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Quantitative Structure Activity Relationships of Chalcones as Antifungal Agents

Santosh Tiwari[1], Vikash Pandey[1], Santosh Kumar Tiwari[2] and Kamlesh Mishra[3]
1, Department of Chemisty, Govt. G.D.C. College, Rewa, (M.P.) - India
2, Department of Chemistry, Govt. S.K. P.G. College, Rewa, (M.P.) - India
3, Department of Chemistry, A.P.S.University, Rewa, (M.P.) - India

Abstract

QSAR/QSPR analysis of a series of chalcones derivatives and there in vitro antifungal activity against *Fusarium proliferatum* are performed by using the computer assisted multiple regression procedure. The activity contributions for either chalcones substituent effects of these compounds were determined from the correlation equation and the predictions for the lead optimization were described. Some of the compounds showed appreciable activity against a fungus resistant strain, and could act a new hit for the design of better analogs.

Key-Words: Chalcones, QSAR/QSPR, Antifungal Agents

Introduction

Over the last three decades, important progress has been made in the therapy of systemic fungal infections. Different kinds of mycoses, especially invasive, have become an important public health problem as their incidence has increased dramatically in the last decades in relation to AIDS, hematological malignancies, transplant recipients and other immunosuppressed individuals[1–8]. Fungal infections remain a major direct cause of death in patients who are treated for a malignant disease, and emerging resistance is also an important problem[9].

*** Corresponding Author**
E.mail: santoshchem1984@gmail.com

Chalcones are 1,3 diaryl-2-propene-1-ones obtained from both synthetic and natural sources which are reported to have therapeutic activities such as antihypertensive and cardiovascular activity, anti-protozoal, anti-inflammatory, anti-diabetic, nitric oxide inhibitory activity, anti-cancer activities as well as antifungal and anti-tubercular activities.[10-15] Anti-fungal activity of chalcones has been investigated by number of researchers.[16-20] anti-fungal activity of the chalcones is related to enone substitution which binds with thiol group of the protein[21].

During the past two decades an increasing number of quantitative structure- activity/property relationship (QSAR/ QSPR) models have been using theoretical molecular descriptors for predicting biomedical, toxicological, and technological properties of chemicals. A quantitative structure-activity relationship, QSAR, is based on the reasonable premise that the biological activity of a compound is a consequence of its molecular structure and that, provided we can identify those aspects of molecular structure that are relevant to a particular biological activity, we can gain a better understanding of the mechanism by which the compound acts.

At present, QSAR, an important area of chemo-metrics, have been widely utilized to study the relationship between chemical structures and biological or other functional activities. Consequently, in recent years, there has been a shift of interest from the use of experimental data to the application of theoretical properties/parameters in the development of QSARs. In this study, the objective of this study were to determine

the influence of various substituents on the antifungal activity of chalcones was performed by multiple regression analysis technique[22-24].

Table:1 Structure of chalcones with different substituents

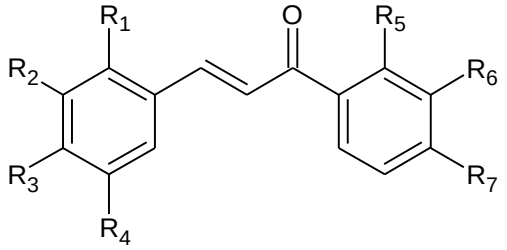


Figure:1 Chemical structure of chalcone

S.No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7
T-1			NMe_2				
2			SMe				
3			SMe				
4							NO_2
T-5			SMe			OH	
6			SMe				OMe
7			SMe		OH		
8			SMe				Me
9			SMe				Cl
10			SMe			NO_2	
11			SMe				
12			SMe		Cl		Cl
13	OMe						
14			SMe				Br
15		OMe	OMe	OMe			
16			SMe				OH
17			OMe	OMe	Cl		Cl
T-18	OMe		OMe			NO_2	
19			OMe	OMe		NO_2	
20			NMe_2			NO_2	
21	OMe						NO_2
22			NMe_2		Cl		Cl
T-23			OMe				Me
T-24			OMe			OH	
S.No.	**R_1**	**R_2**	**R_3**	**R_4**	**R_5**	**R_6**	**R_7**
25	OMe					NO_2	
26		NO_2				OCH_2O	
T-27			Cl			NO_2	
T-28		NO_2				Br	
29	Cl					OMe	
30	Cl						OEt
31			SO_2CH_3				
32			SO_2CH_3				NO_2
33			SO_2CH_3				Cl
34			SO_2CH_3		Cl		Cl
T-35	Cl				Cl		Cl
36	Cl					NO_2	
37	Cl					OH	
38			SMe			OCH_2O	
39			SMe			NH_2	
T-40			SMe			OCH_3	OCH_3
41			SMe			OCH_3	
42			SMe				OEt
T-43			SMe			Br	
44			SMe				F
45	Cl						OCH_2O
46	OMe			Cl			Cl
47			OMe				OCH_2O
T-48			OH				OCH_2O

Material and Methods

The MLR approach in QSAR analysis has been most widely used for the theoretical drug design due to various physico-chemical, topological and indicator parameters. In this study, the model is based on the in vitro activity of certain chalcones derivatives (1-48) against, *Fusarium proliferatum*, where antifungal activity (percentage inhibition at 2 mg/mL) Table-2.

The variables used as descriptors in the analysis are topological ,physico-chemical and indicator parameters. The correlation equation was performed using NCSS statistical software. The overall Statistical descriptor for the calculated best equation was found on the basis of regression coefficient , correlation coefficient , cross validated regression coefficient, PRESS/SSY, F-ratio, adjusted regression coefficient, Spress, which is found significant for the lead optimization in this set of compounds.

The total 48 of chalcones was divided into training and test sets comprising 36 and 12 compounds respectively. The activities in the test set were predicted by using the equations developed using the training set. This is known as external validation process.

Table: 2 Inhibitory activities, calculated topological descriptors, calculated physicochemical descriptors and indicator descriptors.

C.No.	pMIC[M]	J	χ^0	χ^1	Den	IP^1
1	3.892	1.587	10.088	7.433	1.18	0
2	4.001	1.521	13.458	9.038	1.08	0
3	3.924	1.56	10.958	7.826	1.257	0
4	4.059	1.472	14.113	9.614	1.36	0
5	4.024	1.561	11.828	8.22	1.399	0
6	4.04	1.516	13.405	9.131	1.455	0
7	4.282	1.566	12.535	8.737	1.359	0
8	4.308	1.547	13.405	9.131	1.317	0
9	4.375	1.515	15.905	10.342	1.217	0
10	4.31	1.547	13.405	9.131	1.426	0
11	4.342	1.547	13.405	9.131	1.455	0
12	4.406	1.547	13.405	9.131	1.654	0
13	3.979	1.527	12.535	8.758	1.191	0
14	3.96	1.561	11.828	8.22	1.33	0
15	4.005	1.516	13.405	9.131	1.22	0
16	3.95	1.561	11.828	8.22	1.13	0
17	3.977	1.527	12.535	8.758	1.09	0
18	3.98	1.527	12.535	8.758	1.166	0
19	3.958	1.561	11.828	8.22	1.278	0
20	4.027	1.472	14.113	9.614	1.288	0
21	3.979	1.527	12.535	8.758	1.187	0
22	4.004	1.516	13.405	9.131	1.15	0
23	4.225	1.56	10.958	7.826	1.205	1
24	4.253	1.524	11.665	8.365	1.174	1
25	4.257	1.524	11.665	8.365	1.24	1
26	4.283	1.483	12.372	8.865	1.209	1
27	4.227	1.56	10.958	7.826	1.317	1
28	4.285	1.513	12.535	8.737	1.419	1
29	4.11	1.561	11.828	8.22	1.577	0

IP^1 : It is unity when N is present in X, otherwise it becomes zero.

Statistical analysis

The complete regression analysis was carried out by PASS 2005, GESS 2006 and NCSS statistical software.

Results and Discussion

A set of 29 heterocyclic derivatives was used for MLR model generation. The reference drugs were not included in model generation as they belong to a different structural series. The inhibitory activity p MIC [M] was used as a dependent variable in the QSAR study. Different physico-chemical descriptors, topological descriptors and indicator descriptors were used as independent variables and were correlated with antifungal activity.

Developing a QSAR model requires a diverse set of data, and thereby, a large no. of descriptors has to be considered. Pearson's correlation matrix has been performed on all descriptors by using NCSS statistical software. The QSAR models are generated by step wise regression methods are given below:

pMIC [M] =3.4329+0.5322(±0.1966) Den

QSAR Model-1

The QSAR model-1 describes the importance of physico-chemical descriptor Density with the antifungal activity. The positive correlation coefficient shows that as the value of Density increases the antifungal activity also increases.

pMIC [M] = 3.3209+0.5882(±0.1678)Den
+ 0.1924(±0.0569) IP^1

QSAR Model-2

For antifungal activity, the QSAR model-2 show statistically more significant important with comparison QSAR model-1, In this model indicator descriptor IP^1 and physico-chemical descriptor Density both are directly proportional with the antifungal activity, means that as the value of both descriptors increases the antifungal activity also increases.

pMIC [M] = 2.5045+0.0695(±0.0166)X^0
+0.5317(±0.1320) Den
+0.2672(±0.0480) IP^1

QSAR Model-3

The QSAR model-3 demonstrate the importance of used three types of independent variable and shown very important statistical importance. X^0, Den, and IP^1, all descriptors shows positive coefficient with the antifungal activity.

Table: 3 Correlation Analysis

	pMIC[M]	J	X^0	X^1	Den	IP^1
pMIC[M]	1.0000					
J	-0.0757	1.0000				
X^0	0.3160	-0.6251	1.0000			
X^1	0.3395	-0.7020	**0.9895**	1.0000		
Den	0.4619	0.1581	0.1318	0.1064	1.0000	
IP^1	0.4421	-0.1340	-0.3806	-0.3145	-0.0988	1.0000

pMIC [M] = -3.9846+3.7582(±0.6947)J
+ 0.1427(±0.0177)X^0
+ 0.3599(±0.0958)Den
+0.3770(±0.0386)IP1

QSAR Model-4

The generation of QSAR model-4 is the result of addition of topological descriptors balaban index (J) in QSAR model-3 results to get statistically significant result. The regression coefficient of QSAR model-3 (r = 0.8) which is good among all previous developed QSAR models.

pMIC [M] = -9.9319+6.1930(±0.5265)J
-0.2648(±0.0585)X^0
+0.8469(±0.1198)X^1
+0.3283(±0.0551)Den
+ 0.3558(±0.0223)IP^1

QSAR Model-5

The QSAR model-5 show the importance of all used topological, physico-chemical and indicator descriptors, in which only zero order connectivity index show negative correlation coefficient while rest of other show positive coefficient. The regression

coefficient value is higher and cross-validated descriptor shows the validation of developed QSAR model-5. There are five serious outliers compounds are found and after deletion of outlier compound no. 02, 03, 06,15 and 28. The developed QSAR model becomes

pMIC [M] = -10.1116+ 0.0532(±0.0386)J
-0.3141(±0.2884)X^0
+0.9429(±0.0338)X^1
+ 0.4594(±0.0694)Den
+0.3747(±0.0119)IP^1

QSAR Model-6

For antifungal activity against *C. albicans*, the developed QSAR model-6 describes the importance of topological descriptors, physico-chemical descriptor density and indicator descriptors. From the QSAR model-6, we observe that first order connectivity index has mostly affected the antifungal activity which encode for the branching of compounds, while density and IP^1 also show positive coefficient with the antifungal activity and zero order connectivity index shows negative coefficient. The correlation coefficient between the used independent descriptors and antifungal property is maximum in the QSAR model-6.

The generated QSAR model-6 is statistically sounded model which demonstrate the importance of different variable in the generation of antifungal activity of heterocyclic derivatives. The validation of QSAR model is analyzed by cross-validated statistical parameters i.e. PRESS, SSY, PRESS/SSY, Spress, R^2_{cv}, R^2_{adj} etc. The difference between R^2_{cv} and R^2_{adj} illustrate this is a best model for antifungal activity of heterocyclic derivatives.

Even though the sample size and the 'Rule of Thumb' allowed us to go for development of five parametric model in MLR. The 'Rule of Thumb' gives information about the number of parameters to be selected for regression analysis in QSAR based on the number of compounds.[20] According to this rule for QSAR model development one should select one parameter for a five compound data set.

The value of inhibitory activity of a set of heterocyclic derivatives was calculated with the QSAR model-6. These data are compared with experimentally obtained values of antifungal activity against *C. albicans*. From the data presented in Table-6, it is shown that high agreement between the experimental and predicted inhibitory values was obtained.

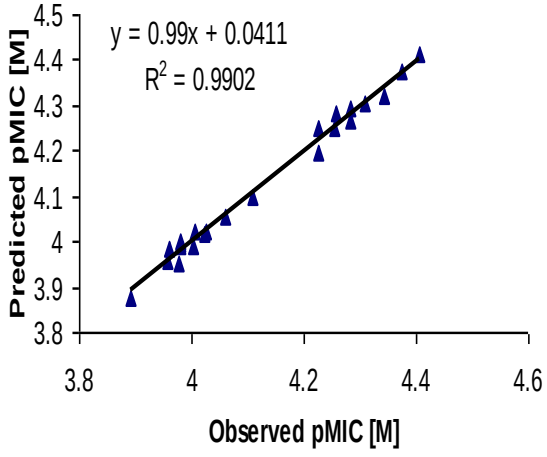
Table: 4 Statistical and Cross- Validated Statistical Descriptors of Generated QSAR Models.

Model	n	Intercept	r	F-ratio	PRESS	SSY	PRESS/SSY	S_{press}	R^2_{cv}	R^2_{adj}
1	29	3.4330	0.46	7.324	0.6511	0.7262	0.8	0.14	0.10	0.18
2	29	3.3210	0.67	10.796	0.4718	0.7262	0.6	0.12	0.35	0.41
3	29	2.5046	0.82	17.596	0.3108	0.7262	0.4	0.10	0.57	0.67
4	29	-3.9847	0.92	35.438	0.1588	0.7262	0.2	0.07	0.78	0.83
5	29	-9.9320	0.97	96..237	0.0556	0.7262	0.07	0.04	0.92	0.94
6	23	-10.1117	0.99	340.935	0.0100	0.5749	0.01	0.02	0.98	0.98

Table: 6 Antifungal Screening Summary

C. No.	Actual	Predicted	Residual
1	3.892	3.877	0.015
2	4.059	4.055	0.004
3	4.024	4.015	0.009
4	4.282	4.293	-0.011
5	4.375	4.373	0.002
6	4.31	4.307	0.003
7	4.342	4.32	0.022
8	4.406	4.411	-0.005
9	3.979	3.999	-0.02
10	3.96	3.984	-0.024
11	4.005	4.024	-0.019
12	3.977	3.953	0.024
13	3.98	3.988	-0.008
14	3.958	3.96	-0.002
15	4.027	4.022	0.005
16	3.979	3.997	-0.018
17	4.004	3.992	0.012
18	4.225	4.197	0.028
19	4.253	4.251	0.002
20	4.257	4.281	-0.024
21	4.283	4.268	0.015
22	4.227	4.248	-0.021
23	4.11	4.097	0.013

Figure:1 Plot of predicted V/S experimentally observed inhibitory activity of heterocyclic derivative against *C.albicans.*



Comparing the activities of the heterocyclic derivatives it was found that (Compound 4, 8, 10, 14, 16, 20, and 22) are more active then other rest compounds. It can be concluded the presence of nitrogen substituents leads to an increase in the activity, in comparison to the presence of a methyl group. These observations revealed that the nature of substituents has an effect on inhibitory activity.

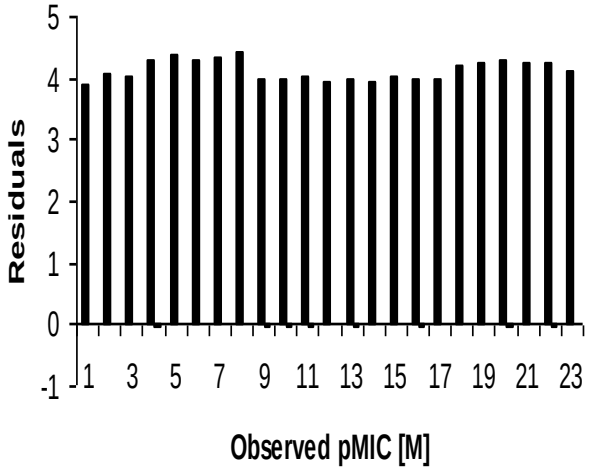


Figure:2 Graph plotted between observed antifungal activity and residual activity

The substitution of $NHCOCH_3$ at R position also increases the antifungal activity and The presence of electron withdrawing group such as NO_2 and Chloro group in R_1 position also influence positively antifungal activity.

Conclusion

From the results and discussion above, we conclude that the heterocyclic derivatives are effective against *C. albicans.* The results obtained from the present investigation of antifungal activity studies indicate that the presence of an electron withdrawing group and Nitrogen atom leads to increase in the activity in comparison of a methyl group. The validity of the models have been established by the determination of suitable statistical descriptors.

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