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Quantitative structure activity relationships study of amino alcohols derivatives as antifungal agents against Candida. Albicans

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ABSTRACT

Quantitative structure activity relationships analysis on a set of synthesized amino alcohols Analogues tested for growth inhibitory antifungal activity was performed by using multiple linear regressions procedure. The activity contributions of these compounds were determined from regression equation and the validation procedures to analyze the predictive ability of QSAR models were described. .The results are discussed on the basis of statistical data. High agreement between experimental and predicted antifungal activity inhibitory values are obtained. To confirm the predictive power of the models, an external set of molecules was used. High agreement between experimental and predicted inhibitory values, obtained in the validation procedure, indicated the good quality of the derived QSAR models.

INTRODUCTION

Quantitative structure activity relationships are also called traditional QSAR or Hansch QSAR. . This is the application of the technique described above to biological activities, such as environmental toxicology or drug activity [1-2]. The discussion above is applicable but a number of other caveats apply; which are addressed in this section. The following discussion is oriented toward drug design, although the same points may be applicable to other areas of research as well. In the case of drug design, it may be desirable to use parabolic functions in place of linear functions. The descriptor for an ideal drug candidate often has an optimum value. Drug activity will decrease when the value is either larger or smaller than optimum. This functional form is described by a parabola, not a linear relationship [3]. The advantage of using QSAR over other modeling techniques is that it takes into account the full complexity of the biological system without requiring any information about the binding site. The disadvantage is that the method will not distinguish between the contribution of binding and transport properties in determining drug activity [4]. QSAR is very useful for determining general criteria for activity, but it does not readily yield detailed structural predictions [5-6].

Amino alcohols derivative regarding their antifungal effect have been screened on pathogenic yeasts *Candida albicans* and the present work addresses the mechanism of antifungal action. There are several known mechanism of actions for commercial antifungal agents such as inhibition of squalene epoxide, egrosterol, folic acid chitin etc. and effect on the protein composition to explore the influence of our amino alcohols on the chitin synthase enzyme in order to get more insight into structure activity relationship [7]. Amino alcohols react with low molecular weight and protein associated thiols to show thereby, activity against pathogenic fungi. Our aim has been to find a class of compounds having a new target specific only for fungi, and started the investigations with our amino alcohols derivatives [8-9]. The mechanism of action of azoles as antifungal agents is based on the disruption of sterol biosynthesis yielding the reduction of the ergosterol production [10]. This blocks the function of ergosterol in fungal membranes and disturbs both the structure and the functions of the membrane. Because ergosterol also plays a hormone like (sparking) role in fungal cell, which stimulates growth [11], the net effect of azole is the inhibition of the fungal growth [12].

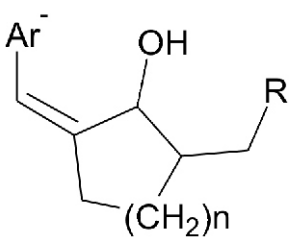

Fig 1: Chemical structure of amino alcohols derivatives for antifungal activity

Table 1: Structural Substitutions and Calculated Descriptors of amino alcohols derivatives for antifungal activity

S.No.	n	R	Ar	Log MIC	IR	$^2X^v$	$^3X^v$
1	1	Pip	Ph	2.0	1.59	6.781	5.143
2	1	Pip	4-OCH_3-C_6H_4	2.0	1.579	7.144	5.460
3	2	Mor	Ph	2.3	1.579	6.524	5.138
4	2	Mor	Ph	2.3	1.579	6.524	5.138
5[b]	2	4-pip	Ph	2.3	1.566	7.040	5.629
6	3	Mor	Ph	2.3	1.573	6.904	5.273
7	3	Pip	Ph	2.3	1.574	7.353	5.618
8	3	Pip	Ph	1.69	1.574	7.353	5.618
9	4	Mor	Ph	2.3	1.568	7.258	5.542
10	4	pip	Ph	2.0	1.568	7.706	5.887

Data set and Methodology

The biological data used in this study were antifungal activity against *Candida albicans,* (in terms of log MIC), of a set ten amino alcohols analogues derivatives are taken from the literature [13]**.** The amino alcohols derivatives, the reduction of the keto group dramatically decreased their antifungal activity.

The best multilinear regression (BMLR) procedure [14] was used to find the best correlation models from selected noncollinear descriptors. The BMLR selects the best two-parameter regression equation, the best three- parameter regression equation, etc., based on the highest r^2 value in the stepwise regression procedure. During the BMLR procedure the descriptor scales are normalized, centered automatically and the final result is given in natural scales. This result has the best representation of the property in the given descriptors pool.

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 [15-16]. By analysis of the plot of the number of descriptors involved in the obtained models versus squared correlation coefficient (and cross-validated squared correlation coefficient) values corresponding to those models, it appears that the statistical parameters of the model improve (steeper ascent of the relationship) up to a certain point ('break point') and after that the improvement is negligible (low ascent of the relationship). Consequently, the model corresponding to the break point is considered the best/optimum model. The QSAR models obtained were validated (i) by the leave-one-out method, (ii) by internal correlation whereby 1/3 of the compounds is predicted with the model fitted with 2/3 of the compounds, and (iii) by external validation.

Table 2: Correlation matrix between different descriptors and antifungal activity

	Log MIC	IR	$^2X^v$	$^3X^v$
Log MIC	1.0000			
IR	-0.2171	1.0000		
$^2X^v$	-0.4286	-0.5767	1.0000	
$^3X^v$	-0.3042	-0.7405	0.9447	1.0000

RESULTS

In the first step, separate stepwise selection-based QSAR analyses were performed using different types of descriptors, and then, an MLR equation was obtained utilizing the pool of all calculated descriptors [17-19].

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. QSAR models against *Candida albicans* have been obtained after removal of few compounds as outliers. In present study, physicochemical descriptor, index of refraction (IR), and topological descriptor second and third order valence connectivity index were selected as independent variables and log MIC as dependent variables. This also shows the dependence of activity on structural features of the molecule as well as justifies the structural numerates of molecules in the form of topological indices. For the QSAR study of the same series we tested the bivariate combinations of the parameters. The results obtained form the bivariate combinations are encouraging and better models are shown below with their statistics.

The correlation coefficient of developed mono-parametric QSAR model no.1 (r = -0.30) are very low with the variance of 18.3 % indicates as the magnitude of second order valence connectivity index decreases the antifungal activity increases. The biparamatric QSAR model listed in table 4 is with the correlation coefficient value (r = 0.71) is low with the variance of 50.67% shows that the topological and physiochemical descriptor is both inversely proportional with the antifungal activity.

The triparametric QSAR model have correlation coefficient value (r = 0.73) with the variance of 53.17 % indicates that

Table 3: Developed QSAR model and Statistical parameters for testing prediction ability of the MLR models of Amino alcohols derivatives.

Log MIC =	n	R^2	F-Ratio	R^2_{cv}	S_{press}	Q
$3.8485-0.2407^3X^v$	10	0.18	1.80	0.14	0.22	2.08
$38.3854-20.9182^3X^v$ -0.4661IR	10	0.51	3.59	0.83	0.18	4.17
$49.1887-27.1491IR-0.1586^2X^v-0.5825^3X^v$	10	0.53	2.27	0.26	0.18	4.06
$47.3220-26.1200IR-0.1402^2X^v-0.5570^3X^v$	08	**0.97**	50.74	0.89	0.04	30.10

physicochemical and topological both descriptors influence inversely with the antifungal activity of amino alcohols derivatives. There are two serious outliers in the series and after deleting the compounds no. 07 and 08 the resulting triparametric QSAR model has significant correlation coefficient (r = 0.98) with the variance of 99.9%. Initially we have used Pogliani's quality factor Q for investigating predictive power of the various parameters and finally we used the cross validation parameters to prove our findings.

DISCUSSIONS

Among the several model generated, the three best were selected for the discussions. The selection was based on the previously mentioned statistical parameters. Initial regression analysis indicated that topological descriptors used, in combination with physicochemical descriptors index of refraction (IR) plays a dominant role in shaping antifungal activity (the greatest value of regression coefficient of the IR).

Table 4: Actual and Predicted antifungal activity

Com. No.	Act. log MIC	Pred. log MIC	Residual
1	2.0	1.975	0.025
2	2.0	2.035	-0.035
3	2.3	2.301	-0.001
4	2.3	2.301	-0.001
5	2.3	2.295	0.005
6	2.3	2.329	-0.029
7	2.3	2.260	0.040
8	2.0	2.005	-0.005

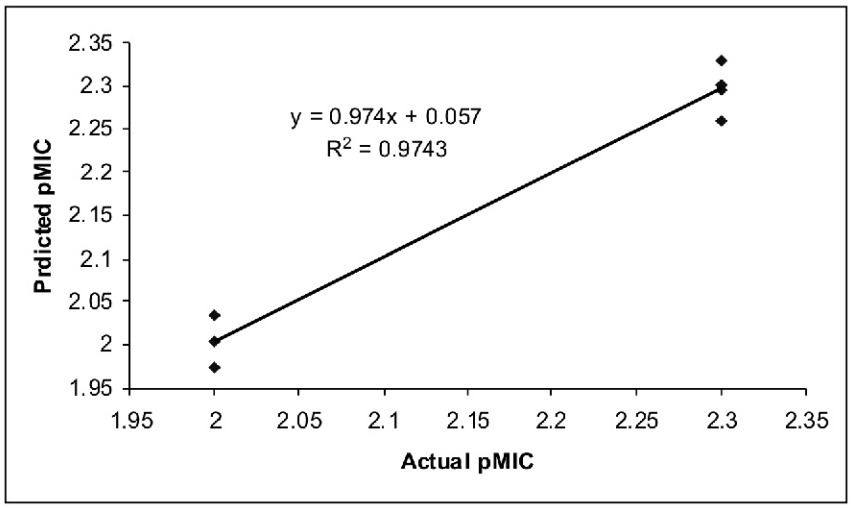

Fig 2: Plots between actual log MIC and predicted log MIC activity

The negative coefficients of IR indicates that the activity increases as the magnitude of those descriptors decreases (Eq-1-4).

In the QSAR study, we sought to correlate potency to inhibit growth of fungus strains of *C. albicans* with molecular properties to include amino alcohols derivatives reported above. Our analysis also increased the number of descriptors compared to the previous effort focusing on antifungal activity of these compounds, meaningful three and two parameter QSAR equations were obtained for fungal strain. Descriptors found to correlate with log MIC for *C. albicans* involved index of refraction, and second/third order valence connectivity index as shown in table 3.

The correlation coefficients were found to be good (0.80-0.98) and excellent correlation was obtained is positive with R^2 value of 0.97 and R^2_{cv} 0.89.

CONCLUSION

Analysis of the descriptors used in Eqns (1)(4) shows close agreement of the results obtained with the known modes of antifungal activity of amino alcohols derivatives. In general terms, these correlation equations contain two types of descriptors: those describing molecular bulk properties and those representing chemical reactivity of the substance under study. Index of Refraction and branching are directly related to hydrophobicity, and topological indices such as those of Kier and Hall make significant positive contributions to the target activity. Taking into account the promising results, we expect that the E-Dragon will also derive satisfactory correlation equations for predicting antifungal activity of different amino alcohol derivatives in various other biological systems using theorectical molecular descriptors calculated from chemical structure.

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