Scientific paper

Quantitative Structure-Activity Relationship (QSAR) Study of a Series of Benzimidazole Derivatives as Inhibitors of *Saccharomyces Cerevisiae*

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Abstract

A quantitative structure activity relationship (QSAR) has been carried out on a series of benzimidazole derivatives to identify the structural requirements for their inhibitory activity against yeast *Saccharomyces cerevisiae.* A multiple linear regression (MLR) procedure was used to model the relationships between various physicochemical, steric, electronic, and structural molecular descriptors and antifungal activity of benzimidazole derivatives. The QSAR expressions were generated using a training set of 16 compounds and the predictive ability of the resulting models was evaluated against a test set of 8 compounds. The best QSAR models were further validated by leave one out technique as well as by the calculation of statistical parameters for the established theoretical models. Therefore, satisfactory relationships between antifungal activity and molecular descriptors were found. QSAR analysis reveals that lipophilicity descriptor (log*P*), dipole moment (*DM*) and surface area grid (*SAG*) govern the inhibitory activity of compounds studied against *Saccharomyces cerevisiae.*

Keywords*:* Benzimidazole derivatives; QSAR, molecular descriptors; antifungals; *Saccharomyces cerevisiae*

1. Introduction

Benzimidazoles and their derivatives are well known to the chemists mainly because of the broad spectrum of the antimicrobial properties exhibited by this class of compounds.[1-13] Interest in the chemistry, synthesis and microbiology of this pharmacophore continues to be fuelled by their biological properties such as antifungal,[14] antitubercular,[15] antioxidant,[16,17] antiallergic,[18,19] and antiparasitic.[20] It is also well known that these molecules are present in a variety of antitumoural,[21] anthelmintic[22] and herbicidal agents[23]. Many derivatives of benzimidazole show antihistaminic, cytostatic, local analgesic, hypotensive and antiinflammatory activity.[24] In recent years, benzimidazole derivatives have been attracted particular interest due to their anticancer activity or may act as *in vitro* anti-HIV agents.[25,26]

Predictions of biological and physicochemical properties of molecules based on their structure are the fundamental and most interesting objectives of chemistry. The conception that there exists a close relationship between bulk properties of compounds and the molecular structure of those compounds is quite rooted in chemistry. This idea allows one to provide a clear connection between the macroscopic and the microscopic properties of matter, and thus has been firmly established as one of the central foundations of chemistry. Therefore, it is the basic tenet of chemistry to attempt to identify these assumed relationships between molecular structure and physico-chemical properties and then to quantify them.

A large number of research studies is needed to analyze the pharmacophore present in these compounds using the Three Dimensional QSAR (quantitative structure-activity relationship) methods.[27–29] The physicochemical properties predicted from structure are helpful in the search for new molecules of similar or increased biological activity. QSAR studies enable the investigators to establish reliable quantitative structure-activity relationships, to derive a QSAR model and predict the activity of novel molecules prior to their synthesis. These studies re-

duce the trial- and error element in the design of compounds by establishing mathematical relationships between physical, chemical, biological, or environmental activities of interest and measurable or computable parameters such as physicochemical, electronic, topological, or stereochemistry. 3D-QSAR methodology has been succesfully used to generate models for various chemotherapeutic agents. Beside importance of QSAR modeling in drug design, computational and *in silico* methods are important contributors to drug discovery processes.[30,31]

To gain insight into the structural and molecular requirement influencing the inhibitory activity, herein we depict QSAR analysis of some benzimidazole derivatives for their inhibitory activity against *Saccharomyces cerevisiae*. The relevance of the model used for design of novel derivatives should be assessed not only in terms of predictivity, either internal or external, but also in terms of their ability to provide a chemical and structural explanation of their binding interaction. These results should provide guidelines for design of more potent and selective antifungals.

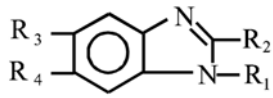
2. Materials and Methods

The structures of the benzimidazoles tested in this study are presented in Table1. All the compounds were synthesized by a general procedure described by Vlaoviæ[32] and these compounds were evaluated for their *in vitr*o growth inhibitory activity against yeast *Saccharomyces cerevisiae* according a procedure described earlier.[33]

2. 1. Molecular Modeling

The molecular modeling study was performed using HyperChem 7.5 software (HyperCube Inc, Version 7.5) running on P-III processor.[34] HyperChem includes a model builder that turns a rough 2Dsketch of a molecule into 3D. The created 3-D models were cleaned up and subjected to energy minimization using molecular mechanics (MM_2). The minimization is executed until the root mean square (RMS) gradient value reaches a value smaller than 0.1 kcal/molÅ. The Austin Model-1 (AM-1) method was used for re-optimization until the RMS gradient attains a

Table 1. Structures of benzimidazole derivatives used in training and test set



Compound	R_1	R_2	R_3	R_4	MIC (μg/ml)
1	NH_2	C_6H_5–CH_2	H	H	100.00
2	NH_2	4–CH_3–C_6H_4–CH_2	H	H	25.00
3	NH_2	4–Cl–C_6H_4–CH_2	H	H	25.00
4	NH_2	C_6H_5–CO	H	H	100.00
5	NH_2	4–CH_3–C_6H_4–CO	H	H	50.00
6	NH_2	4–Cl–C_6H_4–CO	H	H	50.00
7	NH_2	3–CH_3–C_6H_4–CH_2	H	H	25.00
8	NH_2	3–Cl–C_6H_4–CH_2	H	H	25.00
9	NH_2	3–F–C_6H_4–CH_2	H	H	50.00
10	NH_2	3–OCH_3–C_6H_4–CH_2	H	H	100.00
11	CH_3	C_6H_5–CH_2	H	H	25.00
12	CH_3	4–CH_3–C_6H_4–CH_2	H	H	12.50
13	CH_3	4–Cl–C_6H_4–CH_2	H	H	12.50
14	CH_3	C_6H_5–CO	H	H	50.00
15	CH_3	4–CH_3–C_6H_4–CO	H	H	12.50
16	CH_3	4–Cl–C_6H_4–CO	H	H	12.50
17*	H	3–CH_3–C_6H_4–CH_2	CH_3	CH_3	6.25
18*	H	3–Cl–C_6H_4–CH_2	CH_3	CH_3	6.25
19*	H	3–F–C_6H_4–CH_2	CH_3	CH_3	12.50
20*	H	3–OCH_3–C_6H_4–CH_2	CH_3	CH_3	25.00
21*	NH_2	3–CH_3–C_6H_4–CH_2	CH_3	CH_3	6.25
22*	NH_2	3–Cl–C_6H_4–CH_2	CH_3	CH_3	6.25
23*	NH_2	3–F–C_6H_4–CH_2	CH_3	CH_3	12.50
24*	NH_2	3–OCH_3–C_6H_4–CH_2	CH_3	CH_3	25.00
25*	NH_2	H	H	H	3000.00
26*	CH_3	H	H	H	2500.00
27*	NH_2	H	CH_3	CH_3	1000.00
28*	CH_3	H	CH_3	CH_3	500.00

* external test set

value smaller than 0.0001kcal/molÅ using MOPAC.[35,36] The lowest energy structure was used for each molecule to calculate molecular descriptors.

2. 2. Descriptors Generation

The numerical descriptors were calculated for each compound in the data set, using the software HyperChem,[34] Dragon[37] and CS Chem Office Software version 7.0.[38] Since there was a 78 different descriptors for each compound (electronic, constitutional, hydrophobic, and topological), Pearson's correlation matrix was used as a qualitative model, in order to select the suitable descriptors for MLR analysis. One way to avoid data redundancy is to exclude descriptors that are highly intercorrelated with each other before performing statistical analysis. The values of descriptors selected for MLR model are presented in Table 2 (molar refractivity (*MR*), polarizability (*P*), molar volume (*MV*), hydration energy (*HE*), molar weight (*MW*), total energy (TE), surface area grid (*SAG*), dipole moment (*DM*) and partition coefficient (log*P*)).

2. 3. Statistical Methods

The complete regression analysis were carried out by PASS 2005, GESS 2006, NCSS Statistical Softwares.[39] The Elimination Selection Stepwise regression (ES-SWR) algorithm was used to select the most appropriate descriptors. ES-SWR is a popular stepwise technique that combines Forward Selection (FS-SWR) and Backward Elimination (BE-SWR).

For the testing the validity of the predictive power of selected MLR models the LOO technique was used. The developed models were validated by the calculation of following statistical parameters: PRESS, SSY, S_{PRESS}, r^2_{CV}, and r^2_{adj}. These parameters were calculated from the following equations:

$$\mathrm{PRESS} = \sum (Y_{obs} - Y_{calc})^2 \quad (1)$$

$$\mathrm{SSY} = \sum (Y_{obs} - Y_{mean})^2 \quad (2)$$

$$S_{\mathrm{PRESS}} = \sqrt{\frac{\mathrm{PRESS}}{n}} \quad (3)$$

$$r^2_{\mathrm{CV}} = 1 - \frac{\mathrm{PRESS}}{\mathrm{SSY}} \quad (4)$$

$$r^2_{\mathrm{adj}} = 1 - (r^2)\left(\frac{n-1}{n-p-1}\right) \quad (5)$$

where, Y_{obs}, Y_{calc} and Y_{mean} are observed, calculated and

Table 2. Values of inhibitory activities and molecular descriptors used in the regression analysis

Cmpd	Log ($1/c_{MIC}$)	*MR*	*P*	*MV*	*HE*	*MW*	*TE*	*SAG*	*DM*	log*P*
1	3.349	77.28	26.63	675.88	–7.12	223.28	–9.75	416.78	1.45	2.96
2	3.977	81.56	28.46	728.44	–5.95	237.30	–9.81	442.99	1.53	3.44
3	4.013	81.99	28.55	712.38	–6.72	257.72	–9.81	437.70	1.48	3.52
4	3.375	77.21	26.71	666.31	–7.67	237.29	29.80	409.30	2.16	2.84
5	3.701	81.49	28.55	720.15	–6.52	251.29	29.61	437.71	2.13	3.32
6	3.735	80.61	28.64	710.59	–7.35	271.71	30.38	434.96	2.88	3.39
7	3.977	81.56	28.46	744.54	–6.39	237.30	26.35	458.41	4.46	3.44
8	4.013	81.99	28.55	736.31	–7.16	257.72	26.03	450.08	4.43	3.52
9	3.683	77.40	26.53	704.51	–7.31	241.27	26.07	433.17	4.43	3.12
10	3.403	83.65	29.10	771.05	–8.95	253.30	27.94	470.97	4.42	2.83
11	3.949	78.48	27.11	693.35	–2.73	222.29	1.34	423.77	1.32	3.45
12	4.276	82.76	28.94	745.41	–1.61	236.32	1.23	453.96	1.45	3.94
13	4.312	83.19	29.04	737.17	–2.44	256.73	1.63	448.98	1.69	4.01
14	3.674	78.41	27.20	686.80	–3.68	236.27	53.89	422.33	2.40	3.33
15	4.301	82.69	29.03	741.13	–2.53	250.30	53.68	452.01	2.42	3.81
16	4.336	81.81	29.12	731.39	–3.36	270.71	54.42	447.07	2.86	3.89
17	4.603	87.25	30.78	811.60	–1.00	250.34	27.17	490.32	3.98	4.24
18	4.637	87.69	30.87	804.81	–1.86	270.76	26.87	429.54	3.97	4.31
19	4.308	83.10	28.85	777.39	–2.23	254.34	27.02	477.14	3.98	3.91
20	4.028	89.34	31.42	841.79	–3.68	266.38	28.92	507.17	3.97	3.63
21	4.628	90.12	32.13	844.29	–4.26	265.36	27.67	503.71	4.43	4.42
22	4.659	89.24	32.22	833.57	–5.38	285.36	27.18	498.16	4.40	4.49
23	4.333	85.97	30.20	802.16	–5.21	269.32	27.46	480.77	4.41	4.09
24	4.051	92.27	32.77	871.99	–6.83	281.36	29.38	517.74	4.40	3.80
25	1.647	43.63	15.13	430.33	–11.28	133.15	–1.21	292.48	1.04	0.99
26	1.723	44.83	15.62	450.85	–4.75	132.16	10.35	304.78	1.56	1.05
27	2.207	49.54	17.55	478.26	–5.28	161.15	5.59	328.57	2.05	1.54
28	2.505	49.95	19.83	492.38	–6.32	160.16	14.14	372.35	2.58	2.02

mean values; *n*, number of compounds; *p*, number of independent parameters.

PRESS is an acronym for prediction sum of squares. It is used to validate a regression model with regards to predictability. To calculate PRESS, each observation is individually omitted. The remaining n – 1 observations are used to calculate a regression and estimate the value of the omitted observation. This is done n times, once for each observation. The difference between the actual Y value, y_{obs}, and the predicted Y, y_{calc}, is called the prediction error. The sum of the squared prediction errors is the PRESS value. The smaller PRESS is, the better the predictability of the model. Its value being less than SSY points out that the model predicts better than chance and can be considered statistically significant. SSY are the sums of squares associated with the corresponding sources of variation. These values are in terms of the dependent variable, y.

3. Results and Discussion

In order to identify the effect of chemical structure on the inhibitory activity, QSAR studies of title compounds were performed. The compounds was divided into training set of 16 compounds and test set of 8 compounds on the basis of structural diversity. A set of benzimidazoles consisting of 16 molecules was used for multilinear regression model generation. An attempt has been made to find structural requirement for inhibition of yeast *Saccharomyces cerevisiae* using QSAR Hansch approach on benzimidazole derivatives. Different physicochemical, steric, electronic, and structural molecular descriptors were used as independent variables and were correlated with antifungal activity.

The intercorrelation among the descriptors and their correlation with inhibitory activity is investigated by construction of a correlation matrix. From the correlation matrix of the selected descriptors (Table 3), it can be concluded that only one of the aforementioned indices is highly correlated with the activity. This means that is possible to obtain only one statistically significant monoparametric model with log*P* descriptor as independent variable ($r = 0.9706$). A correlation matrix was constructed to find the interrelationship among the parameters, which shows that some parameters selected in the study is highly correlated with the other ($r>0.7$). Therefore, any combination of these descriptors in multiple regression analysis may result with a model suffering from multi-colinearity.

From the QSAR study of the series of benzimidazoles, two best biparametric models were derived. Both the models include lipophilicity descriptor (log*P*). The specifications for the best-selected MLR models are shown in Table 4.

But, only high correlation coefficient is not enough to select the equation as a model and hence various statistical approaches were used to confirm the robustness and practical applicability of the equations.[40,41] There are three important components in any QSAR analysis: development of models, validation of models and utility of developed models. Validation is a crucial aspect of any QSAR analysis.[42–44]

The statistical validity of the resulting models, as depicted in Table 4, is determined by *r*, *s*, and F. It is note-

Table 3. Correlation (r) matrix for the molecular descriptors calculated for benzimidazole derivatives

	Log ($1/c_{MIC}$)	***MR***	***P***	***MV***	***HE***	***MW***	***TE***	***SAG***	***DM***	**log*P***
Log ($1/c_{MIC}$)	1									
MR	0.6021	1								
P	0.6308	0.9719	1							
MV	0.5009	0.9122	0.8569	1						
HE	0.7526	0.2181	0.2448	0.1197	1					
MW	0.3352	0.5657	0.6732	0.4387	–0.1138	1				
TE	0.0303	0.0141	0.1221	0.0965	0.06065	0.3903	1			
SAG	0.4721	0.8888	0.8302	0.9945	0.0792	0.4302	0.1087	1		
DM	–0.1718	0.1151	0.0883	0.4043	–0.4971	0.3007	0.4931	0.4608	1	
log*P*	0.9706	0.5731	0.6196	0.4289	0.8079	0.3448	0.0193	0.3944	0.2755	1

Table 4. Best MLR models for the prediction of antibacterial activity

Model	**Coefficient**		***n***	***r***	***s***	***F***
1	Intercept	0.6758	16	0.9756	0.0787	128.6225
	log*P*	0.9134				
	DM	0.0289				
2	Intercept	0.0174	16	0.9754	0.0794	127.3676
	log*P*	0.8491				
	SAG	0.0022				

Table 5. Cross-validation parameters

Model	PRESS	SSY	PRESS/SSY	S_{PRESS}	r^2_{CV}	r^2_{adj}
1	0.1101	1.6864	0.0653	0.0829	0.9347	0.9445
2	0.1349	1.6864	0.0800	0.0918	0.9200	0.9440

worthy that all these equations were derived using the entire data set of compounds (n = 16) and no outliers were identified. The F-value presented in Table IV is found statistically significant at 99% level since all the calculated F values are higher as compared to tabulated values.

For the testing the quality of the predictive power of selected MLR models the LOO procedure was used (Table 5). The PRESS value above can be used to compute an r^2_{CV} statistic, called r^2 cross validated, which reflects the prediction ability of the model. This is a good way to validate the prediction of a regression model without selecting another sample or splitting your data. In this study, r^2_{adj} and r^2_{CV} is taken as a proof of the high predictive ability of QSAR models. A high value of these statistical characteristic (> 0.5) is considered as a proof of the high predictive ability of the models. Adjustable correlation coefficient (r^2_{adj}) tells us the statistical significance of incorporated physicochemical descriptor in MLR. r^2_{adj} takes into account the adjustment of conventional correlation coefficient (r^2).

Table 6. Predicted log1/c_{MIC} values of training set with residual

Compound	Log (1/c_{MIC}) pred.		Residuals	
	Model 1	Model 2	Model 1	Model 2
1	3.421	3.434	–0.072	–0.085
2	3.862	3.898	0.115	0.079
3	3.934	3.955	0.079	0.058
4	3.332	3.316	0.043	0.059
5	3.769	3.785	–0.068	–0.084
6	3.855	3.838	–0.120	–0.103
7	3.947	3.932	0.030	0.045
8	4.019	3.982	–0.006	0.031
9	3.653	3.605	0.030	0.078
10	3.388	3.441	0.015	–0.038
11	3.865	3.865	0.084	0.084
12	4.316	4.347	–0.040	–0.071
13	4.387	4.395	–0.075	–0.083
14	3.787	3.760	–0.113	–0.086
15	4.226	4.232	0.075	0.069
16	4.311	4.289	0.025	0.047

However, the high r^2_{CV} does not imply automatically a high predictive ability of the model. Thus, the high value of LOO r^2_{CV} is the necessary condition for a model to have a high predictive power, it is not a sufficient condition. In order to verify the predictive power of the developed models, the predicted (log1/c_{MIC}) values of the training set of compounds were calculated and compared with the experimental values (Table 6, Fig. 1).

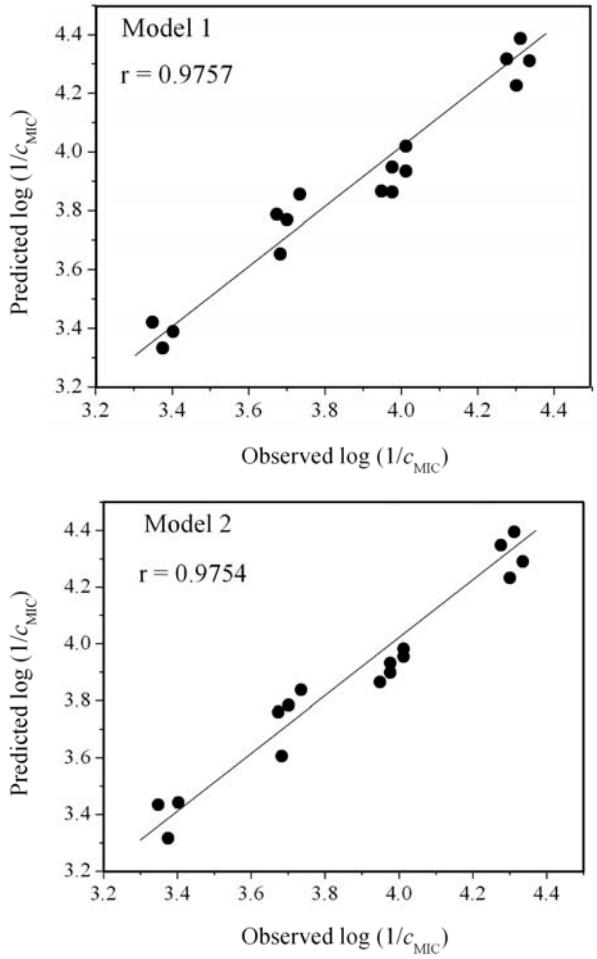


Fig 1. Plots of predicted versus the experimentally observed antifungal activity of training set

Although model showed good internal consistency, they may not be applicable for the analogs which were never used in the generation of the correlation. It is proven that the only way to estimate the true predictive power of a model is to test it on a sufficiently large collection of compounds from an external test set. The test set must include no less than five compounds, whose activities and structures must cover the range of activities and structures of compounds from the training set. This application is necessary for obtaining trustful statistics for comparison between the observed and predicted activities for these compounds. Therefore, the external extrapolation power of the model was further authenticated by a test set of eight compounds (Table 7, Fig. 2).

The values of inhibitory activitiy of a external set of molecules was calculated with the models 1 and 2. These

data are compared with experimentally obtained values of antifungal activity against the same species of fungi. From the data presented in Table 7, it is shown that high agreement between experimental and predicted inhibitory values was obtained (the residual values are small, indicating the good predictability of the established models. According to the reference,[45] without the validation of the QSAR models by using the external test set, we could not have come to a right conclusion about high predictive ability of derived models.

Table 7. Predicted $\log 1/c_{MIC}$ values of external set with residual

Compound	Log ($1/c_{MIC}$) pred.		Residuals	
	Model 1	Model 2	Model 1	Model 2
17	4.664	4.696	–0.061	–0.093
18	4.727	4.622	–0.09	0.015
19	4.362	4.387	–0.054	–0.079
20	4.106	4.215	–0.078	–0.187
21	4.841	4.878	–0.213	–0.250
22	4.904	4.926	–0.245	–0.267
23	4.539	4.548	–0.206	–0.215
24	4.274	4.383	–0.223	–0.332
25	1.610	1.501	0.037	0.146
26	1.680	1.580	0.043	0.143
27	2.142	2.048	0.065	0.159
28	2.595	2.551	–0.090	–0.046

Analysis of the results suggested that for antifungal activity lipophilicity is an essential parameter which is contributing positively. This parameter is usually related to pharmacological activity. This evidence was clearly described in lipid theory advanced by Meyer and Overton.[46,47] According to this theory, log*P* is a measure of hydrophobicity which is important for the penetration and distribution of the drug, but also for the interaction of drug with receptors. The positive contribution of log*P* in both the proposed equations thus suggests its significant participation in the inhibitory activity. The results clearly indicate that compounds with higher lipophilicity values exhibited increased inhibitory action on the growth of the tested yeast.

Other descriptors, *DM* and *SAG,* were effective descriptors combined with log*P*. Both the descriptors are the indicators of lipophilicity/hydrophobicity. They may be related to bind between drug and receptor because polarity is essential factors to bind active site of receptor molecule. Therefore, it can be suggested that simple calculation of log*P*, *DM* and *SAG* might predict the antifungal activity of these class of molecules.

4. Conclusion

From the results discussed above, it can be concluded that the different substituted benzimidazole derivatives showed *in vitro* considerable inhibitory activity against the yeast *Saccharomyces cerevisiae*. Molecular modeling and QSAR analysis were performed to find the quantitative effects of the molecular structure of the compounds on their antifungal activity. Various physicochemical parameters, especially partition coefficient, ionization constant and water solubility can be used successfully for modeling antifungal activity of benzimidazoles. Two best QSAR mathematical models are used to predict inhibitory activity of the benzimidazoles investigated and close agreement between experimental and predicted values was obtained. The low residual activity and high cross-validated r^2 values (r^2_{CV}) observed indicated the predictive ability of the developed QSAR models. It indicates that these models can be successfully applied to predict the antifungal activity of these class of molecules.

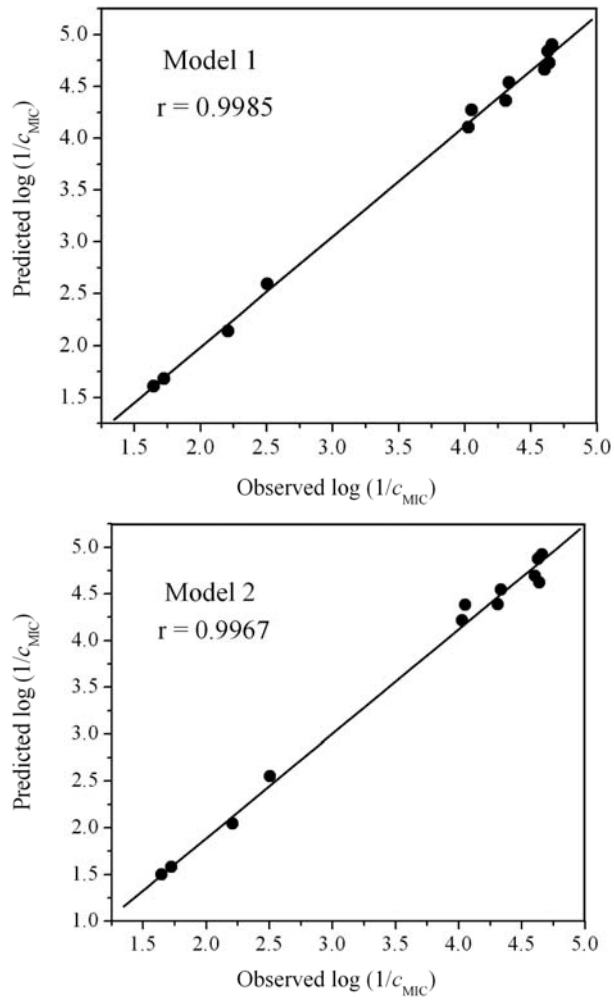


Fig 2. Plots of predicted versus the experimentally observed antifungal activity of test set

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Povzetek

QSAR metoda je bila uporabljena v seriji novih benzimidazolskih derivatov različnih struktur s ciljem ugotavljanja njihovih inhibitorskih aktivnosti na kvasovke *Saccharomyces cerevisiae.* Postopek multiple linearne regresije (MLR) je bil uporabljen za modeliranje odnosa med različnimi fizikalno-kemičnimi, sternimi, elektronskimi in strukturnimi molekularnimi deskriptorji in antifugalne aktivnosti preizkušenih benzimidazolnih derivatov. QSAR odvisnosti so bile dobijene iz poskusnega seta sestavljenega iz 16 spojin. Možnost uporabe dobijenih enačb za predvidevanje inhibitorske aktivnosti je bila nato preizkušena z uporabo testnega niza iz 8 derivatov benzimidazola. Najboljši QSAR model je preverjen z izračunom statističnih parametrov ugotovljenega teoretičnega modela. Tako je določen odgovarjajoč odnos odvisnosti med antifugalno aktivnostjo in molekularnimi deskriptorji. Ugotovljeno je da ima na inhibitorsko aktivnost derivatov benzimidazola na kvasovke *Saccharomyces cerevisiae* največji vpliv deskriptor lipofilnosti (log*P*), dipolni moment (*DM*) in mreža površinskega področja (SAG).