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QSAR study of Antifungal activity of some Heterocyclic Compounds

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ABSTRACT

QSAR analysis on a set of heterocyclic derivatives for antifungal activity was performed by using multiple regression procedure. The activity contribution of these compounds was determined from regression equation and the validation procedure to analyze the predictive ability of QSAR model was described. High agreement between experimental and predicted inhibitory values was obtained. The results of this study indicate that the parameter has a significant effect on antifungal activity of this class of compounds, thus simplifying design of new biologically active molecules.

Keywords: Quantitative structure-activity relationship, Antifungal activity, Multiple linear regressions

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INTRODUCTION

The mycosis diseases are affections caused by body infestation with pathogenic mycosis parasites of pathogenic potential. Some of these fungi live in nature as saprophytes or in the human body or animals and they accidentally become parasite. Recent decades are the witnessed increasing efforts for developing new antifungal drugs that are capable to inhibiting various diseases related to *Candida albicans*.

The conception that there exists a close relationship between bulk properties of compounds and their molecular structure is quite rooted in chemistry. Therefore, it is the basic tenet of chemistry to identify these assumed relationships between the molecular structure and physico-chemical properties and then to quantify them. QSAR approach including multivariate data analysis in combination with statistical design has been extensively employed. This method represents an attempt to correlate biological activities of compounds with structural or molecular descriptors including physico-chemical, electronic, geometrical, topological or thermodynamic parameters.[1-7]

Most fungi are completely resistant to the action of antimicrobial drugs. Only a few substances have been discovered that exert an inhibitory effect on the fungi pathogenic in man and most of these are relatively toxic.[8-10]

In this context, the aim of the present work was to investigate the quantitative effect of structural properties of different substituted heterocyclic derivatives on their antifungal activity against *C.albicans*. The central objective of the study was to select a mathematical model which correlates the best inhibitory activity of this class of molecules with their descriptors[11-13.]

MATERIALS AND METHOD

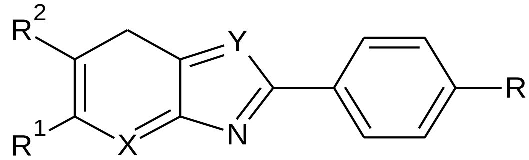
Data set

The heterocyclic compounds 1-29 included in this QSAR study have shown antifungal activity in pMIC [M] value against *C. albicans* comparable to the activity of some commonly used antifungal[14-18]. In this study, QSAR analysis of antifungal heterocyclic derivative is presented in Table-1.

Data analysis

QSAR analysis consists of the following steps;

Table 1: The Structure of Heterocyclic Compounds



C. No.	X	Y	R	R^1	R^2
1	CH	O	H	H	H
2	CH	O	$C(CH_3)$	H	H
3	CH	O	NH_2	H	H
4	CH	O	$NHCOCH_3$	Cl	H
5	CH	O	Cl	Cl	H
6	CH	O	NO_2	Cl	H
7	CH	O	H	NO_2	H
8	CH	O	CH_3	NO_2	H
9	CH	O	$C(CH_3)$	NO_2	H
10	CH	O	NH_2	NO_2	H
11	CH	O	Cl	NO_2	H
12	CH	O	Br	NO_2	H
13	CH	O	C_2H_5	NH_2	H
14	CH	O	F	NH_2	H
15	CH	O	$N(CH_3)_2$	NH_2	H
16	CH	O	CH_3	CH_3	H
17	CH	O	C_2H_5	CH_3	H
18	CH	O	OCH_3	CH_3	H
19	CH	O	F	CH_3	H
20	CH	O	$NHCOCH_3$	CH_3	H
21	CH	O	$NHCH_3$	CH_3	H
22	CH	O	$N(CH_3)_2$	CH_3	H
23	N	O	CH_3	H	H
24	N	O	C_2H_5	H	H
25	N	O	OCH_3	H	H
26	N	O	OC_2H_5	H	H
27	N	O	NH_2	H	H
28	N	O	NO_2	H	H
29	CH	O	Br	NH_2	H

i. Structure optimization using semi-empirical methods. **ii**. Calculation of molecular descriptors. **iii.** Classification using good similarity index. **iv**. Correlation analysis using step forward selection. **v.** Multiple regression analysis by selected descriptors. **vi.** Evaluation of the significance level of the model. **vii.** Validation of the model. **viii.** Interpretation of the results.

Our structures were optimized by using ChemSketch12. The large pool of descriptors, provided by E-Dragon. The descriptors list includes (i.) Topological descriptors (ii) physico-chemical descriptors (iii) indicator descriptors.

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.[19]

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 demonstrates 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	Den
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 .

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-5, shown that high agreement between the experimental and predicted inhibitory values was obtained.

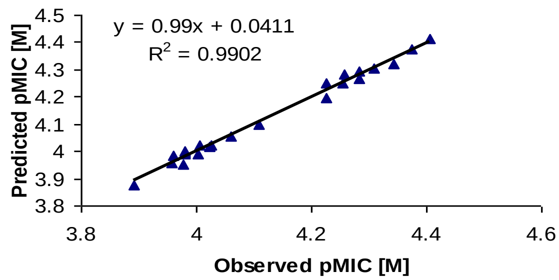


Figure 1. Plot of predicted V/S experimentally observed inhibitory activity of heterocyclic derivative against *C.albicans*

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: 5 Antifungal Screening

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

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

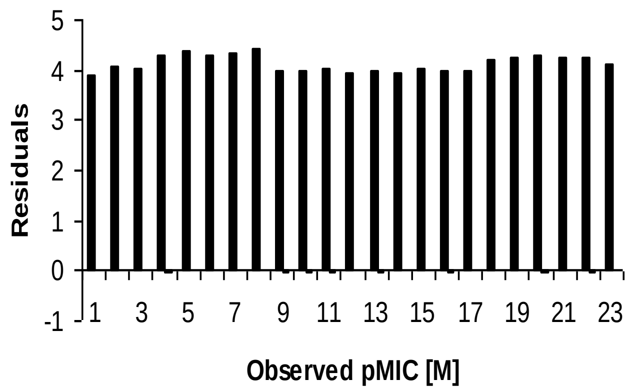


Figure 2. Graph plotted between observed antifungal activity and residual activity

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 has been established by the determination of suitable statistical descriptors.

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REFERENCES

1. Julián-Ortiz J. Virtual Darwinian Drug Design: QSAR Inverse Problem, Virtual Combinatorial Chemistry, and Computational Screening. Comb. Chem. High Throughput Screen 2001; 4:295-310.
2. Dean P.M, Lewis R.A. Molecular Diversity in Drug Design. Kluwer Academic Publishers: Amsterdam, 1999.

3. Walters W. P, Stahl, M.T, Murcko, M.A. Virtual screening: An overview. Drug Discovery Today 1998; 3:160-178.
4. Karelson, M. Molecular Descriptors in QSAR/ QSPR; John Wiley & Sons: New York. 2000.
5. Katritzky A. R, Gordeeva E. V. Traditional Topological Indexes vs Electronic, Geometrical, and Combined Molecular Descriptors in QSAR/QSPR Research. J Chem Inf Comput Sci 1993; 33:835.
6. Kier L. B, Hall L. H. Molecular Connectivity in Chemistry and Drug Research; Academic Press: London. 1976.
7. Balaban A. Topological and Stereochemical Molecular Descriptors for Databases Useful in QSAR, Similarity/Dissimilarity and Drug Design. SAR QSAR Environ Res 1998; 8: 1-21.
8. Gilgado F, Serena C, Cano J. Antifungal susceptibilities of the species of the Pseudallescheria boydii complex. Antimicrob Agents Chemother 2006; 50:4211-3.
9. Ortoneda M, Capilla J, Pastor F. In vitro interactions of approved and novel drugs against Paecilomyces spp. Antimicrob Agents Chemother 2004; 48:2727-9.
10. Meletiadis J, Meis JF, Mouton JW. In vitro activities of new and conventional antifungal agents against clinical Scedosporium isolates. Antimicrob Agents Chemother 2002; 46:62-8.
11. Kullberg BJ, Sobel JD, Ruhnke M. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005; 366:1435-42.
12. Perfect JR, Marr KA, Walsh TJ. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 2003; 36:1122-31.
13. Herbrecht R, Denning DW, Patterson TF. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347:408-15.
14. Cornely OA, Maertens J, Winston DJ. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007; 356:348-59.
15. Nemunaitis J, Shannon-Dorcy K, Appelbaum FR. Long-term follow-up of patients with invasive fungal disease who received adjunctive therapy with recombinant human macrophage colonystimulating factor. Blood 1993; 82: 1422–27.
16. Gallin JI. Interferon-gamma in the management of chronic granulomatous disease. Rev Infect Dis 1991; 13: 973–78.

17. Blasi E, Pitzurra L, Bartoli A, Puliti M, Bistoni F. Tumor necrosis factor as an autocrine and paracrine signal controlling the macrophage secretory response to Candida albicans. Infect Immun 1994; 62: 1199–206.
18. Grazziutti ML, Rex JH, Cowart RE, Anaissie EJ, Ford A, Savary CA. Aspergillus fumigatus conidia induce a Th1-type cytokine response. J Infect Dis 1997; 176: 1579–83.
19. Djeu JY, Liu JH, Wei S. Function associated with IL-2 receptor-beta on human neutrophils. Mechanism of activation of antifungal activity against Candida albicans by IL-2. J Immunol 1993; 150: 960–70.
20. Wuthrich M, Finkel-Jiminez BE, Klein BS. Interleukin 12 as an adjuvant to WI-1 adhesin immunization augments delayed-type hypersensitivity, shifts the subclass distribution of immunoglobulin G antibodies, and enhances protective immunity to Blastomyces dermatitidis infection. Infect Immun 2000; 68: 7172–74.
21. Clemons KV, Brummer E, Stevens DA. Cytokine treatment of central nervous system infection: efficacy of interleukin-12 alone and synergy with conventional antifungal therapy in experimental cryptococcosis. Antimicrob Agents Chemother 1994; 38: 460–64.