WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 3, 904-921. Research Article ISSN 2277– 7105

ANTIFUNGAL ACTIVITY AND QSAR STUDIES ON HETEROCYCLIC DERIVATIVES

Santosh Tiwari*[1], Shailja Sachan[2], Santosh Kumar Tiwari[3], Vikash Pandey[1], Kamlesh Misra[4]

[1]Department of Chemistry, Govt. G.D.C. College, Rewa, (M.P.) PIN- 486001, India.

[2]Department of Chemistry, Govt. M.S.G. College, Rewa (M. P.)PIN- 486001, India.

[3]Department of Chemistry, Govt. S.K.P.G. College, Mauganj, Rewa (M.P.) PIN- 486331 India.

[4]Department of Chemistry, A.P.S.University, Rewa (M.P.) PIN-486003, India.

Article Received on
25 Dec 2015,

Revised on 15 Jan 2016,
Accepted on 06 Feb 2016

***Correspondence for Author**
Dr. Santosh Tiwari
Department of Chemistry, Govt. G.D.C. College, Rewa, (M.P.) PIN-486001, India.

ABSTRACT

QSAR analysis of a set of 94 heterocyclic derivatives tested for growth inhibitory activity against *Candida albicans*. Quantitative structure activity relationship (QSAR) has been used to study the relationships between the antifungal activity with physicochemical descriptors and indicator descriptors by using E-Dragon software. The results are discussed on the basis of statistical data. The best QSAR model for prediction of antifungal activity of the investigated series of heterocyclic derivatives was developed. The resulting QSAR revealed that the heterocyclic ring system with the substitution of a benzyl moiety at position 2 was the most favorable structure among the heterocyclic nuclei. Moreover, the fifth position in the fused ring system is found more significant than the other positions in improving the activity.

KEYWORDS: QSAR, Heterocyclic derivatives, antifungal activity.

INTRODUCTION

Heterocyclic derivatives have shown potential for application in variety of pharmacological target. Fungi are heterophilic organisms which depend on dead or living organisms for their growth.[1] They can quickly develop colonies on all kinds of dead organic matter and play a major role in causing decomposition of organic matter enabling the recycling of nutrients throughout the ecosystem.[2-3] The impact is more acute in developing countries due to non

availability of desired medicines and emergence of widespread drug resistance. Antifungal resistance is a growing problem which necessitates the discovery of new drugs with activity against resistance strain. At present, much of what is known about fungal infections is limited to what happens in human beings.[4-6]

The heterocyclic molecules, is isosteric with indole and purine nuclei, which are present in a number of fundamental cellular components and bioactive compounds which makes the molecules endowed with a variety of biological properties.[7-9] *Candida albicans* has been identified as the major opportunistic pathogen in the etiology of fungal infections; their derivatives block ergosterol biosynthesis causing its depletion. Such sterols alter membrane fluidity with concomitant reduction in the activity of membrane-associated enzymes, increased permeability, and inhibition of cell growth and replication.[10-14]

Quantitative structure-activity relationships (QSAR) derive models which describe the structural dependence of biological activities either by physicochemical parameters (Hansch analysis), by indicator variables encoding different structural features (Free Wilson analysis). The QSAR method assumes that differences in the structural or physical properties measured experimentally account for differences in the observed biological or chemical properties. A QSAR study usually leads to a predictive formula and attempts to model the activity of a series of compounds using measured or computed properties of the compounds.

The other aim of this study is to derive quantitative structure activity relationships (QSARs) from multiple linear regression analysis (MLR) in order to investigate the quantitative effect of structural properties of the heterocyclic derivatives on their antifungal activity.

METHODOLOGY

The antifungal activity has been expressed as the logarithm of the reciprocal of minimal inhibitory concentration, pMIC [M]. The general chemical formula and the different types of substituents X, Y, Z, R_1-R_3 are shown in Table 1. The MLR approach in QSAR analysis has been most widely and effectively used for theoretical drug design due to various physicochemical and indicator descriptors used together. In this study, the model is based on the *in vitro* activity of heterocyclic derivatives against *C. albicans*, where C is the pMIC [M] value expressed in molar concentration units (Table 1) is taken from the literature.[15]

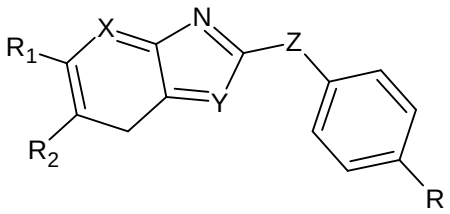
The physcio-chemical descriptors taken into consideration in QSAR study are density and index of refraction, if found to be important in determining the activity, as it is predictive in electrophilic reactions of the drugs with the nucleophilic functions of biomolecules should fulfil the following condition: appropriately describe the structure of chemical compound and the supposed reaction between the drug molecule and the biological system. The physciochemical parameters should be obtained from reproducible measurements or should be accessible from literature.[15] In order to perform statistical analysis it is necessary to have biological activity and physicochemical properties expressed by appropriate quantities.

In further analysis, the multiple linear regression analysis has been used where pMIC[M] was described as a function of selected molecular parameters. The correlation equation was performed using the stepwise technique by entering and removing F level for each variable in the regression. The predictive power of the performed QSAR model was also examined by calculating the r^2 value of heterocyclic derivatives was found significant for the lead optimization in this set of compounds.

The fused ring system has its symmetry potentially broken by the pyridine nitrogen X and the N or O atom Y. The molecules are heterocyclic isosteres and have a possible symmetry bisecting the 5- and 6- membered fused rings. The atom X for CH or N influence activity through an electronic effect that increases or reduces the activity of the drug, and through symmetry if X is CH and Y is NH the molecules is symmetrical and it will be immaterial whether a particular substituent is in the R1 or R2 positions. If X is N and Y is NH the two positions are isosteric, and one of the two possible orientations may or may not be favoured over the other.[16-19]

A major decision in developing successive QSARs is when to stop adding descriptors to the model during the stepwise regression procedure. The lack of an adequate control leads to over-correlated equations, which contain an excess of descriptors and are difficult to interpret in terms of interaction mechanisms. A simple procedure to control the model expansion is the so-called ‘break point’ in improvement of the statistical quality of the model.

Table: 1 The Structure of Heterocyclic Compounds



C. No.	pMIC[M]	X	Y	Z	R	R^1	R^2
1	3.892	CH	O	*	H	H	H
2	4.001	CH	O	*	$C(CH_3)$	H	H
3	3.924	CH	O	*	NH_2	H	H
4	4.059	CH	O	*	$NHCOCH_3$	Cl	H
5	4.024	CH	O	*	Cl	Cl	H
6	4.04	CH	O	*	NO_2	Cl	H
7	4.282	CH	O	*	H	NO_2	H
8	4.308	CH	O	*	CH_3	NO_2	H
9	4.375	CH	O	*	$C(CH_3)$	NO_2	H
10	4.31	CH	O	*	NH_2	NO_2	H
11	4.342	CH	O	*	Cl	NO_2	H
12	4.406	CH	O	*	Br	NO_2	H
13	3.979	CH	O	*	C_2H_5	NH_2	H
14	3.96	CH	O	*	F	NH_2	H
15	4.005	CH	O	*	$N(CH_3)_2$	NH_2	H
16	3.95	CH	O	*	CH_3	CH_3	H
17	3.977	CH	O	*	C_2H_5	CH_3	H
18	3.98	CH	O	*	OCH_3	CH_3	H
19	3.958	CH	O	*	F	CH_3	H
20	4.027	CH	O	*	$NHCOCH_3$	CH_3	H
21	3.979	CH	O	*	$NHCH_3$	CH_3	H
22	4.004	CH	O	*	$N(CH_3)_2$	CH_3	H
23	4.225	N	O	*	CH_3	H	H
24	4.253	N	O	*	C_2H_5	H	H
25	4.257	N	O	*	OCH_3	H	H
26	4.283	N	O	*	OC_2H_5	H	H
27	4.227	N	O	*	NH_2	H	H
28	4.285	N	O	*	NO_2	H	H
29	4.11	CH	O	*	Br	NH_2	H
30	4.282	CH	O	CH_2	OCH_3	H	H
31	4.308	CH	O	CH_2	NO_2	H	H
32	4.29	CH	O	CH_2	H	Cl	H
33	4.34	CH	O	CH_2	OCH_3	Cl	H
34	4.41	CH	O	CH_2	Br	Cl	H
35	4.363	CH	O	CH_2	NO_2	Cl	H
36	4.609	CH	O	CH_2	H	NO_2	H
37	4.657	CH	O	CH_2	OCH_3	NO_2	H
38	4.725	CH	O	CH_2	Br	NO_2	H
39	4.664	CH	O	CH_2	Cl	NO_2	H

40	3.732	CH	O	CH_2O	H	H	NO_2
41	3.831	CH	O	CH_2O	Cl	Cl	NO_2
42	4.359	CH	O	CH_2O	H	NO_2	H
43	4.009	CH	O	CH_2S	H	H	H
44	4.26	N	O	CH_2O	H	H	H
45	4.319	N	O	CH_2O	Cl	CH_3	H
46	4.037	CH	NH	CH_2O	Cl	NO_2	H
47	4.358	CH	NH	CH_2S	H	CH_3	H
48	4.009	CH	NH	CH_2S	H	$COOCH_3$	H
49	4.054	CH	O	CH_2O	H	$COOCH_3$	H
50	4.104	CH	O	CH_2O	Cl	$COOCH_3$	H
51	4.102	CH	NH	CH_2O	Cl	$COOCH_3$	H
52	4.076	CH	NH	CH_2S	H	NO_2	H
53	4.331	CH	O	C_2H_4	H	H	H
54	4.253	N	O	C_2H_4	H	NO_2	H
55	4.283	CH	NH	CH_2O	H	H	H
56	4.015	CH	NH	CH_2O	Cl	Cl	H
57	4.041	CH	NH	CH_2S	H	H	H
58	4.078	CH	NH	C_2H_4	H	H	H
59	3.981	CH	O	CH_2O	H	Cl	H
60	4.071	CH	O	CH_2O	Cl	CH_3	H
61	3.738	CH	O	CH_2O	Cl	H	H
62	3.738	CH	O	CH_2O	Cl	Cl	H
63	4.344	CH	O	CH_2O	H	H	H
64	4.009	CH	O	CH_2S	H	H	H
65	3.955	CH	O	CH_2O	H	NO_2	H
66	4.034	CH	O	CH_2O	H	H	H
67	4.017	CH	O	CH_2O	H	Cl	H
68	4.086	CH	O	CH_2O	Cl	NO_2	H
69	4.286	CH	O	CH_2S	H	H	H
70	4.409	CH	O	CH_2S	H	Cl	NO_2
71	4.379	CH	O	CH_2S	H	$COOCH_3$	H
72	7.742	CH	S	CH_2O	Cl	H	H
73	4.316	CH	NH	CH_2O	H	Cl	H
74	4.053	CH	NH	CH_2O	H	$COOCH_3$	H
75	4.37	CH	NH	CH_2O	Cl	Cl	H
76	3.951	CH	NH	CH_2NH	H	H	H
77	3.977	CH	NH	CH_2NH	H	CH_3	H
78	4.012	CH	O	C_2H_4	H	Cl	H
79	3.952	CH	O	*	$NHCH_3$	H	H
80	4.013	CH	O	*	C_2H_5	Cl	H
81	4.025	CH	O	*	$NHCH_3$	Cl	H
82	4.223	CH	O	CH_2	H	H	H
83	4.29	CH	O	CH_2	Cl	H	H
84	4.68	CH	O	CH_2	NO_2	NO_2	H
85	4.36	CH	O	CH_2	Br	H	H
86	3.98	CH	O	CH_2O	H	CH_3	H
87	3.785	CH	O	CH_2O	H	Cl	NO_2

88	4.016	CH	O	CH_2O	Cl	H	H
89	3.785	CH	O	CH_2O	Cl	Cl	NO_2
90	4.36	CH	O	CH_2S	H	H	NO_2
91	3.953	CH	NH	CH_2O	H	H	H
92	3.979	CH	NH	CH_2O	H	H	H
93	4.284	CH	NH	CH_2S	H	H	H
94	4.277	CH	NH	C_2H_4	H	H	H

RESULTS AND DISCUSSION

In the present study, an attempt has been made to find structural requirement for inhibition of *C. albicans* using QSAR Hansch approach on heterocyclic derivatives with topological, physicochemical and indicator descriptors. QSAR models against *C. albicans* have been obtained. The statistical quality of the regression equations were justified by parameters like regression coefficient (R^2), Fiesher ratio (F-Ratio), cross validated regression coefficient (R^2_{cv}), Adjusted regression coefficient (R^2_{adj}), coefficient of variation (CoV), standard error of estimation (Se).

Use of more than one variable in the multivariate equation was justified by an autocorrelation study. Parameters which encode certain structural features and properties are needed to correlate biological activities with chemical structures in a quantitative manner. Of special value are physicochemical properties which are directly related to the intermolecular forces involved in the drug-receptor interaction as well as to the transport and distribution properties of drugs.[20-23]

Table 2: Descriptor used in present QSAR study

S.No.	Descriptor	Type
1	IR	Index of Refraction
2	ST	Surface Tension
5	IP1	1 if Y is S, 0 otherwise.
6	IP2	1 if Z is CH_2, 0 otherwise.
7	IP3	1 if Z is CH_2O, 0 otherwise.

Using the data (table 3), a correlation matrix was calculated to find the correlation as well as the colinearity between the descriptors. A high interrelationship was observed between IP1 and pMIC [M] (r = 0.8648) as well as the low interrelationship was observed between IP2 and IP3 (r = -0.2724). The correlation matrix indicated the predominance of physicochemical and indicator parameters in describing the antifungal activity of heterocyclic derivatives.

In order to deduce the correlation of the observed antifungal activity, in terms of the pMIC [M] of the reported compounds with different structural parameters, a systemic QSAR investigation has been carried out using the model proposed by Hansch *et. al*[34] the activity data (pMIC [M]) representing the concentration of compound that inhibited the visible growth in various fungal species, was used as dependent variable to get a linear relationship in the QSAR model.

In order to understand the experimental antifungal activity data of 94 substituted heterocyclic derivatives on theoretical basis, we established quantitative structure activity relationships (QSAR) between their activity and descriptors coding for physicochemical and indicator properties of the molecules under consideration using the linear free energy relationship model (LFER). Different physicochemical and indicator descriptors were used as independent variables and were correlated with antifungal activity.[24-28]

Table 3: Correlation matrix for the chosen parameters

	pMIC [M]	IR	ST	IP1	IP2	IP3
pMIC [M]	1.0000	0.1665	0.1539	0.8648	0.2494	-0.0519
IR		1.0000	0.8309	0.0770	-0.0285	-0.1699
ST			1.0000	-0.0045	-0.0605	-0.0428
IP1				1.0000	-0.0433	0.1592
IP2					1.0000	-0.2724
IP3						1.0000

Developing a QSAR model requires a diverse set of data, and, thereby a large number of descriptors have to be considered. Descriptors are numerical values that encode different structural features of the molecules. Selection of a set of appropriate descriptors from a large number of them requires a method, which is able to discriminate between the parameters.[29]

In all equations the following symbols are used: n – the number of regressed data point; c – the regression coefficient; F – the value of the test F; Se – standard error of estimate; R^2_{adj}- adjusted regression coefficient; CoV- coefficient of variation. Using multiple linear regression analysis with physicochemical and indicator descriptors selected by stepwise analysis the above best five equations were derived: for activity against *Candida albicans*:

Hansch analysis correlates biological activity values with physicochemical properties by linear, linear multiple, or nonlinear regression analysis; thus, Hansch analysis is indeed a

property-property relationship model. **As** practically all parameters used in Hansch analysis are linear free energy-related values, the terms "linear free energy-related approach" or "extrathermodynamic approach" are sometimes used as synonyms for Hansch analysis.[30-36]

The Free Wilson approach is a true structure-activity relationship model. An indicator variable is generated for each structural feature that deviates from an arbitrarily chosen reference compound. Values 1, indicating the presence of a certain substituent or structural feature, and 0, indicating its absence, are correlated with the biological activity values by linear multiple regression analysis. The resulting regression coefficients of the indicator variables are the biological activity contributions of the corresponding structural elements.

For a successful application of the mixed approach it is highly recommended to derive Hansch equations for each subset and to compare whether they correspond to each other or not, before combining them into one equation with the help of indicator variables Today the mixed approach is the most powerful tool for the quantitative description of large and structurally diverse data sets. The high R^2_{cv} value is indicative of its reliability in predicting the inhibitory activity. But, the only way to estimate the true predictive power of a model is to test their ability to predict accurately the biological activities of compounds.

Table 4: Developed QSAR model and Statistical parameters for testing prediction ability of the MLR models of Heterocyclic derivatives.

Model No.	p MIC [M] =	n	R^2	F-Ratio	R^2_{cv}	CoV	R^2_{adj}	Se
1.	4.1506+ 3.5913IP1	94	0.74	272.9	0.74	0.05	0.74	0.22
2.	4.098+3.6431IP1+ 0.3441IP2	94	0.83	222.8	0.82	0.04	0.82	0.18
3.	3.5040+ 3.6484IP1 + 0.3569IP2 + 1.0679E-02ST	94	0.86	186.2	0.85	0.03	0.85	0.16
4.	3.5631+ 3.7183IP1+ 0.3199IP2 - 0.1065IP3 + 1.0273E-02ST	94	0.87	153.0	0.86	0.03	0.86	0.15
5.	7.1411+ 3.8036IP1+ 0.3161IP2 - 0.1349IP3-2.4867IR + 0.0200ST	94	0.88	133.8	0.87	0.03	0.87	0.15

However it was interesting to find out how particular classes of activity can be described by means of structural parameters. Therefore for each class of antifungal potency of both fungi species the regression equations of the dependent variable pMIC [M], as a function of structural parameters from molecular modeling, have been derived.

The antifungal activity of heterocyclic derivative is explained by the indicator parameter, IP1 (Model No. 1). As the coefficient of IP1 is positive, therefore the antifungal activity of heterocyclic derivative will increase in value of IP1. The QSAR model expressed by model no.1 was cross validated by its high R^2_{cv} values obtained by leave one out (LOO) method. The value of R^2_{cv} is greater than 0.5 is the basic requirement for qualifying a QSAR model to be valid one. The comparison of observed and predicted antifungal activities is presented in Table 5. It can be seen from the results that the observed and predicted antifungal activities lie close to each other as evidenced by their low residual values (Table 5).

For antifungal activity of heterocyclic derivative, the developed QSAR model (Model No.2-5) indicated the predominance of indicator descriptors and physicochemical descriptors. The coefficient of IP3 and Index of refraction (IR) is negative, which shows that the antifungal activity will increase with the decrease in IP3 and Index of refraction (IR) of heterocyclic derivative, which can be clearly seen from the results of antifungal activity while the coefficient of IP1, IP2 and ST is positive, which shows that the antifungal activity will increase with the increase in IP1, IP2 and ST. Surface tension is the cumulative effect of the different intra and intermolecular forces of two different surfaces.

The perusal of Table 5 is that from the predicted pMIC [M] and residual plot we are able to find the most active heterocyclic derivatives. From the presented table 5, it can be concluded that the strong influence of the substitution of S at the position of Y is predominance with related to antifungal activity of Heterocyclic derivatives, which is usually related to pharmacological activity.[40, 61, 62, 41]

Table 5: Antifungal Screening Summary of Heterocyclic Derivatives

Cmpd	Actual pMIC[M]	QSAR Model No. 1		QSAR Model No. 2		QSAR Model No. 3		QSAR Model No. 4		QSAR Model No. 5	
		Predicted pMIC [M]	Residual	Predicted pMIC [M]	Residual	Predicted pMIC [M]	Residual	Predicted pMIC [M]	Residual	Predicted pMIC[M]	Residual
1	3.892	4.151	-0.259	4.099	-0.207	4.01	-0.118	4.05	-0.158	4.026	-0.134
2	4.001	4.151	-0.150	4.099	-0.098	3.926	0.075	3.969	0.032	4.005	-0.004
3	3.924	4.151	-0.227	4.099	-0.175	4.109	-0.185	4.145	-0.221	4.099	-0.175
4	4.059	4.151	-0.092	4.099	-0.04	4.094	-0.035	4.13	-0.071	4.101	-0.042
5	4.024	4.151	-0.127	4.099	-0.075	4.048	-0.024	4.086	-0.062	4.059	-0.035
6	4.04	4.151	-0.111	4.099	-0.059	4.139	-0.099	4.174	-0.134	4.182	-0.142
7	4.282	4.151	0.131	4.099	0.183	4.126	0.156	4.161	0.121	4.168	0.114
8	4.308	4.151	0.157	4.099	0.209	4.091	0.217	4.128	0.18	4.141	0.167
9	4.375	4.151	0.224	4.099	0.276	4.002	0.373	4.042	0.333	4.097	0.278
10	4.31	4.151	0.159	4.099	0.211	4.229	0.081	4.261	0.049	4.254	0.056
11	4.342	4.151	0.191	4.099	0.243	4.139	0.203	4.174	0.168	4.182	0.16
12	4.406	4.151	0.255	4.099	0.307	4.152	0.254	4.187	0.219	4.169	0.237
13	3.979	4.151	-0.172	4.099	-0.12	4.051	-0.072	4.089	-0.11	4.068	-0.089
14	3.96	4.151	-0.191	4.099	-0.139	4.086	-0.126	4.123	-0.163	4.107	-0.147
15	4.005	4.151	-0.146	4.099	-0.094	4.119	-0.114	4.155	-0.15	4.176	-0.171
16	3.95	4.151	-0.201	4.099	-0.149	3.972	-0.022	4.013	-0.063	4.041	-0.091
17	3.977	4.151	-0.174	4.099	-0.122	3.953	0.024	3.995	-0.018	4.037	-0.06
18	3.98	4.151	-0.171	4.099	-0.119	3.969	0.011	4.01	-0.03	4.035	-0.055
19	3.958	4.151	-0.193	4.099	-0.141	4.023	-0.065	4.062	-0.104	4.113	-0.155
20	4.027	4.151	-0.124	4.099	-0.072	4.104	-0.077	4.14	-0.113	4.151	-0.124
21	3.979	4.151	-0.172	4.099	-0.12	4.021	-0.042	4.06	-0.081	4.002	-0.023
22	4.004	4.151	-0.147	4.099	-0.095	4.001	0.003	4.041	-0.037	4.021	-0.017
23	4.225	4.151	0.074	4.099	0.126	4.041	0.184	4.08	0.145	4.099	0.126
24	4.253	4.151	0.102	4.099	0.154	4.02	0.233	4.059	0.194	4.092	0.161
25	4.257	4.151	0.106	4.099	0.158	4.034	0.223	4.073	0.184	4.113	0.144
26	4.283	4.151	0.132	4.099	0.184	4.018	0.265	4.057	0.226	4.115	0.168

27	4.227	4.151	0.076	4.099	0.128	4.181	0.046	4.214	0.013	4.21	0.017
28	4.285	4.151	0.134	4.099	0.186	4.196	0.089	4.229	0.056	4.281	0.004
29	4.11	4.151	-0.041	4.099	0.011	4.137	-0.027	4.172	-0.062	4.103	0.007
30	4.282	4.151	0.131	4.443	-0.161	4.423	-0.141	4.423	-0.141	4.414	-0.132
31	4.308	4.151	0.157	4.443	-0.135	4.476	-0.168	4.475	-0.167	4.49	-0.182
32	4.29	4.151	0.139	4.443	-0.153	4.387	-0.097	4.39	-0.1	4.373	-0.083
33	4.34	4.151	0.189	4.443	-0.103	4.363	-0.023	4.366	-0.026	4.377	-0.037
34	4.41	4.151	0.259	4.443	-0.033	4.416	-0.006	4.417	-0.007	4.375	0.035
35	4.363	4.151	0.212	4.443	-0.08	4.489	-0.126	4.487	-0.124	4.499	-0.136
36	4.609	4.151	0.458	4.443	0.166	4.476	0.133	4.475	0.134	4.49	0.119
37	4.657	4.151	0.506	4.443	0.214	4.438	0.219	4.438	0.219	4.472	0.185
38	4.725	4.151	0.574	4.443	0.282	4.502	0.223	4.5	0.225	4.491	0.234
39	4.664	4.151	0.513	4.443	0.221	4.489	0.175	4.487	0.177	4.499	0.165
40	3.732	4.151	-0.419	4.099	-0.367	4.134	-0.402	4.063	-0.331	4.069	-0.337
41	3.831	4.151	-0.320	4.099	-0.268	4.101	-0.270	4.031	-0.200	4.149	-0.318
42	4.359	4.151	0.208	4.099	0.26	4.252	0.107	4.282	0.077	4.318	0.041
43	4.009	4.151	-0.142	4.099	-0.09	4.106	-0.097	4.143	-0.134	4.127	-0.118
44	4.26	4.151	0.109	4.099	0.161	4.085	0.175	4.015	0.245	4.027	0.233
45	4.319	4.151	0.168	4.099	0.22	4.101	0.218	4.031	0.288	4.049	0.27
46	4.037	4.151	-0.114	4.099	-0.062	4.094	-0.057	4.024	0.013	3.968	0.069
47	4.358	4.151	0.207	4.099	0.259	4.326	0.032	4.354	0.004	4.458	-0.1
48	4.009	4.151	-0.142	4.099	-0.09	4.166	-0.157	4.2	-0.191	4.182	-0.173
49	4.054	4.151	-0.097	4.099	-0.045	4.046	0.008	3.977	0.077	4.045	0.009
50	4.104	4.151	-0.047	4.099	0.005	4.059	0.045	3.991	0.113	4.071	0.033
51	4.102	4.151	-0.049	4.099	0.003	4.126	-0.024	4.054	0.048	4.056	0.046
52	4.076	4.151	-0.075	4.099	-0.023	4.215	-0.139	4.247	-0.171	4.3	-0.224
53	4.331	4.151	0.18	4.099	0.232	4.114	0.217	4.15	0.181	4.184	0.147
54	4.253	4.151	0.102	4.099	0.154	4.067	0.186	4.105	0.148	4.22	0.033
55	4.283	4.151	0.132	4.099	0.184	4.224	0.059	4.149	0.134	4.131	0.152
56	4.015	4.151	-0.136	4.099	-0.084	4.125	-0.11	4.053	-0.038	3.994	0.021
57	4.041	4.151	-0.11	4.099	-0.058	4.228	-0.187	4.26	-0.219	4.227	-0.186

58	4.078	4.151	-0.073	4.099	-0.021	4.09	-0.012	4.127	-0.049	4.09	-0.012
59	3.981	4.151	-0.17	4.099	-0.118	4.008	-0.027	3.941	0.04	3.974	0.007
60	4.071	4.151	-0.08	4.099	-0.028	4.062	0.009	3.993	0.078	4.075	-0.004
61	3.738	4.151	-0.413	4.099	-0.361	4.024	-0.286	3.957	-0.219	3.937	-0.199
62	3.738	4.151	-0.413	4.099	-0.361	4.024	-0.286	3.957	-0.219	3.937	-0.199
63	4.344	4.151	0.193	4.099	0.245	4.047	0.297	4.085	0.259	4.087	0.257
64	4.009	4.151	-0.142	4.099	-0.09	4.106	-0.097	4.143	-0.134	4.127	-0.118
65	3.955	4.151	-0.196	4.099	-0.144	4.03	-0.075	3.962	-0.007	4.014	-0.059
66	4.034	4.151	-0.117	4.099	-0.065	4.134	-0.100	4.063	-0.029	4.069	-0.035
67	4.017	4.151	-0.134	4.099	-0.082	4.047	-0.030	3.978	0.039	3.952	0.065
68	4.086	4.151	-0.065	4.099	-0.013	4.146	-0.060	4.074	0.012	4.076	0.01
69	4.286	4.151	0.135	4.099	0.187	4.131	0.155	4.166	0.12	4.141	0.145
70	4.409	4.151	0.258	4.099	0.31	4.28	0.129	4.31	0.099	4.352	0.057
71	4.379	4.151	0.228	4.099	0.28	4.157	0.222	4.191	0.188	4.241	0.138
72	7.742	7.742	0.000	7.742	0.000	7.742	0.000	7.742	0.000	7.742	0.000
73	4.316	4.151	0.165	4.099	0.217	4.125	0.191	4.053	0.263	3.989	0.327
74	4.053	4.151	-0.098	4.099	-0.046	4.114	-0.061	4.043	0.01	4.049	0.004
75	4.37	4.151	0.219	4.099	0.271	4.137	0.233	4.066	0.304	4.003	0.367
76	3.951	4.151	-0.200	4.099	-0.148	4.189	-0.238	4.222	-0.271	4.1	-0.149
77	3.977	4.151	-0.174	4.099	-0.122	4.147	-0.17	4.182	-0.205	4.077	-0.1
78	4.012	4.151	-0.139	4.099	-0.087	4.105	-0.093	4.141	-0.129	4.1	-0.088
79	3.952	4.151	-0.199	4.099	-0.147	4.043	-0.091	4.082	-0.13	4.006	-0.054
80	4.013	4.151	-0.138	4.099	-0.086	3.992	0.021	4.033	-0.02	4.034	-0.021
81	4.025	4.151	-0.126	4.099	-0.074	4.06	-0.035	4.098	-0.073	4.026	-0.001
82	4.223	4.151	0.072	4.443	-0.22	4.369	-0.146	4.372	-0.149	4.356	-0.133
83	4.29	4.151	0.139	4.443	-0.153	4.387	-0.097	4.39	-0.1	4.373	-0.083
84	4.68	4.151	0.529	4.443	0.237	4.583	0.097	4.578	0.102	4.628	0.052
85	4.36	4.151	0.209	4.443	-0.083	4.402	-0.042	4.404	-0.044	4.364	-0.004
86	3.98	4.151	-0.171	4.099	-0.119	4.008	-0.028	3.941	0.039	3.925	0.055
87	3.785	4.151	-0.366	4.099	-0.314	4.146	-0.361	4.074	-0.289	4.076	-0.291
88	4.016	4.151	-0.135	4.099	-0.083	4.047	-0.031	3.978	0.038	3.952	0.064

89	3.785	4.151	-0.366	4.099	-0.314	4.146	-0.361	4.074	-0.289	4.076	-0.291
90	4.36	4.151	0.209	4.099	0.261	4.253	0.107	4.283	0.077	4.315	0.045
91	3.953	4.151	-0.198	4.099	-0.146	4.111	-0.158	4.04	-0.087	3.975	-0.022
92	3.979	4.151	-0.172	4.099	-0.12	4.08	-0.101	4.01	-0.031	3.955	0.024
93	4.284	4.151	0.133	4.099	0.185	4.198	0.086	4.231	0.053	4.188	0.096
94	4.277	4.151	0.126	4.099	0.178	4.063	0.214	4.1	0.177	4.067	0.21

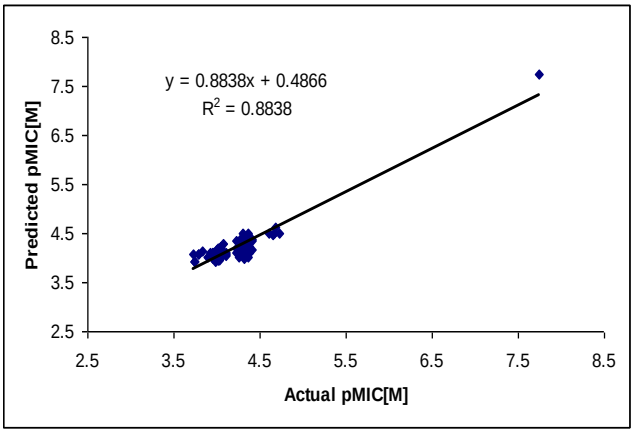


Fig 1: Graph between predicted pMIC[M] and actual pMIC [M] antifungal Activity of QSAR model no.5.

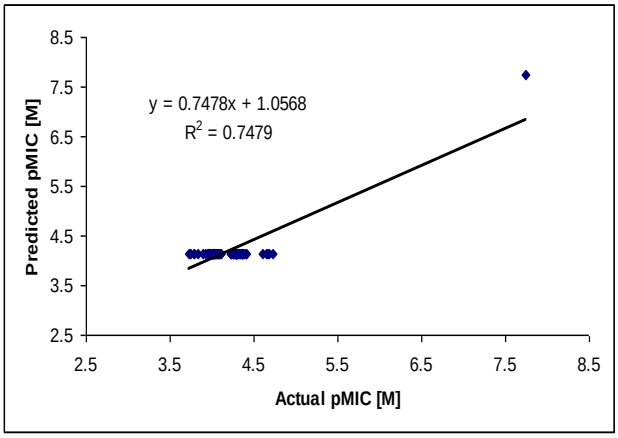


Fig 2: Graph between predicted pMIC[M] and actual pMIC [M] antifungal Activity of QSAR model no.1

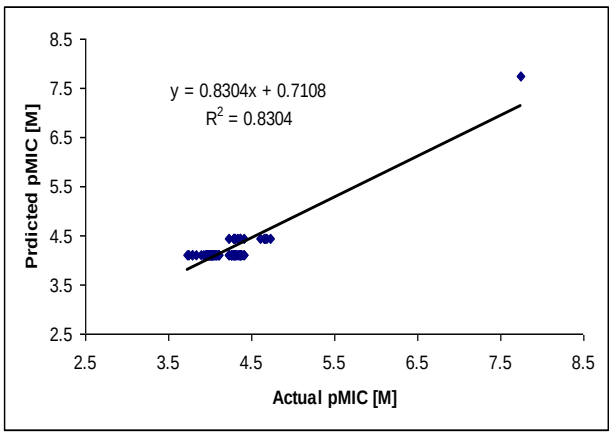


Fig 2: Graph between predicted pMIC[M] and actual pMIC [M] antifungal Activity of QSAR model no.2

CONCLUSION

Classical QSAR methods still play an important role in drug design, despite the progress in protein crystallography, molecular modeling, and structure-based drug design.

Prediction for the lead optimization in the set of compounds can be concluded as follows. Due to the activity contribution of every positive value of regression coefficient of structural parameters IP1, IP2 and physicochemical parameter IR in the developed QSAR model. Holding pyridine ring in the heterocyclic system was found important for the heterocyclic fused system. Moreover, substituting position Y with Sulphur and position Z with a methylene group as a bridge element between the fused heterocyclic ring system and phenyl ring in this set of molecules.

The developed QSAR model revealed that the substituents on postions R_1 were found more indicative and numerical values of physicochemical parameters obtained indicate that thiazole is unfavourable as the 5 membered ring relative to imidazole or oxazole. QSAR neither brings the solution of all our problems, nor can it only be considered as an academic game; *"the great advantage of the QSAR paradigm lies not in the extrapolations which can be made from known QSAR to fantastically potent new drugs, but in the less spectacular slow development of science in medicinal chemistry"*

REFERENCE

1. Emami S, Foroumadi A, Falahati M, Lotfali E, Rajabalian S, Ebrahimi FS, Shafiee A. (2008) 2-Hydroxyphenacyl azoles and related azolium derivatives as antifungal agents. Bioorg Med Chem Lett. 18: 141–146.
2. Gonzalez-Diaz H, Prado-Prado FJ. (2008) Unified QSAR and network-based computational chemistry approach to antimicrobials, part 1: multispecies activity models for antifungals. J Comput Chem. 29(4): 656–667.
3. Hansch C, Fujita T. (1964) p-r-p analysis. A method for the correlation of biological activity and chemical structure. J Am Chem Soc. 86: 1616–1626.
4. Hansch C, Leo A, Unger SH, Kim KH, Nikaitani D, Lien EJ. (1973) Aromatic substituent constants for structure-activity correlations. J Med Chem. 16: 1207–1216.
5. Sortino M, Delgado P, Jaurez S, Quiroga J, Abonia R, Insuasey B, Rodero MN, Garibotto FM, Enriz RD, Zacchino SA. (2007) Synnthesis and antifungal activity of (Z)-5-arylidenerhodanines. Bioorg Med Chem. 15: 484–494.

6. A.M., Enriz R.D. (2001) In vitro antifungal evaluation and structure-activity relationships of a new series of chalcone derivatives and synthetic analogues with inhibitory properties against polymers of the fungal cell wall. Bioorg Med Chem. 9: 1999–2013.
7. Lahtchev KL, Batovska DI., Parushev SP, Ubiyvovk VM, Sibirny AA. (2008) Antifungal activity of chalcones: a mechanistic study using various yeast strains. Eur J Med Chem. 43: 2220–2228.
8. Garc_a-Domenech R, Rios-Santamarina I, Catala A, Calabuig C, del Castillo L, Galvez J. (2003) Application of molecular topology to the prediction of antifungal activity for a set of dicationsubstituted carbazoles, furans and benzimidazoles. J Mol Struct (THEOCHEM). 624: 97–107.
9. Mghazli S, Jaouad A, Mansour M, Villemin D, Cherqaoui D. (2001) Neural networks studies: quantitative structure–activity relationships of antifungal 1-[2-(substituted phenyl)allyl]imidazoles and related compounds. Chemosphere. 43: 385–390.
10. Caballero J, Fernandez M. (2006) Linear and nonlinear modeling of antifungal activity of some heterocyclic ring derivatives using multiple linear regression and Bayesian-regularized neural networks. J Mol Model. 12: 168–181.
11. Duchowicz PR, Vitale MG, Castro EA, Fern_ndez M, Caballero J. (2007) QSAR analysis for heterocyclic antifungals. Bioorg Med Chem. 15: 2680–2689.
12. Purushottamachar P, Kulkarni VM. (2003) 3D-QSAR of N-myristoyltransferase inhibiting antifungal agents by CoMFA and CoMSIA methods. Bioorg Med Chem. 11: 3487–3497.
13. Choi S, Shin JH., Ryu CK., Nam K, Noc KT., Choo HP. (2006) The development of 3D-QSAR study and recursive partitioning of heterocyclic quinine derivatives with antifungal activity. Bioorg Med Chem. 14: 1608–1617.
14. Gaurav G, Kini SG. (2003) Synthesis and Evaluation of certain new 1,3,4-oxadiazole derivatives of Nalidixic acid moiety as potential Antifungal and Antibacterial agents, Indian J. Heterocyclic Chem. 12(3): 289– 290.
15. Deeb G, Clare WC. (2008)QSAR of Heterocyclic Antifungal Agents by Flip Regression. Comput. Aided Mol Des. 22: 885-895.
16. Lazarevic M. Dimova V, Molnar D, (2001) Synthesis of some N1–aryl/heteroarylaminomethyl/ ethyl–1,2,4–triazoles and their antibacterial and antifungal activities, Heterocyclic Communications, **7**(6): 577–582.

17. K. Colanceska, V. Dimova, V. Kakurinov, D. Molnar–Gabor, A. Buzarovska, (2001)Synthesis and antibacterial and antifungal activity of 4–substituted–5–aryl–1,2,4–triazole, Molecules. 6: 815–824.
18. Khan, ZK, Jain P.(2000) Antifungal agents and immunomodulators in systemic mycoses. The Indian J. Chest Dis. Allied Sci., 42: 345-355.
19. Vasanthanathan P, Lakshimi M, (2006)QSAR Study of 3–Phenyl–5–acyloxymethyl–2H,5H–furan–2–ones as Antifungal Agents. Vhem. Pharm. Bull. 54:583–587.
20. Weinberg ED. (1996) Antifungal Agents. Burger's Medicinal Chemistryand Drug Discovery, 5th ed.; Wiley-Interscience: New York. 2: 637-652.
21. Georgopapadakou NH, (1998) Antifungals: mechanism of action and resistance, established and novel drugs. Curr. Opin. Microbiol. 1: 547-557.
22. Sheehan DJ, Hitchcock CA. Silbey. C M. (1999) Current and emerging azole antifungal agents. Clin. Microbiol. Rev., 12: 501-517.
23. Massa S, Stefancich G, Corelli F, Silvestri, R, Mai A, Artico M, Panico S, Simonetti N. (1989) Research on antibacterical and antifungal agents. Synthesis and antifungal activities of 1-{pmethyl- alpha-[4-(1H-pyrrol-1-yl)phenyl]benzyl}azoles and some related products. Arch. Pharm. (Weinheim). 322: 369-373.
24. Stefancich G, Artico M, Ortar G, Silvestri R, Simonetti G, Apuzzo G, Artico M. (1992) Synthesis and antifungal activity of structural analogues of bifonazole and ketoconazole. Arch.Pharm. (Weinheim). 325: 687-694.
25. Artico M, Ragno R, Porretta GC, Massa S, Musiu C, Spiga MG, Corrias S, La Colla P. (1996) Iso-Miconazole and related derivatives: synthesis and antifungal activities. Med. Chem. Res., 137-147.
26. Hall LH, Kier LB. (1991) The molecular connectivity chi indexes and kappa shape indexes in structure-property modeling. In: Lipkowitz K.B., Boyd D.B., editors. Reviews in Computational Chemistry II. New York: VCH. 367.
27. Karelson M, Lobanov VS, Katritzky AR. (1996) Quantum-chemical descriptors in QSAR/QSPR studies. Chem Rev., 96(3): 1027–1044.
28. Kier LB, Hall LH. (1976) Molecular connectivity in chemistry and drug research. Academic Press, New York
29. Hansch C, Fujita T. (1964) p-r-p analysis. A method for the correlation of biological activity and chemical structure. J Am Chem Soc., 86: 1616–1626.
30. Hansch C, Leo A, Unger SH, Kim KH, Nikaitani D, Lien EJ. (1973) Aromatic substituent constants for structure-activity correlations. J Med Chem., 16: 1207–1216.

31. Randic M. (1975) Characterization of molecular branching. J Am Chem Soc., 97: 6609–6615.
32. Randic M. (1993) Comparative regression analysis. Regressions based on a single descriptor. Croat Chem Acta 66: 289–312.
33. Wiener H. (1947) Structural determination of paraffin boiling points. J Am Chem Soc 69: 17–20.
34. Hansch C, Hoekman D, Gao H.(1996) Comparative QSAR: Toward a deeper understanding of chemicobiological interactions. Chem Rev. 96: 1045-35.
35. Kurup A, Garg R, Hansch C.(2001) Comparative QSAR study of tyrosine kinase inhibitors. Chem Rev. 101: 2573-2600.
36. Garg R, Kurup A, Mekapati SB, Hansch C. (2003) Cyclooxygenase (COX) inhibitors: A comparative QSAR study. Chem Rev. 103: 703-731.