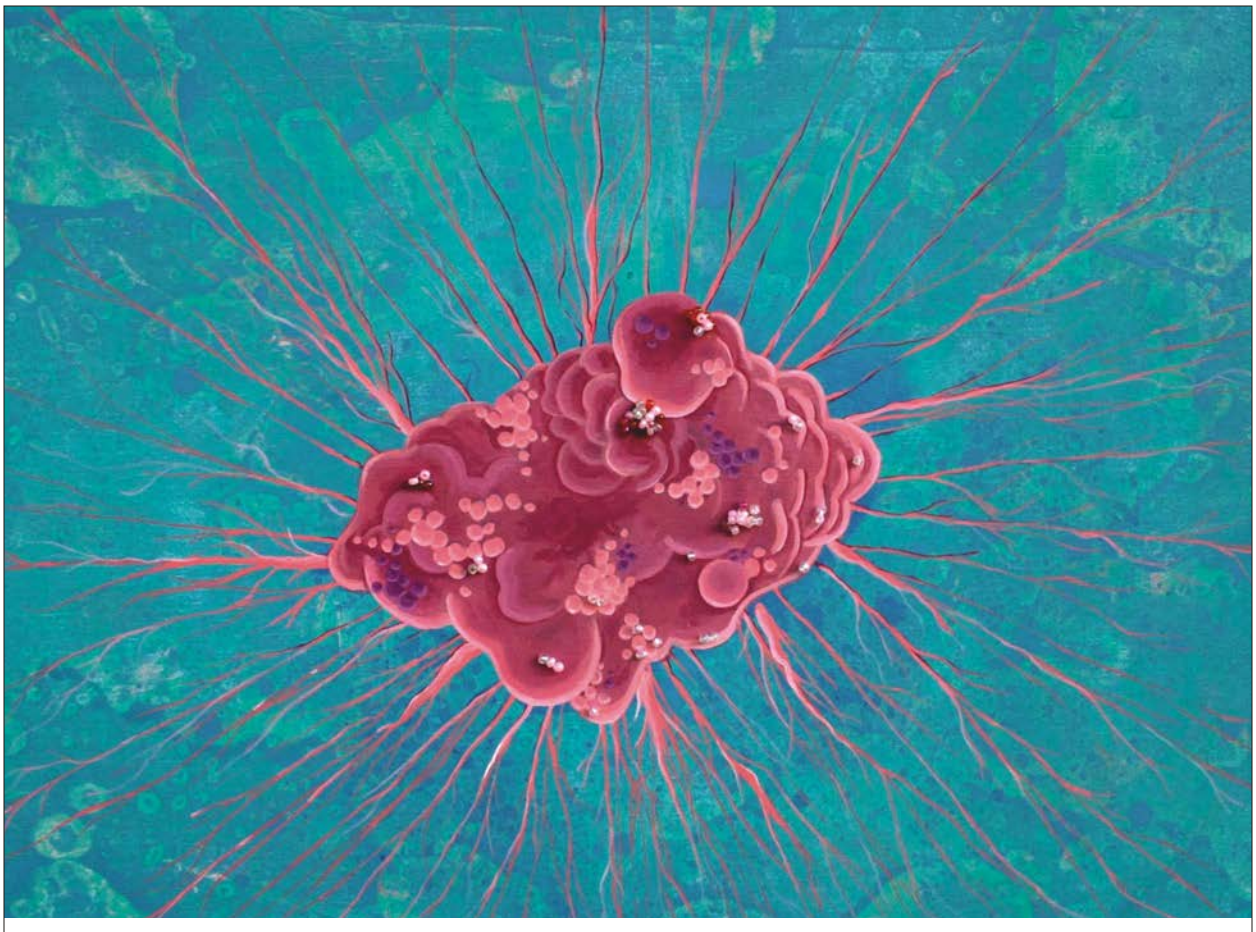

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Quantitative Structure Activity Relationship Analysis of Some Diarylsulphonylurea Derivatives as Tubulin Binding Agents

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Abstract: Quantitative Structure Activity Relationship (QSAR) studies were performed on some tubulin-binding agents. The compounds in the selected series were characterized by topological and Approximate Surface Area descriptors calculated using QuaSAR module of Molecular Operating Environment (MOE). Significant equations were derived from regression analysis shows significance of different descriptors contributing towards the cytotoxic activity. The results of the study show that cytotoxic activity of diarylsulphonylurea can be successfully explained in terms of topology of the molecule. VSA_don contribution towards the activity indicates molecules capable of hydrogen bonding will be beneficial for tubulin polymerization inhibitory activity. Another descriptor contributing beneficially to the cytotoxic action of diarylsulphonylurea is SMR_VSA5. SMR deals with polarizibility; hence increasing polarizibility will increase cytotoxic activity. Negative contribution of a_nN descriptor to the biological activity, signifies that the introduction of nitrogen should be kept minimum while designing new cytotoxic diarylsulphonylurea compounds. The negative coefficient of the descriptor Wiener Path suggests that increased branching in the side chain and resultant decrease in its flexibility is conducive for cytotoxic activity.

Key words: QSAR, tubulin binding, diarylsulphonylurea, topological descriptors

INTRODUCTION

Cancer today is still an important clinical problem with its prognosis remaining relatively poor for the majority of tumors. Surgery, radiotherapy and chemotherapy all have an important role to play in the treatment of cancer, either alone or combined with each other to define more effective strategies. Moreover, remarkable progress in biological knowledge about the exact steps necessary for cancer cells to grow, divide and spread. This has opened the doors for new prospects in chemotherapy to stop or reverse this proliferative process, especially using targeted approaches based on regulation of cancer cell cycle like tubulin dynamic inhibition. Mitotic spindle of eukaryotic cells is an attractive target for development of compounds, which are very useful in anticancer therapy (Hamel, 1996; Rowinsky and Donehower, 1996; Verwij *et al*., 1994). Microtubules show highly dynamic instability and play an essential role in mitosis (Wordenmam and Mitchison, 1994). A group of agents, known as tubulin binding agents, targeting these are very effective in the treatment of cancer. These chemicals attack microtubules through their major component, tubulin, disrupt or suppress both microtubule structure and normal functions by inhibition or promotion of microtubule assembly, resulting in cell arrest in mitosis. The cellular target of tubulin binding agents is the β-tubulin subunit of α/β-tubulin. Tubulin is a heterodimer made up of α and β-tubulin subunits that assemble to form microtubules. Multiple

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isoforms of α and β are present in vertebrate organisms. Six β-tubulin isotypes with a distinct pattern of tissue expression have been identified in human cells (Luduena, 1998). Two main groups of antimicrotubule agents are used in the treatment of cancer; microtubule destabilizers and microtubule stabilizers. Clinically active microtubule destabilizing agents such as vinca alkaloids (isolated from the plant *Catheranthus roseus*) includes chemically related compounds vinblastine and vincristine (Hamel, 1990; Wilson and Jordan, 1994) and a novel semi-synthetic derivative, vinorelbine (Fahy, 2001). Vinca alkaloids bind to tubulin at micro molar concentration (Jordan *et al*., 1986). Vinca alkaloid binding results in self-association of tubulin into non-microtubule polymers, such as spirals and para crystalline aggregates (Ericken, 1975; Na and Timasheff, 1982). Estramustine is another clinically useful synthetic microtubule destabilizing agent that induces microtubule destabilization and inhibits cell growth (Tew *et al*., 1983; Dahlof *et al*., 1993). Microtubule stabilizers include the taxanes. Taxol (paclitaxel) originally isolated from the bark of Western yew tree *Taxus brevifolia* (Wilson and Jordan, 1994) and the semi-synthetic analogue of Taxol, Taxotere (docataxel) (Van Oosterom, 1995). Taxol binds β-tubulin on the microtubule and inhibits cell proliferation by stabilizing spindle microtubules and increasing polymer mass as well as inducing microtubules bundles (Schiff and Horwitz, 1980). In recent years, a significant number of new anti microtubule compounds have been developed and a number of these are in clinical trials. In an attempt to overcome drug resistance in tumour cells, new formulations and routes of delivery of drugs are being investigated (Jordan, 2002; Kavallaris *et al*., 2001).

Diarylsulphonylureas represent a new class of antitumour agents with a broad spectrum of activity against rodent and human models *in vivo* (Mohamadi *et al*., 1992; Houghton and Houghton, 1996; Neeraj *et al*., 2006). The precise mechanism of its anticancer action has not been elucidated. Some prototypic compounds, such as sulofenur and LY295501 have been studied in clinical trials. However, the development of sulofenur was precluded by dose-limiting toxicities including methamoglobinemia and heamolytic anaemia (Talbot *et al*., 1993). Whereas, LY295501 recently showed improved side effects with a specific pattern of myelotoxicity and paucity of nonheamatological toxicity (Forouzesh *et al*., 2003).

A novel derivative of diarylsulfonylurea DW2282 which strongly suppressed the growth of human tumours *in vitro* and *in vivo* (Hwang *et al*., 1999), was recently reported. Experimental studies have proved that DW2282 causes induction of G(2)/M phase arrest and apoptosis promyelocytic leukemia (HL-60) cells (Hwang *et al*., 1999; Wenhua *et al*., 2001).

In view of further progress in the development of these inhibitors (Kim *et al*., 2004) synthesized novel series of diarylsulfonylurea derivatives structurally related to DW2282 and evaluated them for interaction with tubulin and for cytotoxicity against human cancer cell lines. In addition to good inhibitory activity against tubulin polymerization and cancer cell proliferation several compounds were also efficacious against multidrug-resistant cancer cells, which are resistant to many other known microtubule inhibitors. In the present research, a QSAR analysis is proposed on the abovementioned series of diarylsulfonyl urea derivatives to identify the intrinsic molecular properties responsible for the different degree of activities of these analogs against different tumor cell lines.

MATERIALS AND METHODS

QSAR studies were performed on a series of diarylsulphonylurea derivatives reported by Kim *et al*. (2004) at department of pharmacy, SGSITS, Indore in August 2005. The series consists of 15 compounds, which were evaluated for their inhibitory activity on three different cell lines-Human colon carcinoma (HCT116), Human non-small cell lung cancer cell lines (A 549 and NC1-H460) and against Inhibition of Tubulin Polymerization (ITP). The biological activities were expressed in terms of IC_{50} (μM) values. For correlation purposes, the values were converted to negative logarithmic scale-log IC_{50}. These compounds along with their inhibition data are presented in Table 1.

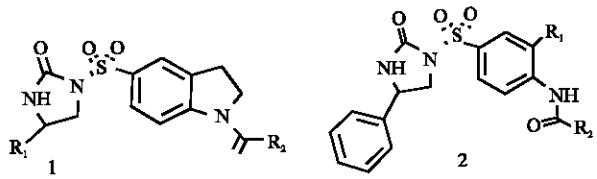

Table 1: Substituents and biological activities

S. No.	R_1	R_2	ITP	Cell line (-log IC_{50})HCT116 A549	NC1-H460	
1a	(S)-Ph	CH_2-Thiophenyl-2-yl	0.000	2.221	2.154	2.154
1b	(S)-Ph	2,6-Dichloropyridin-2-yl	-1.342	0.413	0.413	0.154
1c	(S)-Ph	Pyridin-4-yl	-1.012	1.050	0.876	1.045
1d	(S)-Ph	Thiophen-2-yl	-0.204	1.721	1.552	1.657
1e	(S)-Ph	5-nitrofuran-2-yl	-1.602	0.568	0.022	0.022
1f	(S)-Ph	CH_2NHPh	-0.544	1.259	1.096	0.823
1g	(S)-Ph	NH-Cyclohexyl	-0.301	1.301	1.187	1.096
1h	(S)-Ph	$NH(CH_2)_2$-morpholin-4-yl	-1.477	-0.0791	-0.447	0.000
1i	(S)-Ph	OC_2H_5	-0.176	1.0969	1.096	1.090
1j	(S)-Ph	$O(CH_2)_2$-4-methylpiperazine-1-yl	-1.477	0.000	0.000	0.045
1k	Thiophene-2yl	Furan-2-yl	-0.602	1.124	1.207	1.193
1l	Thiophene-2-l	4-aminophenyl	-1.021	0.522	0.744	0.602
1m	4-fluorophenyl	4-aminophenyl	-1.397	-0.041	-0.079	0.045
2a	CH_3	OC_2H_5	-0.778	0.154	1.318	1.155
2b	Cl	4-aminophenyl	-0.740	1.221	1.221	1.222

ITP: Inhibition of Tubulin Polymerisation, HCT16: Human Colon Carcinoma, A549 and NC1-H460: Human non-small cell lung cancer cell lines

There are three softwares were used for the present study.

MOE

Molecular Operating Environment provides computational tools for optimizing model, conformational searching, molecular dynamics and calculating single point energies of the molecules (MOE, 2002). The package was used for drawing of Structures, energy minimization and QSAR descriptors calculation.

SYSTAT

In the present study, SYSTAT statistical software (SYSTAT, 2003) was used for calculating the correlation coefficient as well as intercorrelation matrix between the parameters. This reduced the data set to a limited number of parameters hence, those data only were selected which were contributing to the biological activity and were statistically significant.

VALSTAT

For the present study, VALSTAT a PC based program developed by using C++ language (VALSTAT, 2004). The program has provision of sequential and stepwise multiple regression analysis with linear and parabolic relationship to generate the QSAR model. VALSTAT computes statistical parameters such as correlation coefficient (R), standard deviation (std) and F-test for statistical significance (F). Additional special statistical parameters such as cross validation-squared correlation coefficient (q^2), randomization test (Chance) and bootstrapping squared correlation coefficient (R^2_{bs}) were incorporated for selection and validation of best QSAR model (Table 4, 5).

Experimental

The molecules were sketched using builder module of MOE. The Molecule Builder constructs molecules by either adding new molecular fragments to the system (if no atoms are selected) or by

substituting fragments onto selected atoms. The Molecule Builder can also be used to change properties of selected atoms (element, hybridization, ionization, etc.) as well as to edit bond lengths, bond angles, torsion angles and stereochemistry. The sketched molecules were energy minimized using the energy minimization option in MOE. Common operation in computational chemistry is energy minimization. Energy minimization is useful for bringing a molecule to, or close to, its equilibrium conformation, which is necessary for stable molecular dynamics simulations or for determining how much energy is needed to take a molecule out of its equilibrium geometry and into another conformation. The energy-minimized structures were stored in a database. The properties of the energy-minimized structure were calculated using the QuaSAR descriptors option in the MOE database. The QuaSAR module of the MOE program provides a widely applicable set of classical molecular descriptors which can be broadly classified into two sets, 2D and internal 3D descriptors (Lin, 1997). However, the present study employs only 2D descriptors since they are simpler for calculation and interpretation. The 2D descriptors used for the present work includes traditional physicochemical properties (atom counts and bond counts, logP, mr etc.), topological descriptor (Weiner path index, Weinerpol index, Kier and Hall connectivity indices, Kappa shape indices), pharmacophore feature descriptors (e.g., hydrogen bond donor, hydrogen bond acceptor, polar, positive, negative, hydrophobic) and partial charge descriptors based on partial equalization of orbital electronegativities method. The purpose of QuaSAR-Descriptor is to calculate properties of molecules that serve as numerical descriptions or characterizations of molecules in other calculations such as QSAR, diversity analysis or combinatorial library design.

Data set generated so was subjected to statistical analysis. Statistical analysis was performed with the help of SYSTAT and VALSTAT. A large number of descriptors were generated by MOE. The descriptor set is reduced by eliminating out the descriptors with constant and near constant values. Further reduction was done by removing the descriptors that are highly degenerate and difficult to interpret. A correlation analysis was performed between inhibitory activities and remaining descriptors. Multiple regression analysis was used as a statistical method in which several parameters were used for regression. Various QSAR models were generated by employing this technique. The statistical quality of the generated models was judged by the parameters like correlation coefficient (R), squared correlation coefficient (R^2), standard deviation, Fischer's value (F) and chance statistics. The best QSAR models were selected on the basis of standard test of significance and the descriptors found in the best models are listed in Table 2. The orthogonal nature of the descriptors in the selected models is determined by the calculation of correlation matrix (Table 3).

Table 2: Contributing descriptors in QSAR models

VSA_Other	Puvsan	a_nN	VSA_don	Puvsaupol	Smruvsa 5	Puvsan 1	Weiner_path
47.19523	57.38982	3	5.682576	0.130824	229.9847	89.96893	3148
65.21675	81.89963	4	5.682576	0.136161	195.3003	120.4384	3673
47.19523	81.89963	4	5.682576	0.147927	229.7290	61.27452	3097
47.19523	61.57442	3	5.682576	0.136468	211.1163	85.78433	2814
75.13507	69.64472	4	5.682576	0.167031	195.3003	95.20557	3726
53.89478	81.89963	4	11.365150	0.123153	248.2298	98.03923	3858
51.68625	74.79245	4	11.365150	0.137284	254.3559	87.37846	3461
51.68625	57.38982	5	11.365150	0.130167	160.0139	61.27452	4289
55.94897	76.13750	3	5.682576	0.163164	160.0139	61.27452	2339
47.19523	80.62851	5	5.682576	0.112199	178.8823	61.27452	4233
58.15751	82.83705	3	5.682576	0.149487	178.0931	28.69441	2551
53.89478	107.34690	4	23.425070	0.147910	226.3703	28.69441	3111
53.89478	130.91930	4	23.425070	0.171027	245.8406	24.50981	3737
55.94897	86.18386	3	11.365150	0.162952	141.1455	61.27452	2184
53.89478	95.49958	4	29.107640	0.144392	244.6154	90.85647	3236

Table 3: Correlation matrix for the models

	A	B	C	D	E	F	G	H
A	1.000							
B	0.106	1.000						
C	0.025	-0.534	1.000					
D	0.110	0.327	0.170	1.000				
E	0.220	0.714	-0.297	0.447	1.000			
F	-0.027	0.060	0.252	-0.227	-0.080	1.000		
G	0.099	0.531	-0.286	-0.055	0.381	0.549	1.000	
H	0.885	-0.014	0.228	0.271	0.092	0.040	0.038	1.000

A: a_nN, B: PEOE_VSAN0, C: PEOE_VSAN-1, D: SMR_VSA5, E: VSA_don, F: VSA_other, G: P_VSA_POL, H: Weiner path

Table 4: Validation parameters of the QSAR Models

Models	r^2bs	Q^2	Chance	S_{PRESS}	S_{DEP}
1	0.941621	0.834610	<0.01	0.314105	0.268983
2	0.931596	0.801883	<0.01	0.356700	0.305459
3	0.916199	0.751739	<0.01	0.371003	0.317708
4	0.787467	0.656565	<0.01	0.354176	0.303298

Table 5: Observed, calculated and predicted activities of the models

	HCT116			A549			NC1-H460			ITP		
S.No.	Obs.	Cal.	Pred.	Obs.	Cal.	Pred.	Obs.	Cal.	Pred.	Obs.	Cal.	Pred.
1	2.221	1.859	1.706	2.154	1.945	1.867	2.154	1.917	1.809	0.000	-0.153	-0.201
2	0.413	0.456	0.462	0.413	0.619	0.638	0.154	0.495	0.694	-1.342	-1.018	-0.975
3	1.050	1.344	1.383	0.876	0.809	0.803	1.045	0.959	0.945	-1.012	-1.018	-1.019
4	1.721	1.803	1.827	1.552	1.842	1.932	1.657	1.889	1.985	-0.204	-0.153	-0.137
5	0.568	0.691	0.709	0.022	0.074	0.094	0.022	-0.152	-0.432	-1.602	-1.512	-1.443
6	1.259	0.957	0.886	1.096	1.222	1.261	0.823	0.886	0.897	-0.544	-0.657	-0.682
7	1.301	1.513	1.580	1.187	1.005	0.961	1.096	0.921	0.896	-0.301	-0.885	-0.935
8	-0.0791	0.080	0.234	-0.447	-0.473	-0.495	0.000	-0.019	-0.028	-1.477	-1.589	-1.638
9	1.0969	1.230	1.282	1.096	1.069	1.059	1.090	1.303	1.346	-0.176	-0.595	-0.722
10	0.000	-0.167	-0.250	0.000	0.029	0.057	0.045	0.195	0.278	-1.477	-1.308	-1.175
11	1.124	1.129	1.130	1.207	1.519	1.607	1.193	0.975	0.849	-0.602	-0.279	-0.203
12	0.522	0.716	0.765	0.744	0.737	0.736	0.602	0.416	0.359	-1.021	-0.817	-0.745
13	-0.041	-0.082	-0.137	-0.079	0.179	0.482	0.045	0.388	0.515	-1.397	-1.419	-1.439
14	0.154	0.896	0.685	1.318	0.957	0.734	1.155	1.302	1.334	-0.778	-0.523	-0.460
15	1.221	1.107	1.085	1.221	0.830	0.763	1.222	0.838	0.788	-0.740	-0.744	-0.747

Obsd: Observed, Calcd: Calculated, Pred: Predicted

RESULTS AND DISCUSSION

The best models found out through multiple regression analysis are summarized below:

Against Human Colon Carcinoma (Model 1)

BA = [2.87397(± 1.00993)] +SMR_VSA5 [0.012273(± 0.00406729)] +PEOE_VSA-0 [-0.0225953 (±0.00754446)] +Weiner path [-0.000806827(±0.000220359)]

n = 15, R = 0.952623, R^2 = 0.907491, variance = 0.0516051, std = 0.227168, F = 35.9691

Against A549, Human Non-Small Cell Lung Cancer Cells (Model 2)

BA = [6.17167(± 1.95864)] +a_nN [-0.816962(± 0.220748)] + PEOE_VSA_POL [-0.0558823 (±0.0270607)] + SMR_VSA5 [0.00552728(±0.00404263)]

n = 15, R = 0.951024, R^2 = 0.904446, variance = 0.0613664, std = 0.247722, F = 34.7063

Against NC1-h460, Human Non-Small Cell Lung Cancer Cells (Model 3)

BA = [5.86412(±1.43982)]+VSA_other[-0.0480036(±0.021159)]+a_nN [-0.76368(±0.227425)] + PEOE_VSAN-1 [0.00677969(± 0.00561285)]

n = 15, R = 0.938054, R^2 = 0.879945, variance = 0.0665622, std = 0.257997, F = 26.8748

Against Inhibition of Tubulin Polymerization (Model 4)

BA = [4.25816 (±2.17467)] +a_nN[-0.577921(± 0.261301)] +VSA_don [0.0141104(± 0.024215)] + PEOE_VSA_POL [-0.0505903(±0.0339525)]

n = 15, R = 0.877888, R^2 = 0.770688, variance = 0.0837568, std = 0.289408, F = 12.3232

In the above models, n represents number of compounds, R is correlation coefficient, R^2 is the Explained Variance (EV) calculated as squared correlation coefficient, std is standard deviation, values given in the parentheses are standard error of the coefficients. The model showed overall significance level better than 99%, as the calculated F-value exceeds the tabulated ($F_{3,11}$= 6.219) value.

The squared correlation coefficient (or coefficient of multiple determination) r^2 is a relative measure of quality of fit by the regression equation. Correspondingly, it represents the part of variation in the observed data that is explained by the regression. The correlation coefficient values close to 1.0 represent the better fit of the regression. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High value of the F-test indicates that the model is statistically significant. Standard deviation is measured by the error mean square, which expresses the variation of the residuals or the variation about the regression line. Thus standard deviation is an absolute measure of quality of fit and should have a low value for the regression to be significant.

Models obtained demonstrate that VSA_don, PEOE_VSAN-1, SMR_VSA5, a_nN, PEOE _VSA-0, PEOE_VSA_POL, Weiner path and VSA_other are contributing towards the biological activity. Among these, VSA_don, PEOE_VSA-1, SMR_VSA5 are beneficial for tubulin binding and a_nN, PEOE_VSA-0, PEOE_VSA_POL, VSA_other and Weiner path are detrimental towards the antimitotic activity.

The individual models along with their parameters are explained below:

Against Human Colon Carcinoma (Model 1)

BA = [2.87397(±1.00993)] +SMR_VSA5 [0.012273(± 0.00406729)] +PEOE_VSA-0 [-0.0225953 (± 0.00754446)] +Weiner path [-0.000806827(±0.000220359)]

n = 15, R = 0.952623, R^2 = 0.907491, variance = 0.0516051, std = 0.227168, F = 35.9691

According to the model generated taking Human colon carcinoma as dependent variable, SMR_VSA5 contributes positively whereas PEOE_VSA-0 and Weiner path has negative contributions towards the cytotoxic activity against colon carcinoma cells.

Weiner path descriptor is contributing towards the activity in the first model. Wiener path index is defined as the half the sum of all entries in a distance matrix.

$$W = \tfrac{1}{2}\sum_{i}\sum_{j} d_{ij}$$

Wiener path index is a global descriptor and has contributions from all the atoms of the molecule. The usual explanation is to why W is so successful in QSAR and QSPR studies is based on the fact that W represents a rough measure of the van der Waals molecular surface area. Consequently in the case of non-polar molecules W is proportional to the intermolecular forces and is thus related to a number of physico-chemical properties of the respective compounds (boiling point, heat of formation, chromatographic retention time, surface tension, vapor pressure, partition coefficients, etc.). It is inversely related to the degree of compactness of the molecule and decreases with increase in the branching and cyclicity of the molecules. Thus, the negative coefficient of the descriptor Wiener path against colon carcinoma cells in the Model suggest increased branching in the side chain or insertion of cyclic structures and resultant decrease in its flexibility is conducive for cytotoxic activity.

SMR_VSA, PEOE_VSA and Slog P_VSA are P_VSA type of descriptors. P_VSA are a set of 32 descriptors derived by summing the approximate exposed surface area for each according to the classification based on Molar refractivity, partial charge and LogP respectively. The Subdivided Surface Areas are descriptors based on an approximate accessible van der Waals surface area calculation for each atom, v_i along with some other atomic property p_i. The v_i is calculated using a connection table approximation. Each descriptor in a series is defined to be the sum of the v_i over all atoms, i such that p_i is in a specified range (a, b).

Suppose that for each atom i in a molecule numeric property P_i is given. The fundamental idea is to create a descriptor for a specific range [u,v] of the property values P; this descriptor will be the sum of the atomic VSA contributions of each atom i with P_i in [u,v). More precisely, the quantity P_VSA(u,v) is defined as;

$$P\_VSA(u,v) = \Sigma V_i\, \delta(P_i\, \varepsilon(u,v))$$

Where, V_i is the atomic contribution of atom i to the VSA of the molecule. A set of n descriptors associated with the property P is as follows:

$$P\_VSA_k = \Sigma Vi\, \delta(P_i\, \varepsilon\, [a_{k-1}, a_k])\ k = 1,2\ldots n$$

Where, $a_0 < a_k < a_n$ are interval boundaries such that $[a_0, a_n]$ bound all values of P_i in any molecule. Each VSA-type descriptor can be characterized as the amount of surface area with P in a certain range. If, for a given set of descriptors, the interval ranges span all values, then the sum of the descriptors will be the VSA of the molecule. Therefore, the VSA-type descriptors correspond to a subdivision of the molecular surface area.

Slog P_VSA intended to capture hydrophobic and hydrophilic effects either in the receptor or on the way to the receptor.

SMR_VSA intended to capture polarizability;

PEOE_VSA intended to capture direct electrostatic interactions.

PEOE_VSA descriptors describe direct electrostatic interaction calculated by the Partial Equalization of Orbital Electronegativities. The method is used for calculating partial atomic charges in which charge is transferred between bonded atoms until equilibrium. The amount of charge transfer dqij between atoms i and j when Xi >Xj

$$dqij=(1/2^k)\,(Xi - Xj)/\, Xj^+$$

Where:

Xj^+ = Electronegativity of positive ion of atom,

j, Xi = Electronegativity of atom i (depending on partial charge),

k = The iteration number of the algorithm.

PEOE charge depends only on the connectivity of the input structures: elements, formal charge and bond orders.

In the PEOE_VSA descriptors calculated for the present study, qi denotes the partial charge of the atom i as defined above and Vi the van der Waals surface area of atom i (as calculated by connection table approximation).

PEOE_VSA-0 is negatively correlated with the biological activity in Model 1 indicating sum of van der Waals surface area should be minimum when partial atomic charge of substituents is in the range (-0.05, 0.00).

Another descriptor contributing to the cytotoxic action of diarylsulphonylurea is SMR_VSA5. It is subdivided surface area descriptor, one that is based on approximate van der Waals surface area calculation for each atom, Vi along with atomic property Pi. S denotes subdivided surface area and MR, Molar refractivity. SMR_VSA5 has positive correlation with the activity as can be seen in the Models 1 and 2 and signifies the sum of Vi such that Ri is in the range (0.44, 0.485) where Ri denotes contribution to molar refractivity for atom i, indicating contribution of substituents having MR values in this range to the VDW area will be favorable, deriving conclusion that molar refractivity is important contributor for tubulin binding activity. As seen above SMR deals with polarizibility, hence increasing polarizibility will increase cytotoxic activity.

Against A549 (Model 2)

BA = [6.17167(±1.95864)] + a_nN [-0.816962(±0.220748)] + PEOE_VSA_POL [-0.0558823 (± 0.0270607)] + SMR_VSA5 [0.00552728(±0.00404263)]

n = 15, R = 0.951024, R^2 = 0.904446, variance = 0.0613664, std = 0.247722, F = 34.7063

Generation of model against human non-small cell lung cancer cells illustrates contribution of a_nN, PEOE_VSA_POL and SMR_VSA5 towards cytotoxiciy.

a_nN is an atom count descriptor, representing the number of nitrogen atoms in the molecule. Negative contribution of this descriptor to the biological activity, signifies that the number of nitrogen atoms should be minimum, while designing new cytotoxic compounds.

PEOE_VSA_POL will be detrimental for activity as can be observed from the regression model, which illustrates negative correlation with the biological activity. PEOE_VSA_POL represents total polar van der Waals surface area of atoms in the molecule. This is the sum of van der Waals surface area such that qi>0.2. This signifies total polar van der Waals surface area should be minimum when qi is more than 0.2.

Another descriptor is SMR_VSA5 that has positive contribution towards human non-small cell lung cancer cell line, the parameter has been explained above in the model 1 and signifying increasing polarizibility will increase cytotoxic activity.

Against NC1-H460 (Model 3)

BA = [5.86412(±1.43982)] + VSA_other [-0.0480036 (±0.021159)] + a_nN [-0.76368 (±0.227425)] + PEOE_VSAN-1 [0.00677969(± 0.00561285)]

n = 15, R = 0.938054, R^2 = 0.879945, variance = 0.0665622, std = 0.257997, F = 26.8748

Regression model obtained against non-small cell lung cancer line indicates VSA_other, a_nN and PEOE_VSAN-1 contributes to cytotoxic activity.

PEOE_VSAN-1 contributes positively towards the activity signifying sum of van der Waals surface area should be maximum when partial atomic charge in the range (-0.10, 0.05). Hence the substituents having increased V when qi is in the range so defined will be favorable for the activity or increased electrostatic interaction with the enzyme.

a_nN is detrimental towards the activity that has been explained in Model 2 also that increasing nitrogen atoms in the ring will decrease activity towards.

VSA_other is Pharmacophore atom type descriptors. These descriptors consider only the heavy atoms of a molecule and assign a type to each atom (using a rule-based system). That is, hydrogens are suppressed during the calculation. The feature set is donor, acceptor, polar (both donor And acceptor), positive (base), negative (acid), hydrophobic and other assignments may take into account.

VSA_other indicates the van der Waals surface area of atoms other than acidic, basic, hydrophobic, H-bond donors, H-bond acceptors and polar atoms. Negative contribution in the Model 3 infers sum of van der Waals surface area of atoms other than those described above will be inimical for the activity.

Against Inhibition of Tubulin Polymerization (Model 4)

BA = [4.25816(±2.17467)] + a_nN [-0.577921 (± 0.261301)] + VSA_don [0.0141104 (± 0.024215)] + PEOE _VSA_POL [-0.0505903(±0.0339525)]

n = 15, R = 0.877888, R^2 = 0.770688, variance = 0.0837568, std = 0.289408, F = 12.3232

a_nN, VSA_don and PEOE _VSA_POL are obtained in the equation elucidating their relation with tubulin binding activity and inhibition of tubulin polymerization.

VSA_don is a pharmacophore feature descriptor. These types of descriptors consider only the heavy atom of a molecule and assign a type to each atom. VSA_don represents an approximation to the sum of van der Waals surface area of pure hydrogen bond donors. Positive correlation towards the inhibition of tubulin polymerization in Model 4 suggests increase in VDW surface area of H-bond donors or H-bond donor substituents attachment will be beneficial for tubulin polymerization inhibitory activity.

a_nN and PEOE_VSA_POL has been explained in above models (Model 2) representing number of nitrogen atoms and total polar van der Waals surface area should be minimum to have better tubulin binding activity.

CONCLUSIONS

Diarylsulphonylureas represent a new class of antitumor agents with a broad spectrum of activity against rodent and human models *in vivo*. Some prototypic compounds, such as sulofenur and LY295501 have been studied in clinical trials. Observing all the features of sulphonylurea, it is elucidated that more effective compounds can be synthesized. Correlations between the dependent variable (biological activity) and independent variables (physicochemical parameters) were found through multiple regression analysis. VSA_don, PEOE_VSAN-1, SMR_VSA5, a_nN, PEOE _VSA-0, PEOE _VSA_POL and VSA_other are contributing towards the biological activity. VSA_don has positive correlation in the models suggests increase in VDW surface area of H-bond donors will be beneficial for the activity. VSA_other negative correlation in the models infers sum of van der Waals surface area of atoms other than acidic, basic, hydrophobic, H-bond donors, H-bond acceptors and polar atoms will be detrimental for the activity. PEOE_VSA-0 is negatively correlated with the biological activity indicating sum of van der Waals surface area should be minimum when partial atomic charge in the range (-0.05, 0.00). PEOE_VSAN-1 contributes positively towards the activity suggesting sum of van der Waals surface area should be maximum when partial atomic charge in the range (-0.10, 0.05). PEOE_VSA_POL will be detrimental for cytotoxic activity due to negative coefficient, it is sum of van der Waals surface area such that qi>0.2. This signifies total polar Van der Waals surface area should be minimum when qi is greater than 0.2. SMR_VSA5 has positive correlation with the activity and signifies the sum of Vi such that Ri is in the range (0.44, 0.485) where Ri denotes contribution to molar refractivity for atom i, indicating substituents having MR values of the atoms with partial charge in this range will be favorable, deriving conclusion that molar refractivity is an important contributor. a_nN represents the number of nitrogen atoms, having negative contribution in the models, signifying the number of nitrogen atoms should be minimum. The negative coefficient of the descriptor Wiener Path suggests that increased branching in the side chain and resultant decrease in its flexibility is conducive for cytotoxic activity.

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