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QSAR studies of cytotoxic acridine 5,7-diones: A comparative study using P-VSA descriptors and topological descriptors

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A comparative QSAR study of a set of reported acridine 5,7-diones tested for cytotoxic activity against human colon adenocarcinoma cell line has been performed using topological descriptors and a novel set of P-VSA descriptors. The QSAR study showed that successful correlations can be achieved for cytotoxic activity of acridine 5,7-diones using P-VSA descriptors ($R>0.9$, $Q^2>0.7$) and in fact the correlations obtained with P-VSA descriptors are of comparable significance to those obtained topological descriptors. The result of the QSAR study suggests the presence of hydrophobic moieties in the molecule and is conducive for the cytotoxic activity of the acridine 5,7-diones whereas increase in molecular surface area bearing a fractional negative charge is detrimental to the biological activity. Additionally, presence of heteroatoms and increase in branching in the molecule appears to have a positive influence in the cytotoxic activity of the acridine 5,7-diones.

Keywords: QSAR, anticancer, acridine 5,7-diones, P-VSA descriptors

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The success of QSAR studies depends on whether the molecular descriptors chosen are appropriate to explain biological activity. Currently there are about 3000 molecular descriptors that have been employed for QSAR studies[1]. Despite the existence of a great number of molecular descriptors they can be broadly classified into two categories, two dimensional (2D) descriptors and three dimensional (3D) descriptors. 2D descriptors are defined to be numerical properties that can be calculated from connection table representation of the molecule and therefore not dependent on conformation of the molecule *e.g.* physicochemical property descriptors, topological descriptors, *etc*[2]. 3D descriptors use the information related to the three dimensional characteristics of the molecule *e.g.* geometric descriptors. Geometric descriptors account for the 3D structural features of molecules in an explicit way such as bond distances, bond angles and torsion angles[3]. However, significant information about a QSAR can be extracted using 2D descriptors and they are advantageous over 3D descriptors since they are quite simple to calculate.

Conventional 2D descriptors presently employed in QSAR/QSPR studies can be classified as: i) size related descriptors: molecular weight, molar refractivity (CMR), molar volume and molecular surface area descriptors *etc.*; ii) hydrophobicity related descriptors: logarithm of octanol-water partition coefficient (ClogP, SlogP); iii) descriptors related to electronic effects: CMR, polarizability descriptors such as apol, bpol and partial atomic charges based on electronegativity equilibration schemes; iv) hydrogen bonding descriptors that estimate the basicity or acidity factors, *e.g.*, counts of hydrogen bond acceptors or donors; v) topological descriptors derived from the molecular graph, usually the hydrogen-depleted molecular graph. The above types of descriptors have been successfully used to derive QSAR models for the past four decades.

Recently Labute *et al.* reported a novel set of descriptors named property labeled surface area descriptors or P-VSA descriptors and successfully applied it to QSAR studies[4]. These descriptors are based upon atomic contributions to Van der Waals

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List of Abbreviations and Symbols Used:
QSAR = Quantitative structure-activity relationships. 2D and 3D = Two dimensional and three dimensional. CMR = Calculated molar refractivity. VSA = Van der Waals surface area. P-VSA = Property labeled Van der Waals surface area. MLR = Multiple linear regression. VIF = Variance inflation factor. χ = Chi.

surface area, logP (octanol/water), molar refractivity and partial charge and can be computed from the connection table information. Neither 3D calculation nor the alignment step is required for the calculation of these descriptors. These descriptors express the structural information in terms of molecular surface and they have been proved to be efficient in describing ligand-macromolecule interactions. Furthermore, even a small number of P-VSA descriptors have been shown to contain much of the information encoded by larger set of popular descriptors[5].

Acridine and its derivatives have long been a well-established class of DNA and RNA binding compounds. Several antitumor agents of clinical importance such as actinomycin-D, daunomycin and adriamycin, belong to this class of compounds. The antitumor property of acridines is mainly because of the ability of the acridine chromophore to intercalate DNA, inhibit topoisomerase[6] and telomerase enzymes[7]. Considering the relevance of acridine derivatives as potential anticancer agents, and the continuing interest in P-VSA descriptors[8], QSAR models have been proposed on the series of acridine 5,7-diones reported by Antonini *et al.*[9] using novel set of P-VSA descriptors. The selection of the above series is based on novelty of the molecules since Antonini and his co-workers have incorporated an additional ring, which mimics intramolecular hydrogen bonding in acridine carboxamides.

The success of topological descriptors in QSAR studies of anticancer acridines have been previously established[10-12]. However till date no QSAR using P-VSA descriptors on this category of compounds has been reported in literature. The above mentioned facts and considerations prompted a comparative QSAR study of acridine 5,7-diones using topological descriptors and P-VSA descriptors. Also explored in the study is the possibility of QSAR modeling using combination of topological and P-VSA descriptors.

The data set comprises of 18 compounds reported by Antonini *et al*[9]. The structure of the compounds in the series of acridine 5,7-diones alongwith their corresponding cytotoxic activity values are illustrated in **Table I**. The nanomolar concentrations of the acridine 5,7-diones required to inhibit cell growth by 50% were transformed to molar units and subsequently converted to free energy related negative logarithmic values for undertaking the QSAR study.

Methodology

All the computations for the present work were performed on a Compaq PIV workstation. The compounds in the series were built using the builder module of the software Molecular Operating Environment (MOE)[13]. The built structures were used for the calculation of P-VSA descriptors in the QuaSAR module of MOE. Topological descriptors used in the study were calculated using QSAR Software DRAGON[14].

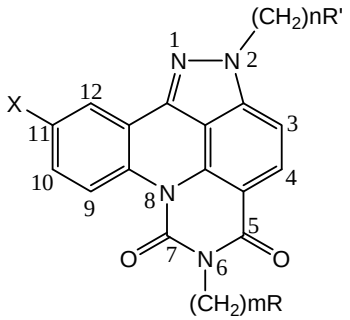
Topological indices are numerical values associated with chemical constitution for correlation of chemical structure with various physical properties, chemical reactivity or biological property. The theory, method of calculation and applications of the topological descriptors used for the present investigation have been extensively reviewed elsewhere[15-17].

Indicator variables were assigned to account for the structural variations in the acridine molecules, which could not be explained by continuous variables. The calculated topological descriptors and indicator variables are defined and summarized in **Table II**.

P-VSA descriptors are based on approximate Van der Waals surface area (VSA) calculation using connection table approximation for an atom V, along with some atomic property P[2,4,5]. Each descriptor in the series is defined to be the sum of VSAi over all atoms i for which Pi is in a specified range [a,b]. The ranges had been determined by percentile subdivision over the Maybridge database[18]. A set of 52 descriptors[5] including 10 SlogP-VSA descriptors describing the hydrophobic and hydrophilic interactions, 26 PEOE_VSA descriptors describing direct electrostatic interactions, 8 SMR_VSA descriptors describing polarizability and 7 P-VSA descriptors describing pharmacophoric features and the total molecular surface area were calculated for the study.

Statistical analysis by multiple linear regressions was performed using statistical software SYSTAT[19]. QSAR models for cytotoxic activity of acridine 5,7-diones were constructed by stepwise variable selection and best regressions were selected on the basis of the statistical quality. The quality of the regression equations was adjudged by the statistical parameters such as correlation coefficient R, squared correlation coefficient R^2, Fischer ratio values, t statistics and standard error of the estimate SEE. Guidelines for the acceptance of regressions were: the correlation coefficient R, above 0.90 or higher

Table I — Structural variations in the acridine 5,7-diones and cytotoxic activity values



Compd	R	R^1	M	n	X	IC_{50}(nm)
1	Me	$N(Me)_2$	2	2	H	37
2	Me	$N(Me)_2$	3	2	H	37
3	Me	$N(Me)_2$	2	3	H	68
4	Me	$N(Me)_2$	3	3	H	135
5	Et	$N(Et)_2$	2	2	H	29
6	Me	N-pyrrolidinyl	2	2	H	9.2
7	Me	N-piperidinyl	2	2	H	4.1
8	Me	$N(Me)_2$	2	2	OMe	11
9	Me	$N(Me)_2$	2	3	OMe	37
10	Me	N-pyrrolidinyl	2	2	OMe	0.17
11	Me	N-piperidinyl	2	2	OMe	0.040
12	Me	$N(Me)_2$	2	2	NO_2	0.98
13	Me	N-pyrrolidinyl	2	2	NO_2	1.4
14	Me	N-piperidinyl	2	2	NO_2	0.21
15	Me	$N(Me)_2$	2	2	OH	39
16	Me	$N(Me)_2$	2	3	OH	61
17	Me	$N(Me)_2$	2	2	NH_2	3.7
18	Me	N-piperidinyl	2	2	NH_2	0.17

Table II — Definitions of conventional 2D descriptors and indicator variables used for the QSAR study

Functional Families of Descriptors	Descriptor (Definition)
Topological Descriptors	Wpath (Weiner Path number) and Wpol (Weiner Polarity Number), BalabanJ (Balaban's Connectivity Topological Index), Radius, Diameter and Petitjean SC (Petitjean Shape Coefficient). Kier Kappa Shape index (1-3 path), Kier alpha modified shape index (1-3 path), S0K (Kier Symmetry Index), PHI (Kier molecular flexibility index), and BLI (Kier Benzene-likeliness index). ZM1 (first Zagreb index M1), ZM2 (Second Zagreb index M2), ZM1V (first Zagreb index M1 by valence vertex degrees) and ZM2V (Second Zagreb index M2 by valence vertex degrees). PW2, PW3, PW4 and PW5 (Randic Shape Index Path/walk 2-5). χ0, χ1, χ2, χ3, χ4 and χ5 (Connectivity Index Chi 0-5) χ0v, χ1v, χ2v, χ3v, χ4v and χ5v (Valence Connectivity Index Chi 0-5). MSD (Mean Square Distance Index), ISIZ (information index on molecular size), IAC (total information index of atomic composition), AAC (mean information index), SMTI (Schultz Molecular Topological Index), SMTIV (Schultz MTI by valence vertex degrees), GMTI (Gutman Molecular Topological Index), GMTIV (Gutman MTI by valence vertex degrees), VAR (Variation).
Indicator Variables	In (Indicator variable having value 1 if the number of methylene groups is 3 in the side chain at position 2, value 0 otherwise) Im (Indicator variable having value 1 if the number of methylene groups is 3 in the side chain at position 6, value 0 otherwise) Ic (Indicator variable having value 1 if cyclic substituents are present at R' position, value 0 otherwise).

Table III—Descriptors for quantitative models of cytotoxic activity of acridine 5,7-diones

Compd	$^5\chi$	$^5\chi_v$	MSD	PEOE_VSA_FNEG	SlogP-VSA8	SMR_VSA5	In
1	10.064	3.381	0.193	0.471611	0	124.2987	0
2	10.119	3.445	0.197	0.502357	18.86841	143.1671	0
3	10.066	3.444	0.198	0.502357	18.86841	143.1671	1
4	10.121	3.508	0.201	0.530825	37.73681	162.0355	1
5	10.297	3.55	0.197	0.476212	0	124.2987	0
6	10.513	3.742	0.196	0.459134	37.73681	162.0355	0
7	11.126	4.216	0.198	0.460874	56.60522	180.9039	0
8	10.504	3.504	0.188	0.417687	0	106.6555	0
9	10.506	3.568	0.192	0.448304	18.86841	125.5239	1
10	10.953	3.865	0.19	0.40674	37.73681	144.3923	0
11	11.566	4.339	0.191	0.410223	56.60522	163.2607	0
12	10.63	3.503	0.186	0.399511	0	106.6555	0
13	11.079	3.864	0.187	0.388696	37.73681	144.3923	0
14	11.692	4.338	0.188	0.392854	56.60522	163.2607	0
15	10.352	3.42	0.189	0.450688	0	106.6555	0
16	10.354	3.483	0.194	0.481548	18.86841	125.5239	1
17	10.352	3.449	0.189	0.444083	0	139.5527	0
18	11.414	4.284	0.194	0.435028	56.60522	196.1579	0

Table IV — Correlation matrix showing the inter-correlation of molecular descriptors used in QSAR study

	$-\log IC_{50}$	$^5\chi$	$^5\chi_v$	*MSD*	SMR_VSA5	SlogP-VSA8	PEOE_VSA_FNEG	In
$-\log IC_{50}$	1.000							
$^5\chi$	0.892	1.000						
$^5\chi_v$	0.806	0.952	1.000					
MSD	-0.515	-0.387	-0.099	1.000				
SMR_VSA5	0.438	0.567	0.759	0.423	1.000			
SlogP-VSA8	0.580	0.768	0.888	0.200	0.888	1.000		
PEOE_VSA_FNEG	-0.800	-0.729	-0.510	0.874	0.046	-0.800	1.000	
In	-0.559	-0.406	-0.342	0.443	-0.070	-0.039	0.562	1.000

(variance, $R^2 > 0.70$), minimum inter-correlation between the descriptors found in the same equation (< 0.6), Fischer ratio and t statistics values indicating 95% level of significance.

The descriptors selected for formulating statistically significant correlations in MLR calculations are given in **Table III**. The orthogonality of the descriptors in multiple regressions was established by generation of correlation matrix (**Table IV**) and calculation of Variance Inflation Factor (VIF) values (**Table V**). VIF value was calculated from $1/1\text{-}R^2$, where R^2 is the multiple correlation coefficient of one descriptor's effect regressed on the remaining molecular descriptors[20]. VIF values larger than 5 indicates that the information of the descriptors may be hidden by the correlation of the descriptors.

Table V — t- and VIF values of generated correlations

Eqn	Intercept/ Descriptor	t- Value	VIF value
1	Intercept	-3.627	-
	$^5\chi$	7.097	1.197
	In	-2.092	1.197
2	Intercept	3.925	-
	$^5\chi_v$	7.362	1.010
	MSD	-4.246	1.010
8	Intercept	12.182	-
	PEOE_VSA_FNEG	-8.635	1.002
	SMR_VSA5	4.995	1.002
9	Intercept	11.882	-
	PEOE_VSA_FNEG	-6.358	1.044
	SlogP-VSA8	3.885	1.044
10	Intercept	3.536	-
	$^5\chi_v$	-4.571	1.351
	PEOE_VSA_FNEG	4.681	1.351

Validation of the selected correlations was performed using the inhouse program VALSTAT[21]. The reliability of the QSAR correlations was tested in a cross validation method with determination of crossvalidated R^2 or Q^2. The values of Q^2 can be considered as a proof of high predictive ability of the QSAR equation. Further confirmation on predictive power of the generated equations was obtained by the calculation of standard deviation based on predicted residual sum of squares (S_{PRESS}) and standard deviation of error of prediction (SDEP) values.

QSAR modeling of the cytotoxic activity of acridine 5,7-diones was carried out using topological descriptors by multiple regression analysis employing stepwise technique. Preliminary statistical analysis of the data by inter-correlation study indicated that the topological descriptors are highly intercorrelated with each other. Hence, using covariant descriptors will produce highly unstable regressions and make it difficult to know the real contribution of the descriptors in the regression models. With due consideration to the above mentioned criterion, the only regressions allowed are those in which the variables do not intercorrelate or intercorrelate weakly (< 0.6).

Result and Discussion

The best regressions for modeling the cytotoxic activity of acridine 5,7-diones is given below.

$-\log IC_{50} = 1.632\ (\pm 0.230)\ {}^{5}\chi\ -0.592\ \pm 0.283)\ In\ -8.988\ (\pm 2.478)$ … (1)

N = 18, R = 0.918, R^2 = 0.842, $F_{(18, 2)}$ = 40.00, P = 0.000, SEE = 0.456

Q^2 = 0.789, S_{PRESS} = 0.527, SDEP = 0.481.

$-\log IC_{50} = 2.368\ (\pm 0.322)\ {}^{5}\chi_v\ -106.629\ (\pm\ 25.113)\ MSD + 20.009\ (\pm 5.098)$ … (2)

N = 18, R = 0.917, R^2 = 0.841, $F_{(18, 2)}$ = 39.59, P = 0.000, SEE = 0.458

Q^2 = 0.766, S_{PRESS} = 0.555, SDEP = 0.507.

Where N is the number of compounds, R is the correlation coefficient, R^2 is the squared correlation coefficient, SEE is the standard error of estimate, F is the Fischer ratio values between the variances of calculated and observed activities, P is the significance probability and the figures within the parentheses are the standard error values of the coefficient. Among the validation parameters given, Q^2 is the cross validation correlation coefficient; S_{PRESS} is standard deviation based on predicted residual sum of squares and SDEP is the standard deviation of error of prediction values.

The correlations explain more than 80% of the total variance in the activity and the F statistics indicate 99% significance level. The significance of the regression coefficients in the models was established by the calculation of t values (**Table V**), which is greater than the tabulated t at 95% confidence interval. **Table V** also shows the VIF values calculated for the descriptors present in the correlation 2, which indicates absence of any inter-correlation among the descriptors.

Eqn 1 is biparametric correlation comprising of the terms molecular connectivity index of order 5 (χ^5) and indicator variable In. The molecular connectivity indices are defined as follows[22]:

$$ {}^{h}\chi = \sum_{s=1} (\delta_i \delta_j .... \delta_{h+1})^{-0.5} \quad \ldots (3)$$

Where ${}^{h}\chi$ is the connectivity index of order h. The product is over the h+1 vertex degrees in the subgraph having h edges and summation is carried out over all subgraphs in the molecule.

The molecular connectivity index of order 5 represents the size of the hydrophobic fragment with five vertices and contains group contribution of all non-hydrogen atoms in the fragment. The coefficient of the descriptor bears a positive sign in the Eqn 1 which suggests that the presence of hydrophobic fragments of five non-hydrogen atoms preferentially carbon favors cytotoxic activity of acridine 5,7-diones. The Indicator variable In takes the value of one for chain length of three carbon atoms at position 2 of the molecules or shall be valued zero otherwise. The negative coefficient of the indicator variable In indicates that the presence of three carbon atom side chain at position 2 is detrimental to the cytotoxic activity of acridine 5,7-diones.

The best biparametric correlation (Eqn. 2) includes the topological descriptor valence molecular connectivity index of order 5 ($^{5}\chi_v$) and mean square distance index (MSD).

The valence connectivity indices are calculated in a similar way to molecular connectivity indices using valence vertex degrees instead of simple vertex degrees[22].

$$ {}^{h}\chi_v = \sum_{s=1} (\delta_i^v\ \delta_j^v ..... \delta^v_{h+1})^{-0.5} \quad \ldots (4)$$

with valence degree of an atom defined as follows

$\delta_i^v = Z_i^v - h_i$ for second row elements … (5)

and $\delta_i^v = (Z_i^v - h_i)/(Z_i - Z_i^v - 1)$ for rest of the atoms … (6)

where Z_i^v is the number of valence electrons, h_i is the number of hydrogen atoms bonded to the atom and Z_i is the atomic number.

The descriptor $^5\chi_v$ encodes information related to molecular branching and can account for heteroatom differentiation. The positive sign of the regression coefficient of the descriptor indicates that presence of five membered fragments with heteroatoms in the molecule favors cytotoxic activity of acridine 5,7-diones.

The topological descriptor mean square distance index is defined by[23]

$$MSD = \frac{\left[\sum_{i=1}^{A}\sum_{j=1}^{A}(D_{ij})^2\right]^{1/2}}{A.(A-1)} \quad \ldots (7)$$

Where A is the number of non-hydrogen atoms and Dij is the entry in the i^{th} row and j^{th} column of the distance matrix. MSD index decreases with increase in branching, thus negative coefficient of the descriptor in the equation suggests that increase in degree of branching is conducive to the cytotoxic activity of acridine 5,7-diones.

The predictive power of the formulated correlation was assessed by cross validation correlation coefficient Q^2 values, which was found to be 0.789 and 0.766 for correlations 1 and 2 respectively. The high Q^2 value and low S_{PRESS}, SDEP values illustrate the good predictive ability of the generated correlation.

The best regressions in case of P-VSA descriptors are given below

$-\log IC_{50}$ = -21.559 (±2.497) PEOE_VSA_FNEG + 0.020(±0.004) SMR_VSA5 + 15.088 (±1.238) … (8)

N = 18, R = 0.930, R^2 = 0.865, $F_{(15, 2)}$ = 47.892, P = 0.000, SEE = 0.422

Q^2 = 0.809, S_{PRESS} = 0.502, SDEP = 0.458.

$-\log IC_{50}$ = -18.428 (±2.977) PEOE_VSA_FNEG + 0.020 (±0.005) SlogP-VSA8 + 7.014 (±1.376) ... (9)

N = 18, R = 0.906, R^2 = 0.820, $F_{(15, 2)}$ = 34.321, P = 0.000, SEE = 0.487

Q^2 = 0.744, S_{PRESS} = 0.580, SDEP = 0.529.

Eqn 8 produces the best description for the cytotoxic activity of acridine 5,7-diones as it explains more than 85% of the variance in the activity. The F value of the equation was found to be 47.892 whereas the tabulated F value is 7.70, which suggest statistical significance of the correlation at 99% level. The significance of the regression coefficients and the absence of any serious muticollinearity between the descriptors present in the correlation were confirmed by the t and VIF values respectively (**Table V**).

Another biparametric Eqn 9 of statistical significance is derived by replacing the subdivided surface area descriptor based on molar refractivity descriptor by another subdivided surface area descriptor based on logP(o/w) in Eqn 8. The equation accounts for more than 80% of the total variance in the activity and also exhibits good predictive potential as established by the high Q^2 value.

The partial charge descriptor PEOE_VSA_FNEG represents the molecular surface bearing a fractional negative charge. The negative contribution of the descriptor in both the correlations suggests that increase in the fractional negative Van der Waals surface area decreases the cytotoxic activity of acridine 5,7-diones.

SMR_VSA5 represents the sum of Van der Waals surface area calculation of atoms with molar refractivity contribution greater than 0.56 (Ref. 2,4). The positive slope of the descriptor in Eqn 8 suggest that increase in the Van der Waals surface area of the atoms contributing to molar refractivity in the above mentioned range will cause a corresponding increase in the cytotoxic activity. Similarly, subdivided divided surface area descriptor SlogP-VSA8 which denotes the sum of Van der Waals surface area over all atoms with logP(o/w) contribution in the range 0.30, 0.40 (Ref. 2,4) has a positive coefficient in Eqn 9. The positive contribution of the descriptor indicates that increase in hydrophobicity of the molecule has a positive impact on the cytotoxic potency of acridine 5,7-diones.

Although P-VSA descriptors have been shown to be useful for physical property and receptor affinity modeling[5,8], not much information regarding steric properties of molecules could be discerned using this set of descriptors. On the other hand, topological descriptors have been shown to be efficient in describing steric phenomenon with acceptable degree of precision[17,18]. So, QSAR analysis using combined set of P-VSA and topological descriptors may yield QSAR models that provide valuable information

regarding the significance of hydrophobicity, polarizability, charge localization and steric properties for molecular properties, including receptor binding. In view of the above, an attempt was made to propose QSAR models for cytotoxic activity of acridine 5,7-diones using a combination of P-VSA descriptors and topological descriptors.

Multiple linear regression treatment of cytotoxic activity values of acridine 5,7-diones alongwith a combined set of P-VSA and topological descriptors resulted in a statistically significant biparametric correlation (Eqn. 10). The molecular descriptors found to be significant in the Eqn 10 are the topological descriptor valence connectivity index of order 5 and partial charge descriptor PEOE_VSA_FNEG. The multicollinearity of the two descriptors in Eqn 5 is represented by their respective VIF values (**Table V**), which indicate the orthogonal nature of the descriptors.

$\log IC_{50}$ = 1.671 (±0.357) $^{5}\chi_{v}$ –13.790 (±3.017) PEOE_VSA_FNEG + 8.245 (±2.332) … (10)

N =18, R = 0.924, R^2 = 0.853, $F_{(18, 2)}$ = 43.676, P = 0.000, SEE = 0.439

Q^2 = 0.781, S_{PRESS} = 0.536, SDEP = 0.489.

The correlation (Eqn 10) explains more than 85% of the variance in the activity and has a good predictive ability ($q^2 > 0.7$). Here again, the topological descriptor valence connectivity index chi-5 carries a positive coefficient, which reaffirms the conclusions drawn earlier from Eqn 2. The P-VSA descriptor based on partial charge of the molecule PEOE_VSA_FNEG represents fractional negative Van der Waals surface area of the molecule. The positive coefficient of the descriptor PEOE_VSA_FPOS which may be regarded as the measure of partial negative charge of the molecule, parallels the earlier findings that increase in molecular surface area having a fractional negative charge decreases the cytotoxic potency of acridine 5,7-diones.

Besides the validation made by the leave-one-out procedure, the generated correlations were also tested for the ability to reproduce $-\log IC_{50}$ values of the compounds in the series and a comparison was made with observed values (**Table VI**).

The results of the QSAR study justify the applicability of the P-VSA descriptors for modeling the cytotoxic activity of acridine 5,7-diones. In spite of the structural complexity of the molecules studied, successful correlations were achieved using P-VSA descriptors and topological descriptors. In fact, QSAR models for the cytotoxic activity of the acridine 5,7-diones with P-VSA descriptors and topological descriptors were comparable in their descriptive and

Table VI — Experimental ($-\log IC_{50}$) and predicted values of cytotoxic activity of acridine 5,7-diones for generated QSAR equations

Compd	$-\log IC_{50}$ Values	Eqn 1	Eqn 2	Eqn 8	Eqn 9	Eqn 10
1	7.432	7.44199	7.43529	7.41047	7.29625	7.38504
2	7.432	7.55081	7.11548	7.07178	7.07989	7.00613
3	7.166	6.73959	7.02723	7.1206	7.12869	7.05336
4	6.870	6.96555	6.88754	6.90372	7.06649	6.74948
5	7.538	7.86135	7.3906	7.28469	7.17789	7.61558
6	8.036	8.18632	7.96327	8.47998	8.36296	8.17426
7	8.387	9.26677	9.07438	8.87299	8.7715	9.12667
8	7.959	8.17785	8.31336	8.28748	8.40665	8.4174
9	7.432	7.61856	8.02525	7.98487	8.19002	8.06938
10	9.77	8.81454	8.82107	9.14056	9.24958	9.00383
11	10.4	9.73592	9.75929	9.36094	9.45753	9.65624
12	9.009	8.31137	8.31696	8.48513	8.54224	8.44146
13	8.854	9.12362	9.28701	9.77216	9.83363	9.45593
14	9.678	10.2716	10.462	9.95018	10.0609	10.2161
15	7.409	7.97488	8.04867	7.5312	7.75047	7.78591
16	7.215	7.35659	7.60296	7.22403	7.55518	7.44633
17	8.432	7.84314	7.95695	8.30518	7.73318	7.81524
18	9.77	9.61698	9.37892	9.58068	9.05842	9.29315

predictive ability. The most statistically significant correlation of the QSAR study was formulated using the P-VSA descriptors (Eqn. 6). The high predictive power of the correlation was established by the leave-one-out cross validated R^2 value and low S_{PRESS} and SDEP values. Another interesting revelation from the study is the utility of P-VSA descriptors and topological descriptors in combination for QSAR studies. Although it has been previously established that P-VSA descriptors are highly correlated to topological descriptors[4], the present study reveals that QSAR modeling is possible in some cases where the descriptors exhibit reasonable orthogonality. Moreover, the correlation comprising of the topological descriptor $^5\chi_v$ and the P-VSA descriptor PEOE_VSA_FNEG exhibited good statistical significance and predictive potential.

The results of the QSAR study suggest presence of hydrophobic moieties in the molecule is conducive for the cytotoxic activity of the acridine 5,7-diones whereas increase in molecular surface area bearing a fractional negative charge is detrimental to the biological activity. Additionally, presence of heteroatoms and increase in branching in the molecule appears to have a positive influence in the cytotoxic activity of the acridine 5,7-diones.

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