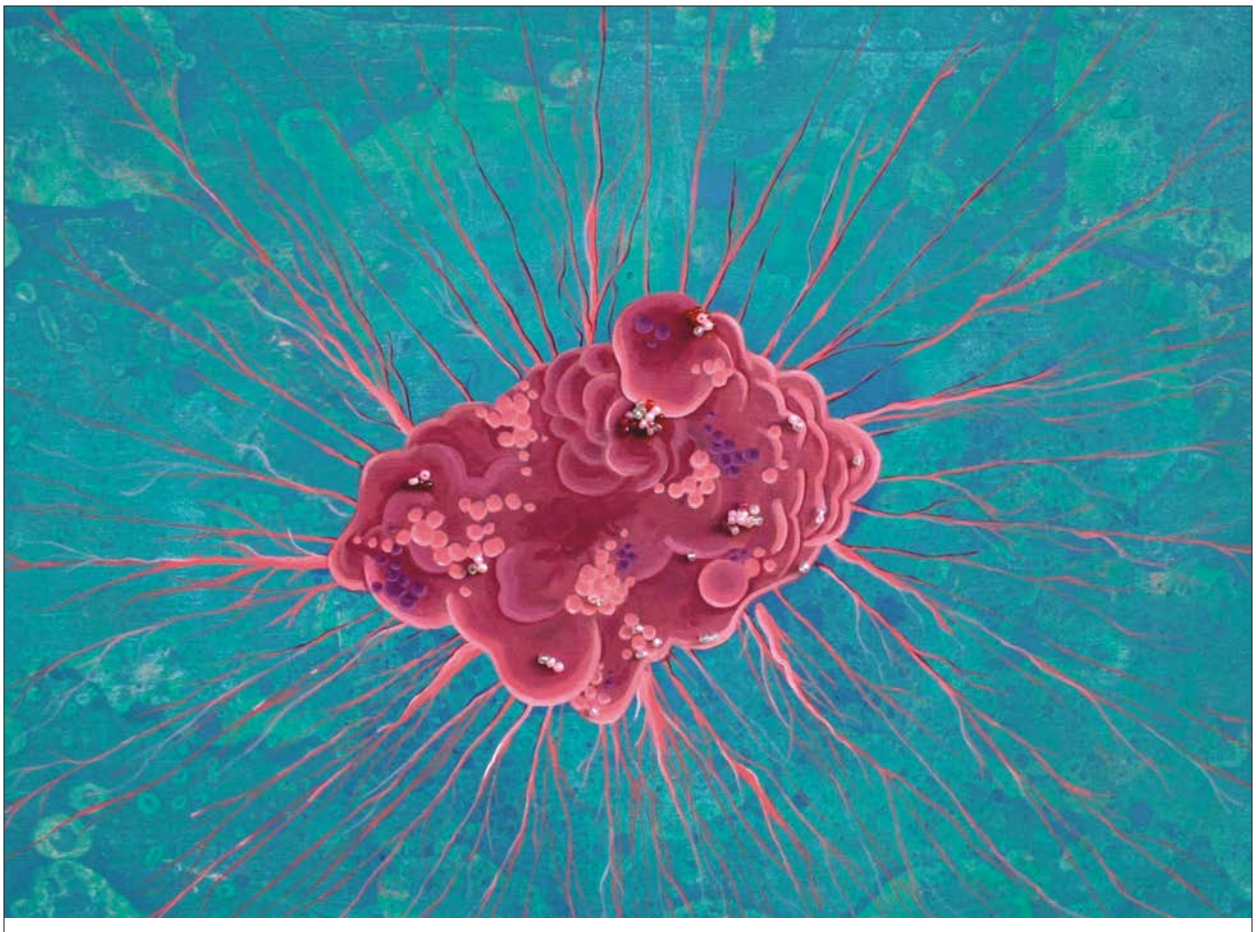

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QSAR Modeling of Some 2-methoxy Acridones: Cytotoxic Agents in Multi Drug Resistant Cells

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Abstract: In pursuit of effective anticancer molecules that can overcome resistance problems, a series of cytotoxic N^{10} substituted 2-methoxy acridone analogues were subjected to quantitative structure activity relationship analysis employing 2D molecular descriptors calculated from QSAR software Dragon. Multiple linear regression analysis of the data following a stepwise technique resulted in statistically significant triparametric models with good predictive power ($r>0.9$, $q^2>0.8$). The results of the study suggest that flexibility of substituent sidechain and four membered methylene bridges between the acridone nucleus and substituents enhances the cytotoxic potency of 2 methoxy acridones. Further, the generated QSAR models also indicate that bulky substituents and the presence of sulfur atoms are disfavored whereas heteroatoms in the molecular extremity are favored for cytotoxic activity.

Key words: 2-Methoxy acridones, QSAR, Dragon

Introduction

The development of novel therapeutic agents for the treatment of cancer is of vital importance since the currently available chemotherapeutic agents only provide palliative cure. Acridines are one of the oldest and most successful classes of bioactive agents. Acridine based chemotherapeutic agents have wide spread use as antimalarial, antibacterial and anticancer agents (Denny, 2002). The clinical utility of the acridines is attributed to their planar structure, which confers the ability to strongly bind with DNA and interfere with critical metabolic processes (Adams, 2002). A large number of acridines have been extensively studied as potential antitumor agents (Demeunynck *et al*., 2001; Demeunynck, 2004). Some noticeable examples this class, clinically used or in the clinical trials are constituted by amsacrine, acridine-4-carboxamide (DACA), imidazoacridines and 5 nitro pyrazolo [3,4,5-kl] acridines (Denny, 2002; Adams, 2002; Demeunynck *et al*., 2001; Demeunynck, 2004). Moreover, studies have shown that cytotoxic activity of acridines may also be related to its ability to inhibit the enzymes topoisomerase and telomerase ((Denny, 1997; Read *et al*., 2001). Notwithstanding the clinical success of the anticancer acridines, their utility is seriously hampered by the development of multidrug resistance in tumor cells. Therefore, there remains a need for the development of new anticancer acridines that can actually circumvent the problem of multidrug resistance. Recently, Krishnagowda *et al*. (2002) reported a series of 2-methoxy N^{10} substituted acridones as modulators of multidrug resistance (Krishnagowda *et al*., 2002). However, the molecules also showed potent

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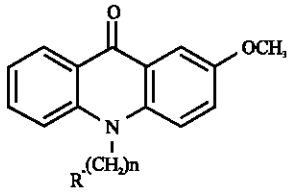
cytotoxic activity against MDR resistant human epidermoid carcinoma (KB-3-1) cells. The ability of these molecules to exhibit cytotoxic activity coupled with intrinsic anti MDR activity makes it a novel lead and the possibility of determining the structural features contributing the cytotoxic activity might help to develop cytotoxic acridones that might overcome the problem of resistance. In the view of above, a quantitative structure activity relationship analysis was proposed for the abovementioned series of compounds. A number of quantitative structure activity relationship studies involving anticancer acridines have been published (Debnath *et al*., 2003; Mazerska *et al*., 1996). However there is a lack of well-defined quantitative structure activity relationship for the group of compounds reported by Krishnagowda *et al*. (2002). It is worth mentioning that authors of the research work considered for the present study had themselves made an attempt to derive QSARs for cytotoxicity of the 2-methoxy acridones but failed to do so. The reason for their failure may be attributed to the fact that they had employed only lipophilicty parameter logP for deriving correlation with biological activity. The structural complexity of the molecules studied warrants for application of molecular descriptors that quantify molecular structure and account for both the geometric and electronic aspects of drug receptor interaction. The aforementioned fundamental and practical considerations have prompted a QSAR analysis employing a varied set of molecular descriptors and the results obtained are reported herein.

Materials and Methods

The data set consists of 19 compounds of 2 methoxy acridones reported by Krishnagowda *et al*. (2002). The activity parameters are given in terms of log (IC_{50}), where (IC_{50}) refers to the molar

Table 1: Structural Modifications in 2-methoxy acridones and its cytotoxic activity against KBChR-8-5 cell lines



Comp. No.	R	n	IC_{50} (μM)
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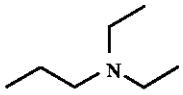
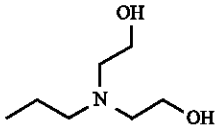
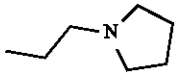
2		3	18
3		3	12.8
4		3	10.8

Table 1: Continue

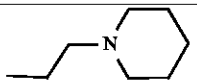
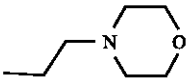
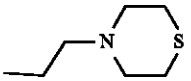
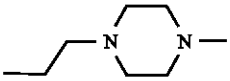
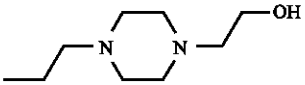
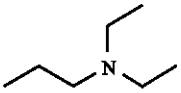
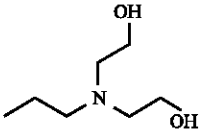
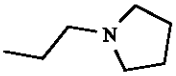
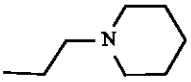
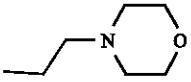
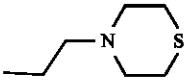
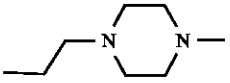
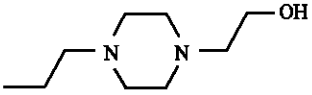
Comp. No.	R	n	IC_{50} (μM)
5		3	12.5
6		3	14.5
7		3	11
8		3	18.5
9		3	15
10		4	8
11		4	15
12		4	8
13		4	5
14		4	7
15		4	5
16		4	5
17		4	9.3
18		4	8

Table 2: Classification and description of the calculated molecular descriptors

Functional families of the descriptors	Descriptor	Definition
Constitutional descriptors	RBN	No. of rotatable bonds
	RBF	rotatable bond fraction
	NDB	No. of double bonds
	NTB	No. of triple bonds
	nAB	No. of aromatic bonds
	nH	No. of Hydrogen atoms
	nC	No. of Carbon atoms
	nN	No. of Nitrogen atoms
	nO	No. of Oxygen atoms
	nS	No. of Sulfur atoms
	nF	No. of Fluorine atoms
	nCL	No. of Chlorine atoms
	nBR	No. of Bromine atoms
	MW	Molecular weight
Topological descriptors	$\chi 0$	Connectivity index chi-0
	$\chi 1$	Connectivity index chi-1 (Randic connectivity index)
	$\chi 2$	Connectivity index chi-2
	$\chi 3$	Connectivity index chi-3
	$\chi 4$	Connectivity index chi-4
	$\chi 5$	Connectivity index chi-5
	$\chi 0v$	Valence connectivity index chi-0
	$\chi 1v$	Valence connectivity index chi-1
	$\chi 2v$	Valence connectivity index chi-2
	$\chi 3v$	Valence connectivity index chi-3
	$\chi 4v$	Valence connectivity index chi-4
	$\chi 5v$	Valence connectivity index chi-5
	ZM1	First Zagreb index M1
	ZM1V	First Zagreb index by valence vertex degrees
	ZM2	Second Zagreb index M2
	ZM2V	Second Zagreb index by valence vertex degrees
	SMTI	Schultz Molecular Topological Index (MTI)
	SMTIV	Schultz MTI by valence vertex degrees
	GMTI	Gutman Molecular Topological Index
	GMTIV	Gutman MTI by valence vertex degrees
	W	Wiener W index
	J	Balaban distance connectivity index
	MAXDN	Maximal electrotopological negative variation
	MAXDP	Maximal electrotopological positive variation
	DELS	Molecular electrotopological variation
	S0K	Kier symmetry index
	S1K	1-path Kier alpha-modified shape index
	S2K	2-path Kier alpha-modified shape index
	S3K	3-path Kier alpha-modified shape index
	PHI	Kier flexibility index
	PJI2	2D Petitjean shape index
	CSI	Eccentric connectivity index
	MR	Molecular refractivity
Molecular properties	PSA	Topological Polar surface area
	MlogP	Log of the octanol/water partition coefficient
	AM1_dipole	Dipole moment
	AM1_E	Total energy
	AM1_Eele	Electronic energy
Quantum chemical descriptors	AM1_HF	Heat of formation
	AM1_IP	Ionization potential
	AM1_LUMO	Energy(eV) of the Lowest Unoccupied Molecular Orbital
	AM1_HOMO	Energy (eV) of the Highest Occupied Molecular Orbital
Indicator variable	Iom	Indicator variable for 4 membered methylene bridge between N^{10} of acridone ring and substituent R.

Table 3: Numerical values of descriptor used in qsar models

Comp. No.	SMTIV	W	CSI	nS	AM1_HF	Iom
1	3658	478	250	0	-12.9089	0
2	5660.494	850	333	0	-21.4365	0
3	9338	1478	479	0	-9.46792	0
4	13132	1878	568	0	-99.5524	0
5	9668	1473	503	0	-6.1973	0
6	10736	1667	568	0	-15.6398	0
7	11532	1667	568	0	-44.3166	0
8	10477.78	1667	568	1	0.46658	0
9	12305	1884	634	0	7.25112	0
10	16185	2400	776	0	-45.7827	0
11	6431.827	993	383	0	-28.4597	1
12	10628	1711	547	0	-17.4417	1
13	14862	2159	640	0	-109.743	1
14	11004	1706	573	0	-13.1959	1
15	12197	1924	640	0	-19.5298	1
16	13089	1924	640	0	-48.2941	1
17	11906.78	1924	640	1	-4.84666	1
18	13942	2166	710	0	6.3228	1
19	18198	2735	858	0	-49.8529	1

concentration of the compound required to produce 50% reduction in the clonogenic survival of KBCh-8-5^R cells. The cytotoxic activity values were transformed to the molar units and subsequently converted in to negative logarithmic scale (pIC_{50}) for the study. Structure of compounds studied with their inhibitory data is summarized in Table 1.

The compounds in the series were sketched using Chem Draw module of software Chem Office, 2001 and the sketched molecules were used for the calculation of molecular descriptors using QSAR software Dragon Web Version 3.0 (2003). Quantum-chemical descriptors were additionally chosen to account for the electronic properties of the molecules, calculated with the semiempirical AM1 Hamiltonian method as implemented by the Molecular Operating Environment program (MOE). The descriptors used in the present study are summarized in Table 2.

Elimination of irrelevant descriptors prior to formulation of QSAR models is significant for obtaining meaningful and statistically significant QSARs. The descriptor pool was reduced by eliminating out the descriptors with constant and near constant values and deletion of the descriptors that are equivalent in their structural meaning (Table 3). Further reduction in the descriptor pool was established by eliminating the descriptors with non-significant correlation with-logIC_{50} values (<0.1). A subset of 36 statistically relevant variables identified from the abovementioned process was used for multiple linear regression analysis. Statistical analysis of the reduced dataset was done using statistical software SYSTAT (SYSTAT 10.2 version). Correlations between the dependent variable (biological activity) and independent variables (molecular descriptors) were found through stepwise multiple regression analysis. The best regression models were selected on the basis of multiple correlation coefficient (R), squared correlation coefficient (R^2), Standard Error of Estimate (SEE) and the Fischer ratio values (F). Multicollinearity among the descriptors in the formulated models was checked by the calculation of correlation matrix and Variance Inflation Factor values (VIF). VIF value was calculated from $1/1-R^2$, where R^2 is the multiple correlation coefficient of one descriptor's effect regressed on the remaining molecular descriptors. VIF values larger than 5 indicates that the information of the descriptors may be hidden by the correlation of the descriptors. In addition, autocorrelation study was also carried out by estimating Durbin Watson statistics (Durbin and Watson, 1950, 1951).

Results

The best multiple linear regressions for modeling the cytotoxicity of 2 methoxy acridones are summarized below.

$$BA = [4.47246\ (\pm 0.142062)] + W\ [0.000258984\ (\pm 8.45712e\text{-}005)] + nS\ [-0.163701\ (\pm 0.132079)] + Iom\ [0.216815\ (\pm 0.0869425)] \quad (1)$$

$$N = 19,\ R = 0.941,\ R^2 = 0.886,\ SEE = 0.082,\ F = 38.82,$$
$$P = 0.00,\ Q^2 = 0.836,\ Spress = 0.098,\ SDEP = 0.087.$$

$$BA = [4.38755(\pm 0.181243)] + CSI\ [0.000805584(\pm 0.000332004)] + AM1\text{-}HF\ [-0.00184883\ (\pm 0.00139764)] + Iom\ [0.217111(\pm 0.0919923)] \quad (2)$$

$$N = 19,\ R = 0.934,\ R^2 = 0.872,\ SEE = 0.087,\ F = 34.12,$$
$$P = 0.00,\ Q^2 = 0.804,\ Spress = 0.108,\ SDEP = 0.096.$$

$$BA = [4.47031\ (\pm 0.134816)] + SMTIV\ [3.88931e\text{-}005\ (\pm 1.19698e\text{-}005)] + Iom\ [0.227032\ (\pm\ 0.0819243)] + nS\ [-0.136952(\pm\ 0.126197)] \quad (3)$$

$$N = 19,\ R = 0.946,\ R^2 = 0.895658,\ SEE = 0.078675,\ F = 42.92,$$
$$P = 0.00,\ Q^2 = 0.849,\ Spress = 0.094,\ SDEP = 0.083.$$

Where N is the number of data points, R is the correlation coefficient, R^2 is squared correlation coefficient, SEE is the standard deviation and F is the Fischer ratio value at 95% significance level. The figures within the parentheses are 95% confidence intervals.

Discussion

All the models manifest good statistical quality and explain more than 80% of variance in the cytotoxic activity of the 2-methoxy acridones. The F-test value of the correlations exceeds the tabulated F-value (F = 5.42) by a large margin as desired in linear regression. The low values of standard error of estimate, a measure of the model error suggests the correctness of the generated models. Further, the obtained p-values (p>0.000) also indicate that there is indeed a significant relationship between the predictor variables and dependent variables in the selected models. No intercorrelation of significance between descriptors is observed in the models as suggested by the correlation matrix and VIF values given in Table 4 and 5, respectively.

From the model 1, it may be observed that the topological descriptor Wiener path is positively correlated with the cytotoxic activity of the 2-methoxy acridones. Wiener path index is defined as the half the sum of all entries in a distance matrix (Wiener, 1947).

$$W = \frac{1}{2}\sum_i \sum_j d_{ij}$$

Wiener path index is a global descriptor and has contributions from all the atoms of the molecule. It is inversely related to the degree of compactness of the molecule and decreases with increase in the

Table 4: Correlation matrix results for descriptors used in the models

	-logIC$_{50}$	AM1_HF	SMTIV	W	nS	CSI	Iom
-logIC$_{50}$	1.000						
AM1_HF	-0.432	1.000					
SMTIV	0.785	-0.401	1.000				
W	0.784	-0.306	0.991	1.000			
nS	-0.192	0.283	-0.012	0.050	1.000		
CSI	0.758	-0.207	0.975	0.989	0.077	1.000	
Iom	0.718	-0.110	0.322	0.361	0.018	0.349	1.00

Table 5: VIF values of descriptors and Durbin-Watson Statistics of QSAR models

Model No.	Descriptor	VIF values	DW statistics
	W	1.152	
1	nS	1.003	1.705
	Iom	1.149	
	CSI	1.186	
2	AM1_HF	1.046	1.899
	Iom	1.149	
	SMTIV	1.116	
3	nS	1.001	1.644
	Iom	1.116	

branching and cyclicity of the molecules. Thus, the positive coefficient of the descriptor Wiener Path suggest that decreased branching in the side chain and resultant increase in its flexibility is conducive for cytotoxic activity. The fragmental descriptor nS, which represent the number of sulfur atoms in the molecule, bear a negative coefficient in the model 1. Thus, it may be inferred that the presence of sulfur atom in the substituent side chain is detrimental to the cytotoxic activity of the 2-methoxy acridones. The model also highlights the contribution of the Indicator variable I_1 which stands for 4-carbon methylene bridge between N^{10} of the acridone ring and the substituent group R to the biological activity. The positive coefficient of the indicator variable in the equation demonstrates the significance of the 4-carbon bridge for the cytotoxic activity of the acridones.

The second QSAR model involves the descriptor terms CSI, AM1-HF and indicator variable I_1. CSI (Sharma *et al*., 1997) refers to eccentric connectivity index based on distance cum adjacency matrix of a molecular graph. The index takes into consideration both eccentricity and valency of each vertex involved in a molecular graph. The eccentricity connectivity index can be mathematically defined as

$$CSI = \sum_{i=1}^{n} E_{(i)} V_{(i)}$$

Where $E_{(I)}$ is the eccentricity and $V_{(I)}$ is the degree of vertex. The magnitude of the CSI increases with increase in the number of vertices and among the isomeric structures the values of the CSI decreases with increase in branching and cyclicity of the molecules. The positive coefficient of the descriptor CSI reaffirms our earlier finding that flexibility of side chain is a factor to be considered while designing potent derivatives of 2-methoxy acridones. The quantum chemical descriptor AM1-HF (Karelson *et al*., 1996) refers to heat of formation is a measure of the stability of the molecule for a given molecular weight calculated by AM1 Hamiltonian method. Heat of formation of a molecule is inversely related to its chemical's stability. As expected, the sign of its coefficient in the generated equation is negative implying that more stable the molecule is; the more will be its cytotoxic potency. Here again, the indicator variable carries a positive coefficient, which suggest that presence of 4-carbon methylene bridge is conducive for the cytotoxic potency of the acridones.

Table 6: Prediction Results obtained using QSAR models (1-3)

Compound No.	-logIC_{50} values	Model 1	Model 2	Model 3
1	4.60206	4.59294	4.61812	4.61768
2	4.744727	4.67841	4.68205	4.67574
3	4.89279	4.85077	4.77752	4.82615
4	4.966576	4.95765	5.07155	4.98353
5	4.90309	4.84808	4.79088	4.83949
6	4.838632	4.91225	4.87852	4.89374
7	4.958607	4.8975	4.92262	4.91373
8	4.732828	4.74998	4.86343	4.75084
9	4.823909	4.98137	4.90129	4.96691
10	5.09691	5.09292	5.0975	5.10091
11	4.823909	5.00154	5.02492	5.00121
12	5.09691	5.13755	5.0745	5.11286
13	5.30103	5.24038	5.34105	5.27097
14	5.154902	5.12763	5.08069	5.12093
15	5.30103	5.17237	5.13645	5.15434
16	5.30103	5.17237	5.19632	5.19353
17	5.031517	5.01437	5.14696	5.01351
18	5.09691	5.27383	5.18524	5.26063
19	5.39794	5.39747	5.38417	5.40793

Another three-descriptor model was found to be statistically appropriate to describe the cytotoxic activity of 2 methoxy acridones (Eq. 3). The model comprises of topological descriptor SMTIV, constitutional descriptors nS and indicator variable Iom. SMTIV (Schultz, 1989; Schultz *et al.,* 1994) is Schulz Molecular Topological Index weighted by valence vertex degrees and unlike Wiener index it is calculated by subjecting the valence, adjacency and distance matrices to matrix algebraic operations. The formula for calculation of the Schultz molecular topological index is given by

$$SMTI = V (D+A).$$

Where V is the vertex degree, A is the adjacency matrix and D is the distance matrix constructed using molecular graph. However, the Schultz molecular topological index used in the present study is valence weighted i.e., valence information and information regarding presence or absence of unshared electron pairs is incorporated in to its distance matrix (Karelson *et al*., 1996). The coefficient of the descriptor bears a positive sign in the model, which suggests that increased cytotoxic activity can be achieved by increasing the heteroatom content and the flexibility of the substituent side chain. Furthermore, it may also be concluded from the positive coefficient of the descriptor that presence of heteroatom in the molecular terminus will be more beneficial than the heteroatom in the intermittent region of the molecule. The constitutional descriptor nS in the model 3 represent the number of sulfur atoms in the molecule. The descriptor bears a negative coefficient indicating that replacement of terminal nitrogen atom by less electronegative sulfur atom as in the case of compound number 7 and 16 is detrimental to the activity.

All the derived regressions indicate that the flexibility of the side chain of 2-methoxy acridones is critical for their cytotoxic activity and bulky substituents in the side chain are not conducive to the cytotoxic activity of 2-methoxy acridones. The observation rules out the role of lipophilicity in the cytotoxic potency as suggested by authors of the research paper since bulky substituents increases the overall lipophilicity of the molecule. Furthermore, the finding probably suggests that side chain might be involved in some kind of interaction with the receptor and flexibility of the side chain is important for proper orientation of the side chain in the receptor space. Moreover, it becomes increasingly prominent from the obtained correlations that the heteroatom in the molecular extremity plays a role in cytotoxic mechanism. Nevertheless, not much could be discerned about the exact role of the heteroatom and the phenomenon merits additional studies.

Although, generation of QSAR models with good statistical significance is of paramount importance, the models should also exhibit good predictive ability. The predictive ability of the models was gauged by a cross-validation procedure following a leave-one-out scheme employing inhouse program VALSTAT. All the models exhibit high Q^2 and low Spress and SDEP values reflecting their good predictive potential and the best being recorded for model 3. Furthermore, a comparison was made between the experimental activity values and predicted activity values calculated using the obtained models in Table 6.

Conclusions

Showing the above discussion, it may be concluded that the QSAR analysis resulted in statistically significant quantitative models with good predictive power. The study also provides remarkable insight into the structural features contributing to the cytotoxic activity of 2 methoxy acridones. While Krishnagowda *et al*. (2002)reported that the cytotoxic activity of 2 methoxy acridones are related to the lipophilicity of the substituent side chain, present findings emphasize on the importance of flexibility of substituent sidechain and the four membered methylene bridge between the acridone nucleus and substituents for the cytotoxic potency of acridones. Further, the generated QSAR models indicate that bulky substituents are disfavored whereas heteroatoms in the molecular extremity are favored for cytotoxic activity. Moreover, the study also reveals that replacement of terminal nitrogen atom by less electronegative sulfur atom lowers the cytotoxic potency of acridone derivatives

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