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Structure-Antifungal Activity Relationships Study of Mannich Bases Containing 1,2,4-Triazoles by Computational Chemistry

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Abstract

1,2,4-triazole moiety and their fused heterocyclic rings derivatives have received great attention due to their effective biological activities such as anti-inflammatory, antimicrobial, antifungal, low toxicity, and good pharmacokinetic and pharmacodynamic profiles. In this study, structure-antifungal activity relationships of a series of eighteen trifluoromethyl-substituted 1,2,4-triazole derivatives with exeperimentally measured fungicidal activity against the *Fusarium oxysporum f. sp. cucumerinum* were explored by multiple linear regression (MLR). Two types of *E* and *Z* isomers were generated by the MMFF94s force field included in the Omega package. Several 0D, 1D, 2D and 3D descriptors were calculated from the minimum energy conformations. The experimental fungicide relative inhibition rate was related to these descriptors using MLR calculations, combined with a genetic algorithm for variable selection. Five out of the eighteen compounds were included in the test set. The more stable and predictive MLR model was developed for the *E* stereoisomers with the following statistical parameters:$r^2_{training}$=0.822, r^2_{test}= 0.899, q^2_{LOO}= 0.747, $RMSE_{tr}$= 0.106, $RMSE_{ext}$= 0.114, r^2_{adj}= 0.804). Geometrical size descriptors provide the highest contribution to the fungicidal activity.

Keywords : QSPR, fungicide, MLR, 1,2,4-triazoles, Omega, QSARINS

1. Introduction

Over the past few years, the chemistry of heterocyclic compounds (i.e. triazole, thiazole, oxazole, etc) has received considerable attention due to their importance in

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pharmacological and agricultural fields (Asif, 2015). A large number of novel Mannich bases have been synthesized and evaluated as potential treatments for a multitude of diseases and medical conditions, as prodrugs, or as molecules eliciting a response from biological targets (Roman, 2015). The 1,2,4-triazolo[5,1-b]-1,3,5-thiadiazines were found to be moderately potent against *C. albicans or Fusarium oxysporum* fungi (Roman, 2015).

1,2,4-Triazole rings, typically planar 6p-electron aromatic systems, represent one of the most bioactive classes of compounds, which display a broad spectrum of biological activities in various fields, including anti-inflammatory (El-Serwy et al., 2013), antiparasitic (Franklim et al., 2013), antifungal (Zhang et al., 2013), herbicidal (Ke et al., 2013), antimicrobial (Wang et al., 2011), cytostatic (Benci et al., 2012) potencies. They are used as dyes, agrochemicals, biological reagents, photostablizers in photographic materials used as light stabilizers, precursors for the synthesis of peptidomimetics and synthesis of polymers (Kumar & Kavitha, 2013).

Fungicides represent one of the most important groups of pesticides, which have played a decisive role for the control of infections caused by a considerable number of extreme pathogen fungal species.

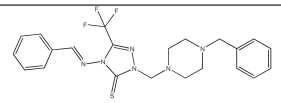
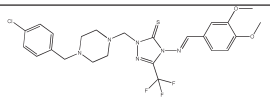
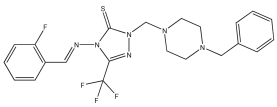
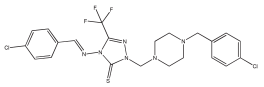
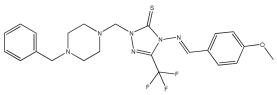
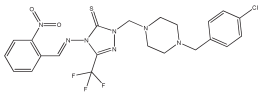
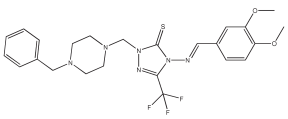
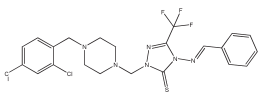
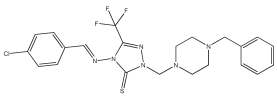
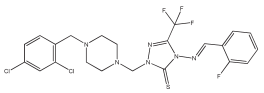
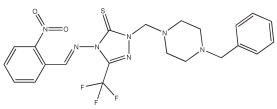
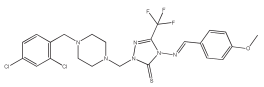
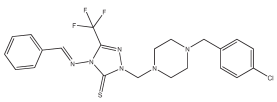
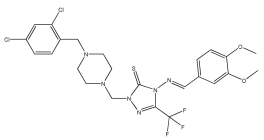
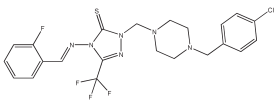
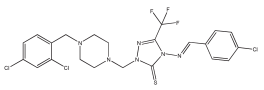
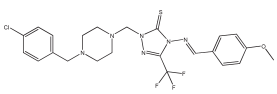
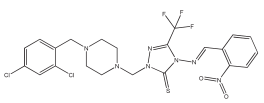
The azole class of fungicides were initially discovered as antifungal compounds, but some derivatives also showed activity on plant growth (Tresch, 2013). Their mechanism of action in fungi was described as inhibitors of the cytochrome P450-dependent 14 α -lanosterol demethylase in sterol biosynthesis. They act not only as specific sterol biosynthesis inhibitors, but also with other cytochrome P450-dependent enzymes. Depending on the specific derivative, effects in plants were primarily caused by the inhibition of cytochrome P450 enzymes in gibberelin or in brassinolide biosynthesis.

The presence of the asymmetrically substituted carbon atoms in the triazol alkyl moiety makes almost all triazole-type fungicides to be chiral. These chiral compounds consist of two or four stereoisomers. Even if the enantiomers have identical physical and chemical properties, their interactions with biological macromolecules are often chiral-selective, leading to enantiomer selectivity in biodegradation, ecotoxicity and human health effects. These interactions may also contribute to differences in biological activity, toxicity on beneficial or nontarget organisms and environmental fate. The introduction of inactive isomers into the environment may result in unwanted side effects. Therefore, there is an increasing interest in evaluating the enantioselective behavior of chiral pesticides in the environment (Zhang et al., 2015).

Rapid developments in molecular mycology showed that triazole scaffolds have increased the ability to treat many fungal infections, for example, *Candidiasis, Cryptococcal meningitis, Aspergillosis* etc. (Shalini et al., 2011).

A series of trifluoromethyl-substituted 1,2,4-triazole Mannich bases containing substituted benzylpiperazine ring with herbicidal and fungicidal activity have been synthesized (Wang et al., 2011) (Table 1).

Table 1. Structure of trifluoromethyl-substituted 1,2,4-triazole Mannich bases and their experimental *Fusarium oxysporum f. sp. cucumerinum* relative inhibition rate (RIR, % inhibition)

No	Structure	RIR	No	Structure	RIR
1		0.101	10		0.401
2		0.804	11		0.303
3		0.187	12		0.502
4		0.000	13		0.708
5		0.000	14		0.826
6		0.402	15		0.504
7		0.509	16		0.705
8		0.719	17		0.607
9		0.604	18		0.608

The present paper describes a structure-fungicidal activity relationships study for this series of trifluoromethyl-substituted 1,2,4-triazole Mannich bases using multiple linear regression (MLR). The molecular structures of the compounds were pre-optimized using a rule-based algorithm in combination with variants of the Merck force field 94. Several descriptors were calculated for the minimum energy geometries and were related to the mycelial growth inhibition activity against the *Fusarium oxysporum f. sp. cucumerinum fungi* test.

2. Materials and Methods

Definition of target property and molecular structures

A series of 18 trifluoromethyl-substituted 1,2,4-triazole Mannich bases containing substituted benzylpiperazine ring was used, having the fungicidal *Fusarium oxysporum f. sp. Cucumerinum* relative inhibitation rate (RIR, expressed in %) as dependent variable.

The title fungicides were energy pre-optimized by molecular mechanics calculations using the MMFF94s force field included in the OMEGA (version 2.5.1.4, OpenEye Scientific Software, Santa Fe, NM. http://www.eyesopen.com) software (Hawkins et al., 2010; Hawkins & Nicholls, 2012). Structural 0D, 1D, 2D and 3D descriptors were calculated for the minimum energy structures using the DRAGON (Dragon Professional 5.5 (2007), Talete S.R.L., Milano, Italy), InstantJchem (which was used for structure database management, search and prediction) (InstantJchem 6.0.0, 2013, ChemAxon (http://www.chemaxon.com) and ChemProp (UFZ Department of Ecological Chemistry 2014. ChemProp 6.2, http://www.ufz.de/index.php?en=6738) software .

The data are normalized based on the autoscaling method, which can be described as:

$$XT_{mj} = \frac{X_{mj} - \overline{X}_m}{S_m} \quad (1)$$

where for each variable m, XT_{mj} and X_{mj} are the values j for the variable m after and before scaling, respectively; $\overline{X}_m$ is the mean and S_m the standard deviation of the variable.

Compound descriptors were related by multiple linear regression (MLR) to the fungicide relative inhibition rate. MLR calculations were combined with a genetic algorithm for variable selection included in the QSARINS v.2.2 program (Gramatica et al.., 2013a). The RQK fitness function, with leave-one-out cross-validation correlation coefficient was used as constrained function to be optimized. The dataset was divided in training and a randomly selected test set (30% of the total number of compounds in the test set). Compounds: 1, 3, 7, 13, 17 for the *E* set and 4, 9, 11, 12, 17 for the *Z* set were

included in the test set. It is well known that the success of any structure-activity relationship model depends on some factors such as: (i) the accuracy of the input data, (ii) the selection of appropriate descriptors, (iii) selection of adequate statistical tools and, (iv) the validation of the developed model. Validation is the most important step for judging quality of the QSAR model (Roy, 2007). In this light, the developed MLR models were validated using internal and external validation.

Model validation

All the statistical tests were performed at a significance level of 5 %. In MLR models, outliers were detected by a value of residual greater than 2.5 times the value of standard error in calculation.

For internal validation results several measures of robustness were employed: leave-one-out cross-validation (Q^2_{LOO}), Y-scrambling and Q^2_{LMO} leave-more-out (LMO) cross-validation (carried out for 30% of data out of training, each run). A QSAR model can be considered robust when its performance remains satisfactory and stable when heavy perturbations (for instance by leave-many-out) in the training composition is made.

Y-scrambling testing is a technique for checking the robustness of a QSAR model and the statistical significance of the estimated predicted power. In this test, the dependent variable vector, Y-vector, is randomly shuffled and a new QSAR model is developed using the original independent variable matrix. The process was repeated 2000 times. It is expected that the resulting QSAR models will generally have low R^2 and low Q^2 (leave-one-out, LOO) values. If the new models developed from the data set with randomized responses have significantly lower R^2 and Q^2 than the original model, then this is strong evidence that the proposed model is well founded, and not just the result of chance correlation. Satisfactory leave-one-out cross-validation values are stable and predictive if validated by the leave-more-out procedure.

Models based on chance correlation can be detected using the QUIK rule (Todeschini et al., 1999), a simple criterion that allows the rejection of models with high predictor collinearity, which could lead to chance correlation. The QUIK rule is based on the K multivariate correlation index (Table 2) that measures the total correlation of a set of variables. The rule is derived from the assumption that the total correlation in the set given by the model predictors X plus the response Y (K_{XY}) should always be greater than that the one measured only in the set of predictors (K_{XX}). Therefore, according to the QUIK rule, only models with the K_{XY} correlation among the [X+Y] variables greater than the K_{XX} correlation among the [X] variables can be accepted.

The data over fitting and model applicability was controlled by comparing the root-mean-square errors (RMSE) of training and validation sets. To test the predictive power of the model, the concordance correlation coefficient (CCC) (Chirico & Gramatica, 2011) was used.

The Multi-Criteria Decision Making (MCDM) (Keller et al.., 1991) is a technique that summarizes the performances of a certain number of criteria simultaneously, as a single number (score) between 0 and 1. This is done associating to every validation criteria a desirability function which values range from 0 to 1 (where 0 represents the worst validation criteria value and 1 the best). The geometric average of all the values obtained from the desirability functions gives the MCDM value. The ‚MCDM all' scores were calculated based on the criteria: fitting, cross validated and external and were used to choose the best MLR models.

The domain of applicability (a theoretical region in chemical space, defined by the model descriptors and modeled response for which a QSAR model should makes predictions with a given reliability) was checked using the Williams plots (standardized crossvalidated residuals versus leverage (Hat diagonal) values) (Gramatica, 2013b).

3. Results and Discussion

Two types of *E* and *Z* isomers were found by Omega, with respect to the C=N bond and therefore two series of compounds were built. The X-ray diffraction analysis of compound 18 (Wang et al., 2011) revealed that the C=N bond is in the *E* configuration. A training set of 12 compounds and 5 test compounds (no.: 1, 3, 7, 13, 17 for the *E* set and 4, 9, 11, 12, 17 for the *Z* set) were used in the calculations. Compound 2 was found as outlier in both datasets and was excluded from the final MLR models. Several one and two descriptor models were found. Structural parameters were derived by InstantJChem, Dragon and ChemProp programs from the structures of the minimum energy. MLR calculations were performed for each type of isomer. Variable selection was carried out by the genetic algorithm, using the leave-one-out fit criterion as constrained function to be optimized. Following satisfactory MLR models were obtained for the *E* isomers:

MLR_E model (for *E* isomers):

RIR = 0.848(±0.07) - 0.747(±0.11)Mor19m
$N_{training}$ = 12 N_{test} = 5 SEE 0.12 r^2_{adj} 0.804 F = 46.13 q^2_{LOO} = 0.747

and for Z isomers:

MLR_Z model (for Z isomers):

RIR = 0.608(±0.05) - 0.45(±0.07)Strongest basic pKa + 0.256(±0.08)T(N..F)
$N_{training}$ = 12 N_{test} = 5 SEE = 0.107 r^2_{adj} = 0.8358 F = 28.99 q^2_{LOO} = 0.767

where Mor19m represents the 3D-MoRSE - signal 19/weighted by atomic masses, T(N..F) – the sum of topological distances between N..F.

Several fitting and predictivity criteria were employed for the model validation (see Tables 2-4).

Table 2. Internal validation parameters of the MLR models (training set)*

Model	$r^2_{training}$	q^2_{LOO}	$RMSE_{tr}$	MAE_{tr}	CCC_{tr}	r^2_{scr}	q^2_{scr}	K_{XX}	Delta K
MLR_Z	0.866	0.767	0.093	0.082	0.928	0.180	−0.480	0.193	0.357
MLR_E	0.822	0.747	0.106	0.095	0.902	0.092	−0.321	0.000	0.907

* $r^2_{training}$-correlation coefficient; q^2_{LOO}- leave-one-out correlation coefficient; $RMSE_{tr}$-root-mean-square errors; MAE_{tr}-mean absolute error; CCC_{tr}-the concordance correlation coefficient (Chirico & Gramatica, 2011); K_{XX}-the K multivariate correlation index that measures the total correlation given by the set of predictors; Delta K- the difference between the total correlation in the set given by the model predictors X plus the response Y (K_{XY}) and that of the set of predictors (K_{XX}).

Table 3. External validation parameters of the MLR models (test set)*

Model	Q^2_{F1}	Q^2_{F2}	Q^2_{F3}	$RMSE_{ext}$	MAE_{ext}	CCC_{ext}
MLR_Z	0.740	0.716	0.766	0.123	0.100	0.808
MLR_E	0.776	0.769	0.795	0.114	0.089	0.861

* Q^2_{F1}(Shi et al., 2001), Q^2_{F2}(Schüürmann et al., 2008), Q^2_{F3}(Consonni et al., 2009)-external validation parameters; $RMSE_{ext}$-root-mean-square errors; MAE_{ext} -mean absolute error; CCC_{ext}-the concordance correlation coefficient

Table 4. Golbraikh and Tropsha (Tropsha & Golbraikh, 2010) criteria calculated for external validation of the MLR models (test set)*

Model	r^2_{test}	$\frac{r^2 - r_0^2}{r^2}$	$\frac{r^2 - r_0'^2}{r^2}$	k	k'	$\lvert r_0^2 - r_0'^2 \rvert$
MLR_Z	0.762	0.060	0.451	0.987	0.943	0.299
MLR_E	0.899	0.001	0.019	1.217	0.802	0.016

*r^2_{test} -squared correlation coefficient between the predicted and observed activities; r_0^2-coefficient of determination for linear regressions with intercepts set to zero, i.e. (predicted versus observed activities); $r_0'^2$-coefficient of determination for linear regressions with intercepts set to zero (observed versus predicted activities); k and k'-slopes of the above mentioned two regression lines

In order to verify the reliability of the developed equations, experimental versus predicted RIR values, Williams plots and Y-scramble plots for the MLR_E and MLR_Z final models are presented in Figure 1, 2 and 3, respectively.

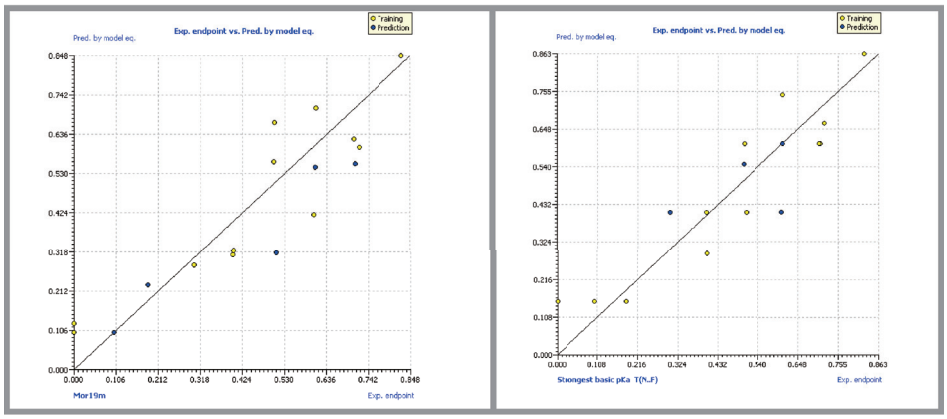


Figure. 1. Experimental versus predicted RIR values for the MLR_E (left) and MLR_Z (right) models.

The Williams plot is used to identify compounds with the greatest structural influence ($h_i > h^*$; h_i =leverage of a given chemical; h^*= the warning leverage) in the QSAR model. The Williams plot for the training sets presented in Figure 2 (for the MLR_E and MLR_Z models), establishes the applicability domain of the models within $\pm$ 2.5 σ and a leverage threshold h* of 0.500 and 0.750, respectively. The analysis of Figure 2 suggests that all the compounds in the dataset are within the applicability domain of the models.

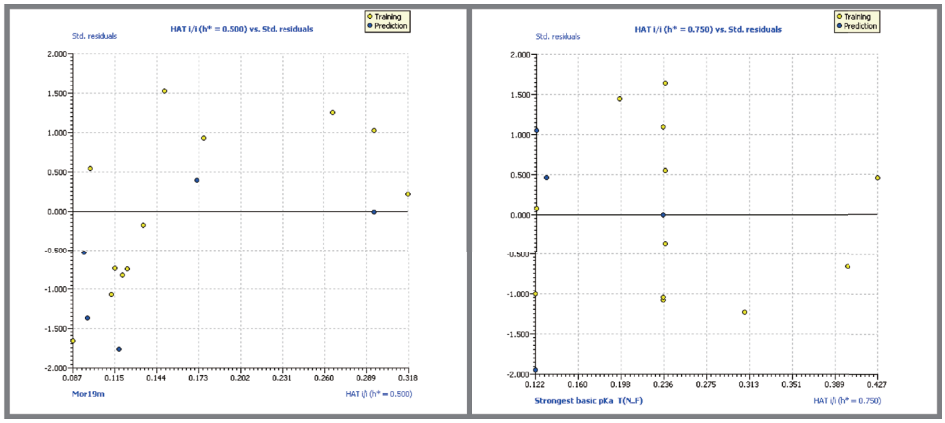


Figure. 2. Williams plot predicted by the final MLR_E (left) and MLR_Z (right) models.

The y-scrambling test indicates the robustness of a QSAR model, being a measure of the model overfit. The robustness of the developed models is confirmed by a significant low scrambled r^2 (r^2_{scr}) and cross-validated q^2 (q^2_{scr}) values obtained for 2000 trials. Figure 3 suggest that in case of all the randomized models, the values of r^2_{scr} and q^2_{scr} were < 0.5. The low calculated r^2_{scr} and q^2_{scr} values (r^2_{scr}/q^2_{scr} of 0.092/- 0.321 and 0.180/- 0.480) indicates

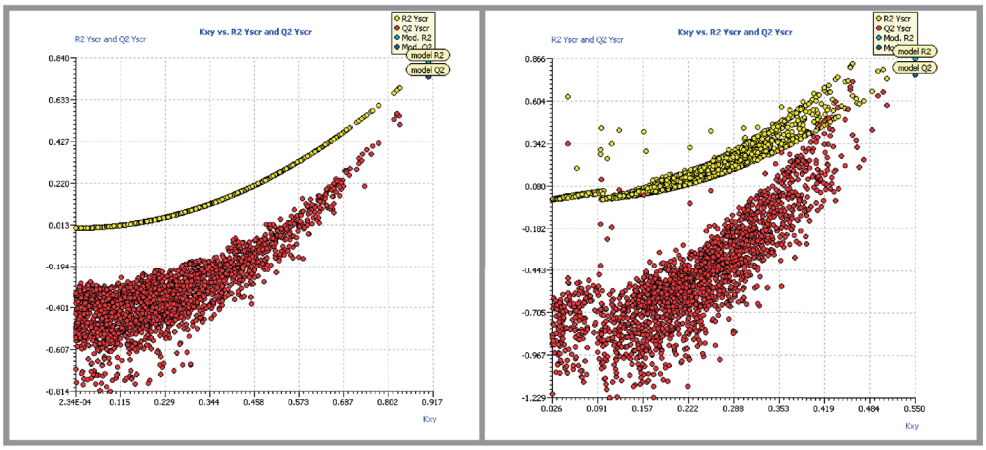


Figure. 3. Y-scramble plots for the MLR_E (left) and MLR_Z (right) models.

no chance correlation for the chosen models.

Insufficient experimental information on the stereoselectivity of all synthesized compounds is presented in the original paper (Wang et al., 2011). The statistical parameters obtained after variable selection by genetic algorithm for the *E* and *Z* datasets indicate good fitting results in both cases. The MLR_E model is more stable compared to the MLR_Z model from fitting and especially predictive model power points of view. Therefore the fungicidal activity of this series of pesticides could be expected to be influenced by the *E* stereoisomers.

The 3D-MoRSE (3D-MOlecule Representation of Structures based on Electron diffraction) descriptors were used owing to the flexibility of these descriptors, since they afford the possibility for choosing an appropriate atomic property and in this way we could adapt them to the specific problem under study.

4. Conclusion

In this study the fungicidal activity (the relative inhibition rate) of Mannich bases containing trifluoromethyl-1,2,4-triazoles was explored by multiple linear regression (MLR). *E* and *Z* stereoisomers were found by molecular mechanics calculations using the MMFF94s force field. 0D, 1D, 2D and 3D descriptors were derived from the minimum energy structures and were related to the fungicidal activity using MLR calculations, combined with a genetic algorithm for variable selection. Geometrical size descriptors have an important contribution to the fungicidal activity for the data set studied herein. 1,2,4-triazole stereoisomerism influences the fungicidal relative inhibition rate.

Acknowledgements

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和文要旨

1,2,4-トリアゾール基を有するマンニッヒ塩基の構造ー抗真菌性相関の計算化学による解析

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1,2,4-トリアゾール基とその縮合複素環誘導体は、消炎性、抗菌性、抗真菌性のような生物活性を有し、低毒性であり、しかも優れた薬物動態および薬理学的な性質を持つため注目が高まっている。 本研究では、18種のトリフルオロメチル置換基を有する1,2,4-トリアゾール誘導体の*Fusarium oxysporum f. sp. cucumerinum*に対する構造―抗真菌性を重回帰分析（MLR）モデルを構築して検討した。Omegaパッケージに含まれているMMFF94sを使った分子力場計算による分子の立体配座の安定性を検討し、２種の*E*体、Z体のシス-トランス異性体について種々の0D、1D、2D、3D記述子を計算した。それらの記述子と実験により求められた抗真菌性との間の定量的構造活性相関を変数選択のための遺伝的アルゴリズムを用いた重回帰分析（MLR）によりモデル化した。18化合物のうち５種をテストセットとして用い、MLRモデルの安定性と予測性を評価したところ、*E*体についてのモデルが最も統計的に優れていることを見出した。分子の幾何学的なサイズに関する記述子が抗真菌性に最も大きな寄与があることが明らかになった。