399	0.75	1
2	212.247	-630.43	-249.35	1.6500	-0.3984	1	2
3	226.274	-651.07	-240.93	1.6584	-0.3980	0.8	3
4	240.257	-736.65	-340.45	2.5385	-0.5718	1	4
5	246.260	-455.82	-111.68	-4.5169	-0.4887	0.8	1
6	262.264	-633.13	-266.30	-3.2313	-0.5241	0.8	1
7	276.291	-620.15	-217.89	-3.3930	-0.5691	1	2
8	280.709	-483.03	-133.24	-3.3974	-0.6735	1	1
9	291.262	-628.40	-199.97	9.7689	-1.2630	0.83	2
10	260.291	-487.96	-112.89	-4.1057	-0.5589	1	1
11	325.160	-440.96	-106.99	-2.7546	-0.5589	1	1
12	264.255	-663.40	-316.99	-3.3821	-0.6964	1	1
13	296.324	-358.78	19.02	-12.361	-0.6911	1	1
14	289.333	-441.04	6.310	-2.0141	-0.5033	0.83	2
15	272.302	-379.88	-14.62	-3.8853	-0.4326	0.83	2
16	292.290	-797.46	-372.51	-1.1052	-0.6068	1	2
17	306.317	-784.48	-324.10	2.8234	-0.6082	0.83	3
18	274.275	-573.51	-212.41	0.2407	-0.5173	1	2
19	236.225	-598.16	-232.50	4.1078	-0.4941	1	1
20	252.293	-420.90	-106.52	7.5429	-0.6170	1	1
21	247.252	-402.39	-43.05	4.4045	-0.6249	0.8	1

Table 4: Pearson correlation matrix of six significant descriptors.

	pIC$_{50}$	***HF***	***G***	***Et***	***LUMO Energy***	***ShpC***	***RotB***
pIC$_{50}$	1.000						
HF	0.199	1.000					
G	0.130	0.960	1.000				
Et	0.294	-0.333	-0.333	1.000			
LUMOEnergy	0.097	0.063	0.001	-0.225	1.000		
ShpC	0.112	-0.043	-0.122	-0.179	0.033	1.000	
RotB	0.223	-0.570	-0.428	0.262	-0.051	-0.106	1.000

Table 5: Pearson correlation matrix of six significant descriptors.

Descriptor	**Description**
HF	Heat of formation (ΔH_f^o), the enthalpy change (amount of heat absorbed or evolved at 25° C (77° F) and at one atmosphere pressure when one mole of a compound is formed) when a compound is formed from its constituent elements
Et	Torsional energy, the energy it takes to overcome torsional strain (resistance to rotation about a single bond caused by steric hindrance of eclipsing interactions), or the difference in energy between eclipsed and staggered conformations
RotB	Number of rotatable bonds, the number of bonds which allow free rotation around themselves, these are defined as any single bond, not in a ring, bound to a non-terminal heavy atom

Table 6: Observed and predicted antimalarial activity with residual values

Comp.	pIC_{50} observed	pIC_{50} predicted	Residual
1	-1.569	-1.595	0.026
2	-1.678	-1.202	-0.475
3	-0.854	-0.809	-0.044
4	0.547	-0.617	1.165
5	-1.174	-1.361	0.187
6	-2.260	-1.976	-0.282
7	-2.119	-1.463	-0.656
8	-1.495	-1.401	-0.093
9	-1.420	-0.709	-0.711
10	-1.276	-1.462	0.186
11	-1.237	-1.198	-0.037
12	-1.420	-2.103	0.683
13	-1.119	-1.451	0.332
14	-1.796	-0.681	-1.113
15	0.127	-0.555	0.682
16	-2.959	-2.018	-0.940
17	-1.222	-1.261	0.038
18	-1.333	-1.064	-0.268
19	0.406	-1.402	1.807
20	0.551	-0.505	1.056
21	-2.164	-0.620	-1.534

Results and Discussion

The 2D-QSAR analysis was performed by conventional Hansch's extra-thermodynamic (Linear Free Energy Relationship) method (Hansch and Fujita 1964) to describe the antimalarial effectiveness of a set of structural analogues of trioxane. This method relates the biological activity within a homologous series of compounds to a set of theoretical molecular parameters which describe essential properties related to chemical structure of drug molecules. In Hansch's analysis, structural features of a

set of bioactive molecules are quantified in terms of different parameters that are in turn correlated to their quantified biological activity through simple linear regression analysis.

In our study, MLR *mt*-QSAR model was developed to predict the antimalarial activity of 1,2,4-trioxane derivatives. Literature reports (Khatkar et al 2014) indicate that the *mt*-QSAR models are better than one-target (*ot*) models in describing the biological activity. In *mt*-QSAR study, the biological activity is predicted using a single linear regression equation.

It is well known that there are three important components in the QSAR study: development of correlation models, validation of models and utility of developed models. Before calculation of descriptors, energy minimization of structure was carried out since this is an important requirement in QSAR analysis. The basis of energy minimization is that the drug binds to receptors in the most stable form, i.e., the minimum energy form. The selection of potential descriptors from a large set of multiple descriptors is also critical step in developing a good QSAR model. The results of correlation matrix analysis indicate that six descriptors have better contribution to the antimalarial activity than other descriptors. They are combination of constitutional (*RotB*), thermodynamic (*HF*, *G*), steric (*Et*), electronic (*LUMOEnergy*) and topological (*ShpC*) properties of molecules. *Et* can also be considered as thermodynamic descriptor and *LUMOEnergy* as semi-empirical descriptor. Table 4 shows that among six parameters *HF*, *Et* and *RotB* contribute more significantly to the activity as compared to others. Low collinearity ($r < 0.5$) is observed between these descriptors. The regression equation was therefore obtained with *HF*, *Et* and *RotB*. The QSAR model developed for the predictive study ensures a reasonable correlation of antimalarial activity (pIC_{50}) with above three selected descriptors. These independent variables allowed physical explanation of constitutional, thermodynamic and steric properties contributing to the antimalarial activity. Electronic and topological descriptors described above also have some degree of contribution to the activity.

The best *mt*-QSAR model obtained from tri-parametric MLR analysis is as follows [Equation (3)]. The±data within parentheses represents standard error of coefficient.

$$pIC_{50} = 0.004\ (\pm 0.002)\ HF + 0.060\ (\pm 0.042)\ Et + 0.501\ (\pm 0.269)\ RotB - 0.213\ (\pm 0.906) \quad (3)$$

n =21 r = 0.524 r^2 = 0.275 r^2_{adj} = 0.147

F = 2.147 SEE = 0.238 $PRESS$ = 20.77 q^2 = 0.648

MLR estimates the values of the regression coefficients by applying least square curve fitting [best fit of dependent variable (antimalarial activity) to a combination of independent variables (descriptors)] method. An MLR equation with high r (0.524) and low SEE (0.238) values is said to be statistically significant. The r and SEE values for Equation (1) indicate the statistical significance of the model. The r^2 value also indicates the quality of fit of the model. Fischer's test (F value = 2.147) which represents F-ratio between the variance of observed and calculated activity shows statistical significance of the model at 5% level of probability.

An ideal QSAR model should be robust enough to be capable of making accurate and reliable predictions of the biological activities of new compounds. Thus, QSAR models constructed from the data set should be validated with some statistical indexes in order to check the predictivity of the developed models. $PRESS$ and r^2_{cv} were also found significant for Equation (3). $PRESS$ was found lowest and r^2_{cv} (q^2) was higher indicating the predictive power of the model. The overall $PRESS$ value was 20.77. The value of q^2 (0.648) more than 0.5 indicates that the model developed is a valid one (Tuga et al 2009). The value of q^2 also shows quality of fitness of the model. Further, Table 6 shows high agreement between experimental (observed) and predicted (calculated) antimalarial values (pIC_{50}) exists (the residual values are small) indicating good predictability of the established model.

Our study reveals that there is a positive correlation between constitutional/thermodynamic/steric property and antimalarial activity of the trioxane derivatives. The antimalarial activity increases with increase in Number of Rotable Bonds (*RotB*) and Torsional Energy (*Et*) to a considerable extent. It is important to note here that good descriptors should characterize molecular properties important for molecular interactions with receptors. *RotB* and *Et* define quantified steric features of drug molecules for it's complementary fit with receptor. Heat of Formation (thermodynamic property) plays an important role in defining free energy change that takes place during drug-receptor complex formation (Silakari et al 2003). Eletronic and topological parameters like *LUMOEnergy* and Shape Coefficient (*ShpC*) parameters also plays dominant role in antimalarial activity. Electronic properties are responsible for weak non-covalent bonding between drug molecules and receptor (Silakari et al 2003). Moreover, electronic character (for example, electron density over >C=O function at C-6 of trioxane ring system) relates directly to the electron distribution of interacting molecules. Molecular topology considering size, shape and symmetry of molecules probably defines binding affinities for interactions. The difference of substituting groups or structure units of compounds leads to the variance of molecular properties that in turn modulates permeability of biological membrane and eventual interaction with biological targets (receptors) with enhanced/reduced activity. Both bulk of groups (steric) and electron density on attachment group (electronic) are largely responsible for interaction studies. Hydrophobic property (due to presence ring substituents) plays a vital role for biodistribution of drug molecules across cell membrane (Hansch and Fujita 1964).

Conclusion

Finally, it can be concluded that to develop a good QSAR analysis, multi-parametric linear regression is carried out using two or more descriptors depending on the number of observations in the data set in order to obtain a better predictive model avoiding chances of spurious correlations. From above observations it is apparent that the tri-parametric MLR-based *mt*-QSAR model developed for antimalarial activity is a valid one. This *mt*-

QSAR model developed can therefore be used for predicting the antimalarial activity of 1,2,4-trioxane derivatives. In addition, this study may be useful in rational design and optimization of trioxane analogues as newer antimalarial agents or for their development as antimalarial lead molecules.

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