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## QSARs of Some 5- or 6-Methyl-2-Substituted Benzoxazoles/Benzimidazoles against *Candida albicans*

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**Abstract:** QSAR analysis of some 5- or 6-methyl-2-substituted benzoxazoles/benzimidazoles was studied for the antifungal activity against *C. albicans* using Hansch analysis. Prediction for the lead optimization in this QSAR analysis was described by the description of various hydrophobic, electronic, steric and structural parameters related to positions R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, X, Y. The cross-validation method was also applied to the data set in order to prove the predictive power by

using the BILIN statistical software. The resulting QSAR revealed that substitution at position Y with the CH<sub>2</sub> group was significant for the improved antifungal activity. Moreover, hydrophobic properties of the substituents at position R<sub>2</sub> are indicative for the antifungal activity against *C. albicans*.

**Key Words:** Benzoxazole, Benzimidazole, Antifungal activity, QSAR, Hansch analysis

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### Introduction

Mycotic illnesses in humans are divided into three groups: contagious skin and hair infections, noncontagious soilborne or airborne systemic infections and noncontagious foodborne toxemias. The responsible organisms and methods of prevention and treatment differ with each group. The prevalence of systemic fungal infections has increased significantly during the past decade. This increase is due to greater use of broad-spectrum antibiotics, immunosuppressive agents, central venous catheters, intensive care low birth weight infants, organ transplantation and the acquired immunodeficiency syndrome (AIDS) epidemic (1-13).

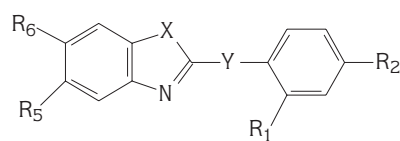
Significant antifungal chemotherapy began in 1903, with the successful use of potassium iodide for the treatment of sporotrichosis. Except for the development of flucytosine, there was little progress until the early 1970s and the development of the azole drugs. The current era, which is characterized largely by the modifications of azole drugs, began with miconazole and ketoconazole and brought the agents fluconazole and itraconazole and ravuconazole, which can be given orally and have increased potency, decreased toxicity and a broader spectrum of activity (14-19).

In the past 10 years there has been a major expansion in the development of antifungal drugs, but there are still weaknesses in the range and scope of current antifungal

chemotherapy (5). New developments have included the modification of existing drug molecules to eliminate toxicity and improve activity. In short, antifungal therapy has advanced rapidly in the last few years compared to previous years and recommendations for treatment of fungal infections are likely to change in the near future as our understanding of fungal infections improves and new antifungal therapies are discovered.

Biologically active benzoxazoles have been known for a long time and it was seen that position 2 is decisive for the biological activity, whereas position 5 determines the intensity of their activity (20-22).

Recently, we reported the synthesis and in vitro antifungal activities of different 5- or 6-methyl-2-substituted benzoxazoles/benzimidazoles against the fungus *Candida albicans* (23-25) (Figure 1).



R<sub>1</sub>=H, Cl, F, NO<sub>2</sub>, CH<sub>3</sub>, OCH<sub>3</sub>  
R<sub>2</sub>=H, Cl, Br, NH<sub>2</sub>, CH<sub>3</sub>, OCH<sub>3</sub>  
R<sub>5</sub>=H, CH<sub>3</sub>  
R<sub>6</sub>=H, CH<sub>3</sub>

Y= —, CH<sub>2</sub>, CH<sub>2</sub>O, CH<sub>2</sub>S  
X= O, NH

Figure 1. Antifungal active some benzoxazole and benzimidazole derivatives against *C. albicans*.

An extrathermodynamic approach in the analysis of quantitative structure activity relationships (QSAR) has been most widely and effectively used for theoretical drug design. This method has also been called the Hansch approach and it assumes that the potency of a certain biological activity exerted by a series of congeneric compounds can be expressed in terms of a function of various physicochemical (electronic, steric and hydrophobic) effects (26-29). This assumption is summarized in an equation as follows:

$$f(\text{biological activity}) = f(\text{electronic}) + f(\text{steric}) + f(\text{hydrophobic}) + [f(\text{structural}) + f(\text{therotical})]$$

If these functions could be formulated in an equation showing certain effects favorable for the activity, structural modifications that enhance such properties would be expected to generate potent active compounds.

Multiple regression analysis involving finding the best fit of a dependent variable (microbiological activity) to a linear combination of independent variables (descriptors) by the least squares method was used (30). This is formally expressed as follows:

$$y = a_0 + a_1x_1 + a_2x_2 + a_3x_3 + \dots + a_nx_n$$

where y is related to the microbiological activity of a compound,  $x_1, x_2, \dots, x_n$  are the descriptor values related to the activity and  $a_0, a_1, a_2, \dots, a_n$  are the regression coefficients determined by the least square analysis. This equation is developed for each compound in our QSAR study.

In this present study, QSAR analysis of some antifungal active 5- or 6-methyl-2-substitutedbenzoxazoles/benzimidazoles, 1-25 given in Figure 1, against *C. albicans* were determined using Hansch analysis.

### Experimental

Multivariate Hansch analysis in QSAR has been most widely and effectively used for theoretical drug design due to various physicochemical (electronic, steric and hydrophobic) parameters and structural indicator parameters being used together. The assumption can be formulated as given in the equation below.

$$\log 1/C = \sum a_i I_i + \sum b_j X_j + c$$

where  $I_i$  is the structural indicator parameters and  $X_j$  is the physicochemical variables.

For the procedure of descriptor selection related to the activity among the candidate set of variables, forward step-wise multiple regression of elimination was applied. During the development of the best fit model of correlation equation, the minimum F value for entering and removing the variables in the step-wise multiple regression was taken to be 8.0, which is statistically significant at the 1% level of probability (31).

In order to judge the validity of the predictive power of the QSAR, the cross-validation method is also applied to the original data set by removing a group of compounds from the data in such a way that each observation (compound) is deleted once and once only. For each reduced data set, a model is developed and the response values of the deleted observations are predicted from this model. The cross-validation method was also applied to the data set in order to judge the validity of predictive power of the model and overall PRESS (Predictive Residual Sum of Square) values were calculated (32).

Regression analysis and calculations were run on a PC using the BILIN statistical program package (33,34). In the equations, the figures in parentheses are the standard errors of the regression coefficients. For a given equation, n is number of compounds,  $r^2$  denotes square of the multiple correlation coefficients, F is the significance test and s represents the residual standard deviation.

A congeneric set of 5- or 6-methyl-2-substitutedbenzoxazoles/benzimidazoles 1-25 were considered in this study. The candidate set of variables used in this analysis includes hydrophobic, electronic, steric and structural parameters. For the structural variables  $I_{R6}$  was defined as 0 for possessing H, 1 for possessing  $CH_3$  at position  $R_6$ ;  $I_{R5}$  was defined as 0 for possessing H, 1 for possessing  $CH_3$  at position  $R_5$ ;  $I_{yO}$  was defined as 1 for possessing O atom;  $I_{yCH_2}$  was defined as 1 for possessing  $CH_2$  group;  $I_{yCH_2O}$  was defined as 1 for possessing  $CH_2O$  group;  $I_{yS}$  was defined as 1 for possessing  $CH_2S$  group at position Y and  $I_x$  was defined as 1 for possessing O atom, 0 for NH atoms at position X. The hydrogen donating/accepting capabilities ( $H_{DONOR}/H_{ACCEPT}$ ) of the substituents at  $R_1, R_2, R_5, R_6$  were the indicator variables.

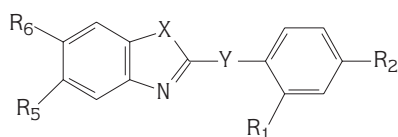
The screened physicochemical parameters in this QSAR study were  $\pi$  for the hydrophobic effects, F (field

effect), R (resonance effect) and  $\sigma$  as the electronic influence and MR, MW, Es, Es-V, Verloop's STERIMOL parameters ( $L$ ,  $B_1$ ,  $B_4$ ) for the steric interactions of the substituents  $R_1$ ,  $R_2$ ,  $R_5$  and  $R_6$ . Values for all candidate physicochemical variables used in this QSAR study were taken from the table of Hansch et al. (14). The values of the descriptors related to the activity among the candidate test set of variables of the best results in the QSAR analysis are shown in the Table.

## Results and Discussion

Predictions for the lead optimization in this QSAR analysis of antifungal active 5- or 6-methyl benzoxazoles/benzimidazoles were described by the description of various hydrophobic, electronic, steric and structural parameters related to positions  $R_1$ ,  $R_2$ ,  $R_5$ ,  $R_6$ , X, Y. One leave out cross-validation method was also applied to the data set in order to prove the predictive power by using the BILIN statistical software. Compounds

Table. Compounds and the parameters used in the best equation.



Com. No:	$R_1$	$R_2$	$R_5$	$R_6$	X	Y	$\pi R_2$	lyCH <sub>2</sub>	MIC $\mu\text{g/mL}$	Obs. log <sub>1</sub> /C	Cal. log <sub>1</sub> /C	Residual
1	Cl	H	CH <sub>3</sub>	H	O	—	0	0	25	3.989	3.996	-0.007
2	OCH <sub>3</sub>	H	CH <sub>3</sub>	H	O	—	0	0	25	3.980	3.996	-0.015
3	NO <sub>2</sub>	H	CH <sub>3</sub>	H	O	—	0	0	25	4.007	3.996	0.011
4	Cl	Cl	CH <sub>3</sub>	H	O	—	0.71	0	25	4.046	4.024	0.023
5	CHH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	H	O	—	0.56	0	25	3.977	4.018	-0.041
6	OCH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	H	O	—	-0.02	0	25	4.032	3.995	0.037
7	Cl	H	H	CH <sub>3</sub>	O	—	0	0	25	3.989	3.996	-0.007
8	OCH <sub>3</sub>	H	H	CH <sub>3</sub>	O	—	0	0	25	3.980	3.996	-0.015
9	F	H	H	CH <sub>3</sub>	O	—	0	0	25	3.958	3.996	-0.038
10	NO <sub>2</sub>	H	H	CH <sub>3</sub>	O	—	0	0	25	4.007	3.996	0.011
11	Cl	Cl	H	CH <sub>3</sub>	O	—	0.71	0	25	4.046	4.024	0.023
12	CH <sub>3</sub>	CH <sub>3</sub>	H	CH <sub>3</sub>	O	—	0.56	0	25	3.977	4.018	-0.041
13	OCH <sub>3</sub>	OCH <sub>3</sub>	H	CH <sub>3</sub>	O	—	-0.02	0	25	4.032	3.995	0.037
14	H	H	CH <sub>3</sub>	H	O	CH <sub>2</sub>	0	1	12.5	4.251	4.298	-0.047
15	H	Br	CH <sub>3</sub>	H	O	CH <sub>2</sub>	0.86	1	12.5	4.383	4.332	0.051
16	H	NH <sub>2</sub>	CH <sub>3</sub>	H	O	CH <sub>2</sub>	-1.23	1	12.5	4.280	4.250	0.030
17	H	H	H	CH <sub>3</sub>	O	CH <sub>2</sub>	0	1	12.5	4.251	4.298	-0.047
18	H	H	CH <sub>3</sub>	H	NH	CH <sub>2</sub>	0	1	12.5	4.249	4.298	-0.049
19	H	Cl	CH <sub>3</sub>	H	NH	CH <sub>2</sub>	0.71	1	12.5	4.312	4.326	-0.014
20	H	Br	CH <sub>3</sub>	H	NH	CH <sub>2</sub>	0.86	1	12.5	4.382	4.332	0.049
21	H	NH <sub>2</sub>	CH <sub>3</sub>	H	NH	CH <sub>2</sub>	-1.23	1	12.5	4.278	4.250	0.028
22	H	H	CH <sub>3</sub>	H	O	CH <sub>2</sub> O	0	0	25	3.980	3.996	-0.015
23	H	H	CH <sub>3</sub>	H	O	CH <sub>2</sub> S	0	0	25	4.009	3.996	0.013
24	H	H	CH <sub>3</sub>	H	NH	CH <sub>2</sub> S	0	0	25	4.007	3.996	0.011
25	H	Cl	CH <sub>3</sub>	H	NH	CH <sub>2</sub> O	0.71	0	25	4.037	4.024	0.014

and parameters used in the best equation and observed, calculated and residual values are given in the Table. The plot of the observed and calculated C values of the growth inhibitory activity of compounds 1-25 against *C. albicans* using the best equation is shown in Figure 2.

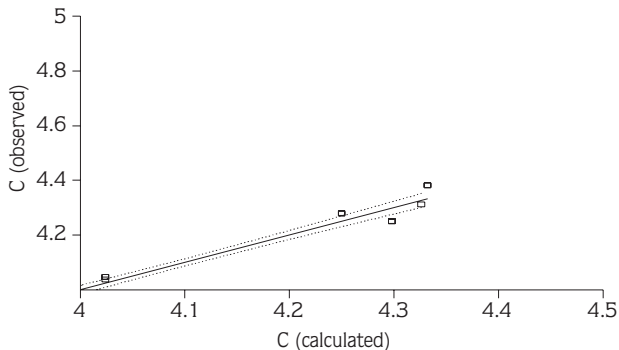


Figure 2. Plot of the observed and calculated C values of the growth inhibitory activity of compounds 1-25 against *C. albicans*.

The best equation and cross-validation results observed in this QSAR study are:

$$\log 1/C = +0.0393 (\pm 0.027) \pi R_2 + 0.303 (\pm 0.030) I_{yCH_2} + 3.996 (\pm 0.017)$$

$$n=25; \quad r=0.97; \quad s=0.03; \quad F=224.38;$$

$$p < 0.001; \quad Q^2=0.93; \quad s\text{-PRESS} = 0.03$$

n: number of compounds

r: correlation coefficient

s: standard deviation

F: Fischer value (measure of the statistical significance)

$Q^2$ : squared cross-validation regression coefficient

s-PRESS: standard deviation of cross-validation predictions

Calculated  $Q^2$  and s-PRESS values show that the predictive power of this QSAR model is significant. Predictions for the lead optimization in this set of compounds can be summarized as follows:

- The activity contributions obtained in this QSAR model show that the indicator structural parameter  $I_{yCH_2}$  is significant for the activity. So substitution at position Y with the  $CH_2$  group is more important than with  $CH_2O$  and  $CH_2S$  groups for the antifungal activity against *C. albicans*.

- The substitution at  $R_2$  is found to be more significant than  $R_1$ ,  $R_5$ ,  $R_6$  and X in improving the antifungal activity.

- Hydrophobic properties of the substituents at position  $R_2$  are more indicative than electronic and steric properties of the antifungal activity against *C. albicans*.

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