Molecular Topology QSAR Strategy for Crop Protection: New Natural Fungicides with Chitin Inhibitory Activity

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ABSTRACT: Nowadays, crop protection is a major concern and how to proceed is a delicate point of contention. New products must be safe and ecofriendly in accordance with the actual legislation. In this context, we present a quantitative structure—activity relationship strategy based on molecular topology as a tool for generating natural products as potential fungicides following a mechanism of action based on the synthesis of chitin inhibition (chitinase inhibition). Two discriminant equations using statistical linear discriminant analysis were used to identify three potential candidates (1-methylxanthine, hematomnic acid, and antheraxanthin). The equations showed accuracy and specificity levels above 80%, minimizing the risk of selecting false active compounds.

INTRODUCTION

Nowadays fungi cause crop losses worldwide, with fungal diseases having a significant economic impact on plant yield and quality; thus, managing such diseases is an essential component of production for most crops. The identification of molecules targeting enzymes and/or biochemical processes almost exclusive in fungi is a useful approach for agrochemical companies when fighting resistant infestations. Fungal cell walls are primarily composed of polysaccharides, namely chitin, glucans, mannans, and glycoproteins. Chitin is one of the main components, and it is not present in plant cells. Basically, it is a eukaryotic extracellular amino sugar biopolymer, massively produced by most fungal systems and invertebrates, notably arthropods. For its importance in fungi life cycle, chitin has been considered as a selective target for pesticide action. It is synthesized by chitin synthase and cleaved by chitinase which degrades or remodels the cell wall. This way, it is capable to maintain cell wall plasticity during growth. Fungal chitinases are crucial for cell division and replication and also for cell wall remodeling. In addition, they play an important role in cell nutrition, morphogenesis, and development processes; so, the importance as potential targets is clear. Chitin synthesis inhibitors were considered new since 1977. Over the past few decades, a variety of chitinase inhibitors were identified and characterized. The majority of potent chitinase inhibitors are naturally derived products such as pseudotrisaccharide allosamidin and cyclic peptides such as arginin, psammaplin, and argadin. Chemically, many reported chitinase inhibitors share the imine functionality, either in acyclic or cyclic form. Moreover, several diverse mechanisms of action (MOA) related to chitin synthase have been described till today:

- Prevention of the permeation of the substrate through the cytoplasmic membrane so that it is unable to reach the target enzyme.
- Inhibition of chitin biosynthesis and chitin deposition.
- Postpolymerization event, the translocation of chitin chains across the cell membrane.
- Stimulation of the immune system of the plant by inhibiting chitin-related enzymes, the plant elicitors.

The last one is probably the latest and one of the most interesting MOA. The present paper presents two quantitative structure—activity relationship (QSAR) discriminant equations, designed by molecular topology (MT), as tools to identify the potential fungicides and new inhibitors of chitin formation. The MT paradigm consists in characterizing molecules through numerical descriptors called topological indices. These descriptors are based on simple and intuitive notions of a structure having to do with connections between different atoms in a molecule (molecular connectivity). The key elements are not geometrical or physical features of molecules, such as interatomic distances, bond angles or energies, and so forth (which usually play a main role in most QSAR approaches), but features such as the number of links between two atoms, the presence or absence of cycles, the possibility of connecting two particular atoms by a certain path, and so forth. It can be said that MT goes beyond standard QSAR approaches, allowing the generation of a huge number of new and interesting inhibitors. The two discriminant equations presented here provide a procedure to generate new natural products as potential fungicides and new inhibitors of chitinase with interesting MOA.
of descriptors and increasing the chance of strong correlations. In addition, it must be noted that topological descriptors only rely on structure; so, no experimental measures are required. They are rentable, flexible (it is possible to use topological descriptors for every kind of structure), and contrary to the general assumption, and they can be used to predict three-dimensional properties. Latest results showed the potential of MT in antimicrobial resistance control, fungi resistance control, and biodegradability prediction as a powerful tool for research related with health, crop, and environment safety.

## MATERIALS AND METHODS

The MT approach consists of the following steps

- **Step I:** creation of a specific database. Compounds with fungicide and chitin synthase inhibition activity were retrieved from the literature and “The pesticide manual” reported by the British Crop Protection Council.
- **Step II:** calculation of topological descriptors using the Dragon software.
- **Step III:** division of the data set into two groups: training and test sets.
- **Step IV:** calculation of the topological predictive models, applying the linear discriminant analysis (LDA) technique: DF$_1$ and DF$_2$.
- **Step V:** performance of external and internal validation to assess the robustness of the predictive equations.
- **Step VI:** virtual screening of database (The Natural Product Collection from MicroSource Discovery System Inc.)
- **Step VII:** selection of potential candidates as fungicides with inhibitory activity against the chitin formation.

### Compound Analysis

The first QSAR model (DF$_1$) was developed from a database of 295 heterogeneous active and inactive structural compounds with fungicidal activity. The data were split into two subsets: training set (215 molecules) and external test set (80 molecules). Each set was again split into two groups: active and inactive, taking into account different chemical features in order to reach a coherent balance on chemical diversity between the groups. All active compounds were collected from the literature. The second QSAR model (DF$_2$) was calculated using a dataset of 41 molecules (training set) retrieved from the literature. For both models, the inactive molecules were retrieved from the Sigma-Aldrich compound collection. After a comprehensive analysis of the dataset, a study of molecular descriptors is provided.

### Molecular Descriptors

Topological descriptors codify information about the molecular structure in a purely numerical way. The numerical format makes the search of new hits and leads easier. The structure of molecules was drawn using ChemDraw Ultra (version 10.0) and characterized by a set of descriptors such as constitutional and topological descriptors. Among the last stand edge-adjacency indices, walk and path counts, connectivity indices, and topological charge indices. Other graph-theoretical descriptors were also calculated but not depicted here because of their lack of effectiveness. All indices were calculated with the Dragon software version 5.4, and their values for the selected equations for every compound included in this study (training set, external test set, and virtual screening set) are shown in the Supporting Information.

### Modeling Techniques

In the present work, LDA was used to calculate QSAR models. LDA allows calculation of a discriminant function (DF), which best separates two categories or objects in a specific case into active and inactive groups. The software used was Statistica 9.0. Discriminant capability was assessed as the percentage of correct classifications in each set of compounds. Its classification criterion is based on the minimum Mahalanobis distance (the distance of each case to the mean of all cases in a category), and the quality of discrimination was evaluated using Wilks’ lambda ($\lambda$) parameter, which is related with the multivariate analysis of variance that tests the equality of group means for the variable in the discriminant model. The smaller the Wilks parameter value, the smaller is the overlap between the active and inactive groups ($\lambda = 0$ would mean a perfect separation between the groups). The descriptor selection was carried out according to the Fisher–Snedecor parameter ($F$), which establishes the relevance of candidate variables. The stepwise procedure is “guided” by the respective $F$ to introduce and remove values. The $F$ value for a variable indicates its statistical significance in the discrimination between groups, that is, it is a measure of the extent to which a variable makes a unique contribution to the prediction of group membership. The descriptors included to compute the linear classification function are chosen in a stepwise manner: at each step, the variable making the largest contribution in discriminating between groups is introduced into the equation (or the variable that makes the smallest contribution is removed).

### Model Validation

Validation of DFs was performed using external (test set) and internal (y-randomization) validation techniques. In addition, the sensitivity, specificity, and predictive precision of the models are reported. In order to determine the capability of the model for identifying true positive compounds (true active), sensitivity has been calculated, following the formula: sensitivity = $\frac{\text{true positives}}{\text{true positives} + \text{false negatives}} \times 100$. Furthermore, to assess the capability of the model in identifying true negative (true inactive) compounds, the specificity has also been calculated: specificity = $\frac{\text{true negatives}}{\text{true negatives} + \text{false positives}} \times 100$. Finally, the model accuracy is calculated to quantify the ability to identify the true positives and negatives (real active and inactive compounds): accuracy = $\frac{\text{true positives} + \text{true negatives}}{\text{true positives} + \text{true negatives} + \text{false positives} + \text{false negatives}} \times 100$.

### ROC Curve

Receiver operating characteristic (ROC) curve is a graphical display of sensitivity on y-axis and (1—specificity) on x-axis for varying cutoff points of values. It is depicted as a square box, with both axes from 0 to 1. The area under the curve (AUC) is a measure of sensitivity and specificity for assessing the robustness of a predictive test. Maximum AUC = 1 means the prediction test is perfect in differentiating active cases from inactive cases. This implies that both sensitivity and specificity are 1 and that both errors—false positive and false negative—are 0. The closer AUC is to 1, the better is the performance of the test. The diagonal joining the point (0, 0) to (1, 1) divides the square in two equal parts, and each has an area equal to 0, 5. When the ROC meets with this line (AUC = 0, 5), there is a 50–50 chance that the test will discriminate the active and nonactive cases: random classification.

### Activity Distribution Diagram

LDA in topological QSAR allows plotting frequency distribution diagrams. The diagrams represent a function of the number of molecules within an interval of values of DF versus these values. It is
called activity distribution diagram (ADD). For structurally heterogeneous groups of molecules, the diagram shows skewed Gaussian shapes or present several maxima. The maxima afford intervals of DF in which exists a good expectancy to find new active molecules.  

**Virtual Screening.** Once a maximum expectancy range of DF for finding fungicide and chitin inhibitor activities is defined, a virtual screening of a commercial database is performed. The natural product collection from MicroSource Discovery System Inc.  was used here to find new natural compounds with fungicidal activity and inhibitory activity of chitin formation.

**RESULTS AND DISCUSSION**

**QSAR Topological Models.** The two QSAR models, one for predicting fungicidal activity (DF1) and the other for predicting the inhibitory activity of chitin formation (DF2), are presented below. The first DF (DF1), a six-variable equation, is reported

\[
DF_1 = \left( \frac{D}{Dr05} \times 0.020 \right) + \left( \piPC04 \times 1.319 \right) - \left( MPC10 \times 0.037 \right) - \left( EEig03r \times 2.862 \right) + \left( EEig14r \times 2.366 \right) + \left( JGI3 \times 23.364 \right) + 3.321
\]

(1)

The parameters accounting for the significance of this equation were

\[
N = 215; \ \lambda = 0.732; \ F = 12.7; \ p < 0.00001
\]

where N is the number of training set compounds; λ, Wilks’ lambda; F, Fisher–Snedecor parameter; p, statistical significance; D/Dr05, distance/detour ring index of order 5; πPC04, molecular multiple path count of order 4; MPC10, molecular path count of order 10; EEig3r, eigenvalue 3 from edge adjacency matrix weighted by resonance integrals; EEig14r, eigenvalue 14 from edge adjacency matrix weighted by resonance integrals; and JGI3, the mean topological charge index of order 3.

Although it is not easy to establish an explanation in terms of structure–activity relationship for an equation with as many variables as DF1, some observations can be made. Among the descriptors, D/Dr05, πPC04, EEig14r, and JGI3 contribute positively to fungicidal activity, whereas MPC10 and EEig3r contribute negatively. D/Dr05, for example, the distance/detour ring index of order 5 is a topological descriptor. The positive coefficient of this descriptor suggests that the presence of five-member rings contribute to increase the fungicidal activity. Although the presence of five-member rings may not be a conditio sine qua non for fungicidal activity, it can be observed how compounds that do have five-member rings and values of D/Dr05 (45–150) are classified as active by the model. On the contrary, compounds with values of the descriptor <45 or >150 are classified as inactive (Figure 1).

πPC04, a member of the walk and path family descriptors, is defined as the sum of weights of the paths of length 4. Therefore, the πPC04 value is expected to increase according to the increasing size, branching, and length of carbon chains in molecules (Figure 2). When analyzing the value adopted by this index in the training set, it can be seen how molecules with values of πPC04 (0–2.8) are always classified as fungicides by the model. However, compounds which adopt values (2.8–5.4) are classified as active or inactive depending on the overall
calculation of the rest of the descriptors present in the equation (Figure 2).

JGI3 (mean topological charge index of order 3) is a descriptor that provides information about the exchange of charges between atoms located at a topological distance 3, per bond, that is, it represents an average value of the charge transferred at distance 3 in the molecule.

In addition, it should be noted how the descriptors that less contribute to the discrimination of fungicidal activity are two of the three most statistically relevant in the model (F > 25). MPC10 provides pure topological information of the compounds, whereas EEig3r is related with the resonant effect. Finally, the descriptor which contributes greater to the model is EEig14r (F > 30), which describes the degree of conjugation of the molecules related with the resonance effect. In fact, as shown in Figure 3, molecules with higher conjugation (Blasticidin-S or S102385) adopt larger values of these indices than less-conjugated ones (ampropyfos or 1067-47-6).

All the compounds of the training and test sets are reported in Table S1 in the Supporting Information, showing: the
probability of activity, the DF\textsubscript{1} value, and the value of each respective descriptor of the discriminant equation.

According to the results of DF\textsubscript{1}, a molecule will be classified as a potential fungicide if DF > 0 and as a nonfungicide if DF < 0. By applying this criterion to the training set of 215 compounds, 73 out of 104 active compounds were correctly classified as fungicides (70.2% accuracy), whereas 90 out of 111 inactive compounds were correctly classified (81.1% accuracy), as can be seen in Table 1. To evaluate the robustness of the discriminant equation, an external validation was run using an external test set. The group was made up of 80 compounds (40 active and 40 inactive, as fungicides, respectively) which were not included in the training set. A random selection of about 30% of all dataset was made. The model yields a correct classification of 67.5% for the active group (27 out of 40 compounds) and 77.5% for the inactive group (31 out of 40 compounds), as shown in Table 1.

As illustrated in Table 1, the model has a higher specificity than sensitivity both for the training and test sets (81.1 and 77.5%, respectively). This is important because it minimizes the risk of selecting false active compounds. Figure 4 gives visual insights about the whole specificity and sensitivity of the model.

| % correct class* | no active class | no inactive class |
|------------------|----------------|------------------|
| Training Set (DF\textsubscript{1}) | | |
| active group | 70.2 | 73 | 31 |
| inactive group | 81.1 | 21 | 90 |
| External Test Set (DF\textsubscript{1}) | | |
| active group | 67.5 | 27 | 13 |
| inactive group | 77.5 | 9 | 31 |
| Training Set (DF\textsubscript{2}) | | |
| active group | 82.3 | 14 | 3 |
| inactive group | 83.3 | 4 | 20 |

To identify the DF\textsubscript{1} applicability domain, ADD is developed.\textsuperscript{28} Molecules showing fungicide activity are represented in black, whereas inactive molecules are represented in white. In Figure 6A it can be seen how the model’s range of applicability is for DF\textsubscript{1} values between −6 and 4. In addition, the graphic gives information about the range of DF\textsubscript{1} in which the expectancy of finding fungicides is higher (0.5–4.0). Furthermore, a zone of overlap between the

From these results, it is clear that when using the model to screen the database for potential antifungal agents, there is an 18.9% probability of selecting false active compounds. Figure 5A shows the ROC curve for DF\textsubscript{1}. A value of AUC = 0.893 represents an 89.3% probability that two compounds, one active and the other inactive, are correctly classified by the DF\textsubscript{1} function.

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Figure 4. Graphic of the accuracy, specificity, and sensitivity for DF\textsubscript{1} and DF\textsubscript{2}.

Figure 5. ROC curves for DF\textsubscript{1} (A) and DF\textsubscript{2} (B) for different thresholds of class function (between −10 and +10). AUC (DF\textsubscript{1}) = 0.893 and AUC (DF\textsubscript{2}) = 0.946.

Figure 6. ADD for DF\textsubscript{1} (A) and DF\textsubscript{2} (B) (the black color represents the fungicide or inhibitor of the chitin formation compounds, and the white color compounds without these activities).
fungicidal and nonfungicidal compounds (0.5 and −3.5) is present. DF1 values <−6 and >4.0 will be considered outside the range of applicability of the model; therefore, these molecules are nonclassifiable by the model.

Once the fungicidal activity is modeled, the other main objective of the present work is addressed: to develop a predictive model to find the potential inhibitors of chitin formation. A new discriminant equation of three descriptors was made (eq 2)

\[
DF_2 = (ATS4m \times 13.534) - (ATS5m \times 8.907) - (GATS5m \times 3.040) - 17.050
\]  

(2)

The statistics of this equation were

\[ N = 41; \lambda = 522; F = 11.3; p < 0.00001 \]

where \( N \) is the number of training set compounds; \( \lambda \), Wilks’ lambda; \( F \), Fisher–Snedecor parameter; \( p \), statistical significance; ATS4m, the Broto–Moreau autocorrelation index of topological structure – lag 4/weighted by atomic masses; ATS5m, the Broto–Moreau autocorrelation index of topological structure – lag 5/weighted by atomic masses; and GATS5m, the Geary autocorrelation index – lag 5/weighted by atomic masses.

The descriptors in DF2 are related to the atomic mass of atoms present in the molecules. As illustrated in Figure 7, molecules with a larger size, and therefore larger atomic mass, adopt higher values of the descriptors in the model for predicting the inhibitory activity against chitin. However, there is no direct relationship between a greater value of these descriptors and a greater value of DF2 because two of the descriptors (ATS5m and GATS5m) contribute negatively to the equation.

All the compounds of the training set are reported in Table S2 in the Supporting Information, showing the probability of activity, the DF2 value, and the value of each respective descriptor in the discriminant equation.

The discriminant model classifies those molecules with DF2 > 0 as potential inhibitors of chitin formation, whereas those with DF2 < 0 as inactive. By applying this criterion to the training set (41 compounds), 14 out of 17 have been correctly classified as inhibitors of chitin formation (82.3% accuracy), and 20 out of 24 inactive compounds were also correctly classified (83.3% accuracy), as can be seen in Table 1.

As shown in Table 1 and Figure 4, DF2 shows high specificity and sensitivity. DF2 has a probability to select false active and inactive compounds for values of DF > 0 or <0 of 17%.

Considering the small size of the database of chitin formation inhibitors, the external validation of the model could not be done. Therefore, an internal validation was performed. \( y \)-Scrambling or \( y \)-randomization test was performed, in which 10 molecules between the active and inactive groups are interchanged randomly. This is a form of arrangement test, where the values of the dependent variable \( y \) are randomly assigned to different compounds, whereas the descriptor values \( x \) are left unchanged.\(^{29}\) The rearranged data are then used for training QSAR models. As shown in Table 2, the value of \( \lambda \) (Wilks) increases significantly in all the validation models. This gives some insights about the absence of randomness of the model, thereby assuring reliability and stability. When changing some molecules from the active group to the inactive one, the predictive capability decreases. Hence, it can be concluded that the presence of a particular molecule does not alter the DF2 value significantly. Moreover, in the validation models, both the sensitivity and specificity decrease significantly.

Figure 5B shows the ROC curve for DF2. The value of AUC = 0.946 represents a probability of 94.6% of correct classification with DF2.

Next, Figure 6B shows the ADD for DF2. Here, the domain of applicability ranges between −6 and 6. In addition, information about the range of DF2 in which a higher expectancy of finding inhibitors of the formation of chitin (1.5–6) is depicted. Moreover, the overlap zone (−2.5 and 1.5) between the active and inactive compounds is present. DF2 values <−6 and >6 will be considered outside the range of applicability of the model and are therefore considered as nonclassifiable by the model.

Virtual Screening. After validating the predictive models and identifying the range of application, the commercial database, The Natural Product Collection from MicroSource Discovery System Inc.,\(^{17}\) was screened, searching for new fungicides and chitin formation inhibitors of natural origin.

Table S3 in the Supporting Information shows the DF1, \( y \) DF2 values obtained for each natural compound of the dataset (some 700 molecules).

In Tables 3 and S4 is reported the selection using the two discriminant equations DF1 and DF2, respectively. A molecule will be considered active if the following conditions of ADD are met: DF1 values from 0.5 to 4 and DF2 from 1.5 to 6.

Only 16 compounds pass the filter of the topological model for the selection of potential natural fungicides by the inhibition of chitin formation (2.3% of the screen data). In addition, 13 of the 16 selected compounds (81.2%) have already been described with antifungal activity in the literature, suggesting that the topological model presented is highly predictive.

Table 2. \( y \)-Randomization Test Performed to DF2

| series     | \( \lambda \) (Wilks) | sensitivity (%) | specificity (%) |
|------------|----------------------|-----------------|-----------------|
| Training   | 0.522                | 82.3            | 83.3            |
| random_1   | 0.816                | 64.7            | 66.7            |
| random_2   | 0.939                | 64.7            | 62.5            |
| random_3   | 0.812                | 58.8            | 66.7            |
| random_4   | 0.828                | 64.7            | 70.8            |
| random_5   | 0.837                | 77.8            | 69.6            |
Figure 8 shows the chemical structure of three new potential fungicides acting as the inhibitors of chitin formation, identified using DF1 and DF2.

![Chemical structures](image)

**Figure 8.** Potential fungicides and chitin formation inhibitors of natural origin.

Even if the antifungal activity for the three molecules is not recorded in the literature, these natural compounds had been reported to show some pharmacological activity. 1-Methylxanthine, well known as the major metabolite of caffeine, has positive effects against asthma and diuretic activity. 43 Hematommic acid is described as an effective antioxidant agent,44 as well as antheraxanthin, which also has a carotenoid profile.45

A similarity study on the three potential fungicides is carried out using SciFinder Scholar and ChemSpider database. Tanimoto and Euclidean parameters46 are used, searching for similarity in a range between 80 and 99% among the commercially available molecules. For 1-methylxanthine, no antifungal activity among similar molecules was found; however, several methyl xanthine derivatives are described in the literature as fungicides, with activity as chitin inhibitors.47,48 As for the antheraxanthin similar, no antifungal activity is described, while for the hematommic acid one molecule, the 2,4-dihydroxy-6-methylbenzoic acid (CAS number: 480-64-8) with a similarity of 82%, is reported as antibacterial and antifungal.49,50

**CONCLUSIONS**

In the present work, the authors show how MT can be a key paradigm in developing QSAR strategies, searching for new fungicides. Considering the urgent situation in crop field protection, they decided to develop an in silico strategy to search new molecules capable to inhibit the synthesis of chitin in fungi. To do so, the authors calculated two discriminant equations using statistical LDA. The two equations were validated with external and internal methods and then used for the screening of The Natural Product Collection from MicroSource Discovery,17 searching for the potential inhibitors of the formation of chitin. Only 16 molecules pass the topological filters, and almost 80% of the candidates was later confirmed, as already described in the literature, for some antifungal activity. Three best candidates are selected as new, natural agents to control fungi growth in crop protection: 1-methylxanthine, hematommic acid, and antheraxanthin. In the authors’ opinion, the present results offer an insight about the potential of MT as an effective methodology in designing new agrochemical agents. The identification of the three new potential fungicides that inhibit the chitin synthesis may be an attractive starting point for the development of new products in crop protection, above all, considering that the molecules are natural products.

**ASSOCIATED CONTENT**

*Supporting Information*

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00177.

All indices calculated with Dragon software version 5.4.15 and their values for the selected equations for every compound (training set, external test set, and virtual screening set) (XLSX)

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### Table 3. Selection of Potential Natural Fungicides by Inhibiting Chitin Formation

| compound                  | Cas# no | DF1  | DF2  | reported activity |
|---------------------------|---------|------|------|-------------------|
| 1-methylxanthine          | 6136-37-4 | 2.14 | 1.47 | no info registered |
| 4-O-methylphloracetophenone | 7507-89-3 | 3.19 | 2.80 | 30                 |
| antheraxanthin            | 640-03-9 | 2.87 | 3.01 | no info registered |
| atractanorin              | 479-20-9 | 0.52 | 2.38 | 31                 |
| beaemysic acid            | 644-66-6 | 0.69 | 2.07 | 32                 |
| camphor                   | 76-22-2 | 3.27 | 4.73 | 33                 |
| cantharidin               | 56-25-7 | 0.64 | 6.76 | 34                 |
| evernic acid              | 537-09-7 | 1.07 | 3.55 | 35                 |
| evernic acid              | 570-10-5 | 3.19 | 2.74 | 36                 |
| hematommic acid           | 479-25-4 | 0.56 | 1.93 | no info registered |
| lecanoric acid            | 480-56-8 | 0.62 | 4.09 | 37                 |
| menthol(−)                | 1490-04-6 | 1.46 | 4.60 | 38                 |
| Menthone                  | 14073-97-3 | 1.51 | 4.60 | 39                 |
| methyl orsellinate        | 3187-58-4 | 3.08 | 2.11 | 40                 |
| orsellinic acid           | 480-64-8 | 3.29 | 3.96 | 41                 |
| orsellinic acid, ethyl ester | 2524-37-0 | 0.73 | 2.34 | 42                 |

*As far as we know, no information about antifungal or chitin inhibition activity is present in the literature.*
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Notes
The authors declare no competing financial interest.

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■ ABBREVIATIONS
MOA, mechanism of action; QSAR, quantitative structure–activity relationship; MT, molecular topology; LDA, linear discriminant analysis; DF, discriminant function; ADD, activity distribution diagram; ROC, receiver operating characteristic; AUC, area under the curve

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