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HOLOGRAM QSAR MODEL FOR THE ANTIFUNGAL ACTIVITY OF COUMARIN-1,2,4-TRIAZOLES

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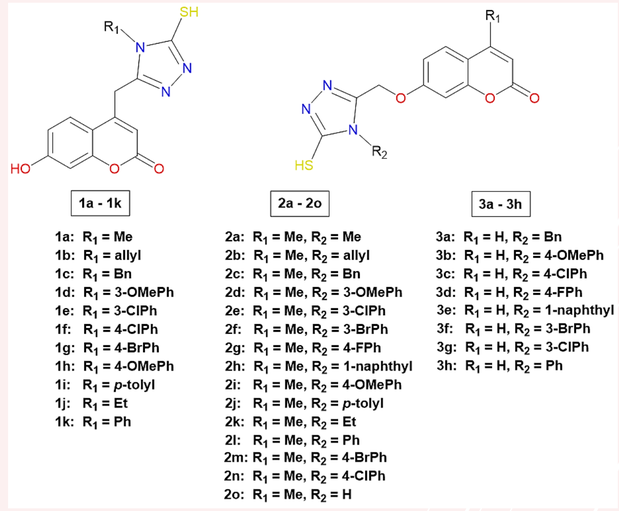
INTRODUCTION

The hologram quantitative structure-activity relationship (HQSAR) is a two-dimensional QSAR method that uses substructural fragments in a molecule as descriptors relevant to its biological activity. Generated molecular holograms encode all possible fragments within a determined radius, including branched, cyclic, and overlapping fragments. Therefore, HQSAR can help identify the most significant fragment or atom contribution in explaining the variation in activity [1].

Sclerotinia sclerotiorum is a nonspecific, highly destructive plant pathogen infecting over 500 plant species, causing severe crop damage and production loss. Recently, we tested the antifungal activity of coumarin-1,2,4-triazoles on several phytopatogenic fungi and obtained very good results of the *S. sclerotiorum* growth inhibition [2]. The aim of this work was to employ the HQSAR to elucidate the structural features important for the observed antifungal activity of coumarin-1,2,4-triazoles against *S. sclerotiorum*.



General structures of coumarin-1,2,4-triazoles

METHODS

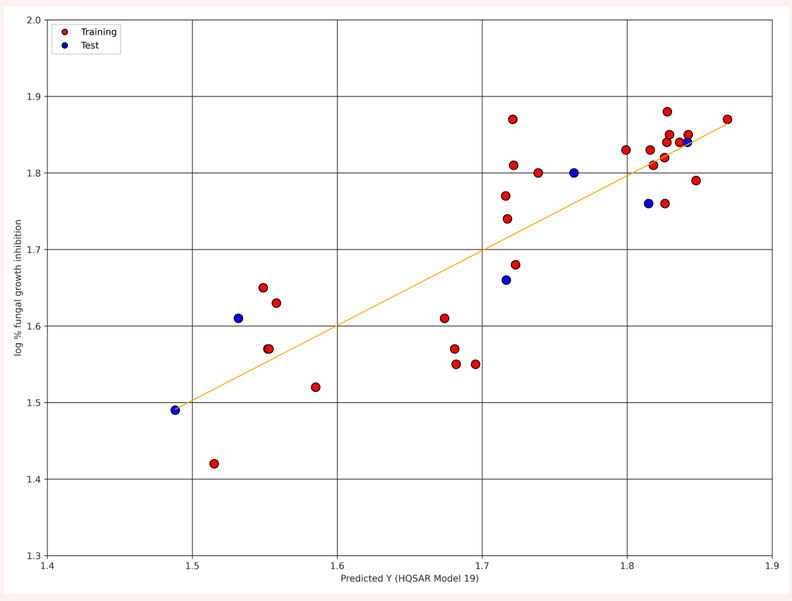
The models were generated by ChemMaster Basic 1.2 software on a set of 28 compounds (model training set) using circular fragment selection within the topological radius of 4 (including bond order and chirality). The logarithmic values of mycelial growth inhibition percentage [2] were used as the response variable. The best model underwent internal and external validation.

RESULTS

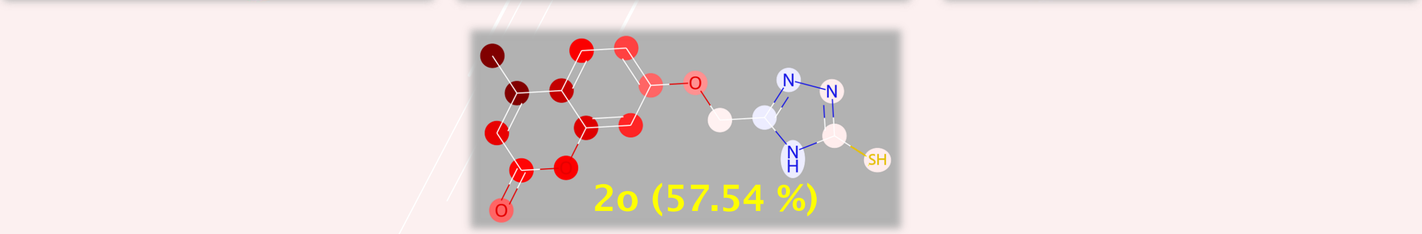
Statistical parameters for the best obtained HQSAR model

	Training (28 compounds)	Cross-validation*	External validation**
R^2	0.734	0.602	0.762
RMSE	0.068	0.086	0.055
MAE	0.052	0.071	0.049

R^2 – correlation coefficient; *RMSE* – root-mean-square error; *MAE* – mean absolute error
* Internal validation of the model
** performed on the randomly chosen test set (**1k**, **2h**, **2m**, **2o**, **3a**, **3c**)



Observed versus predicted values of *S. sclerotiorum* inhibition for coumarin-1,2,4-triazoles calculated by the HQSAR model



Graphical representation of atom contributions according to the HQSAR model, for the least and the most active coumarin-1,2,4-triazoles (observed percent growth inhibition of *S. sclerotiorum* in brackets)

CONCLUSIONS

- The analysis indicated that the coumarin moiety contributed more to the increased activity than the triazole part.
- Triazole moiety had a more prominent role when linked to C-7 of the coumarin core.
- Contribution of coumarin moiety to the antifungal activity was significantly reduced if the methyl group at C-4 was absent.

REFERENCES AND ACKNOWLEDGEMENTS

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