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QSAR/QSPR Modeling of 2-Phenylindoles as Anticancer Agents

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Abstract

In a continuing effort to develop novel 2-phenylindoles endowed with better pharmacological profiles. A series of 2-phenylindoles derivatives were designed on the basis of previously developed QSARs.These drugs offer novel mechanisms of action and expanded spectrums of activity over traditional treatment option. However, with these new agents comes the need for increased awareness of the potential interactions and toxicities associated with these drugs. The best models for different cancer cell were first validated by leave-one-out cross validation procedure. It was revealed that topological, physicochemical and indicator parameters were found to have overall significant correlationship with anticancer activity and these studies provide an insight to design new molecules.

Key-Words: QSAR, Hansch Approach, Anticancer Activity

Introduction

Tubulins consist of a small group of globular proteins with approximate molecular weight of 55 kilodaltons. The most common members of the tubulin family are α-tubulin and β-tubulin. Microtubules are assembled as dimers of α- and β-tubulin subunits**.[1]** Microtubule is the generic name of a class of subcellular components that occur in a wide variety of eukaryotic cells. Such structures are straight cylinders, 240 ± 20 Å in diameter, with a hollow 150 Å core.

They have diverse biochemical functions which include chromosome movements in cell division, intracellular transport of materials, development and maintenance of cell form, cellular motility, and sensory transduction. It is well known that the disruption of microtubules by antimitotic drugs or physical factors results in disruption of cellular function**.[2]**

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Various tubulin binding ligands with antimitotic and anticancer properties have been reported in the literature. **[3–6]** Regarding the binding sites of the various ligands, these can be classified into three main groups: those that bind tubulin at the colchicine-binding site; those that bind at the vinblastine site, and those that bind at the taxol site. The inhibition of microtubule formation via tubulin polymerization results in mitotic arrest which, in turn, promotes vascular disruption, leading to cell death by apoptosis.

Hence, tubulin has emerged as a popular target for anticancer drug design**.[7-8]** Von Angerer et al. synthesized a group of 2-phenylindole derivatives and determined their anticancer activities in human breast cancer cells**.[9–11]**

One of their critical observations was that these compounds prevent the polymerization of the α/β -tubulin dimers to functional microtubules by binding to the colchicine-binding site and all have pronounced cytotoxicity, indicating their good potential as a new class of anticancer drugs.

Consequently, there has been a lot of interest in understanding the structural basis of the anticancer activity of 2-phenylindoles using quantitative structure-activity relationship (QSAR) modeling. In fact, **Liao *et al.* [12]** applied the comparative molecular field analysis (CoMFA) approach to a set of 43 analogs of 2-phenylindole with reasonable results.

In our previous studies we found that mathematical molecular descriptors, invariants of simple and weighted molecular graphs in particular, which can be calculated directly from chemical structure without the input of any other experimental data, can predict property/ bioactivity/toxicity of various congeneric and structurally diverse classes of chemicals. **[13–24]** So in this paper we carried out QSAR modeling on the set of 43 2-phenylindoles using a diverse collection of mathematical structural invariants.

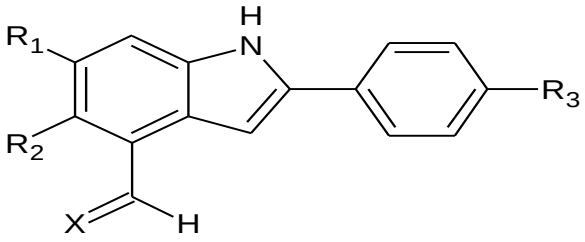

Fig.1. Molecular structure of 2-phenylindole derivatives

Table 1: Substitution in the structure of 2-phenylindole derivatives against human breast cancer cell line MDA-MB 231

S.No.	R_1	R_2	R_3	X
1	H	H	H	$C(CN)_2$
2	H	H	OCH_3	$C(CN)_2$
3	H	OCH_3	OCH_3	$C(CN)_2$
4	OCH_3	H	OCH_3	$C(CN)_2$
5	H	F	OCH_3	$C(CN)_2$
6	F	H	OCH_3	$C(CN)_2$
7	OCH_3	H	CH_3	$C(CN)_2$
8	H	CH_3	OCH_3	$C(CN)_2$
9	Cl	CH_3	OCH_3	$C(CN)_2$
10	H	n-Pr	OCH_3	$C(CN)_2$
11	H	i-Pr	OCH_3	$C(CN)_2$
12	H	n-Bu	OCH_3	$C(CN)_2$
13	H	n-Pentyl	OCH_3	$C(CN)_2$
14	H	n-Hexyl	OCH_3	$C(CN)_2$
15	H	n-Bu	CH_3	$C(CN)_2$
16	H	n-Bu	CH_2CH_3	$C(CN)_2$
17	H	n-Bu	CF_3	$C(CN)_2$
18	H	n-Pentyl	CF_3	$C(CN)_2$
19	H	n-Hexyl	CF_3	$C(CN)_2$
20	H	OCH_3	OCH_3	O
21	OCH_3	H	OCH_3	O
22	F	H	OCH_3	O
23	H	F	OCH_3	O
24	Cl	H	OCH_3	O
25	Cl	CH3	OCH_3	O
26	H	CH3	OCH_3	O
27	H	Pr	OCH_3	O
28	H	n-Bu	OCH_3	O
29	H	sec-Bu	OCH_3	O
30	H	t-Bu	OCH_3	O
31	H	n-Pentyl	OCH_3	O
32	H	n-Hexyl	OCH_3	O
33	OCH_3	OCH_3	OCH_3	O
34	OCH_3	H	CH_3	O
35	H	CH3	CH_3	O
36	H	n-Bu	CH_3	O
37	H	n-Bu	CH_2CH_3	O
38	H	CH_2CH_3	n-Bu	O
39	H	n-Bu	CF_3	O
40	H	n-Pentyl	CF_3	O
41	H	n-Hexyl	CF_3	O
42	OCH_3	H	H	O
43	H	H	H	O

Material and Methods

The Database

The 43 compounds used for the QSAR models in this study were taken from the published work of von Angerer and his coworkers.**[25–31]** Liao *et al*.**[12]** carried out a QSAR using this set of compounds. The anticancer activity of the 43 2-phenylindole derivatives was measured as the level of cytotoxicity against human breast cancer cell line.

The range of IC_{50} values was 5.5 to 720 nM, more than two orders of magnitude between the most and least potent derivatives. We used pIC_{50} values of the compounds (pIC_{50}= – $logIC_{50}$) as dependent variable in our models. The structural formula of the studied

compounds is shown in Fig 1. The structure of each compound is listed in Table1. Standardized by auto scaling to zero mean and unit standard deviation.

Statistical Analysis

Three regression methods that are appropriate when the number of descriptors exceeds the number of observations are ridge regression (RR**),[32-37]** principal component regression (PCR),**[38]** and partial least squares (PLS) regression**. [38-39]** These are shrinkage methods that avoid over fitting by imposing a penalty on large fluctuations of the estimated parameters. They are designed to utilize all available descriptors, as opposed to subset regression wherein variable selection is employed, and can be used with descriptors that are inter-correlated. RR, Statistical theory suggests that RR is the best of the three methods, and we have found in comparative studies that RR outperforms PCR and PLS in the vast majority of cases. **[21, 39, 40–45]** Therefore, we report only the ridge regression results in the current study. The leave-one-out (LOO) method was used for model cross-validation. Unfortunately, it is a widely held belief that the use of a hold-out test set is always the best method of model validation. However, theoretic argument and empiric study46 have shown that the LOO cross-validation approach is *preferred* to the use of a hold-out test set unless the data set to be modeled is very large.

The drawbacks of holding out a test set include:

1) Structural features of the held out chemicals are not included in the modeling process, resulting in a loss of information,

2) Predictions are made on only a subset of the available compounds, whereas LOO predicts the activity value for all compounds,

3) There is no scientific tool that can guarantee similarity between the training and test sets, and

4) Personal bias can easily be introduced in selection of the external test set.

The reader is referred to ***Hawkins et al.*** **[46]** and ***Kraker et al.*** **[47-62]** for further discussion of proper model validation techniques. The reader is cautioned to be critical of research studies which involve descriptor selection and cross-validation.

In many such studies, the q^2 is obtained via a two-step process wherein a subset of descriptors is first selected, followed by cross-validation of the model which is developed based on those descriptors. When using cross-validation and descriptor selection, it is essential that the descriptor selection step be included in the validation procedure.

Descriptors with large R^2 values are highly significant in the predictive model and, as such, can be examined in order to gain some understanding of the nature of the property or activity of interest.

It must be noted, however, that no conclusions may be drawn with respect to descriptors associated with small values. For the sake of clarity, it should be re-stated that the ridge regression method used in the current study does not involve variable selection, as this is a shrinkage method which is designed to use all available descriptors **[63-79].**

Results and Discussion

The calculated descriptors and bioactivity of each compound used in stepwise MLR are given in Table 2. The correlation matrix is given in Table 3 while Table 4 represents validated and cross-validated statistical descriptors of developed QSAR/QSPR models.

After 2D QSAR study by Multiple Linear Regression method using forward-backward stepwise variable selection method, the final QSAR equation developed QSAR/QSPR models was as follows. The highest correlation coefficient ($r \geq 0.8$) between the descriptors as illustrated in Table 3.

Table2: Experimental anticancer activities against human breast cancer cell line with Calculated topological and indicator descriptors

C.No	pIC_{50}	DEN	X_3	X_0v	X_1v	X_2v	X_3v	IP_1	IP_2	IP3	IP_4
1	6.367	1.28	7.649	11.168	6.507	4.639	3.323	0	0	0	0
2	6.143	1.27	8.467	12.499	7.03	5.002	3.64	0	0	0	0
3	6.229	1.27	9.27	13.83	7.559	5.336	3.956	0	0	0	0
4	6.585	1.27	9.167	13.83	7.553	5.371	3.921	1	0	0	0
5	6.398	1.33	8.955	12.799	7.135	5.115	3.723	0	0	0	0
6	6.553	1.33	8.728	12.799	7.129	5.149	3.677	0	1	0	0
7	6.745	1.25	8.759	13.421	7.44	5.509	3.883	1	0	0	0
8	6.553	1.25	8.955	13.421	7.446	5.451	3.994	0	0	0	0
9	7.125	1.32	9.479	14.478	7.93	5.959	4.495	0	1	1	0
10	7.081	1.2	9.405	14.836	8.507	6.043	4.385	0	0	1	0
11	6.678	1.2	9.405	14.836	8.507	6.043	4.385	0	0	0	0

12	7.585	1.18	9.674	15.543	9.007	6.396	4.666	0	0	1	0
13	7.377	1.16	9.924	16.25	9.507	6.75	4.916	0	0	1	0
14	7.337	1.15	10.174	16.957	10.007	7.103	5.166	0	0	1	0
15	7.187	1.16	9.265	15.135	8.895	6.534	4.627	0	0	1	0
16	7.119	1.14	9.674	15.842	9.455	6.718	4.938	0	0	1	0
17	7.252	1.27	10.202	15.768	9.212	6.743	4.788	0	0	1	0
18	7.108	1.25	10.452	16.476	9.712	7.096	5.038	0	0	1	0
19	6.824	1.23	10.702	17.183	10.212	7.45	5.288	0	0	1	0
20	6.585	1.24	7.981	11.844	6.559	4.672	3.544	0	0	0	1
21	7.456	1.24	7.901	11.844	6.553	4.707	3.507	1	0	0	1
22	7.229	1.3	7.461	10.813	6.129	4.486	3.263	0	1	0	1
23	6.268	1.3	7.666	10.813	6.135	4.452	3.311	0	0	0	1
24	7.569	1.33	7.461	11.569	6.507	4.922	3.481	0	1	0	1
25	7.585	1.3	8.19	12.492	6.93	5.295	4.083	0	1	0	1
26	7.066	1.21	7.666	11.435	6.446	4.787	3.582	0	0	0	1
27	7.699	1.2	8.116	12.85	7.507	5.379	3.974	0	0	0	1
28	8.174	1.14	8.385	13.557	8.007	5.733	4.254	0	0	1	1
29	7.143	1.14	8.738	13.72	7.928	5.868	4.541	0	0	0	1
30	6.553	1.14	8.42	13.935	7.696	6.767	4.172	0	0	0	1
31	8.26	1.13	8.635	14.264	8.507	6.086	4.504	0	0	1	1
32	8.131	1.11	8.885	14.971	9.007	6.44	4.754	0	0	1	1
33	6.658	1.24	8.699	13.174	7.088	5.016	3.825	1	0	0	1
34	7.509	1.21	7.492	11.435	6.44	4.845	3.469	1	0	0	1
35	7.319	1.18	7.258	11.027	6.334	4.924	3.544	0	0	0	1
36	7.469	1.12	7.977	13.148	7.894	5.87	4.216	0	0	1	1
37	7.569	1.1	8.385	13.855	8.455	6.054	4.526	0	0	1	1
38	6.523	1.1	8.369	13.855	8.455	6.054	4.518	0	0	0	1
39	7.481	1.24	8.913	13.782	8.211	6.079	4.376	0	0	1	1
40	7.377	1.22	9.163	14.489	8.711	6.433	4.626	0	0	1	1
41	7.367	1.2	9.413	15.196	9.211	6.786	4.876	0	0	1	1
42	6.62	1.24	7.082	10.513	6.029	4.345	3.191	1	0	0	1
43	6.377	1.24	6.382	9.182	5.506	3.975	2.91	0	0	0	1

IP_1: When OCH_3 is present in R_1 taken as unity, otherwise it is zero., IP_2: When F and Cl is present in R_1 taken as unity, otherwise it is zero., IP_3: When n is present in R_2 taken as unity, otherwise it is zero., IP_4: When O is present in R_3 taken as unity, otherwise it is zero.

Table 3: Correlation Matrix

	pIC_{50}	DEN	X^3	X^3v	IP_1	IP_2	IP3	IP_4
pIC_{50}	1.0000							
DEN	-0.4520	1.0000						
X^3	0.0868	-0.1194	1.0000					
X^3v	**0.3983**	-0.5006	0.8685	1.0000				
IP_1	-0.1104	0.1441	-0.2075	-0.3411	1.0000			
IP_2	0.1811	0.4596	-0.1770	-0.1647	-0.1289	1.0000		
IP_3	0.5358	-0.4349	0.6245	0.7920	-0.3417	-0.1094	1.0000	
IP_4	0.3670	-0.2602	**-0.6660**	-0.3325	0.0880	0.1237	-0.1942	1.0000

The developed QSAR/QSPR model no. 1 is biparametric which represents the importance of connectivity indices X^3_V and X^3 which is directly proportional with the magnitude of log of 50% of inhibitory concentration of anticancer activity.

QSAR Model No.1

pIC_{50} = 7.3315+ 1.1806X^3v-0.5925X^3

Eq……..1

The developed QSAR/QSPR model no.2 is also biparametric QSAR model shows the importance of indicator descriptors which is directly proportional with the anticancer activity reveals that as the magnitude of indicator descriptors increases the inhibitory activity also increases

QSAR model No.2.

pIC_{50} = 6.4957+0.6826IP_3+0.5261IP_4

Eq……..2

With reference to Table 3 the selected descriptors are used for biparamatric QSAR model no.1 development which show the importance of IP_3 and IP_4 which is directly proportional with the anticancer activity with the anticancer activity. The Biparametric

low statistical results indicates needs for the development of Triparametic and more QSAR models follow rule of thumb. The QSAR model no.2 has significant importance in which IP_2, IP_3 and IP_4 has positive contribution with the anticancer activity. The statistical descriptors are given in Table no.4 (Model No.3).

QSAR Model No.3

pIC_{50} = 6.4672+0.3565IP_2+0.7012IP_3+0.5039IP_4

Eq…….3

The four parametric QSAR/QSPR model no.4 reveals the importance of indicator descriptors and physicochemical descriptors in which density shows the negative correlation coefficient while the indicator descriptors IP_2, IP_3 and IP_5 show positive correlation coefficient with the indicator descriptors.

QSAR Model No.4

pIC_{50} = 9.3958+0.5973IP_2+0.5581IP_3+0.3791IP_4-2.3161DEN Eq…4

The above developed QSAR/QSPR model no. 04 have four serious outliers in the series and after ommiting it the resulted developed QSAR/QSPR model no.5 is statistically significant.

After deletion of compound no.21, 29, 35 and 38

QSAR Model No.5

pIC_{50} = 10.6870+0.7577IP_2+0.5393IP_3+0.2739IP_4-3.3584DEN Eq……..5

The developed QSAR/QSPR model 05 show positive correlation coefficient of indicator descriptors and negative correlation coefficient between the anticancer activity and density. The overall statistical and cross-validated descriptors are given in Table 4

Table 4: Statistical and Cross-Validated descriptors of Developed QSAR/QSPR Models

Model	n	Intercept	R^2	F-Ratio	PRESS	R^2_{CV}	R^2_{ADJ}
1	43	7.3315	0.4321	15.218	8.1433	0.3351	0.4037
2	43	6.4957	0.5178	21.476	6.7447	0.4493	0.4937
3	43	6.4672	0.5546	16.187	6.5796	0.4628	0.5203
4	43	9.3958	0.5938	13.886	6.4076	0.4768	0.5511
5	39	10.687	0.7127	21.083	4.3936	0.6077	0.6789

The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. Statistical data is shown in Table 4.The observed and predicted pIC_{50} along with residual values are shown in Table 5. The plot of observed vs. predicted activity is shown in Fig. (2). From the plot it can be seen that MLR model is able to predict the activity of training set quite well (all points are close to regression line) as well as external.

The above study leads to the development of statistically significant QSAR model, which allows understanding of the molecular properties/features that play an important role in governing the variation in the activities. In addition, this QSAR study allowed investigating influence of very simple and easy-to-compute descriptors in determining biological activities, which could shed light on the key factors that may aid in design of novel potent molecules.

Table 5: Results of Regression Analysis

No.	Para. Used	Ai (1,…..3)	Intercept	F-Ratio	R^2	AR^2
1	X_3V X^3	1.1806 -0.5925	7.3315	15.218	0.4321	0.4037
2	IP_3 IP_4	0.6826 0.5261	6.4957	21.476	0.5178	0.4937
3	IP_2	0.3565	6.4672	16.187	0.5546	0.5203

	IP_3 IP_4	0.7012 0.5039				
4	IP_2 IP_3 IP_4 DEN	0.5973 0.5581 0.3791 -2.3161	9.3958	13.886	0.5938	0.5511
5.	IP_2 IP_3 IP_4 DEN	0.7577 0.5393 0.2739 -3.3584	10.6870	21.083	0.7127	0.6789

Table 6: Predicted pIC_{50} and Actual pIC_{50} of QSAR model No.5

Comp. No.	Actual pIC_{50}	Predicted pIC_{50}	Residual
1	6.367	6.388	-0.021
2	6.143	6.422	-0.279
3	6.229	6.422	-0.193
4	6.585	6.422	0.163
5	6.398	6.22	0.178
6	6.553	6.22	0.333
7	6.745	6.489	0.256
8	6.553	6.489	0.064
9	7.125	7.551	-0.426
10	7.081	6.657	0.424
11	6.678	7.196	-0.518
12	7.585	7.263	0.322
13	7.377	7.33	0.047
14	7.337	7.364	-0.027
15	7.187	7.33	-0.143
16	7.119	7.398	-0.279
17	7.252	6.961	0.291
18	7.108	7.028	0.08
19	6.824	7.095	-0.271
20	6.585	6.796	-0.211
22	7.229	7.353	-0.124
23	6.268	6.595	-0.327
24	7.569	7.252	0.317
25	7.585	7.353	0.232
26	7.066	6.897	0.169
27	8.174	7.672	0.502
28	7.143	7.132	0.011
30	6.553	7.132	-0.579
31	8.26	7.705	0.555
32	8.131	7.772	0.359
33	6.658	6.796	-0.138
34	7.319	6.998	0.321
36	7.469	7.739	-0.27
37	7.569	7.806	-0.237
39	7.481	7.336	0.145
40	7.377	7.403	-0.026
41	7.367	7.47	-0.103
42	6.62	6.796	-0.176
43	6.377	6.796	-0.419

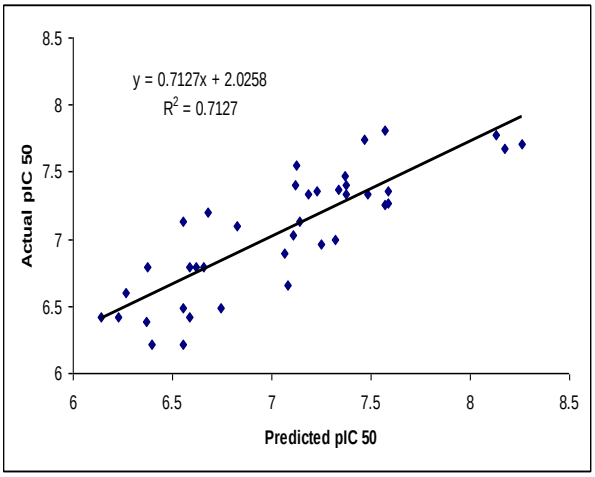

Fig 2: Graph plotted between predicted pIC_{50} and Actual pIC_{50}

Conclusion

Topological indices and atom pairs derived from chemical graph theory produced high-quality models for the prediction of anticancer activity of a set of 43 phenylindole derivatives which act by the disruption of tubulin working through the colchicine binding site. The QSAR formulated using TIs and APs together was superior to the QSAR model developed from the same set of chemicals. Easily calculated molecular descriptors like TIs and APs used in this paper may find application in the QSAR and *in silico* prediction of bioactivity of potential therapeutic agents in new drug discovery protocols as well as other toxic substances.

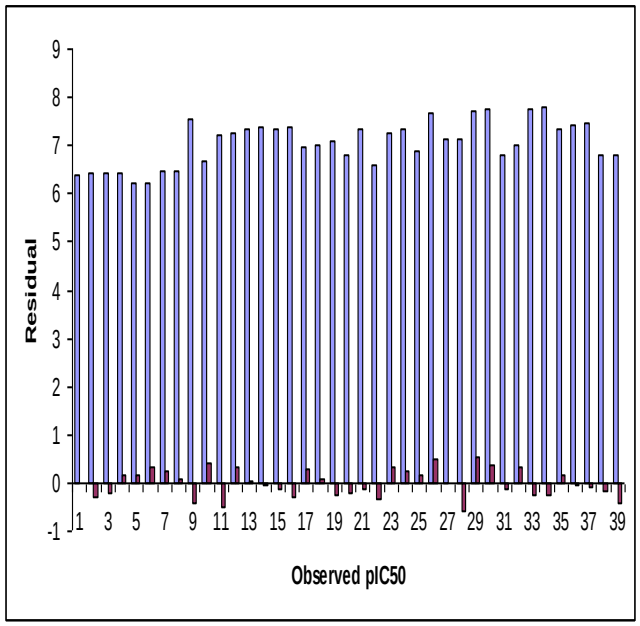

Fig 3: Graph plotted between Observed pIC$_{50}$ and Residual.

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