QSAR MODELING OF FUNGICIDAL ACTIVITY OF MANNICH BASES

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INTRODUCTION

- 1,2,4-triazole and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities, including anti-inflammatory, antiviral, analgesic, antimicrobial, anticonvulsant, anticancer, antioxidant, antitumoral and antidepressant activity, the last usually being explored by the forced-swim test [1]. Some of the complexes containing 1,2,4-triazole ligands have rather peculiar structures and specific magnetic properties.
- Triazoles are used in the control of variety of fungal diseases in fruits, vegetables, legumes and grain crops, both as pre- and postharvest applications [2]. The biochemical mechanism of their antifungal effect is based on the inhibition of ergosterol biosynthesis thereby interfering with fungal cell-wall formation. They also inhibit sterol 14α–demethylase and hence considered steroid demethylation inhibitor. 3- amino-1,2,4-triazole is an inhibitor of mitochondrial and chloroplast function.

[1]. M. Koparir, C. Orek, P. Koparir, K. Sarac, *Spectrochim. Acta A*, 2013, *105*, 522–531.
[2]. S.S. Kumar, H.P. Kavitha, *Mini-Rev. Org. Chem.*, 2013, *10(1)*, 40-65.

AIM:

- **The fungicide activity of trifluoromethyl-substituted 1,2,4-triazole Mannich bases containing substituted benzylpiperazine ring (Table 1), expressed by the mycelial growth inhibition activity against the *Fusarium oxysporum f. sp. cucumerinum* fungi test was studied by partial least squares (PLS).**

- **These fungicides were previously energy optimized [3] by the RM1 semiempirical quantum chemical approach, using the Schrödinger software (Schrödinger, LLC, New York, NY, 2008). Structural descriptors of these compounds were correlated to the relative inhibition rate (RIR) values.**

[3]. S. Funar-Timofei, A. Borota, A. Bora, R. Curpan, S. Avram, Modeling of Mannich bases fungicidal activity by the MLR approach, *21st International Symposium on Analytical and Environmental Problems (ISAEP)*, Szeged, Hungary, 28 September, 2015.

METHODS

Table 1. Mannich bases structures including trifluoromethyl-substituted 1,2,4-triazoles

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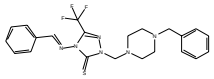
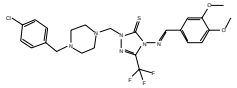
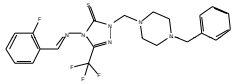
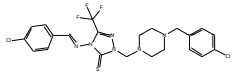
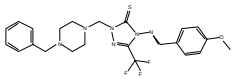
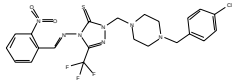
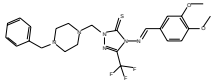
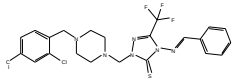
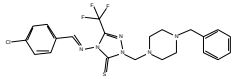
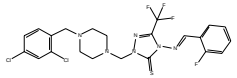
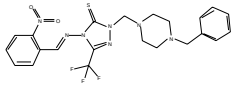
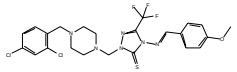
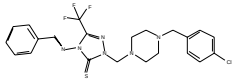
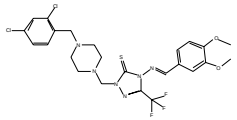
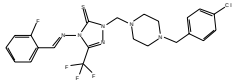
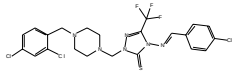
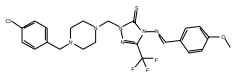
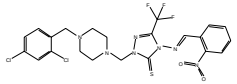
1		10	
2		11	
3		12	
4		13	
5		14	
6		15	
7		16	
8		17	
9		18	

METHODS

- ***Definition of target property and molecular structures***

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

- **Quantum chemical descriptors were derived for the energy optimized structures using previously [3] the RM1 semiempirical quantum chemical approach.**

[4]. B.–L. Wang, X.–H. Liu, X.–L. Zhang, J.–F. Zhang, H.–B. Song, Z.–M. Li, *Chem. Biol. Drug. Des.* 2011, *78*, 42–49.

METHODS

- **Compound descriptors were calculated by several programs: Dragon (Dragon Professional 5.5/2007, Talete S.R.L., Milano, Italy), Instant JChem (Instant JChem v. 15.7.27, 2015, 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).**

- **Partial Least Squares (PLS) [5] was employed to relate the structural descriptors to the mycelial growth inhibition activity against the *Fusarium oxysporum f. sp. cucumerinum* fungi test.**

[5]. H. Wold, Partial Least Squares, in: S. Kotz and N. L. Johnson (Eds.), *Encyclopedia of Statistical Sciences* (Vol. 6), Wiley, New York, 1985, pp. 581-591.

METHODS

- ***Model validation***
- **The leave-seven-out cross-validation procedure was employed for internal validation, the data over fit and model applicability was controlled by comparing the root-mean-square errors (RMSE) and the mean absolute error (MAE) of training and validation sets and the predictive power of the model by the concordance correlation coefficient (CCC) [6].**
- **Y-scrambling was used to check the model robustness and predictive power.**
- **In addition, to test the predictive power of the model, the predictive r^2 (r^2_{pred}) test [7] was employed. It is considered that for a predictive QSAR model, its value should be higher than 0.5.**

[6]. N. Chirico, P. Gramatica, *J. Chem. Inf. Model.* 2011, *51*, 2320-2335.
[7]. P. P. Roy, S. Paul, I. Mitra, K. Roy, *Molecules* 2009, *14,* 1660-1701.

RESULTS AND DISCUSSION

- **PLS calculations were performed to correlate the RIR values with all the calculated descriptors. Compounds: 4, 8, 11, 14, 16 were included in the test set.**

- **A two-components PLS model with acceptable statistical quality was obtained: $R^2X(Cum) = 0.805$, $R^2Y(cum) = 0.823$, $Q^2(Cum) = 0.735$.**

- **Y-randomization test and leave-seven-out crossvalidation runs were performed to check the robustness and internal predictive ability of the PLS models. The Y-scrambling procedure, which was repeated 999 times. The extremely low calculated scrambled R^2 (0.158) and Q^2 (-0.346) values indicate no chance correlation for the chosen model.**

RESULTS AND DISCUSSION

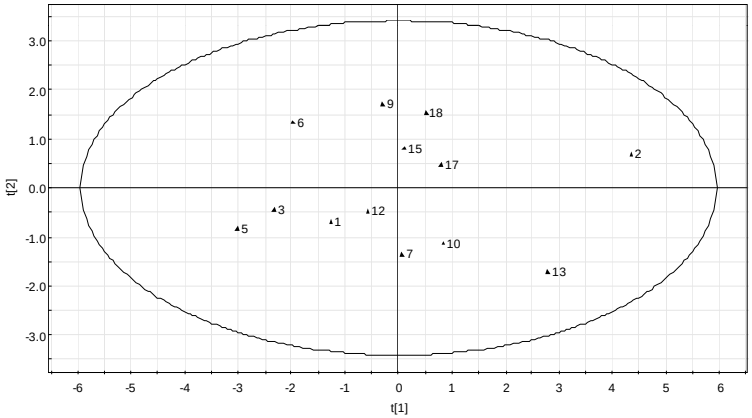


Figure 1. Score scatter plot of the final PLS model

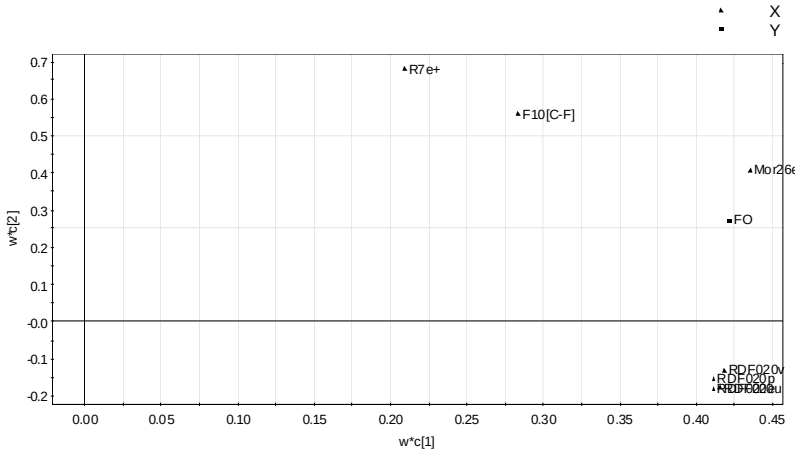


Figure 2. Loading scatter plot of the final PLS model.

RESULTS AND DISCUSSION

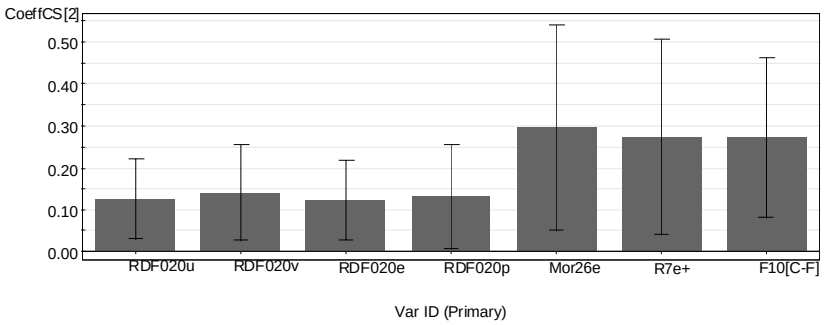


Figure 3. PLS regression coefficients plot of the model with 2 components. The bars indicate 95% confidence intervals based on jack-knifing.

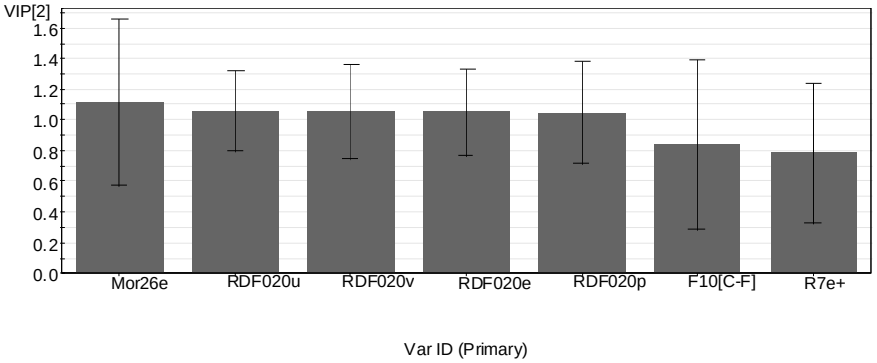


Figure 4. VIP plot of the x-variables of the two-component PLS model.

RESULTS AND DISCUSSION

- The data over fitting and model applicability was controlled by comparing the root-mean-square errors (RMSE) and the mean absolute error (MAE) [8] calculated for the training ($RMSE_{tr}$ = 0.096, MAE_{tr} = 0.079) and validation ($RMSE_{ext}$ = 0.178, MAE_{ext} = 0.140) sets.

- The calculated concordance correlation coefficient values for the training (CCC_{tr} = 0.903), crossvalidation (CCC_{L7O} = 0.832) and test (CCC_{ext} = 0.853) sets indicate a robust model with predictive power, which was confirmed by the r^2_{pred} value of 0.681, too.

[8]. P. Gramatica, In: Reisfeld B, Mayeno AN, editors. Computational Toxicology, Volume II, *Methods in Molecular Biology*, Vol. 930, "On the Development and Validation of QSAR Models", Springer, 2013, pp. 499-526.

RESULTS AND DISCUSSION

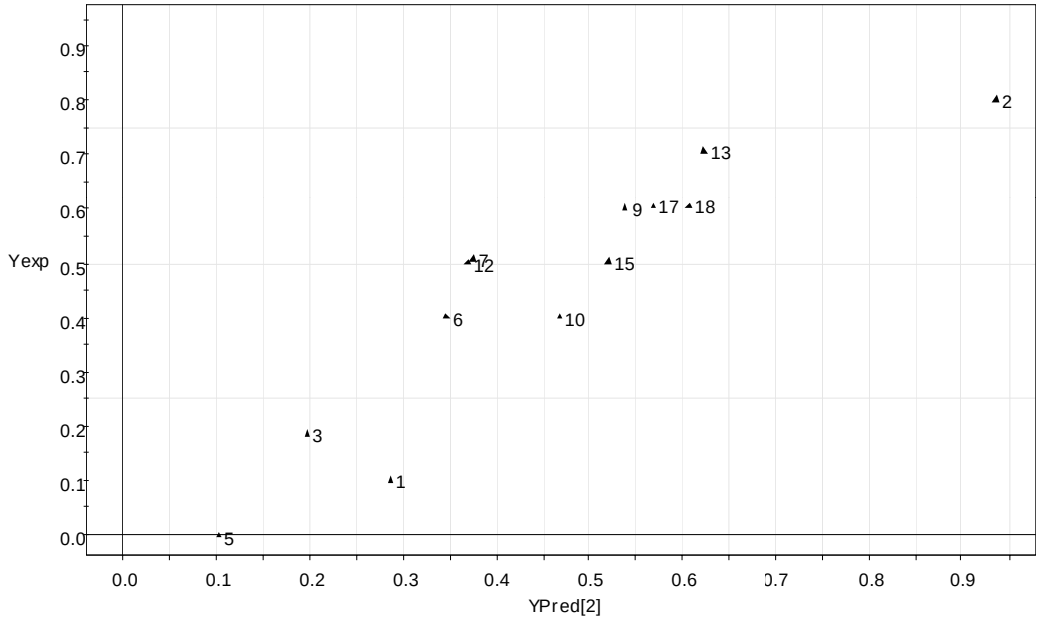


Figure 5. Experimental *versus* predicted RIR values obtained by the final PLS model.

CONCLUSIONS

- **The obtained two-components PLS model is satisfactory in the fitting and has predictive power.**
- **In the final PLS model the selected molecular descriptors capture 3D information (3D-Morse, GETAWAY, RDF), supplying information about interatomic distances, topological distances, types of atoms and which encode chemical information (2D-frequency fingerprints).**
- **The fungicidal activity can be raised by molecular conformation in 3D descriptors weighted by atomic van der Waals volumes, atomic Sanderson electronegativities and atomic polarizabilities, geometrical descriptors referring to the effective position of substituents and fragments in the molecular space.**

ACKNOWLEDGEMENTS

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