

Quantitative Structure–Activity Relationships of Mosquito Larvicidal Chalcone Derivatives

Gustavo Pasquale,[†] Gustavo P. Romanelli,^{†,‡} Juan C. Autino,[†] Javier García,[§] Erlinda V. Ortiz,[⊥] and Pablo R. Duchowicz^{*,§}

[†]Cátedra de Química Orgánica, Facultad de Ciencias Agrarias y Forestales, Universidad Nacional de La Plata (UNLP), 60 y 119 (B1904AAN) La Plata, Buenos Aires, Argentina

[‡]Centro de Investigación y Desarrollo en Ciencias Aplicadas “Dr. Jorge J. Ronco” (CINDECA), CONICET-CCT La Plata, Universidad Nacional de La Plata (UNLP), 47 No. 257, (B1900AJK), La Plata, Argentina

[§]Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas INIFTA (UNLP, CCT La Plata-CONICET), Diag. 113 y 64, Sucursal 4, C.C. 16, 1900 La Plata, Argentina

[⊥]Facultad de Tecnología y Ciencias Aplicadas, Universidad Nacional de Catamarca, Av. Maximio Victoria 55, (4700) Catamarca, Argentina

S Supporting Information

ABSTRACT: The mosquito larvicidal activities of a series of chalcones and some derivatives were subjected to a quantitative structure–activity relationship (QSAR) study, using more than a thousand constitutional, topological, geometrical, and electronic molecular descriptors calculated with Dragon software. The larvicidal activity values for 28 active compounds of the series were predicted, showing in general a good approximation to the experimental values found in the literature. Chalcones having one or both electron-rich rings showed high toxicity. However, the activity of chalcones was reduced by electron-withdrawing groups, and this was roughly diminished by derivatization of the carbonyl group. A set of six chalcones being structurally similar to some of the active ones, with a still unknown larvicidal activity, were prepared. Their activity values were predicted by applying the developed QSAR models, showing that two chalcones of such set, both **32** and **34**, were expected to be highly active.

KEYWORDS: chalcone derivatives, mosquito larvicidal activity, QSAR theory, molecular descriptors

1. INTRODUCTION

Chalcones or 1,3-diaryl-2-propen-1-ones are a family of aromatic ketones with two aromatic groups bridged by an enone linkage (Ar–COCH=CH–Ar').¹ The numbering of chalcones and the designation of the aryl ring as A and B are indicated for the unsubstituted compounds **1** (Figure 1).

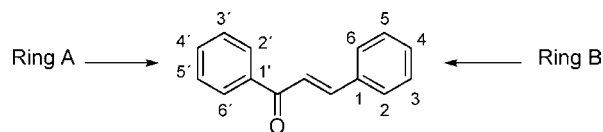


Figure 1. Chalcone structure.

Chalcone is commonly synthesized via the Claisen–Schmidt aldol condensation between acetophenone and benzaldehyde (Scheme 1). This reaction is catalyzed by bases and acids under

Scheme 1. Chalcone Synthesis



homogeneous conditions. The condensation reaction in basic medium is usually carried out in the presence of sodium hydroxide, potassium hydroxide, or alkali alcoholate,^{2,3} and the acid-catalyzed

methodologies include the use of dry HCl,⁴ a Lewis acid such as TiCl₄,⁵ *p*-toluenesulfonic acid,⁶ and more recently BF₃–Et₂O.⁷

Chalcones have attracted increasing attention due to numerous pharmacological applications. They are the main precursors for the biosynthesis of flavonoids, which are common pharmacologically active components of the human diet.⁸ For example, licochalcone A isolated from the roots of *Glycyrrhiza inflata* (licorice) has *in vitro* and *in vivo* antimalarial⁹ and anti-leishmanial activities,¹⁰ and 3-methoxy-4-hydroxyoncocarpin isolated from the roots of *Lonchocarpus utiliz* inhibits NADH:ubiquinone oxidoreductase activity (Figure 2).¹¹

Compounds with the backbone of chalcones, which possess various biological activities such as antimicrobial,¹² anti-inflammatory,¹³ antiplatelet,¹⁴ antimalarial,¹⁵ anticancer,¹⁶ antileishmanial,¹⁷ antioxidant, antifungal,¹⁸ and inhibition of leukotriene B₄, have been reported. Chalcones also find several application in agriculture; for example, chalcones exhibit allelopathic activity,¹⁹ and many chalcones are used as insecticides and fungicides;²⁰ in this way chlorochalcones are potent insect antifeedants.^{18,21}

The well-known basis of the quantitative structure–activity relationships (QSAR) theory^{22–25} is the hypothesis that the biological activity exhibited by a chemical compound is mainly

Received: August 22, 2011

Revised: December 7, 2011

Accepted: December 7, 2011

Published: January 3, 2012

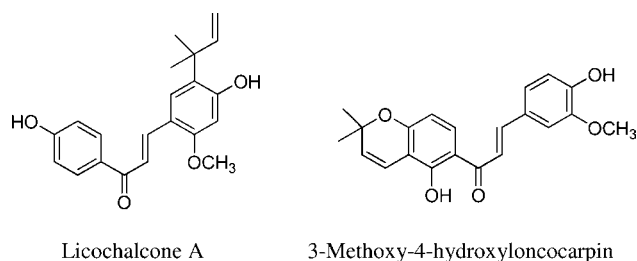


Figure 2. Licochalcone A and 3-methoxy-4-hydroxyloncocarpin.

determined by its molecular structure. This fact does not offer specific details on the usually complex mechanism/path of the process that leads to the final biological effect. However, it is possible to get some insight into the underlying mechanism of action by means of the QSAR-based predicted activities. Although chalcones have been widely studied in the past, there are not many QSAR studies on the insecticide activity of these compounds. Only a recent publication of Begum and co-workers²⁶ described a QSAR for mosquito larvicidal activity of some chalcone derivatives.

In this work, we studied the larvicidal activity of some chalcone-type compounds with various substitution patterns along with some of their derived products against the larvae of *Culex quinquefasciatus*. We collected experimental information from the literature²⁶ and established useful QSARs, with the main purpose of applying this structure–activity relationship to a set of six chalcone derivatives with unknown experimental larvicidal activities recently synthesized in our laboratory.²⁷ We employed multiparametric linear regression models, as this is considered one of the most popular statistical techniques, and explored more than a thousand theoretical descriptors.^{28–30}

2. MATERIALS AND METHODS

2.1. Materials and Reagents. All solvents and chemicals were commercially available and used without further purification unless otherwise stated. Catalyst was prepared according to the literature.²⁷

2.2. General Procedure for Chalcone Synthesis. Chalcone synthesis was performed in a sealed tube in solvent-free conditions. A mixture of the corresponding aldehyde (1.3 mmol), acetophenone (1 mmol), and catalyst (100 mg) was warmed at 140 °C for 4 h. The reaction mixture was diluted with hot toluene (10 mL), the catalyst was filtered off, and then the solution was washed and dried with anhydrous Na₂SO₄, the solvent was evaporated, and the residue was purified by column chromatography (silica gel, ethyl acetate/hexanes) to afford pure chalcones. All yields were calculated from isolated products.

2.3. Quantitative Structure–Activity Relationships Analyses. The initial conformations of the compounds were drawn by means of the “model build” modulus available in HyperChem 7.³¹ Each molecular structure was first preoptimized with the molecular mechanics force field (MM+) procedure, and the resulting geometry was further refined by means of the semiempirical method PM3 (parametric method 3). We chose a gradient norm limit of 0.01 kcal mol⁻¹ Å⁻¹. The numerical descriptors for each compound were calculated with Dragon software³² and included several variable types characterizing the multidimensional aspects of the chemical structure: constitutional, topological, geometrical, charge, GETAWAY (geometry, topology, and atom-weighted assembly), WHIM (weighted holistic invariant molecular descriptors), 3D-MoRSE (3D molecular representation of structure based on electron diffraction), molecular walk counts, BCUT descriptors, 2D autocorrelations, aromaticity indices, Randic molecular profiles, radial distribution functions, functional groups, and atom-centered fragments. We also added quantum chemical descriptors to the pool such as the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbital energies, HOMO–LUMO gap (Δ HOMO–LUMO), total dipole

moment, and number of electrons. The total number of calculated descriptors was 1502.

We resorted to the replacement method (RM)³³ as the molecular descriptor selection approach, an algorithm that was proposed by our research group some years ago for generating multivariable linear regression QSAR models with minimized standard deviation (*S*). The quality of the results achieved with this technique is quite close to that obtained by performing an exact (combinatorial) full search (FS) of molecular descriptors, although, of course, it requires much less computational work.³⁴ In addition, the RM provides models with statistical parameters better than those from the forward stepwise regression procedure and similar to those from the more elaborated genetic algorithms approach.^{35,36}

All of the models presented here were properly validated by means of the leave-one-out (loo) cross-validation technique³⁷ and more strictly by using an external test set of selected compounds (test). We also practiced the *Y*-randomization³⁸ technique, which consists of scrambling the experimental activity values in such a way that they no longer correspond to the respective compounds. The smallest standard deviation *S*^{Rand} obtained after analyzing 1000 cases of *Y* randomization for each developed QSAR turned out to be poorer (greater) than the one found in the true calibration (*S*). This result supports the assumption that the correlations derived here are not fortuitous but the result of actual structure–activity relationships.

To determine the relative importance of each descriptor in the linear regression model, we calculated standardized regression coefficients³⁹ as

$$b_j^s = \frac{s_j \times b_j}{s_Y} \quad j = 1, \dots, d \quad (1)$$

where *b_j* is the regression coefficient for the descriptor *j* and *s_j* and *s_Y* are the standard deviations for that descriptor and for the experimental activity, respectively. The larger the value of *b_j^s*, the greater is the importance of the descriptor *j*.

3. RESULTS AND DISCUSSION

The set of six chalcone derivatives **29–34** was prepared by the Claisen–Schmidt condensation reaction of benzaldehydes and acetophenone under solvent-free conditions catalyzed by amino-propylated silica sol–gel materials according to the literature.²⁷ The reactivity of different benzaldehydes and methyl aryl ketones was tested under the same conditions (140 °C, benzaldehyde/acetophenone ratio 1.3:1, catalyst 100 mg, and 240 min). Results of the obtained yields are listed in Table 1. The results showed

Table 1. Chalcone Synthesis by Claisen–Schmidt Procedure

entry	product	R	R ₁	yield (%)
29	29	–H	–CH ₃	83
30	30	–H	–OCH ₃	83
31	31	–H	–OH	84
32	32	–H	–Cl	88
33	33	–CH ₃	–H	90
34	34	–Cl	–Cl	84

that, in general, the reactions were clean and products were isolated by liquid column chromatography in pure form without further purification (¹H and ¹³C NMR).

As a first step, we partitioned the complete set of 28 chalcone derivatives having experimental activities into 23 training (82%) and 5 test set compounds (18%). The members of such sets were chosen by exploring the structure–activity relationship

present in these observations. Afterward, we searched various predictive linear QSAR models for the chalcone structures that obey the “rule of thumb”. This rule states that at least five or six data points should be present for each fitting parameter to avoid overfitting problems.

The optimal linear regression equations were established by means of the replacement method approach, which minimized its standard deviation (S) and included the best “representative” $d = 1-3$ molecular descriptors. We proceeded by using two different approaches: (a) extracted d descriptors from the complete pool containing $D = 1502$ variables (0D–3D QSAR); (b) extracted d descriptors from a pool containing $D = 762$ variables, which included only topochemical (conformation independent) type of descriptors (0D–2D QSAR). Tables 2

Table 2. Statistical Characteristics for 0D–3D QSAR Models on $\text{Log}_{10}\text{LC}_{50}$ of Chalcone Derivatives

	regression coefficient (standard error)	statistical quality
QSAR-1		
intercept	3.425 (0.2)	$N/d = 23, R^2 = 0.59, S = 0.54, o \geq 2.5S = 0, S^{\text{Rand}} = 0.58, R_{\text{loo}}^2 = 0.50, S_{\text{loo}} = 0.60, R_{\text{test}}^2 = 0.50, S_{\text{test}} = 0.60$
Mor22p	8.644 (2)	
QSAR-2		
intercept	6.941 (1)	$N/d = 11.5, R^2 = 0.69, S = 0.47, R_{\text{max}}^2 = 0.14, o \geq 2.5S = 0, S^{\text{Rand}} = 0.52, R_{\text{loo}}^2 = 0.58, S_{\text{loo}} = 0.56, R_{\text{test}}^2 = 0.63, S_{\text{test}} = 1.03$
PJI3	-4.239 (2)	
Mor22p	7.134 (2)	
QSAR-3		
intercept	2.523 (0.4)	$N/d = 7.7, R^2 = 0.79, S = 0.40, R_{\text{max}}^2 = 0.55, o \geq 2.5S = 0, S^{\text{Rand}} = 0.46, R_{\text{loo}}^2 = 0.73, S_{\text{loo}} = 0.46, R_{\text{test}}^2 = 0.59, S_{\text{test}} = 0.82$
RDF030e	-0.319 (0.1)	
Mor22p	9.523 (1)	
RSe	3.336 (0.8)	

and 3 summarize the main statistical results found for the various QSAR via these two alternative procedures. Here, N denotes the number of training set molecules, R^2 is the squared correlation

coefficient, $o > xS$ indicates the number of molecules with a predicted residual being greater than x times S , R_{max}^2 represents the maximum squared correlation coefficient between two given descriptors of the model, and S^{Rand} stands for Y randomization. Table 1S of the Supporting Information includes a brief description for each molecular descriptor involved in the QSAR models for the larvicidal activity of the chalcone-type compounds. Table 2S of the Supporting Information includes the numerical values of such molecular descriptors.

It is clearly appreciated from Table 2 that the 0D–3D QSAR models tended to overfit the 23 training set compounds and, as revealed by the test set results, had a lower predictive power on structurally related molecules than the 0D–2D QSAR of the same dimension (d) shown in Table 3. Therefore, we concluded that topochemical descriptors worked better for modeling the larvicidal activity of chalcone derivatives. This was explained by considering that these variables did not depend upon 3D geometry optimization artifacts that may affect the calculation of the more sophisticated conformation-based molecular descriptors.

We decided to adopt the QSAR-5 model as the best one, which included the following two molecular descriptors: the Balaban U index, U_{index} ,⁴⁰ and the highest eigenvalue 1 of the Burden matrix/weighted by atomic masses, $BEHm1$.⁴¹ The U_{index} is a molecular descriptor calculated as information content of molecules, based on the calculation of equivalence classes from the molecular graph. This kind of descriptor may be characterized as not having degeneracy for alkanes with up to 15 vertices. $BEHm1$ is the highest eigenvalue 1 of the Burden matrix (B), weighted by atomic masses. As is well-known, B is a modified adjacency matrix (A) with the main diagonal elements being weighted with a given atomic property, in the present case by using atomic masses.

A comparison of our results with those found by Begum et al. in their QSAR study²⁶ revealed that the authors established a model solely based on 3D molecular descriptors, characterizing the shape and electronic structure of chalcone derivatives. This set of descriptors were two Jurs descriptors ($Jurs_PPSA_1$ and

Table 3. Statistical Characteristics for 0D–2D QSAR Models on $\text{Log}_{10}\text{LC}_{50}$ of Chalcone Derivatives

regression coefficient (standard error)		statistical quality
QSAR-4		
<i>Intercept</i>	0.737 (0.5)	$N/d = 23, R^2 = 0.37, S = 0.67, o \geq 2.5S = 0, R_{\text{loo}}^2 = 0.26, S_{\text{loo}} = 0.73, R_{\text{test}}^2 = 0.63, S_{\text{test}} = 0.50$
<i>RBN</i>	0.388 (0.1)	
QSAR-5		
<i>Intercept</i>	53.607 (10)	$N/d = 11.5, R^2 = 0.55, S = 0.58, R_{\text{max}}^2 = 0.46, o \geq 2.5S = 0, S^{\text{Rand}} = 0.61, R_{\text{loo}}^2 = 0.41, S_{\text{loo}} = 0.67, R_{\text{test}}^2 = 0.72, S_{\text{test}} = 0.57$
<i>Uindex</i>	0.101 (0.02)	
<i>BEHm1</i>	-13.980 (4)	
QSAR-6		
<i>Intercept</i>	79.267 (10)	$N/d = 7.7, R^2 = 0.64, S = 0.53, R_{\text{max}}^2 = 0.57, o \geq 2.5S = 0, S^{\text{Rand}} = 0.55, R_{\text{loo}}^2 = 0.52, S_{\text{loo}} = 0.62, R_{\text{test}}^2 = 0.86, S_{\text{test}} = 0.57$
<i>Ms</i>	2.411 (0.7)	
<i>BEHm4</i>	2.769 (0.6)	
<i>MATS1m</i>	-96.554 (20)	

Jurs RPCG) and the highest occupied molecular orbital (HOMO) energy. Such *Jurs* -based descriptors were calculated by mapping atomic partial charges on solvent-accessible surface areas of individual atoms. Although that model reported its statistical calibration results, it did not include any result on validation. Therefore, we checked the predictive capability of this model by applying these three descriptors to the training and test sets of the present work. The results were as follows: $N/d = 7.7$, $R^2 = 0.58$, $S = 0.57$, $\sigma \geq 2.5S = 0$, $S^{\text{Rand}} = 0.59$, $R_{\text{loo}}^2 = 0.43$, $S_{\text{loo}} = 0.68$, $R_{\text{test}}^2 = 0.67$, $S_{\text{test}} = 0.73$. The predictive performance of the model based on *Jurs* descriptors was lower than that provided by QSAR-5 in Table 3.

Chalcones showing high larvicidal activity presented enhanced electron densities on one or both rings, in general having electron-releasing group(s), as **8**, **11**, and **17**; in some cases an *o*-hydroxyl group at the A ring enhanced the activity, suggesting that the resonance-assisted H-bond at ring A could raise the electron density at ring B (**2** vs **1**, **5** vs **4**, etc.). However, chalcone **11**, having a *p*-Cl at ring B, was one of the most active, and an *o*-HO group at the A ring lowered its activity in the same manner as occurred with **8** and **9**. Besides, the presence of electron-withdrawing group(s) in general decreased the activity of chalcones, only slightly in some cases such as **13** and **16**, where a *p*-HO group was at the A ring, or more greatly for **6**, **7**, **12**, and **14**. Derivatization of the carbonyl group roughly decreased the activity, and extension of the branched chromophore of **1** to both vinylogous **19** and **20** neither gave a relevant activity.

It was possible to perform a mathematical interpretation of these structure–activity findings. A proper standardization of the regression coefficients of the QSAR-5 model enabled the assignment of greater importance to the molecular descriptors that exhibited larger (absolute) standardized coefficients. The resulting order was

$$Uindex (0.99) > BEHm1 (0.81) \quad (2)$$

where the standardized values of the regression coefficients (b_j^*) are shown in parentheses. It was seen that the most important descriptor for the larvicidal activity of this set of chalcone derivatives was *Uindex*, the numerical values of which changed most in accordance with the numerical variations of the experimental activity. However, the relative magnitudes of the b_j^* (0.99 and 0.81) suggested that these numerical variables complemented each other inside the linear equation, and that resulted in comparable relevance for predicting the studied property.

According to Table 2S of the Supporting Information, both descriptors took positive numerical values: the range of *Uindex* was 19.349–57.823, whereas the range of *BEHm1* was 3.815–3.979. In addition, from Table 3 it was noted that *Uindex* had a positive regression coefficient in the QSAR-5 model and *BEHm1* a negative one. Therefore, we concluded that a simultaneous decrease of the numerical value for *Uindex* and an increase of the *BEHm1* descriptor would lead to structures having a highly predicted activity. Also, a poor predicted activity would be found for a simultaneous increase of *Uindex* and a decrease of *BEHm1*. This result was in line with the predictions found for the four most active structures: **8** (*Uindex*, 28.031; *BEHm1*, 3.915), **11** (*Uindex*, 28.654; *BEHm1*, 3.947), **17** (*Uindex*, 26.070; *BEHm1*, 3.884), and **2** (*Uindex*, 28.551; *BEHm1*, 3.878), for which QSAR-5 tended to predict low $\log_{10}LC_{50}$ values. The four least active structures were **28** (*Uindex*, 57.823; *BEHm1*, 3.976), **23** (*Uindex*, 52.152; *BEHm1*, 3.979), **25** (*Uindex*, 48.648; *BEHm1*, 3.971), and **22** (*Uindex*, 36.607; *BEHm1*, 3.891).

Table 4 includes the predicted $\log_{10}LC_{50}$ values achieved for both the training and test sets of chalcone analogues, according to

Table 4. Experimental and QSAR Predicted $\log_{10}LC_{50}$ Insecticidal Activities of Chalcones

entry	compound	exptl	QSAR-5	QSAR-1
1	(2E)-1,3-diphenylprop-2-en-1-one	1.954	2.255	2.223
2 ^a	(2E)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one	1.740	2.291	2.465
3	(2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one	2.017	2.334	2.327
4	(2E)-3-(4-hydroxy-3-methoxyphenyl)-1-phenylprop-2-en-1-one	3.168	2.674	1.929
5 ^a	(2E)-3-(4-hydroxy-3-methoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one	2.836	2.826	2.093
6	(2E)-3-(3-nitrophenyl)-1-phenylprop-2-en-1-one	2.998	2.225	2.137
7	(2E)-1-(2-hydroxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one	2.721	2.447	2.405
8	(2E)-3-(3,4-methylenedioxyphenyl)-1-phenylprop-2-en-1-one	0.699	1.721	1.013
9	(2E)-3-(3,4-methylenedioxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one	2.994	1.867	2.699
10 ^a	(2E)-1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one	2.377	2.370	2.145
11	(2E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one	0.699	1.337	1.635
12	(2E)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one	2.982	2.281	2.197
13	(2E)-1-(4-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one	1.959	2.538	2.310
14 ^a	(2E)-1-(2-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one	2.945	2.504	2.569
15	(2E)-3-(4-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one	1.908	1.566	2.102
16	(2E)-1-(4-hydroxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one	1.949	2.483	2.457
17	(2E)-3-(furan-2-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one	1.279	1.955	1.921
18	(3E)-4-phenylbut-3-en-2-one	2.680	2.238	2.759
19	(1E,4E)-1,5-diphenylpenta-1,4-dien-3-one	3.315	2.990	2.846
20	(2E,4E)-1,5-diphenylpenta-2,4-dien-1-one	2.640	2.940	2.949
21	(2E,4E)-1-(2-hydroxyphenyl)-5-phenylpenta-2,4-dien-1-one	3.050	2.985	2.863
22	phenylhydrazone of 1	3.329	2.927	3.356
23 ^a	2,4-dinitrophenylhydrazone of 1	3.403	3.274	4.030
24	phenylhydrazone of 18	2.667	3.116	2.318
25	2,4-dinitrophenylhydrazone of 18	3.370	3.031	3.165
26	semicarbazone of 18	3.320	3.381	3.114
27	oxime of 18	2.538	2.477	3.010
28	2,4-dinitrophenylhydrazone of 19	3.421	3.892	3.926
29	(2E)-3-(4-methylphenyl)-1-phenylprop-2-en-1-one		2.344	1.834
30	(2E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one		2.608	1.307
31	(2E)-3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one		2.385	2.154
32	(2E)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one		1.279	1.817
33	(2E)-1-(4-methylphenyl)-3-phenylprop-2-en-1-one		2.314	1.886
34	(2E)-1-(4-chlorophenyl)-3-(4-chlorophenyl)-prop-2-en-1-one		1.294	1.350

^aMember of test set.

the most predictive models appearing in Tables 2 and 3: QSAR-5 (OD–2D) and QSAR-1 (OD–3D). We included the QSAR-1

predictions in the table just for comparison. Figures 3A and 4A plot the predicted activities as functions of the observed ones for

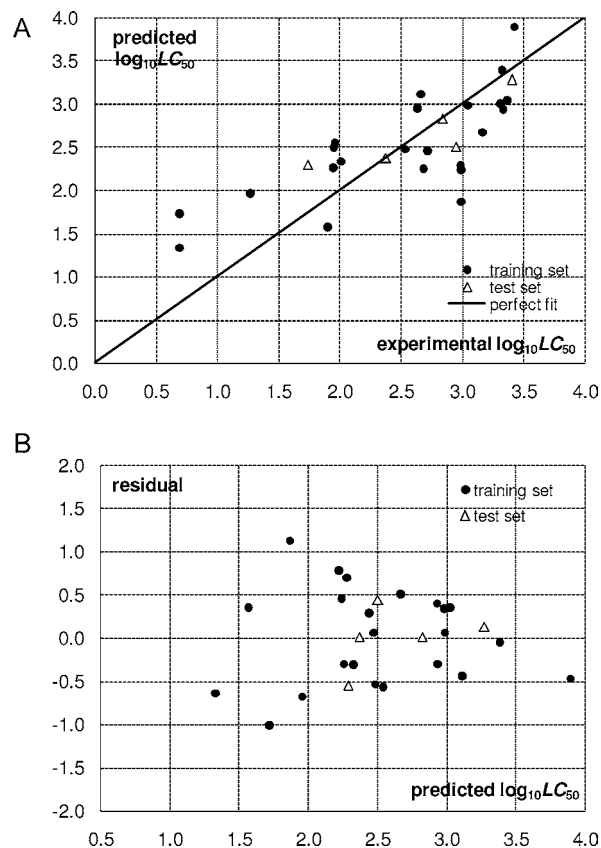


Figure 3. (A) Predicted $\log_{10}LC_{50}$ according to QSAR-5 as a function of experimental values. (B) Residuals and predicted $\log_{10}LC_{50}$.

such models, respectively; Figures 3B and 4B reveal that the residuals were randomly distributed and did not follow any kind of strange pattern, which would indicate the presence of nonmodeled factors.

Finally, the established QSAR enabled us to predict the set of six chalcone derivatives **29**–**34** synthesized in our group, the experimental biological data of which were still not obtained. Such compounds were structurally similar to some of the training compounds (**29** to **1**; **30** and **31** to **4** or **8**; **32** to **10**, **11**, or **12**; **33** to **2** or **10**; **34** to **1**, **10**, **11**, or **12**). Their activity values were predicted by the application of the novel QSAR models (QSAR-5 and -1), showing that the expected activity of **29** fitted with **1** (active), that of **30** and **31** fitted with **4** (low activity), **32** fitted well with **11** (highly active), **33** was between **2** and **10** (active), and **34** also showed a good fitting with **11** (high activity). Table 4 includes the results for such predictions. It was seen that both QSAR-5 and QSAR-1, although being based on different types of descriptors, tended to achieve comparable predictions for most structures of this unknown set, with the exception of **30** ((*2E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one), having predicted $\log_{10}LC_{50}$ values of 2.608 for QSAR-5 and 1.307 for QSAR-1. Obviously, we adopted the result of QSAR-5 (i.e., 2.608) due to the higher statistical quality of this model. Now, such findings deserve to be experimentally analyzed in forthcoming bioassays.

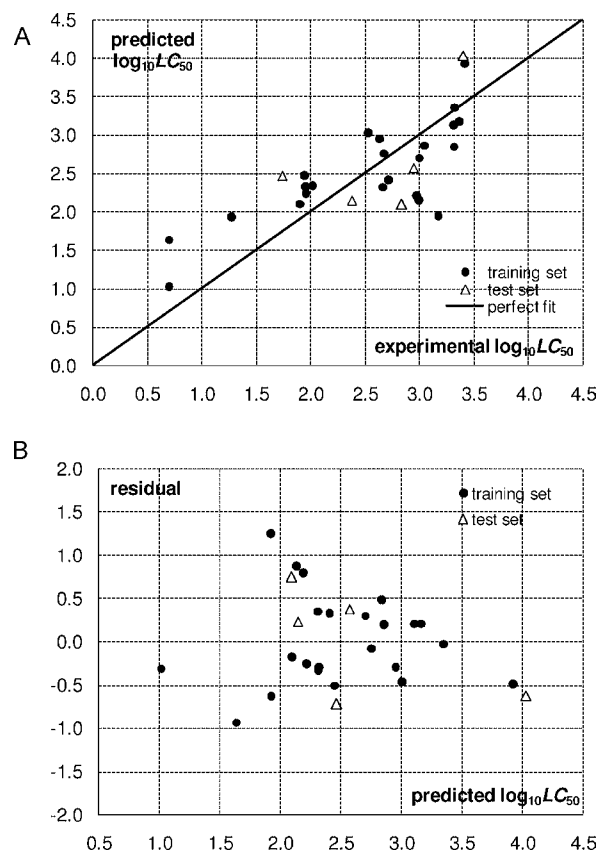


Figure 4. (A) Predicted $\log_{10}LC_{50}$ according to QSAR-1 as a function of experimental values. (B) Residuals and predicted $\log_{10}LC_{50}$.

■ ASSOCIATED CONTENT

Supporting Information

Table giving details of the molecular descriptors employed in the QSAR models established in this work and NMR spectra of representatives chalcones **29**–**34**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +54 221 425 7430, +54 221 425 7291. Fax: +54 221 425 4642. E-mail: pabloducho@gmail.com.

Funding

We gratefully acknowledge financial support by the Research Council of Argentina (Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)), PIP11220100100151 project. We also thank Universidad Nacional de La Plata.

■ REFERENCES

- (1) Dimmock, J. R.; Elias, D. W.; Beazely, M. A.; Kandepu, N. M. Bioactivities of chalcones. *Curr. Org. Chem.* **1999**, *6*, 1125–1149.
- (2) Cave, G. W.; Raston, C. L. Toward benign syntheses of pyridines involving sequential solvent free aldol and Michael addition reactions. *Chem. Commun.* **2000**, *22*, 2199–2200.
- (3) Mitsutani, A. Future possibilities of recently commercialized acid/base-catalyzed chemical processes. *Catal. Today* **2002**, *73*, 57–63.
- (4) Calloway, N. O.; Green, L. D. Reactions in the presence of metallic halides. α,β -Unsaturated ketone formation as a side reaction in Friedel-Crafts acylations. *J. Am. Chem. Soc.* **1937**, *59*, 809–811.

- (5) Sipos, G.; Sirokman, F. Chalcon formation of different substituted acetophenones and p-hydroxy-benzaldehyde. *Nature* **1964**, *202*, 489.
- (6) Le Gall, E.; Texier-Boullet, F.; Hamelien, J. ChemInform abstract: simple access to α,β -unsaturated ketones by acid-catalyzed solvent-free reactions. *Synth. Commun.* **1999**, *29*, 3651–3657.
- (7) Narender, T.; Papi Reddy, K. A simple and highly efficient method for the synthesis of chalcones by using borontrifluoride-etherate. *Tetrahedron Lett.* **2007**, *48*, 3177–3180.
- (8) Rao, Y. K.; Fang, S.-H.; Tzeng, Y.-M. Differential effects of synthesized 2'-oxygenated chalcone derivatives: modulation of human cell cycle phase distribution. *Bioorg. Med. Chem.* **2004**, *12*, 2679–2686.
- (9) Chen, M.; Theander, T. G.; Christensen, S. B.; Hviid, L.; Zhai, L.; Kaharazmi, A. A new antimalarial agent, inhibits in vitro growth of the human malaria parasite *Plasmodium falciparum* and protects mice from *P. yoelii* infection. *Antimicrob. Agents Chemother.* **1994**, *38*, 1470–1475.
- (10) Fang, N.; Casida, J. E. New bioactive flavonoids and stilbenes in cubé resin insecticide. *J. Nat. Prod.* **1999**, *62*, 205–210.
- (11) Chen, M.; Zhai, L.; Christensen, S. B.; Theander, T. G.; Kharazmi, A. Inhibition of fumarate reductase in *Leishmania major* and *L. donovani* by chalcones. *Antimicrob. Agents Chemother.* **2001**, *45*, 2023–2029.
- (12) Bandgar, B. P.; Patil, S. A.; Korbad, B. L.; Nile, S. H.; Khobragade, C. N. Synthesis and biological evaluation of β -chloro vinyl chalcones as inhibitors of TNF- α and IL-6 with antimicrobial activity. *Eur. J. Med. Chem.* **2010**, *45*, 2629–2633.
- (13) Hsieh, H. K.; Tsao, L. T.; Wang, J. P.; Lin, C. N. Synthesis and anti-inflammatory effect of chalcones. *J. Pharm. Pharmacol.* **2000**, *52*, 163–171.
- (14) Zhao, L.-M.; Jin, H.-S.; Sun, L.-P.; Piao, H.-R.; Quan, Z.-S. Synthesis and evaluation of antiplatelet activity of trihydroxychalcone derivatives. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5027–5029.
- (15) Liu, M.; Wilairat, P.; Go, L. M. Antimalarial alkoxyated and hydroxylated chalcones: structure-activity relationship analysis. *J. Med. Chem.* **2001**, *44*, 4443–4452.
- (16) Nielsen, S. F.; Chen, M.; Theander, T. G.; Kharazmi, A.; Christensen, S. B. Synthesis of antiparasitic licorice chalcones. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 449–452.
- (17) Miranda, C. L.; Aponso, G. L.; Stevens, J. F.; Deinzer, M. L.; Buhler, D. R. Antioxidant and prooxidant actions of prenylated and nonprenylated chalcones and flavonoids in vitro. *J. Agric. Food Chem.* **2000**, *48*, 3876–3884.
- (18) Svetaz, L.; Tapia, A.; López, S. N.; Furlán, R. L. E.; Petenatti, E.; Pioli, R.; Schmeda-Hirschmann, G.; Zacchino, S. A. Antifungal chalcones and new caffeic acid esters from *Zuccagnia punctata* acting against soybean infecting fungi. *J. Agric. Food Chem.* **2004**, *52*, 3297–3300.
- (19) Thirunarayanan, G.; Vanangamudi, G. Insect antifeedant potent chalcones. *J. Indian Chem. Soc.* **2008**, *85*, 447–451.
- (20) Jin, H.; Geng, Y.; Yu, Z.; Tao, K.; Hou, T. Lead optimization and anti-plant pathogenic fungi activities of daphneolone analogues from *Stellera chamaejasme* L. *Pest Biochem. Physiol.* **2009**, *93*, 133–137.
- (21) Thirunarayanan, G.; Surya, S.; Srinivasan, S.; Vanangamudi, G.; Sathiyendiran, V. Synthesis and insect antifeedant activities of some substituted styryl 3,4-dichlorophenyl ketones. *Spectrochim. Acta Part A* **2010**, *75*, 152–156.
- (22) Hansch, C.; Leo, A. *Exploring QSAR. Fundamentals and Applications in Chemistry and Biology*; American Chemical Society: Washington, DC, 1995.
- (23) Hansch, C.; Fujita, T. Classical and three-dimensional QSAR in agrochemistry. *J. Am. Chem. Soc.* **1995**, *606*, 318–329.
- (24) Kubinyi, H. *QSAR: Hansch Analysis and Related Approaches*; Wiley-Interscience: New York, 2008.
- (25) Puzyn, T.; Leszczynski, J.; Cronin, M. T. *Recent Advances in QSAR Studies: Methods and Applications*, 1st ed.; Springer: New York, 2009.
- (26) Begum, N. A.; Roy, N.; Laskar, R. A.; Roy, K. Mosquito larvicidal studies of some chalcone analogues and their derived products: structure-activity relationship analysis. *Med. Chem. Res.* **2011**, *20*, 184–191.
- (27) Romanelli, G. P.; Pasquale, G.; Sathicq, A.; Thomas, H.; Autino, J. C.; Vázquez, P. Synthesis of chalcones catalyzed by aminopropylated silica sol-gel under solvent-free conditions. *J. Mol. Catal. A: Chem.* **2011**, *340*, 24–32.
- (28) Duchowicz, P. R.; Goodarzi, M.; Ocsachoque, M. A.; Romanelli, G. P.; Ortiz, E. V.; Autino, J. C.; Bennardi, D. O.; Ruiz, D.; Castro, E. A. QSAR analysis on *Spodoptera litura* antifeedant activities for flavone derivatives. *Sci. Total Environ.* **2009**, *408*, 277–285.
- (29) Goodarzi, M.; Duchowicz, P. R.; Wu, C. H.; Fernández, F. M.; Castro, E. A. New hybrid genetic based support vector regression as QSAR approach for analyzing flavonoids-GABA(A) complexes. *J. Chem. Inf. Model.* **2009**, *49*, 1475–1485.
- (30) Romanelli, G. P.; Virla, E. G.; Duchowicz, P. R.; Gaddi, A. L.; Ruiz, D. M.; Bennardi, D. O.; Ortiz, E. V.; Autino, J. C. Sustainable synthesis of flavonoid derivatives, QSAR study and insecticidal activity against the fall armyworm, *Spodoptera frugiperda* (Lep.: Noctuidae). *J. Agric. Food Chem.* **2010**, *58*, 6290–6295.
- (31) Hyperchem 7 (Hypercube, Inc.), <http://www.hyper.com> (last accessed on Oct 31, 2011).
- (32) Dragon Milano Chemometrics and QSAR Research Group, <http://michem.disat.unimib.it/chm> (last accessed on Oct 31st, 2011).
- (33) Duchowicz, P. R.; Castro, E. A.; Fernández, F. M.; González, M. P. A new search algorithm of QSPR/QSAR theories: normal boiling points of some organic molecules. *Chem. Phys. Lett.* **2005**, *412*, 376–380.
- (34) Duchowicz, P. R.; Castro, E. A.; Fernández, F. M. Alternative algorithm for the search of an optimal set of descriptors in QSAR-QSPR studies. *MATCH Commun. Math. Comput. Chem.* **2006**, *55*, 179–192.
- (35) Mercader, A. G.; Duchowicz, P. R.; Fernández, F. M.; Castro, E. A. QSPR study of solvent quenching of the 5D0 \rightarrow 7F2 emission of Eu(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)3. *Chem. Phys. Lett.* **2008**, *462*, 352–357.
- (36) Mercader, A. G.; Duchowicz, P. R.; Fernandez, F. M.; Castro, E. A. Replacement method and enhanced replacement method versus the genetic algorithm approach for the selection of molecular descriptors in QSPR/QSAR theories. *J. Chem. Inf. Model.* **2010**, *50*, 1542–1548.
- (37) Hawkins, D. M.; Basak, S. C.; Mills, D. Assessing model fit by cross validation. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 579–586.
- (38) Wold, S.; Eriksson, L. Statistical validation of QSAR results. In *Chemometrics Methods in Molecular Design*; van de Waterbeemd, H., Ed.; VCH: Weinheim, Germany, 1995; pp 309–318.
- (39) Draper, N. R.; Smith, H. *Applied Regression Analysis*; Wiley: New York, 1981.
- (40) Balaban, A. T.; Balaban, T. S. New vertex invariants and topological indices of chemical graphs. Based on information on distances. *J. Math. Chem.* **1991**, *8*, 383–397.
- (41) Burden, F. R. Molecular identification number for substructure searches. *J. Chem. Inf. Comput. Sci.* **1989**, *29*, 225–227.