

Sustainable Synthesis of Flavonoid Derivatives, QSAR Study and Insecticidal Activity against the Fall Armyworm, *Spodoptera frugiperda* (Lep.: Noctuidae)

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A simple, clean, solvent-free preparation of flavones by the use of a silica-supported Preyssler heteropolyacid as reusable catalyst is described. High selectivity and very good yields (87–94%) were obtained in short reaction times (7–13 min). Bioassays for insecticidal activity against *Spodoptera frugiperda* were carried out with a set of flavones. Bioassays showed that some of the flavones had moderate insecticidal activity. Quantitative structure–activity relationships were established on the available data with the purpose of predicting the insecticidal activity of a number of structurally related flavones. A relationship between the molecular structure and biological activity is proposed.

KEYWORDS: Fall armyworm; flavones; heteropolyacid; insecticidal activity; Preyssler catalyst; QSAR; *Spodoptera frugiperda*; sustainable synthesis

1. INTRODUCTION

The compounds that contain the chromone (4*H*-benzopyran-4-one) skeleton constitute part of the flavonoid family and are widely spread in nature, mainly in green plants (1). Flavonoids exert a protective effect toward both UV light and microbial invasion by pathogens in plants (2, 3). In addition, some natural and synthetic flavonoid derivatives have shown a promising activity as insecticides. It is known that some flavonoids have a repelling property against certain species of phytophagous insects (4) and subterranean termites (genus *Coptotermes*) (5). There is an important amount of data about the role of flavonoids in insect–plant interactions (6). Simmonds studied the bioactivity of different flavonoids and confirmed that these compounds could modulate the feeding and oviposition behavior of insects (7). Sosa et al. investigated natural and synthetic flavone derivatives and demonstrated that all the studied compounds decreased *Tenebrio molitor* larvae weight (8). In the past decade several papers were published about the antifeedant activity of flavonoid derivatives: various chromone and aurone derivatives showed activity against *Spodoptera litura* (Oriental leafworm moth) (4, 9–11), *Spodoptera littoralis* (Egyptian armyworm) (12), *Mythimna separate* (Oriental armyworm) (13), *Ctenoposteustis*

obliquana (leafroller) (14), *Spilarctia obliqua* (hairy caterpillar) (15), and other insects.

The fall armyworm *Spodoptera frugiperda* (FAW) (16) is a polyphagous pest that causes important damage in different regions of America and mainly affects corn crops in both tropical and subtropical areas. Currently, control relies on both transgenic plants and/or chemical pesticides. The significance of this pest in Argentina was pointed out by Virila et al (17–19).

As part of a research project in sustainable agrochemistry, we planned to synthesize different compounds with probable insecticidal activity against crop-damaging pests in Argentina. The research objectives were to synthesize a set of flavones using a clean procedure, to perform a theoretical estimation of the insecticidal activity of flavones against FAW, and to check their insecticidal activity against FAW larvae. To the best of our knowledge, the literature lacks previous reports on this subject.

In this work, we report a simple, clean, and environmentally friendly procedure for the solvent-free preparation of a set of flavones from 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones (Figure 1). Silica-supported Preyssler heteropolyacid (H₁₄P₅NaW₂₉MoO₁₁₈) was employed as a reusable catalyst. We theoretically estimated the insecticidal activity of a number of flavones against FAW and performed insecticidal activity bioassays against FAW. Both theoretical and experimental LT₅₀ values are reported.

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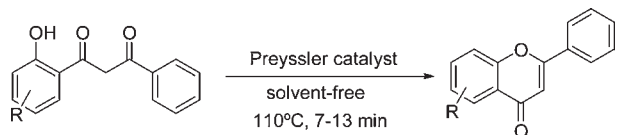


Figure 1. Clean synthesis of flavone derivatives.

The importance of flavones has led to the development of various methods for their synthesis. The Baker–Venkataraman synthesis involves the acylation of an *o*-hydroxyacetophenone to an aryl ester and its rearrangement by base to a 1,3-diaryl-1,3-diketone (20–22). Diketones are further cyclized under strongly acidic conditions to afford the corresponding flavones, using both conventional and microwave heating (23–25). Greener procedures have been described (26–29), and catalysis by clay (30), heteropolyacids (31, 32), or ionic liquids under microwave irradiation (33) have been investigated.

In the realms of the quantitative structure–activity relationships (QSAR) theory (34), there exists a continuous interest in correlating the variation of the behavior of chemical compounds, as expressed by any experimental biological activity, or physico-chemical property, with numerical entities related to some aspects of the chemical structure, termed molecular descriptors (35). We established a QSAR model on the insecticidal activities against FAW, with the main purpose of applying this structure–activity relationship to a set of flavone derivatives with unknown experimental data. For the inhibitory activity analysis we employed multiparametric linear regression equations, as this is considered one of the most popular statistical techniques, and explored more than 1000 descriptors of the structure (36, 37).

2. MATERIALS AND METHODS

2.1. General Procedures. All the yields were calculated from crystallized products. All the products were identified by comparison of analytical data (mp, TLC, NMR) with those reported or with authentic samples prepared by the conventional method using sulfuric acid as catalyst. All the starting 1,3-diketones were prepared by following a procedure described elsewhere (38). Melting points of the compounds were determined in sealed capillary tubes and were uncorrected. ^{13}C NMR and ^1H NMR spectra were recorded at 20 °C on a Bruker AC-250 spectrometer (62.5 and 250 MHz, respectively) using TMS as internal standard. Chromone was prepared by the Claisen condensation between the phenol and alkyl ester, followed by dehydroxygenation with a strong acid (4). 7-Hydroxyflavone was synthesized from the corresponding chalcone by the Dao method (39), and xanthone was prepared by dilithiation and carbonylation of diphenyl ether (40).

2.2. Catalyst Preparation. The Mo-doped Preyssler heteropolyacid $\text{H}_{14}[\text{NaP}_5\text{W}_{29}\text{MoO}_{110}]$ (H14PMo) was prepared by following a literature method (41). In a typical experiment, 56 g (0.169 mol) of $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ and 2 g (0.008 mol) of $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ were dissolved in 70 mL of water and then mixed at 60 °C for 30 min. The solution was cooled to room temperature, and 45 mL of concentrated phosphoric acid was added. The resulting yellow solution was refluxed for 48 h. The color changed to dark green at the end of the reaction. The solution was brought to room temperature and diluted with 30 mL of water, and then 20 g of potassium chloride was added with stirring. The mixture was stirred for 30 min and then heated to dryness; a greenish solid was obtained. This raw product was dissolved in 70 mL of warm water, and upon cooling to room temperature, yellow crystals were formed; they were collected and recrystallized from boiling water (yield 18%). The molybdenum-substituted heteropolyanion $\text{K}_{14}[\text{NaP}_5\text{W}_{29}\text{MoO}_{110}]$ was converted to its corresponding acid by passing it through a column filled with Dowex-50W-X8 ion-exchange resin. A complete characterization of this heteropolyacid has been reported (42).

2.3. General Procedure for the Preparation of Substituted Flavones. A mixture of 1,3-diketone (1 mmol) and H14PMo (0.5% mmol) was stirred at 110 °C for the indicated time (see Table 1). The reaction mixture was extracted with hot toluene (3 × 2 mL). The solution

Table 1. Solvent-Free Preparation of Flavones using 0.5% of Supported Preyssler Heteropolyacid as Catalyst

Entry (and Compd. Nr.)	Flavone	Reaction Time (min)	Yields (%)
1		10	89 (88.85) ^a
		30	85 ^b
2		10	92
3		10	94
4		7	88
5		13	93
6		13	90
7		13	88
8		13	87
9		13	90

^a Yields obtained in both the first and second reuse of the Preyssler catalyst.
^b Yields attained using 0.5% of bulk catalyst.

was washed with 3 M NaOH (1 × 2 mL) and then with water (1 × 2 mL); then it was dried with anhydrous sodium sulfate and concentrated under vacuum. All the solid crude products were recrystallized from methanol. Yields of the pure flavones 1–9 are reported in Table 1.

2.4. Bioassay. Test insect: FAW larvae were obtained from PROIMI laboratory population. The employed larvae were from the corn strain (19) from the El Manantial site (Tucumán, Argentina) and were bred in the laboratory for four to five generations. The population had not been previously exposed to insecticides. Laboratory FAW larvae were fed on bean flour based artificial diet in a controlled room environment at 25 ± 3 °C, 60–70% relative humidity, and 14/10 h (L/D) of artificial photoperiod.

2.5. Evaluation Test of Compounds. For the bioassays all the compounds were dissolved in acetone at a concentration of 2000 mg/kg. The insecticidal activity was tested against FAW, first instar larvae individually isolated in glass tubes 100 mm in length and 12 mm in diameter. For the foliar application, the whole corn leaves, nearly 50 cm in length and 7–9 cm maximum width, were sprayed to homogeneous dampening and, after the complete removal of the solvent, they were cut into pieces of approximately 1.5 cm². Compounds were checked by 10 repetitions of six larvae each, fed on treated fresh corn leaf pieces. An equal number of larvae fed on pieces of leaves sprayed with distilled water was used as control A, and larvae fed on similar leaf pieces treated only with acetone were used as control B. The tubes were closed using wet cotton,

and the leaf pieces were not renewed until the end of the assay. Assessments were made on a dead/alive basis, and mortality rates (0 = no activity and 100 = total kill) were corrected using Abbott's formula. Mortality was scored twice a day over 4 days. In addition, the 50% lethal times (LT_{50}) were determined by Probit analysis. This median lethal time is the statistically derived average time interval during which 50% of a given population may be expected to die following acute administration of a chemical agent at a given concentration under a defined set of conditions.

2.6. Quantitative Structure–Activity Relationship Analysis.

The initial conformations of the compounds were drawn by means of the "model build" modulus available in HyperChem 6.03 (43). 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 $0.01 \text{ kcal } \text{Å}^{-1}$.

The numerical descriptors for each compound were calculated with Dragon software (35) and included several variable types characterizing the multidimensional aspects of the chemical structure: constitutional, topological, geometrical, charge, GETAWAY (geometry, topology and atoms-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 and HOMO–LUMO gap ($\Delta_{\text{HOMO-LUMO}}$). The total number of calculated descriptors resulted in 1500 variables.

We resorted to the replacement method (RM) (44) 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 (45). 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 (36, 37, 46, 47). All the models presented here were properly validated.

3. RESULTS AND DISCUSSION

3.1. Synthesis and Evaluation of Insecticidal Activity.

Initially we conducted blank experiments without the presence of Preyssler acid. No product was detected when 1 mmol of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione was warmed to $120 \text{ }^\circ\text{C}$ for 30 min. When this compound was also warmed in the presence of silica (support), no product was detected by TLC, in the same time. Afterward, the catalytic activity of the bulk Preyssler acid (H14PMo) was tested in the preparation of substituted flavones, in the absence of solvent. The obtained results are shown in **Table 1**. The temperature and mole ratio of H14PMo to substrates were checked to optimize the reaction, using 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione as substrate; no reaction was detected at room temperature. The use of just 0.5% mmol of Preyssler heteropolyacid was enough to push the reaction forward at $110 \text{ }^\circ\text{C}$; higher amounts of the catalyst did not improve the results. The experiments were run until 1,3-diketone was consumed or until no changes in the composition of the reaction mixture were observed. In all the cases, the desired products were obtained with high selectivity, almost free of secondary products (7–13 min). Recycling of the catalyst was checked in two consecutive batches after the first one; the catalyst showed almost constant activity.

An assessment of the insecticidal activities of chromone, xanthone, and flavone against FAW was carried out (**Table 2**, entries 1–3). Since the most active compound was flavone, we therefore synthesized a series of nine substituted flavones, and

Table 2. Insecticidal Activity of Chromanoids against *S. frugiperda*

entry	compd	LT_{50} (h)
1	chromone	55.42
2	xanthone	53.78
3	flavone	51.19
4	6-methylflavone	93.00
5	7-methylflavone	105.46
6	7-hydroxyflavone	106.94
7	7-methoxyflavone	114.38
8	7-fluoroflavone	63.76
9	6-chloroflavone	53.36
10	7-chloroflavone	29.33
11	6-bromoflavone	43.86
12	7-bromoflavone	89.73
13	acetone control	114.93
14	H_2O control	146.64

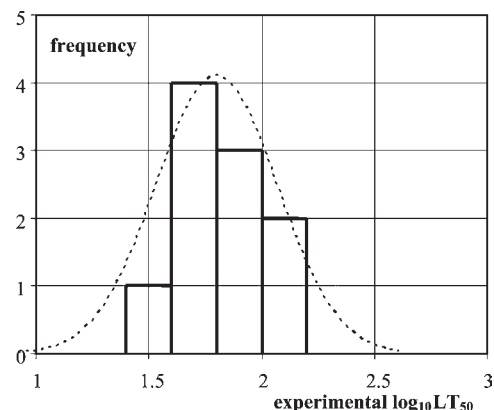


Figure 2. Histogram revealing the normal distribution trend in the training set of insecticidal effects.

then we evaluated their insecticidal activities and that of 7-hydroxyflavone against FAW. The results are given in **Table 2**. These data showed that efficacy was strongly influenced by both the nature and location of the substituent at the benzene ring of the chromanoid. Relationships between structure and activity were established in the set of flavones for the carbocyclic moiety of the heterocyclic ring system. Some flavones substituted by halogen at C-6 and C-7 in the carbocycle led to an increase of the insecticidal activity, especially for 7-chloroflavone ($LT_{50} = 29.33$, **Table 2**, entry 10). In contrast, electron-donating substituents in the carbocyclic moiety caused a considerable decrease of the insecticidal activity, the 7-methoxyflavone being the least active, rendering the FAW larvae as long-lived as those subjected to the acetone control.

3.2. QSAR Analysis.

As a previous step of the QSAR analysis, we verified that the experimental insecticidal activities of the training set compounds (the dependent variable of the linear regression model) followed the assumption of normal distribution. This fact could be appreciated from the histogram given by **Figure 2**, which plotted the number of compounds having the experimental data in a certain range.

We established the optimal linear regression equation by means of the replacement method approach, which minimized its standard deviation (S) and included the best "representative" molecular descriptors, extracted from the pool containing $D = 1500$ variables. The best resulting QSAR involved two descriptors that were able to acceptably predict the $\log_{10} LT_{50}$ insecticidal activity of 10 flavone derivatives employed in the training set. The following statistical results were found: correlation coefficient (R) equal to 0.882, $S = 0.093 \text{ log unit}$, and a Fisher parameter (F) of 27.898. **Table 3** summarizes the details of this QSAR, and **Table 4**

Table 3. Statistical Characteristics for the Proposed Linear QSAR

descriptor	Mor28p	intercept
regression	-3.843	1.807
std error	0.7	0.03
P value	7.445×10^{-4}	5.562×10^{-12}

Table 4. Experimental and QSAR Predicted \log_{10} LT_{50} Insecticidal Activities of Flavone Derivatives^a

entry	compd	exptl	pred	loo pred	Mor28p
1	chromone	1.744	1.830	1.840	-0.006
2	xanthone	1.731	1.619	1.580	0.049
3	flavanone	1.656	1.684	1.690	0.032
4 ^b	flavone	1.709	1.892		-0.022
5	6-methylflavone	1.968	1.988	1.993	-0.047
6	7-methylflavone	2.023	2.049	2.062	-0.063
7 ^b	7-hydroxyflavone	2.029	1.899		-0.024
8	7-methoxyflavone	2.058	2.034	2.023	-0.059
9	7-fluoroflavone	1.805	1.796	1.795	0.003
10	6-chloroflavone	1.727	1.673	1.660	0.035
11	7-chloroflavone	1.467	1.634	1.685	0.045
12 ^b	6-bromoflavone	1.642	1.853		-0.012
13	7-bromoflavone	1.953	1.826	1.812	-0.005
14	chrysin		1.673		0.035
15	luteolin		1.553		0.066
16	wogonin		1.792		0.004
17	isowogonin		1.888		-0.021
18	norwogonin		1.623		0.048
19	baicalein		1.799		0.002
20	mosloflavone		2.038		-0.060
21	nobiletin		2.549		-0.193
22	apigenin		1.611		0.051
23	moslosoflavone		1.972		-0.043
24	oroxylin A		1.903		-0.025
25	6-hydroxyflavone		1.865		-0.015
26	7-methoxychromone		1.892		-0.022

^aNumerical values of molecular descriptors are provided. ^bMember of external test set.

includes the predicted \log_{10} LT_{50} values achieved for both the training and test sets of flavonoids. **Figure 3a** plots the predicted activities as function of the observed ones; **Figure 3b** revealed that the residuals were randomly distributed and did not follow any kind of strange pattern which would indicate the presence of nonmodeled factors.

It is to be noted that the QSAR so developed obeys the “rule of thumb”, stating that at least five or six data points should be present for each fitting parameter. In this way, one avoids overfitting problems.

Regarding the necessary validation of the structure–activity relationship, the leave-one-out cross-validation parameters (loo) (48) were suitable for measuring the stability of the model upon the inclusion or exclusion of compounds from the training set. As is known, the loo procedure consists in a step-by-step removal of a molecule from the training set and the subsequent prediction of the removed molecule with the model recalibrated through the remaining molecules. Therefore, both the loo correlation coefficient ($R_{loo} = 0.812$) and the associated standard deviation ($S_{loo} = 0.116$) indicated that the QSAR was predictive and deteriorated little upon the removal of compounds from the model. Furthermore, according to the specialized literature R_{loo}^2 should be higher than 0.50 for obtaining a validated model (49).

Table 4 demonstrates this fact when the experimental \log_{10} LT_{50} and the loo predictions are compared for each training flavonoid. In addition, after analysis of 5000 cases of Y randomization (48) for the developed QSAR, the smallest standard

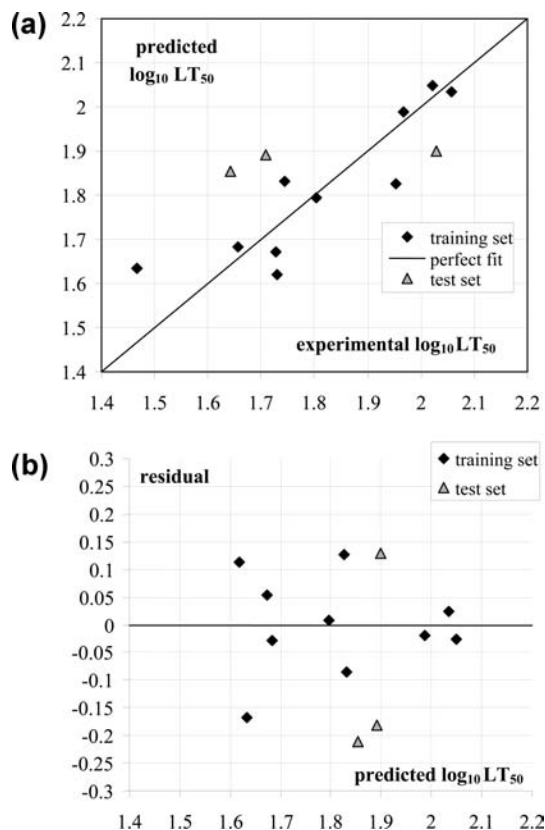


Figure 3. (a) Predicted \log_{10} LT_{50} insecticidal activities as a function of experimental values. (b) Residuals as a function of predicted \log_{10} LT_{50} data.

deviation of randomization (S_{rand}) achieved was compared to the one found when considering the true calibration (S). Therefore, as $S_{rand} = 0.112$ was greater than $S = 0.093$, it was expected that the QSAR found did not result from happenstance and constituted a real structure–activity relationship. The test set for validating the established QSAR involved three flavone derivatives (compounds 4, 7, and 12) that were not considered during the model fitting. **Table 4** shows that these compounds were acceptably predicted, and thus the structure–activity relationship would have predictive capability on new data.

The descriptor involved in the QSAR is a 3D molecule representation of structure based on electron diffraction (3D-MoRSE) (50): Mor28p, 3D-MoRSE-signal 28/weighted by atomic polarizabilities. This sort of theoretically defined code provides 3D information from the optimized geometry using a molecular transform derived from an equation used in electron diffraction studies. Various atomic properties can be taken into account, giving great flexibility to this kind of structural representation, such as Sanderson electronegativities, van der Waals volumes, masses, and polarizabilities. The numerical values that took this descriptor on the flavone derivatives are also included in **Table 4**.

Finally, the importance of the derived QSAR was that, from the development of a simple model based on the knowledge of the available experimentally measured insecticidal action, it enabled the prediction of some flavone derivatives having a structure similar to that of the training compounds. **Table 4** includes the predictions for such estimation molecules, compounds 14–26. For instance, it was found that compounds exhibiting low predicted \log_{10} LT_{50} were luteolin (predicted \log_{10} $LT_{50} = 1.553$) and apigenin (predicted \log_{10} $LT_{50} = 1.611$), resulting in promising molecules that deserve to be experimentally analyzed in forthcoming bioassays.

The aforementioned method provides a clean, simple, and useful alternative for preparing substituted flavones; the use of silica-supported Preyssler heteropolyacid ($H_{14}P_5NaW_{29}MoO_{118}$) catalysts provides very good yields, also leading to an easy separation and recovery of the catalysts for further use. The catalytic activity, which was practically constant in consecutive reaction batches, and the high recovery of the catalysts allow for both low environmental impact and low cost. Other “green” advantages of the method are the low formation of wastes and the replacement of corrosive, soluble mineral acids. Some title compounds, especially halogenated flavones, exhibited insecticidal activities against FAW in the concentration of 2 g L^{-1} .

The appropriate development of a linear QSAR model on the available experimental insecticidal activities enabled the prediction of these values for some proposed flavone structures that still do not have experimental data. Two of them exhibited favorable potencies.

ACKNOWLEDGMENT

We thank Eduardo Frías for his assistance in the insecticidal activity assays.

Supporting Information Available: Text, figures, and a table giving details of QSAR, the replacement method, validation of QSAR results, NMR spectra of the flavones **1–9**, and characterization of the Preyssler catalyst. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Received for review January 8, 2010. Revised manuscript received April 9, 2010. Accepted April 16, 2010. We thank the Agencia Nacional de Promoción Científica y Tecnológica (Argentina), Universidad Nacional de La Plata, and Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) for financial support. G.P.R., E.G.V., and P.R.D. are Research Members of CONICET.