# Antileishmanial Chalcones: Statistical Design, Synthesis, and Three-Dimensional Quantitative Structure−Activity Relationship Analysis

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A large number of substituted chalcones have been synthesized and tested for antileishmanial and lymphocyte-suppressing activities. A subset of the chalcones was designed by using statistical methods. 3D-QSAR analyses using 67 (antileishmanial activity) and 63 (lymphocyte-suppressing activity) of the compounds for the training sets and 9 compounds as an external validation set were performed by using the GRID/GOLPE methodology. The Smart Region Definition procedure with subsequent region selection as implemented in GOLPE reduced the number of variables to approximately 1300 yielding 3D-QSAR models of high quality (lymphocyte-suppressing model, $R^2 = 0.90$, $Q^2 = 0.80$; antileishmanial model, $R^2 = 0.73$, $Q^2 = 0.63$). The coefficient plots indicate that steric interactions between the chalcones and the target are of major importance for the potencies of the compounds. A comparison of the coefficient plots for the antileishmanial effect and the lymphocyte-suppressing activity discloses significant differences which should make it possible to design chalcones having a high antileishmanial activity without suppressing the proliferation of lymphocytes.

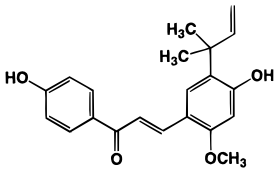
## Introduction

Various species of the protozoan parasite *Leishmania* cause a broad spectrum of diseases ranging from the cutaneous healing skin lesions caused by *L. major* to a fatal visceral form called kala azar caused by *L. donovani*.[1,2] Leishmaniases are widespread in many parts of the world with the highest prevalence in Africa, Asia, and Latin America. It is estimated that 12 million people suffer from the disease, with 400 000 new cases and 100 000 deaths each year.[3] Not less than 350 million individuals in 88 countries, including some southern European countries, are at risk of infection.[4]

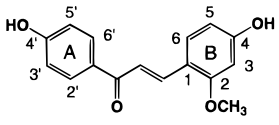
Therapy of patients with leishmaniasis still poses a serious problem. The drugs of first choice are pentavalent antimonial compounds, which require long-term treatment and have severe side effects.[4] The reported large-scale clinical resistance to antimonial agents in India and Sudan[5] has created an urgent need for the development of new, efficient, and safe drugs for the treatment of the diseases.[6]

Licochalcone A (**1**; Chart 1), isolated from Chinese licorice, efficiently inhibits proliferation of *L. donovani* and *L. major* promastigotes and amastigotes in vitro by interfering with the function of the parasite mitochondria. In vitro tests have revealed that licochalcone A at lower concentrations inhibits phytohemmagglutinin A-induced proliferation of human lymphocytes.[7] Thus, the use of chalcones for the treatment of leishmania infections may result in a suppression of the immune system as an undesirable side effect. Preliminary studies reveal that changes of the substitution pattern of the chalcones appear to affect the activities against leishmania promastigotes and lymphocytes differently, indicating that it should be possible to prepare chalcones with a high selectivity. Since the binding sites of the chalcones at the targets are unknown, the design of optimal ligands based on the topographies of the binding sites is excluded.

**Chart 1**




Licochalcone A (1)




Echinatin (2)

In the present work, the synthesis of a large number of chalcones, partly designed by statistical methods, was undertaken and 3D-QSAR analyses of the data were performed in order to reveal structure−activity relationships for antileishmanial activity and for the inhibition of proliferation of lymphocytes. The aim of this study is to elucidate how selectivity might be optimized by appropriate substitution of the chalcone skeleton. The 3D-QSAR analyses were performed by using the GRID program[8,9] to generate molecular descriptors (variables) and the GOLPE program[10−12] for the multivariate data (PLS) analyses. To obtain a comprehensive data material for the multivariate 3D-QSAR analysis, 30 substituted chalcones were designed by statistical methods.[13−15]

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**Table 1.** Properties of the Principal Components: Weights ($w$) and Loadings ($p$)

| variable | mean | $w$ | $p_1$ | $p_2$ |
|---|---|---|---|---|
| MR | 15.4 | 0.13 | 0.42 | 0.59 |
| $\pi$ | 0.53 | 0.95 | 0.47 | 0.49 |
| $\sigma_m$ | 0.13 | 4.46 | −0.57 | 0.38 |
| $\sigma_p$ | 0.01 | 2.84 | −0.52 | 0.51 |

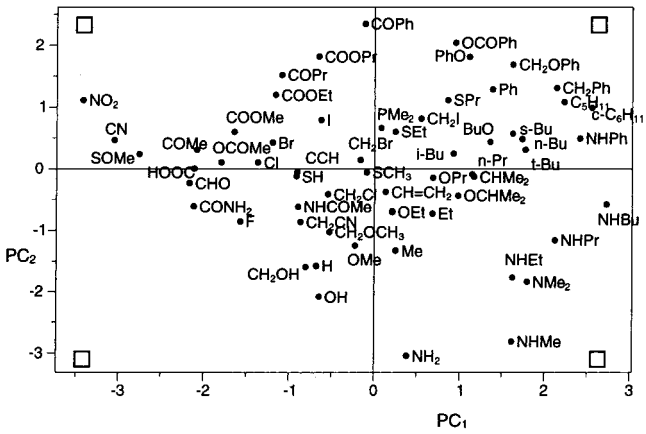



**Figure 1.** Substituents in the space of the principal components.

**Table 2.** $2^{4-1}$ Design in the 4- and 4′-Position[a]

| | 4-position | | 4′-position | | | | IC$_{50}$ ± SD ($\mu$M) | |
|---|---|---|---|---|---|---|---|---|
| compd | PC$_1$ | PC$_2$ | PC$_1$ | PC$_2$ | 4-position | 4′-position | leish | lymph |
| **7** | + | + | + | + | $OC_6H_5$ | $C_6H_{11}$ | NS | NS |
| **8** | − | + | + | − | $NMe_2$ | $NO_2$ | NS | NS |
| **9** | + | − | + | − | $NMe_2$ | $NMe_2$ | 30 ± 4 | NS |
| **10** | − | − | + | + | $OC_6H_5$ | F | 42 ± 6 | 33 ± 2 |
| **11** | + | + | − | − | F | $C_6H_{11}$ | 27 ± 2 | 74 ± 2 |
| **12** | − | + | − | + | $NO_2$ | $NO_2$ | 26 ± 4 | 51 ± 3 |
| **13** | + | − | − | + | $NO_2$ | $NMe_2$ | NS | NS |
| **14** | − | − | − | − | F | F | 15 ± 2 | 22 ± 1 |

[a] A plus (+) represents a high value and a minus (−) a low value of the parameters. NS indicates that the compound could not be tested due to low solubility in the test medium.

## Results and Discussion

**Statistical Design.** The chalcones studied contain a common skeleton, and the description of the molecules can therefore be based on substituent parameters.[16,17] The substituents were described by four parameters which may be related to the biological activity of the compounds, the molar refractivity (MR) describing steric effects, the lipophilicity constant $\pi$, and the Hammett constants $\sigma_p$ and $\sigma_m$ describing electronic effects. Sixty-two substituents, which can be introduced on the chalcone skeleton, were selected for the analysis, and a principal components analysis (PCA)[18] was performed on the 62 × 4 matrix. Parameter values for the substituents were taken from ref 18. The two first principal components, which explain 89% of the variance in the four original parameters (Table 1), were used for the statistical design. Figure 1 displays the substituents in the space of the principal components (PCs).

Since a preliminary 2D-QSAR analysis (data not shown) reveals that positions 4 and 4′ are the most important ones for the biological activity, a $2^{4-1}$ fractional factorial design[14] (FFD) in these positions was first performed (Table 2). However, poor solubility of some of the compounds (e.g., **7**−**9** and **13**) prevented this approach, and instead a more simple approach was employed. Substituents with high and low values of the two principal components were placed in each of the three positions of one of the rings according to a $2^2$ factor design. At the same time a substitution pattern known to afford chalcones with high activity was kept in the other ring (Tables 3 and 4). The advantage of selecting chalcones with medium to high activities is that the poor solubility in the test medium will be sufficient for determination of the IC$_{50}$ values. In ring B, the 3,5- or 2,4-dimethoxy substitution (Table 3) and in ring A, the 2′,3′,4′-trimethoxy pattern (Table 4) were chosen.

**Table 3.** Substituents in Ring A According to Three $2^2$ Factorial Designs[a]

| | | | | | IC$_{50}$ ± SD ($\mu$M) | |
|---|---|---|---|---|---|---|
| compd | PC$_1$ | PC$_2$ | ring A | ring B | leish | lymph |
| **15** | + | + | 2′-$OC_4H_9$ | 3,5-$OCH_3$ | 7.2 ± 1.2 | 13 ± 1 |
| **16** | + | − | 2′-$N(CH_3)_2$ | 3,5-$OCH_3$ | 7.3 ± 1.0 | 5.7 ± 0.3 |
| **17** | − | + | 2′-$NO_2$ | 3,5-$OCH_3$ | 3.4 ± 0.5 | 3.7 ± 0.2 |
| **18** | − | − | 2′-F | 3,5-$OCH_3$ | 3.5 ± 0.8 | 6.0 ± 0.4 |
| **19** | + | + | 3′-$OC_4H_9$ | 2,4-$OCH_3$ | 20 ± 3 | 65 ± 4 |
| **20** | + | − | 3′-$N(CH_3)_2$ | 3,5-$OCH_3$ | 5.8 ± 0.7 | 5.0 ± 0.2 |
| **21** | − | + | 3′-$NO_2$ | 2,4-$OCH_3$ | 8.6 ± 1.1 | 18 ± 2 |
| **22** | − | − | 3′-F | 3,5-$OCH_3$ | 5.5 ± 0.3 | 9.2 ± 0.5 |
| **23** | + | + | 4′-$C_6H_{11}$ | 3,5-$OCH_3$ | 31 ± 2 | 39 ± 2 |
| **24** | + | − | 4′-$N(CH_3)_2$ | 3,5-$OCH_3$ | NS | NS |
| **25** | − | + | **4′-$NO_2$** | **3,5-$OCH_3$** | **16 ± 1** | **20 ± 1** |
| **26** | − | − | 4′-F | H | 15 ± 1 | 23 ± 21 |

[a] A plus (+) represents a high value and a minus (−) a low value of the parameters. NS indicates that the compound could not be tested due to low solubility in the test medium. The substituents and test data of the compounds in the validation set are in bold type.

**Chemistry.** The chalcones **7**−**71** were synthesized by a Claisen−Schmidt condensation[19] of the appropriate benzaldehyde with the appropriate acetophenone. The chalcones **8**, **12**, **17**, and **29** were prepared using hydrochloric acid as a catalyst, whereas the remaining chalcones **7**−**71** were prepared by a sodium hydroxide-catalyzed condensation. To increase the yield, the hydroxy groups in the starting materials for the hydroxychalcones **72**−**82** were masked as tetrahydropyranyl ethers before condensation. The hydroxy group was demasked by acid hydrolysis.

The procedure developed for the syntheses of the naturally occurring licorice chalcones **1** and **2**[7] were followed for the preparation of the alkylated chalcones **3**−**6** (Scheme 1). The alkylated 2,4-dihydroxybenzaldehydes **3b**−**6b** were prepared by a Vilsmeier formylation[20] of the resorcinols **3a**−**6a**. In all cases a rapid regioselective acylation was obtained. Reaction with dihydropyran selectively afforded the 4-*O*-tetrahydropyranyl ethers **3c**−**6c**, which were methylated at O-2 to give the starting materials **3d**−**6d**.

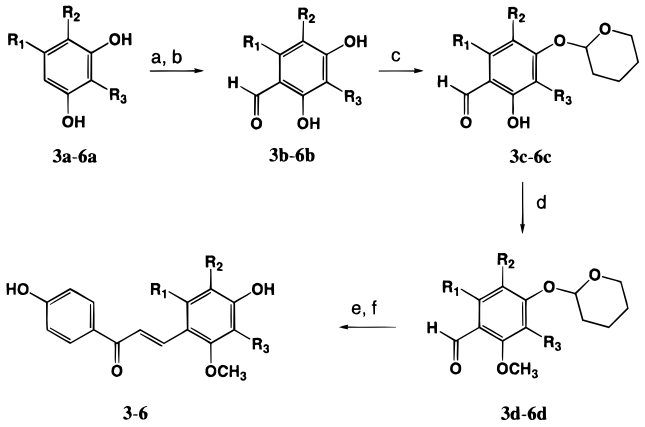
**3D-QSAR Analyses.** The 30 chalcones designed by statistical methods (**7**−**36**, Tables 2−4) supplemented with 52 chalcones (**1**−**6** and **38**−**82**) prepared for opening studies were used for the 3D-QSAR analyses. Conformational analysis of the compounds and the molecular alignments employed were performed as described in the Experimental Section. The interaction energies between the compounds and three different probes (water, methyl, and ammonium ion) were calculated by using the GRID program employing a grid spacing of 1 Å. The probes were selected to reflect possible interactions with the target. The GRID calculations give 57 200 variables for each compound. A

**Table 4.** Substituents in Ring B According to Three $2^2$ Factorial Designs[a]

| compd | $PC_1$ | $PC_2$ | ring B | ring A | $IC_{50} \pm SD$ ($\mu$M) leish | $IC_{50} \pm SD$ ($\mu$M) lymph |
|---|---|---|---|---|---|---|
| **27** | + | + | 2-$OC_4H_9$ | 2′,3′,4′-$OCH_3$ | 26 ± 1 | 52 ± 3 |
| **28** | + | − | 2-$N(CH_3)_2$ | 2′,3′,4′-$OCH_3$ | | |
| **29** | − | + | 2-$NO_2$ | 2′,3′,4′-$OCH_3$ | 5.9 ± 0.4 | 7.0 ± 0.6 |
| **30** | − | − | 2-F | 2′,3′,4′-$OCH_3$ | 15 ± 1 | 11 ± 1 |
| **31** | + | + | 3-$OC_6H_5$ | 2′,3′,4′-$OCH_3$ | 8.7 ± 0.5 | 17 ± 1 |
| **32** | + | − | 3-$N(CH_3)_2$ | 2′,3′,4′-$OCH_3$ | 20 ± 3 | 26 ± 1 |
| **33** | − | + | 3-$NO_2$ | 2′,3′,4′-$OCH_3$ | 17 ± 2 | 36 ± 2 |
| **34** | − | − | 3-F | 2′,3′,4′-$OCH_3$ | 9.7 ± 0.9 | 6.4 ± 0.4 |
| **10**, Table 2 | + | + | | | | |
| **35** | + | − | **4-$N(CH_3)_3$** | **2′,3′,4′-$OCH_3$** | **21 ± 2** | **35 ± 2** |
| **36** | − | + | 4-CN | 2′,3′,4′-$OCH_3$ | 8.6± 0.9 | 5.4 ± 0.3 |
| **11** and **14**, Table 2 | − | − | | | | |

[a] A plus (+) represents a high value and a minus (−) a low value of the parameters. Substituents and test data of the compounds in the validation set are in bold type.

**Scheme 1**[a]




[a] **3**: $R_2 = C_3H_7$, $R_1 = R_3 = H$. **4**: $R_2 = C_6H_{13}$, $R_1 = R_3 = H$. **5**: $R_3 = CH_3$, $R_1 = R_2 = H$. **6**: $R_1 = CH_3$, $R_2 = R_3 = H$. Reagents: (a) $POCl_3$, DMF; (b) $H_2O$; (c) 3,4-dihydro-2*H*-pyran, pyridinium *p*-toluenesulfonate, $CH_2Cl_2$; (d) $CH_3I$, NaOH, DMSO; (e) 4-[(tetrahydropyranyl)oxy]acetophenone, NaOH, ethanol; (f) 4 M HCl.

major part of these variables is not important for describing the interaction between the chalcone and the target and is only introducing noise in the PLS model.[21] These variables are eliminated using the GOLPE algorithm, and the resulting models are of higher quality than models calculated without variable selection.

The QSAR was calculated using GOLPE on 67 (antileishmanial activity) and 63 (lymphocyte-suppressing activity) of the chalcones, using the Smart Region Definition (SRD) procedure for variable preselection,[22] followed by a FFD variable selection[11] (see Experimental Section). The data pretreatment reduces the number of variables to approximately 10%, and region selection was then applied to eliminate regions which are not significantly contributing to the predictivity. This is done by building a large number (twice the number of variables) of reduced models according to a FFD procedure in which some regions are left out and the predictivity of the reduced models is calculated. This makes it possible to evaluate the effect of each individual region, and only the regions that contribute in a positive way to the predictivity of the model are included. Scaling did not improve the quality of the models and was not used.

Nine chalcones, compounds **2**, **25**, **35**, **44**, **55**, **56**, **67**, **68**, and **73**, were chosen to form an external validation set. These compounds are shown in bold in Tables 3, 4, and 7. The compounds were chosen to cover the entire activity interval as well as to represent different substituent types and patterns.

**Table 5.** Properties of the 3D-QSAR Models for Antileishmanial Activity

| | number of variables | number of components | $R^2$ | $Q^2$ |
|---|---|---|---|---|
| initial model | 39 950 | 2 | 0.68 | 0.48 |
| after SRD pretreatment | 4 077 | 2 | 0.68 | 0.49 |
| after FFD region selection | 1 365 | 2 | 0.73 | 0.63 |

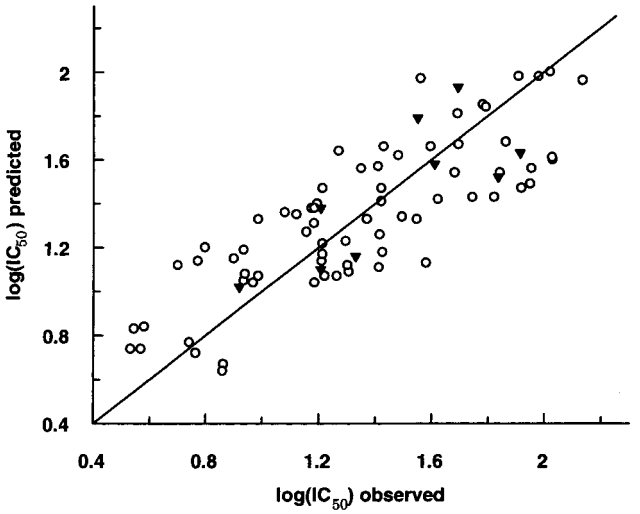



**Figure 2.** Observed and predicted antileishmanial activities: ○, training set; ▼, validation set.

**3D-QSAR Model for Antileishmanial Activity.** Using the SRD preselection procedure, the number of variables was reduced from 39 950 variables (after rejection of variables having a total sum of squares (SS) lower than $10^{-7}$; see Experimental Section) to 4 077 variables without any significant change in the quality of the model (Table 5). Region selection based on the FFD procedure further reduced the number of variables to 1365 with a major improvement in the quality of the model (Table 5). The correlation between observed and predicted activities is shown in Figure 2. The prediction of the activity of the external validation set is good (SDEP = 22.2), and the model is able to predict the activity of both high- and low-potency compounds.

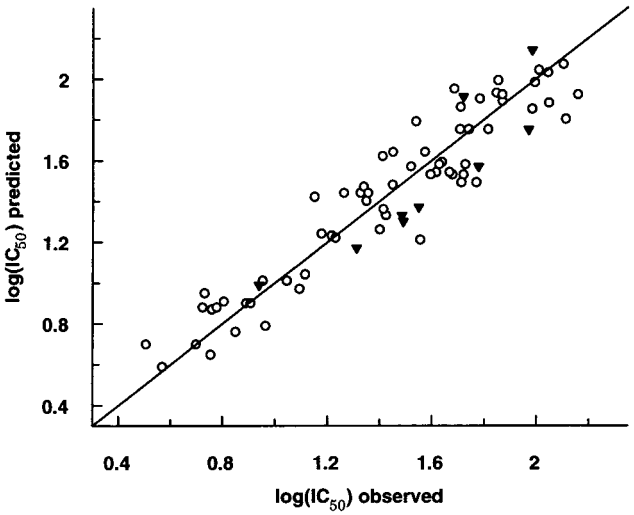



**Figure 3.** Observed and predicted antilymphocytic activities: ○, training set; ▼, validation set.

The coefficient plots for the three probes used in the GRID calculations are almost identical indicating that the difference in activity between the chalcones is mainly due to steric interactions with the target. The interpretation of the model is thereby simplified since the coefficient plot for the methyl probe contains almost all relevant information. This is confirmed by calculating a model using only the methyl probe. The coefficent regions are essentially identical to those obtained by using the more complex model based on three probes. The quality of the model using only the methyl probe is only slightly lower ($R^2 = 0.68$, $Q^2 = 0.53$ compared to $R^2 = 0.73$, $Q^2 = 0.63$) indicating that electrostatic interactions with the target play a minor role in the activity.

The regions with the highest positive and negative coefficients are located around the A-ring (Figure 4) indicating that substituents on the A-ring are mainly responsible for the differences in the antileishmanial activity of the chalcones. The negative coefficient regions around the 2′- and 3′-positions (Figure 4, top) indicate that substituents which in these regions give unfavorable interactions with the methyl probe, i.e., bulky substituents, are predicted to increase the activity of the compound. The positive coefficients (Figure 4, bottom) illustrate regions around the molecule in which introduction of substituents is predicted to reduce the activity of the compounds. Thus, a bulky substituent in the 4′-position is predicted to reduce the antileishmanial activity of the compound.

**Table 6.** Properties of the 3D-QSAR Models for the Suppression of Proliferation of Lymphocytes

| | number of variables | number of components | $R^2$ | $Q^2$ |
|---|---|---|---|---|
| initial model | 46 062 | 3 | 0.85 | 0.52 |
| after SRD pretreatment | 4 021 | 3 | 0.86 | 0.57 |
| after FFD region selection | 1 454 | 3 | 0.90 | 0.80 |

**3D-QSAR Model for Lymphocyte-Suppressing Activity.** The SRD preselection method applied to the lymphocyte data reduces the number of variables from 46 062 (after rejection of variables having SS lower than $10^{-7}$) to 4 021 with preserved quality of the model, and subsequent FFD region selection results in a model of very high quality ($R^2 = 0.90$, $Q^2 = 0.80$) using 1 454 variables (Table 6). Examination of the plot in Figure 3 indicates that the prediction of the external validation set is good (SDEP = 25.0) and that the model is able to predict the activities of high- as well as low-potency compounds.

The coefficient plots for the three different probes are also in this case very similar indicating that the interaction with the lymphocyte target is determined mainly by steric factors. The coefficient plots for the methyl probe are displayed in Figure 5. In contrast to the coefficient plots for antileishmanial activity (Figure 4), examination of the plots in Figure 5 indicates that the antilymphocytic activity of the chalcones is influenced by substituents on the A- as well as the B-ring. Negative coefficient regions around the 2′-position (ring A) as well as the 5- and 6-positions (ring B) indicate that

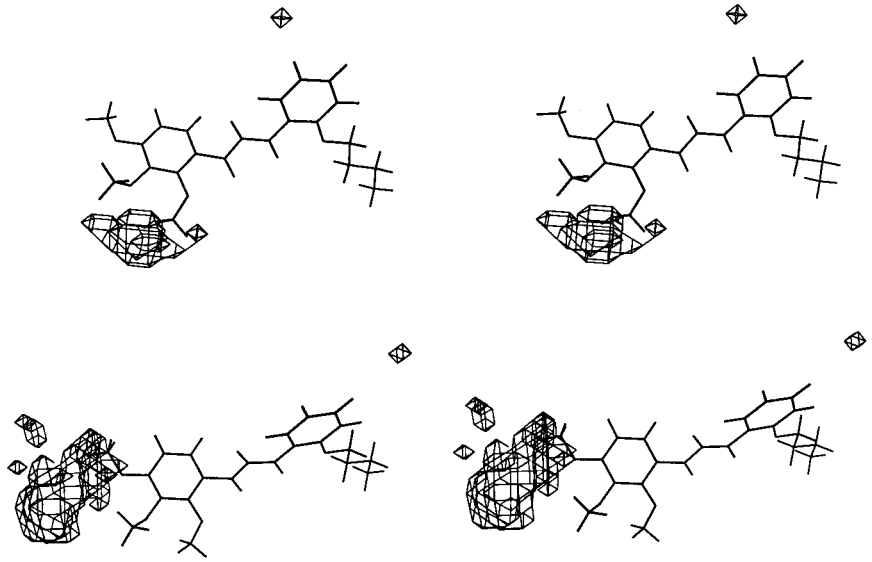


**Figure 4.** Contour maps (stereoview) for antileishmanial activity. The negative (top) and positive (bottom) coefficients at the 0.0005 level for the methyl probe are shown. An unfavorable interaction (positive interaction energy) between a substituent and the probe in regions with negative coefficients will reduce the $IC_{50}$, i.e., increase the activity of the compound, and vice versa for positive coefficients. The chalcone **27** is drawn to illustrate the size of the regions.

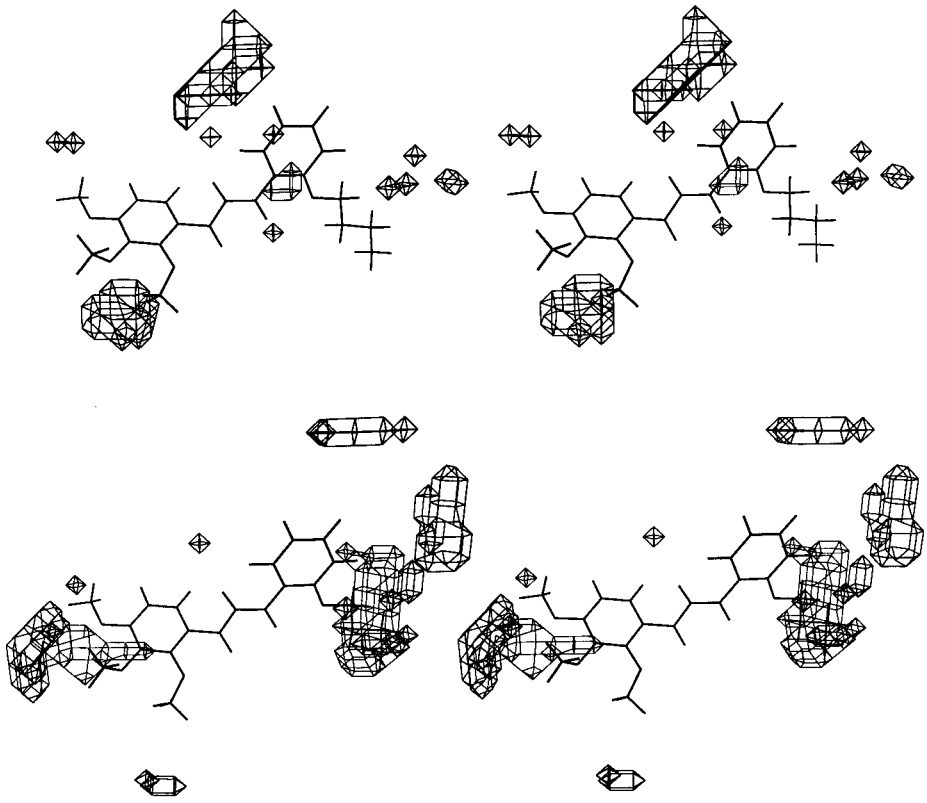


**Figure 5.** Contour maps (stereoview) for lymphocyte suppression activity. The negative (top) and positive (bottom) coefficients at the 0.0005 level for the methyl probe are shown. An unfavorable interaction (positive interaction energy) between a substituent and the probe in regions with positive coefficients will increase the $IC_{50}$, i.e., reduce the activity of the compound, and vice versa for the negative coefficients. The chalcone **27** is drawn to illustrate the size of the regions.

bulky groups giving unfavorable interactions with the methyl probe will cause an (undesirable) increase in the antilymphocytic activity of the compound (Figure 5, top). The presence of positive coefficient regions around the 4′-, 2-, 3-, and 4-positions (Figure 5, bottom) indicates that bulky groups in these positions will lead to less active and thereby less toxic compounds.

## Conclusions

The 3D-QSAR models developed for the antileishmanial activity and the lymphocyte-suppressing activity of substituted chalcones show high predictability, indicating that the models can be expected to give reliable predictions of the activities of new chalcones. The coefficient plots for the three probes employed indicate that steric interactions between the chalcones and the target are of major importance for the potencies of the compounds. A comparison of the coefficient plots for the antileishmanial effect (Figure 4) and the lymphocyte-suppressing activity (Figure 5) discloses that large substituents in positions 4′, 2, 3, and 4 are predicted to decrease the activity toward lymphocytes, whereas the antileishmanial activity should not be affected. These observations make it possible to separate the antileishmanial activity and the antilymphocyte properties of the chalcones. The coefficient plots in Figures 4 and 5 may then be employed to design chalcones with high selectivity against the parasites.

## Experimental Section

**Chemistry.** $^1$H NMR, $^{13}$C NMR, and DEPT (135) spectra were recorded on a Bruker AC-200F spectrometer. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (b); NMR values are given in $\delta$ units. An asterisk indicates that signals with similar shifts may be interchanged. The uncorrected melting points are determined on an Electrothermal melting point apparatus. Column chromatography was performed on silica gel (Merck, 0.040−0.063 mm) using a mixture of toluene and ethyl acetate as an eluent. All moisture-sensitive reactions were performed under nitrogen using oven-dried glassware. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone.

The following chalcones were prepared as previously described: licochalcone A (**1**),[23] echinatin (**2**),[23] licochalcone C (**37**),[23] 2,4-dimethoxy-2′,4′-difluorochalcone (**48**),[24] 2,4-difluoro-2′,4′-dimethoxychalcone (**49**),[24] 2,4-dichloro-2′,3′,4′-trimethoxychalcone (**50**),[24] 3,4-difluoro-2′,4′-dimethoxychalcone (**51**),[24] 2,4-dichloro-2′,5′-dimethoxychalcone (**52**),[24] 4,4′-dimethoxychalcone (**54**),[25] 2,4-dimethoxy-4′-butoxychalcone (**62**),[26] 2,4-dimethoxychalcone (**64**),[27] 2,4-dimethoxy-2′-hydroxychalcone (**69**),[28] 4,4′-dihydroxychalcone (**72**),[29] 4′-hydroxychalcone (**77**),[30] 2,5-dimethoxy-4′-hydroxychalcone (**78**),[31] and 2,3-dimethoxy-4′-hydroxychalcone (**74**).[32] Chalcone (**57**) was purchased from Aldrich; butein (**53**) and homobutein (**55**) were from Roth.

**2,4-Dihydroxy-5-propylbenzaldehyde (3b). General Procedure A.** Phosphorus oxychloride (0.800 mL, 8.6 mmol) was added dropwise with stirring to dimethylformamide (2.6 mL, 33.6 mmol), the temperature being kept at 10−20 °C. This reagent was slowly added to a solution of 2,4-dihydroxy-5-propylbenzene[33] (0.59 g, 3.9 mmol) in dimethylformamide (2.6 mL), the temperature being kept at 20−30 °C. After 30 min the mixture was poured in 2 M NaOH (20 mL). The organic phase was extracted with 2 M NaOH (210 mL). The combined aqueous phases were neutralized with hydrochloric acid 4 M and extracted with ethyl acetate (320 mL). The combined organic phases were concentrated in vacuo, and the residue was purified by column chromatography to give **3b** (0.44 g, 63%) as gray crystals: mp 92.8−93.6 °C (water−ethanol),[33] mp 71−76 °C; $^1$H NMR ($CD_3OD$) 9.65 (s, −CHO), 7.28 (s, H6), 6.28 (s, H3), 4.94 (b, OH), 2.48 (t, $J$ = 7.3 Hz, H1′), 1.56 (sext,

**Table 7.** Structure and Activity of Chalcones for Opening Studies[a]

| compd | structure: substituents on chalone | $IC_{50} \pm SD$ ($\mu$M) leish | lymph |
|---|---|---|---|
| **1** | licochalcone A | 13 ± 1 | 48 ± 5 |
| **2** | **2-$OCH_3$-4,4′-OH** | **68 ± 4** | **94 ±4** |
| **3** | 2-$OCH_3$-4,4′-OH-5-propyl | 26 ± 2 | 41 ± 3 |
| **4** | 2-$OCH_3$-4,4′-OH-5-hexyl | 9.7 ± 0.9 | 46 ± 3 |
| **5** | 2-$OCH_3$-3-methyl-4,4′-OH | 22 ± 3 | 27 ± 4 |
| **6** | 2-$OCH_3$-4,4′-OH-6-methyl | 39 ± 5 | 53 ± 6 |
| **37** | licochalcone C | 55 ± 3 | 53 ± 2 |
| **38** | 3,5-$OCH_3$-4′-allyloxy | 27 ± 2 | 25 ± 2 |
| **39** | 4-$C_4H_9$-3,5-$OCH_3$-4′-allyloxy | 90 ± 14 | NS |
| **40** | 4-$C_6H_{13}$-3,5-$OCH_3$-4′-allyloxy | 19 ± 4 | 15 ± 1 |
| **41** | 2′-OH-3,5-$OCH_3$ | 3.8 ± 0.9 | 8.1 ± 0.8 |
| **42** | 3′-OH-3,5-$OCH_3$ | 3.7 ± 0.6 | 3.2 ± 0.4 |
| **43** | 2-OH-2′,3′,4′-$OCH_3$ | 9.3 ± 1.0 | 9.0 ± 0.7 |
| **44** | **2′,3′,4′,3,5-$OCH_3$** | **8.3 ± 0.9** | **8.7 ± 0.5** |
| **45** | 3′,2,4-$OCH_3$ | 18 ± 3 | 42 ± 2 |
| **46** | 2′-Br-2,4-$OCH_3$ | 14 ± 2 | 35 ± 3 |
| **47** | 3′-Br-2,4-$OCH_3$ | 16 ± 1 | 37 ± 2 |
| **48** | 2′,4′-F-2,4-$OCH_3$ | 26 ± 2 | 74 ± 4 |
| **49** | 2′,4′-$OCH_3$-2,4-F | 27 ± 4 | 12 ± 0 |
| **50** | 2′,3′,4′-$OCH_3$-2,4-Cl | 6.3 ± 0.6 | 7.8 ± 0.9 |
| **51** | 2′,4′-$OCH_3$-3,4-F | 16 ± 1 | 5.3 ± 0.6 |
| **52** | 2′,5′-$OCH_3$-2,4-Cl | 7.8 ± 0.7 | 5.7 ± 0.5 |
| **53** | 2′,4′,3,4-OH | 66 ± 2 | 16 ± 1 |
| **54** | 4′,4-$OCH_3$ | 106 ± 9 | 112 ± 8 |
| **55** | **2′,4′,4-OH-3-$OCH_3$** | **16 ± 2** | **31 ± 2** |
| **56** | **3,4,5-$OCH_3$-4′-allyloxy** | **41 ± 4** | **30 ± 1** |
| **57** | chalcon | 20 ± 1 | 21 ± 2 |
| **58** | 2,5-$OCH_3$-4′-allyloxy | 73 ± 4 | 55 ± 2 |
| **59** | 3,4-$OCH_3$-4′-allyloxy | 60 ± 5 | 51 ± 6 |
| **60** | 2,4,2′-$OCH_3$ | 16 ± 1 | 26 ± 2 |
| **61** | 2,4-$OCH_3$-4′-$OC_6H_{13}$ | 136 ±15 | NS |
| **62** | 2,4-$OCH_3$-4′-$OC_4H_9$ | 95 ± 10 | NS |
| **63** | 4′-$OC_6H_{13}$ | 62 ± 5 | 99 ± 7 |
| **64** | 2,4-$OCH_3$ | 15 ± 0 | 48 ± 2 |
| **65** | 2,6-$OCH_3$-4′-$OC_4H_9$ | 104 ± 9 | 127 ± 10 |
| **66** | 2,6-$OCH_3$-4′-allyloxy | 81 ± 7 | 96 ± 8 |
| **67** | **2,3-$OCH_3$-4′-allyloxy** | **49 ± 3** | **96 ± 6** |
| **68** | **3,5-$OCH_3$-4′-$OC_4H_9$** | **35 ± 3** | **52 ± 3** |
| **69** | 2,4-$OCH_3$-2′-OH | 35 ± 2 | 144 ± 9 |
| **70** | 2,4-$OCH_3$-2′-allyloxy | 5.0 ± 0.7 | NS |
| **71** | 2,5,4′-allyloxy | 38 ± 2 | 61 ± 3 |
| **72** | 4′,4-OH | 83 ± 5 | 59 ± 3 |
| **73** | **2,6-$OCH_3$-4′OH** | **82 ± 8** | **60 ± 2** |
| **74** | 2,3-$OCH_3$-4′OH | 89 ± 9 | 70 ± 4 |
| **75** | 3,5-$OCH_3$-4′OH | 12 ± 1 | 14 ± 1 |
| **76** | 2,4,6-$OCH_3$-4′-OH | 106 ± 8 | 44 ± 2 |
| **77** | 4′-OH | 16 ± 1 | 28 ± 1 |
| **78** | 2,5-$OCH_3$-4′-OH | 23 ± 2 | 22 ± 1 |
| **79** | 2,4,5-$OCH_3$-4′OH | 16 ± 2 | 28 ± 2 |
| **80** | 2,4-$OCH_3$-4′-OH | 48 ± 3 | 71 ± 5 |
| **81** | 2-$OCH_3$-4-OH-4′-$N(CH_3)_2$ | 49 ± 4 | 111 ± 7 |
| **82** | 4-$N(CH_3)_2$-4′OH | 79 ± 6 | 130 ± 13 |

[a] NS indicates that the compound could not be tested due to low solubility in the test medium. The substituents and test data of the compounds in the validation set are in bold type.

$J$ = 7.3 Hz, H2′), 0.91 (t, $J$ = 7.3 Hz, H3′); $^{13}$C NMR ($CD_3OD$) 193.5 (C═O), 163.4*(C4), 161.8*(C2), 134.0 (C6), 121.8 (C5), 113.7 (C1), 100.7 (C3), 30.4 (C1′), 21.9 (C2′), 12.3 (C3′).

**2-Hydroxy-4-[(2-tetrahydropyranyl)oxy]-5-propylbenzaldehyde (3c). General Procedure B.** A solution of **3b** (0.45 g, 2.5 mmol), pyridinium *p*-toluenesulfonate (20 mg, 0.1 mmol), and 3,4-dihydro-2*H*-pyran (0.34 mL, 4.0 mmol) in methylene chloride (5 mL) was stirred for 4 h at room temperature. The solution was washed with 1 M sodium carbonate (5 mL) and concentrated in vacuo to give 1.25 g of a yellow oil, which according to the $^1$H NMR spectrum consisted of **3c**: $^1$H NMR ($CDCl_3$) 11.30 (s, −OH), 9.68 (s, −CHO), 7.21 (s, H6), 6.68 (s, H3), 5.49 (bt, H2′), 3.85 (b, H6a′), 3.60 (b, H6e′), 2.55 (t, $J$ = 7 Hz, H1″), 1.58 (hext, $J$ = 7 Hz, H2″), 2.1−1,4 (m, H3′−5′), 0.91 (t, $J$ = 7 Hz, H3″).

**2-Methoxy-4-[(2-tetrahydropyranyl)oxy]-5-propylbenzaldehyde (3d). General Procedure C.** The crude product **3c** (1.25 g), sodium hydroxide (0.4 g), and iodomethane (0.31 mL, 5 mmol) were suspended in DMSO (5 mL), stirred for 60 min at room temperature, and added to water (20 mL). The mixture was extracted with methylene chloride (420 mL), and the combined organic phases were washed with water (320 mL) and concentrated in vacuo to give 1.26 g of a brown oil, which according to the $^1$H NMR spectrum consisted of **3d**: $^1$H NMR ($CDCl_3$) 10.28 (s, CHO), 7.58 (s, H6), 6.73 (s, H3), 5.55 (b, H2′), 3.81 (s, $OCH_3$), 3.8 (b, H6a′), 3.6 (b, H6e′), 2.55 (t, $J$ = 7 Hz, H1″), 1.61 (m, H2″), 2.1−1.4 (m, H3′−5′), 0.91 (t, $J$ = 7 Hz, H3″).

**2-Methoxy-4,4′-dihydroxy-5-propylchalcone (3). Procedure D.** A solution of the crude product **3d** (1.26 g), 4-[(2-tetrahydropyranyl)oxy]acetophenone (0.48 g, 2.2 mmol), and sodium hydroxide (50 mg) in anhydrous ethanol (10 mL) was stirred for 18 h at room temperature. The solution was added to 4 M hydrochloric acid (2 mL), stirred for an additional 15 min, and added to water (40 mL). The mixture was extracted with ethyl acetate (450 mL), and the combined organic phases were concentrated in vacuo to give **3** (0.32 g, 41% overall yield based on **3b**): orange-brown crystals; mp 126.5−128.0 °C (ethanol−water); $^1$H NMR ($(CD_3)_2CO$) 8.11 (d, $J$ = 15.5 Hz, H$\beta$), 8.06 (m, H2′ and H6′), 7.73 (d, $J$ = 15.5 Hz, H$\alpha$), 7.63 (s, H6), 6.97 (m, H3′ and H5′), 6.59 (s, H3), 3.85 (s, $OCH_3$), 2.58 (t, $J$ = 7.3 Hz, H1″), 1.64 (sext, $J$ = 7.3 Hz, H2″), 0.95 (t, $J$ = 7.3 Hz, H3″); $^{13}$C NMR ($(CD_3)_2CO$) 188.4 (CHO), 162.3*(C4′), 159.7*(C2), 159.5*(C4), 139.5 (C$\beta$), 131.7 (C1′), 131.6 (C2′, C6′), 131.3 (C6), 122.4 (C5), 119.1 (C$\alpha$), 116.3 (C1), 116.0 (C3′, C5′), 99.7 (C3), 55.9 ($OCH_3$), 32.2 (C1″), 23.9 (C2″), 14.3 (C3″). Anal. ($C_{19}H_{20}O_4 \cdot 0.5H_2O$) C, H, N.

**2,4-Dihydroxy-5-hexylbenzaldehyde (4b)** was synthesized according to procedure A using 2,4-dihydroxy-5-hexylbenzene (1.39 g, 7.2 mmol) as starting material: yellow-white crystals (0.74 g, 46%); mp 108.2−109.5 °C (ethanol−water),[34] mp 109 °C; $^1$H NMR ($CD_3OD$) 9.65 (s, OH, CHO), 7.30 (s, H6), 6.29 (s, H3), 4.94 (b, OH), 2.50 (t, $J$ = 7.3 Hz, H1′), 1.56 (m, H2′), 1.30 (m, H3′−H5′), 0.91 (t, $J$ = 7.3 Hz, H6′); $^{13}$C NMR ($CD_3OD$) 193.5 (C═O), 163.3*(C4), 161.8*(C2), 133.8 (C6), 122.0 (C5), 113.7 (C1), 100.7 (C3), 30.9 (C1′), 28.8 (C2′), 28.2 (C3′, C4′), 21.7 (C5′), 12.5 (C6′).

**2-Hydroxy-4-[(2-tetrahydropyranyl)oxy]-5-hexylbenzaldehyde (4c)** was synthesized according to procedure B using **4b** (0.23 g, 1 mmol) as starting material: yellow oil (0.62 g); $^1$H NMR ($CDCl_3$) 11.28 (s, −OH), 9.69 (s, −CHO), 7.23 (s, H6), 6.66 (s, H3), 5.50 (bt, H2′), 3.9 (b, H6a′), 3.6 (b, H6e′), 2.55 (t, $J$ = 7 Hz, H1″), 2.1−1.4 (m, H3′−5′, H2″−H5″), 0.90 (t, $J$ = 7 Hz, H6″).

**2-Methoxy-4-[(2-tetrahydropyranyl)oxy]-5-hexylbenzaldehyde (4d)** was synthesized according to procedure C using crude **4c** (0.62 g) as starting material: brown oil (0.61 g); $^1$H NMR ($CDCl_3$) 10.28 (s, CHO), 7.58 (s, H6), 6.75 (s, H3), 5.58 (b, H2′), 3.88 (s, $OCH_3$), 3.80 (b, H6a′), 3.61 (b, H6e′), 2.60 (m, H1″), 2.1−1.4 (m, H3′−H5′, H2″−H5″), 0.90 (bt, $J$ = 7.1 Hz, H6″).

**2-Methoxy-4,4′-dihydroxy-5-hexylchalcone (4)** was synthesized according to procedure D using crude **4d** (0.61 g) and 4-[(2-tetrahydropyranyl)oxy]acetophenone[23] (0.10 g, 0.45 mmol) as starting materials: an orange amorphous powder (0.19 g, 51% overall yield based on **4b**); $^1$H NMR ($(CD_3)_2CO$) 8.10 (d, $J$ = 15.6 Hz, H$\beta$), 8.05 (m, H2′ and H6′), 7.73 (d, $J$ = 15.6 Hz, H$\alpha$), 7.64 (s, H6), 6.96 (m, H3′ and H5′), 6.58 (s, H3), 3.85 (s, $OCH_3$), 2.60 (t, $J$ = 7 Hz, H1″), 1.33 (m, H2″), 1.1 (m, H3″−H5″), 0.88 (bt, $J$ = 7 Hz, H6″); $^{13}$C NMR ($(CD_3)_2CO$) 188.5 (CHO), 162.3*(C4′), 159.6*(C2), 159.4*(C4), 139.6 (C$\beta$), 131.7 (C1′), 131.6 (C2′, C6′), 131.3 (C6), 122.6 (C5), 119.0 (C$\alpha$), 116.2 (C1), 116.0 (C3′, C5′), 99.7 (C3), 55.9 ($OCH_3$), 32.5 (C1″), 30.9 (C2″), 30.1 (C3″), 29.9 (C4″), 23.3 (C5″), 14.4 (C6″). Anal. ($C_{22}H_{26}O_4$) C, H.

**3-Methyl-2,4-dihydroxybenzaldehyde (5b)** was synthesized according to procedure A using 3-methyl-2,4-dihydroxybenzene (1.48 g, 11.9 mmol) as starting material: white crystals (1.46 g, 80%); mp 149.6−150.3 °C (ethanol−water),[35] mp 150 °C; $^1$H NMR ($CD_3OD$) 9.61 (s, OH, CHO), 7.30 (d $J$ = 8.6 Hz, H6), 6.47 (d $J$ = 8.6 Hz, H5), 4.94 (b, OH), 2.04 (s,

$CH_3$); $^{13}C$ NMR ($CD_3OD$) 196.1 (C═O), 164.9*(C4), 163.2*(C2), 134.2 (C6), 115.7 (C1), 112.1 (C3), 108.9 (C5), 7.3 ($CH_3$).

**2-Hydroxy-3-methyl-4-[(2-tetrahydropyranyl)oxy]benzaldehyde (5c)** was synthesized according to procedure B using **5b** (0.38 g, 2.5 mmol) as starting material: yellow oil (0.60 g); $^1H$ NMR ($CDCl_3$) 9.68 (s, OH, CHO), 7.31 (d, $J$ = 9.1 Hz, H6), 6.78 (d, $J$ = 9.1 Hz, H5), 5.58 (bt, H2′), 3.9 (b, H6a′), 3.6 (b, H6e′), 2.18 (s, $CH_3$), 2.1−1.4 (m, H3′−5′).

**2-Methoxy-3-methyl-4-[(2-tetrahydropyranyl)oxy]benzaldehyde (5d)** was synthesized according to procedure C using crude **5c** (0.60 g) as starting material: brown oil (0.69 g); $^1H$ NMR ($CDCl_3$) 10.2 (s, CHO), 7.70 (d, $J$ = 8.9 Hz, H6), 6.98 (d, $J$ = 8.9 Hz, H5), 5.55 (bt, H2′), 3.85 (s, $OCH_3$), 3.82 (b, H6a′), 3.64 (b, H6e′), 2.20 (s, $CH_3$), 2.1−1.4 (m, H3′−5′).

**2-Methoxy-3-methyl-4,4′-dihydroxychalcone (5)** was synthesized according to procedure D using crude **5d** (0.69 g) and 4-[(2-tetrahydropyranyl)oxy]acetophenone[23] (0.38 g, 1.7 mmol) as starting materials: yellow crystals (0.38 g, 54% overall yield based on **5b**); mp 185.4−186.7 °C (ethanol−water); $^1H$ NMR ($(CD_3)_2CO$) 8.07 (m, H2′ and H6′), 8.03 (d, $J$ = 15.6 Hz, H$\beta$), 7.71 (d, $J$ = 15.6 Hz, H$\alpha$), 7.67 (d, $J$ = 8.5 Hz, H6), 6.98 (m, H3′ and H5′), 6.76 (d, $J$ = 8.5 Hz, H5), 3.77 (s, $OCH_3$), 2.18 (s, $-CH_3$); $^{13}C$ NMR ($(CD_3)_2CO$) 188.6 (C═O), 162.3*(C4), 160.6*(C4′), 159.4*(C2), 139.3 (C$\beta$), 131.7 (C2′, C6′), 131.6 (C1′), 127.0 (C6), 120.9 (C1), 120.3 (C$\alpha$), 118.9 (C3), 116.1 (C3′, C5′), 112.4 (C5), 61.8 ($OCH_3$), 9.1 ($CH_3$). Anal. ($C_{17}H_{16}O_4$) C, H.

**2,4-Dihydroxy-6-methylbenzaldehyde (6b)** was synthesized according to procedure A using 2,4-dihydroxy-6-methylbenzene (2.9 g, 20.8 mmol) as starting material: orange crystals (65%); mp 173.7C −177.3 °C (water−ethanol),[36] mp 178−180 °C; $^1H$ NMR ($CD_3OD$) 10.2 (s, OH, CHO), 6.18 (d $J$ = 2 Hz, H5), 6.08 (d $J$ = 2 Hz, H3), 4.95 (s, OH) 2.47 (s, $CH_3$); $^{13}C$ NMR ($CD_3OD$) 192.3 (C═O), 165.8*(C4), 165.2*(C2), 144.3 (C6), 112.0 (C1), 109.9 (C5), 99.5 (C3), 16.4 ($CH_3$).

**2-Hydroxy-4-[(2-tetrahydropyranyl)oxy]-6-methylbenzaldehyde (6c)** was synthesized according to procedure B using **6b** (0.76 g, 5.0 mmol) as starting material: yellow oil (1.80 g); $^1H$ NMR ($CDCl_3$) 10.09 (s, OH, CHO), 6.45 (d, $J$ = 2 Hz, H5), 6.37 (d, $J$ = 2 Hz, H3), 5.49 (bt, H2′), 3.9 (b, H6a′), 3.6 (b, H6e′), 2.52 (s, $CH_3$), 2.1−1.4 (m, H3′−5′).

**2-Methoxy-4-[(2-tetrahydropyranyl)oxy]-6-methylbenzaldehyde (6d)** was synthesized according to procedure C using crude **6c** (1.80 g) as starting material: brown oil (1.74 g); $^1H$ NMR ($CDCl_3$) 10.5 (s, CHO), 6.48 (b, H3, H5), 5.55 (bt, H2′), 3.85 (s, $OCH_3$), 3.8 (b, H6a′), 3.6 (b, H6e′), 2.55 (s, $CH_3$), 2.1−1.4 (m, H3′−5′).

**2-Methoxy-4,4′-dihydroxy-6-methylchalcone (6)** was synthesized according to procedure D using crude **6d** (1.74 g) and 4-[(2-tetrahydropyranyl)oxy]acetophenone[23] (0.80 g, 3.6 mmol) as starting materials: yellow crystals (0.73 g, 51% overall yield based on **6b**); mp 197.0−197.9 °C (ethanol−water); $^1H$ NMR ($(CD_3)_2CO$) 8.02 (d, $J$ = 15.7 Hz, H$\beta$), 8.00 (m, H2′ and H6′), 7.83 (d, $J$ = 15.7 Hz, H$\alpha$), 6.97 (m, H3′ and H5′), 6.46 (d, $J$ = 2 Hz, H5), 6.40 (d, $J$ = 2 Hz, H3), 3.93 (s, $OCH_3$), 2.43 (s, $CH_3$); $^{13}C$ NMR ($(CD_3)_2CO$) 188.8 (CHO), 162.7*(C4), 162.1*(C4′), 160.5*(C2), 142.8 (C6), 138.0 (C$\beta$), 131.8 (C1′), 131.5 (C2′, C6′), 122.9 (C$\alpha$), 116.1 (C3′, C5′), 115.5 (C1), 111.2 (C5), 98.1 (C3), 55.9 ($OCH_3$), 21.5 ($-CH_3$). Anal. ($C_{17}H_{16}O_4 \cdot 0.5H_2O$) C, H.

**4-Phenoxy-4′-cyclohexylchalcone (7). Procedure E.** To a solution of 4-phenoxybenzaldehyde (0.86 mL, 4.9 mmol) and 4-cyclohexylacetophenone (1.0 g, 4.9 mmol) in anhydrous ethanol (5 mL) was added sodium hydroxide (30 mg). The solution was stirred for 16 h, neutralized with 4 M hydrochloric acid, added to water (10 mL), and extracted four times with ethyl acetate (20 mL). The combined organic phases were concentrated in vacuo, and the residue was purified by column chromatography to give **7** (1.47 g, 79%) as white crystals: mp 160.9−161.1 °C (ethanol−water); $^1H$ NMR ($CDCl_3$) 8.11 (m, H2′ and H6′), 7.96 (d, $J$ = 15.5 Hz, H$\beta$), 7.9 (m, H2, H6, H3′, H5′), 7.79 (m, H3 and H5), 7.70 (d, $J$ = 15.5 Hz, H$\alpha$), 7.41 (m, H3″, H5″), 7.26 (m, H2″, H4″, H6″), 2.61 (b, H1$^c$), 1.9 (m, H2$^c$, H6$^c$), 1.5 (H3$^c$−H5$^c$). Anal. ($C_{27}H_{26}O_2$) C, H.

**4-(Dimethylamino)-4′-nitrochalcone (8). Procedure F.** A solution of 4-nitroacetophenone (0.50 g, 3.0 mmol) and 4-(dimethylamino)benzaldehyde (0.45 g, 3.0 mmol) in ethanol (3 mL) was saturated with hydrochloric acid. After 24 h, **8** (0.28 g, 32%) was isolated by filtration as brown crystals: mp 214.0−214.7 °C (acetonitrile−water); $^1H$ NMR ($CDCl_3$) 8.34 (m, H3′ and H5′), 8.12 (m, H2′ and H6′), 7.82 (d, $J$ = 15.3 Hz, H$\beta$), 7.60 (m, H2 and H6), 7.28 (d, $J$ = 15.3 Hz, H$\alpha$), 6.71 (m, H3 and H5), 3.09 (s, $NCH_3$). Anal. ($C_{17}H_{16}N_2O_3$) C, H, N.

**4,4′-Bis(dimethylamino)chalcone (9)** was synthesized according to procedure E using 4-(dimethylamino)benzaldehyde (0.12 g, 0.8 mmol) and 4-(dimethylamino)acetophenone (0.13 g, 0.8 mmol)[37] as starting materials: orange crystals (0.18 g, 76%); mp 149.8−150.7 °C (ethanol−water); $^1H$ NMR ($CDCl_3$) 8.00 (m, H2′ and H6′), 7.77 (d, $J$ = 15.4 Hz, H$\beta$), 7.54 (m, H2 and H6), 7.40 (d, $J$ = 15.4 Hz, H$\alpha$), 6.70 (m, H3 and H5, H3′ and H5′), 3.06 (s, $NCH_3$), 3.02 (s, $NCH_3$); $^{13}C$ NMR ($CDCl_3$) 188.9 (C═O), 152.3*(C4′), 148.4*(C4), 143.4 (C$\beta$), 130.5*(C3′, C5′), 130.0*(C3, C5), 127.1 (C1′), 123.0 (C1), 117.0 (C$\alpha$), 111.9*-(C2, C6), 110.8*(C2′, C6′), 40.5 ($NCH_3$), 40.1 ($NCH_3$). Anal. ($C_{19}H_{22}N_2O$) C, H, N.

**4-Phenoxy-4′-fluorochalcone (10)** was synthesized according to procedure E using 4-phenoxybenzaldehyde (0.29 mL, 1.5 mmol) and 4-fluoroacetophenone (0.18 mL, 1.5 mmol) as starting materials: white crystals (0.42 g, 90%); mp 115.7−116.0 °C (ethanol−water); $^1H$ NMR ($CDCl_3$) 8.26 (m, H2′ and H6′), 7.90 (m, H2 and H6), 7.84 (d, $J$ = 15.4 Hz, H$\beta$), 7.3−7.0 (remaining H). Anal. ($C_{21}H_{15}O_2F$) C, H.

**4-Fluoro-4′-cyclohexylchalcone (11)** was synthesized according to procedure E using 4-fluorobenzaldehyde (0.53 mL, 4.9 mmol) and 4-cyclohexylacetophenone (1.0 g, 4.9 mmol) as starting materials: white crystals (1.3 g, 86%); mp 166.8−167.9 °C (ethanol−water); $^1H$ NMR ($CDCl_3$) 7.95 (m, H2′ and H6′), 7.78 (d, $J$ = 15.7 Hz, H$\beta$), 7.60 (m, H3′ and H5′), 7.45 (d, $J$ = 15.7 Hz, H$\alpha$), 7.38 (dd, $J$ = 8.3, 6.5 Hz, H2, H6), 7.05 (dd, $J$ = 9.9, 8.3 Hz), 2.55 (b, H1$^c$), 1.87 (m, H2$^c$, H6$^c$), 1.41 (m, H3$^c$−H5$^c$); $^{13}C$ NMR ($CDCl_3$) 189.9 (C═O), 160.4 (C4), 153.4 (C4′), 143.7 (C$\beta$), 136.1 (C1′), 129.8 (C1), 128.7 (C2′, C6′), 127.0 (C2, C6), 124.1 (C$\alpha$), 119.7 (C3′, C5′), 118.4 (C3, C5), 44.7 (C1$^c$), 34.1 (C2$^c$, C6$^c$), 26.7 (C3$^c$, C5$^c$), 26.0 (C4$^c$). Anal. ($C_{21}H_{21}OF$) C, H.

**4,4′-Dinitrochalcone (12)** was synthesized according to procedure F using 4-nitrobenzaldehyde (0.46 g, 3.0 mmol) and 4-nitroacetophenone (0.50 g, 3.0 mmol) as starting materials: yellow crystals (0.35 g, 40%); mp 175−178 °C dec; $^1H$ NMR ($CDCl_3$) 8.39 (m, H3′ and H5′), 8.31 (m, H3 and H5), 8.16 (m, H2′ and H6′), 7.84 (d, $J$ = 15.8 Hz, H$\beta$), 7.80 (m, H2 and H6), 7.62 (d, $J$ = 15.8 Hz, H$\alpha$). Anal. ($C_{15}H_{10}N_2O_5$) C, H, N.

**4-Nitro-4′-(dimethylamino)chalcone (13)** was synthesized according to procedure E using 4-nitrobenzaldehyde (0.17 g, 1.1 mmol) and 4-(dimethylamino)acetophenone (0.20 g, 1.1 mmol)[37] as starting materials: orange crystals (0.29 g, 80%); mp 198.5−199.5 °C (acetonitrile−water); $^1H$ NMR ($CDCl_3$) 8.40 (d, $J$ = 15.5 Hz, H$\beta$), 8.30 (m, H3 and H5), 8.1 (m, H2, H6, H2′, H6′), 7.74 (d, $J$ = 15.5 Hz, H$\alpha$), 6.81 (m, H3′ and H5′), 3.11 (s, $NCH_3$). Anal. ($C_{17}H_{16}N_2O_3$) C, H, N.

**4,4′-Difluorochalcone (14)** was synthesized according to procedure E using 4-fluoro-benzaldehyde (0.78 mL, 7.2 mmol) and 4-fluoroacetophenone (0.89 mL, 7.2 mmol) as starting materials: white crystals (1.2 g, 68%); mp 112.0−112.9 °C (ethanol−water); $^1H$ NMR ($CDCl_3$) 8.05 (dd, $J$ = 8.7, 5.6 Hz, H2′, H6′), 7.78 (d, $J$ = 15.7 Hz, H$\beta$), 7.63 (dd, $J$ = 8.7, 5.6 Hz, H2, H6), 7.43 (d, $J$ = 15.7 Hz, H$\alpha$), 7.1 (m, H3, H5, H3′, H5′). Anal. ($C_{15}H_{10}OF_2$) C, H.

**3,5-Dimethoxy-2′-butoxychalcone (15)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (2.0 g, 12.0 mmol) and 2′-butoxyacetophenone (2.3 g, 12.0 mmol) as starting materials: yellow crystals (3.8 g, 92%); mp 69.5−70.1 °C (ethanol−water); $^1H$ NMR ($CDCl_3$) 7.66 (dd, $J$ = 7.6, 1.8 Hz, H6′), 7.57 (d, $J$ = 15.9 Hz, H$\beta$), 7.44 (d, $J$ = 15.9 Hz, H$\alpha$), 7.43 (t, $J$ = 7.7 Hz, H4′), 7.00 (bt, $J$ = 7.7 Hz, H5′), 6.95 (bd, $J$ = 7.7 Hz, H3′), 6.73 (d, $J$ = 2.2 Hz, H2, H6), 6.49 (t, $J$ = 2.2 Hz, H4), 4.03 (t, $J$ = 6.3 Hz, H1″), 3.79 (s, $OCH_3$), 1.77 (pent, $J$ = 7.3 Hz, H2″), 1.45 (hext, $J$ = 7.3 Hz, H3″),

0.87 (t, $J = 7.3$ Hz, H4″); $^{13}$C NMR ($CDCl_3$) 192.4 (C═O), 160.7 (C3, C5), 157.7 (C2′), 142.1 (C$\beta$), 136.9 (C1), 132.9 (C4′), 130.4 (C6′), 128.9 (C1′), 127.4 (C$\alpha$), 120.4 (C5′), 112.1 (C3′), 105.9 (C2, C6), 102.2 (C4), 68.0 (C1″), 55.1 ($OCH_3$), 31.1 (C2″), 19.1 (C3″), 13.5 (C4″). Anal. ($C_{21}H_{24}O_4$) C, H.

**3,5-Dimethoxy-2′-(dimethylamino)chalcone (16)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (1.5 g, 8.9 mmol) and 2′-(dimethylamino)acetophenone[38] (1.45 g, 8.9 mmol) as starting materials: yellow crystals (1.9 g, 66%); mp 159.8−160.5 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.63 (d, $J = 15.9$ Hz, H$\beta$), 7.53 (dd, $J = 7.6$, 1.6 Hz, H6′), 7.37 (dt, $J = 7.6$, 1.7 Hz, H4′), 7.33 (d, $J = 15.9$ Hz, H$\alpha$), 6.98 (bt, $J = 7.6$ Hz, H5′), 6.75 (bd, $J = 7.6$ Hz, H3′), 6.72 (d, $J = 2.2$ Hz, H2, H6), 6.48 (t, $J = 2.2$ Hz, H4), 3.78 (s, $OCH_3$), 2.80 (s, $NCH_3$); $^{13}$C NMR ($CDCl_3$) 194.8 (C═O), 160.9 (C3, C5), 152.2 (C2′), 142.4 (C$\beta$), 137.1 (C1), 132.0 (C4′), 131.3 (C1′), 130.4 (C6′), 126.6 (C$\alpha$), 120.0 (C5′), 116.9 (C3′), 106.1 (C2, C6), 102.1 (C4), 55.3 ($OCH_3$), 44.3 ($NCH_3$). Anal. ($C_{19}H_{21}NO_3$) C, H.

**3,5-Dimethoxy-2′-nitrochalcone (17)** was synthesized according to procedure F using 3,5-dimethoxybenzaldehyde (1.0 g, 6.1 mmol) and 2′-nitroacetophenone (1.0 g, 6.1 mmol) as starting materials: yellow crystals (0.45 g, 23%); mp 98.4−98.9 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.18 (dd, $J = 8.0$, 1.2 Hz, H3′), 7.78 (td, $J = 7.4$, 1.2 Hz, H5′), 7.66 (td, $J = 8.0$, 1.5 Hz, H4′), 7.50 (dd, $J = 7.4$, 1.5 Hz, H6′), 7.11 (d, $J = 15.9$ Hz, H$\beta$), 6.92 (d, $J = 15.9$ Hz, H$\alpha$), 6.61 (d, $J = 2.2$ Hz, H2, H6), 6.49 (t, $J = 2.2$ Hz, H4), 3.79 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 192.9 (C═O), 160.9 (C3, C5), 146.4 (C2′), 146.2 (C$\beta$), 136.1 (C1), 135.6 (C1′), 134.0 (C5′), 130.5 (C4′), 128.7 (C6′), 126.6 (C$\alpha$), 124.4 (C3′), 106.2 (C2, C6), 103.2 (C4), 55.3 ($OCH_3$). Anal. ($C_{17}H_{15}NO_5$) C, H.

**3,5-Dimethoxy-2′-fluorochalcone (18)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (2.4 g, 14.4 mmol) and 2′-fluoroacetophenone (2.0 g, 14.4 mmol) as starting materials: yellow crystals (2.9 g, 71%); mp 71.6−72.5 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.81 (dt, $J = 7.6$, 1.8 Hz, H6′), 7.64 (d, $J = 15.7$ Hz, H$\beta$), 7.57 (m, H4′), 7.34 (d, $J = 15.7$ Hz, H$\alpha$), 7.3−7.1 (m, H3′, H5′), 6.76 (d, $J = 2.2$ Hz, H2, H6), 6.53 (t, $J = 2.2$ Hz, H4), 3.83 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 189.0 (C═O), 161.0 (C3, C5), 158.6 (C2′), 144.8 (C$\beta$), 136.5 (C1), 134.1 (C4′), 131.0 (C6′), 126.9 (C1′), 125.9 (C$\alpha$), 124.5 (C5′), 116.3 (C3′), 106.4 (C2, C6), 102.9 (C4), 55.4 ($OCH_3$). Anal. ($C_{17}H_{15}O_3F$) C, H.

**2,4-Dimethoxy-3′-butoxychalcone (19)** was synthesized according to procedure E using 2,4-dimethoxybenzaldehyde (1.62 g, 9.7 mmol) and 3′-butoxyacetophenone (1.87 g, 9.7 mmol) as starting materials: yellow crystals (3.0 g, 92%); mp 80.4−81.3 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.07 (d, $J = 15.8$ Hz, H$\beta$), 7.56 (m, H2′, H6′, H6), 7.51 (d, $J = 15.8$ Hz, H$\alpha$), 7.36 (t, $J = 7.8$ Hz, H5′), 7.07 (ddd, $J = 8.2$, 2.6, 0.9 Hz, H4′), 6.50 (dd, $J = 2.2$ Hz, H5), 6.43 (d, $J = 2.2$ Hz, H3), 4.00 (t, $J = 6.4$ Hz, H1′), 3.85 (s, $OCH_3$), 1.78 (pent, $J = 7.2$ Hz, H2″), 1.47 (hext, $J = 7.2$ Hz, H3″), 0.97 (t, $J = 7.2$ Hz, H4″); $^{13}$C NMR ($CDCl_3$) 190.5 (C═O), 162.8*(C4), 160.1*(C2), 159.1 (C3′), 140.1 (C$\beta$), 139.9 (C1′), 130.5 (C5′), 129.1 (C6), 120.5 (C$\alpha$), 119.9 (C6′), 118.9 (C4′), 116.7 (C1), 113.2 (C2′), 105.2 (C5), 98.1 (C3), 67.6 (C1″), 55.2 ($OCH_3$), 55.1 ($OCH_3$), 31.0 (C2″), 19.0 (C3″), 13.6 (C4′). Anal. ($C_{21}H_{24}O_4$) C, H.

**3,5-Dimethoxy-3′-(dimethylamino)chalcone (20)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (2.0 g, 12.3 mmol) and 3′-(dimethylamino)acetophenone[39] (2.0 g, 12.3 mmol) as starting materials: yellow crystals (2.6 g, 49%); mp 81.8−82.6 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.70 (d, $J = 15.7$ Hz, H$\beta$), 7.45 (d, $J = 15.7$ Hz, H$\alpha$), 7.33 (m, H2′, H4′, H5′), 6.76 (d, $J = 2.2$ Hz, H2, H6), 6.51 (t, $J = 2.2$ Hz, H4), 6.93 (m, H6′), 3.82 (s, $OCH_3$), 3.00 (s, $-N(CH_3)_2$); $^{13}$C NMR ($CDCl_3$) 191.1 (C═O), 160.8 (C3, C5), 150.5 (C3′), 144.1 (C$\beta$), 138.7 (C1′), 136.8 (C1), 128.9 (C5′), 123.0 (C$\alpha$), 116.7 (C6′, C4′), 111.5 (C2′), 106.1 (C2, C6), 102.4 (C4), 55.3 ($OCH_3$), 40.4 ($-N(CH_3)_2$). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

**2,4-Dimethoxy-3′-nitrochalcone (21)** was synthesized according to procedure E using 2,4-dimethoxybenzaldehyde (0.5 g, 3.0 mmol) and 3′-nitroacetophenone (0.5 g, 3.0 mmol) as starting materials: gray crystals (0.61 g, 64%); mp 88.1−88.7 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.82 (t, $J = 2.0$ Hz, H2′), 8.52 (dt, $J = 8.0$, 1.4 Hz, H4′), 8.46 (ddd, $J = 8.0$, 2.0, 1.4 Hz, H6′), 8.17 (d, $J = 15.6$ Hz, H$\beta$), 7.87 (d, $J = 8.0$ Hz, H6), 7.86 (t, $J = 8.0$ Hz, H5), 7.80 (d, $J = 15.6$ Hz, H$\alpha$), 6.64 (bs, H3), 6.62 (dd, $J = 8.0$, 2.1 Hz, H5′), 3.97 (s, $OCH_3$), 3.89 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 186.0 (C═O), 162.9*(C4), 159.6*(C2), 143.3 (C3′), 139.9 (C$\beta$), 139.2 (C1′), 133.2 (C6′), 129.6 (C5′), 129.3 (C6), 125.7 (C4′), 121.8 (C$\alpha$), 117.3 (C2′), 115.3 (C1), 105.3 (C5), 97.2 (C3), 54.4 ($OCH_3$), 54.2 ($OCH_3$). Anal. ($C_{17}H_{15}NO_5$) C, H, N.

**3,5-Dimethoxy-3′-fluorochalcone (22)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (2.4 g, 14.4 mmol) and 3′-fluoroacetophenone (1.78 mL, 14.4 mmol) as starting materials: white crystals (2.3 g, 56%); mp 89.5−90.3 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.79 (bd, $J \sim 8$ Hz, H6′), 7.73 (d, $J = 15.7$ Hz, H$\beta$), 7.69 (dt, $J \sim 9$, 3 Hz, H2′), 7.49 (m, H4′), 7.48 (d, $J = 15.7$ Hz, H$\alpha$), 7.28 (td, $J \sim 8$, ~2 Hz, H5′), 6.78 (d, $J = 2.2$ Hz, H2, H6), 6.51 (t, $J = 2.2$ Hz, H4), 3.84 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 189.0 (C═O), 165.1 (C3′), 160.9 (C3, C5), 145.5 (C$\beta$), 139.9 (C1′), 136.4 (C1), 130.3 (C5′), 124.1 (C$\alpha$), 121.8 (C6′), 119.9 (C4′), 115.4 (C2′), 106.3 (C2, C6), 102.9 (C4), 55.4 ($OCH_3$). Anal. ($C_{17}H_{15}O_3F$) C, H.

**3,5-Dimethoxy-4′-cyclohexylchalcone (23)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (0.82 g, 4.9 mmol) and 4-cyclohexylacetophenone (1.0 g, 4.9 mmol) as starting materials: brown crystals (1.6 g, 92%); mp 75.5−76.2 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.95 (m, H2′ and H6′), 7.64 (d, $J = 15.9$ Hz, H$\beta$), 7.48 (d, $J = 15.9$ Hz, H$\alpha$), 7.33 (m, H3′ and H5′), 6.78 (d, $J = 2.2$ Hz, H2, H6), 6.52 (t, $J = 2.2$ Hz, H4), 3.84 (s, $OCH_3$), 2.58 (b, H1′), 1.8 (m, H2″, H6″), 1.4 (m, H3″−H5″); $^{13}$C NMR ($CDCl_3$) 189.9 (C═O), 161.0 (C3, C5), 153.7 (C4′), 144.3 (C$\beta$), 137.0 (C1), 136.0 (C1′), 128.8 (C2′, C6′), 127.1 (C3′, C5′), 122.6 (C$\alpha$), 106.3 (C2, C6), 102.6 (C4), 55.5 ($OCH_3$), 44.7 (C1″), 34.1 (C2″, C6″), 26.7 (C3″, C5′), 26.0 (C4″). Anal. ($C_{23}H_{26}O_3$) C, H.

**3,5-Dimethoxy-4′-(dimethylamino)chalcone (24)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (0.67 g, 4.0 mmol) and 4-(dimethylamino)acetophenone[37] (0.66 g, 4.0 mmol) as starting materials: orange crystals (0.91 g, 73%); mp 155.1−156.2 °C (ethanol−water); $^1$H NMR ($(CD_3)_2CO$) 8.10 (m, H2′ and H6′), 7.92 (d, $J = 15.6$ Hz, H$\beta$), 7.63 (d, $J = 15.6$ Hz, H$\alpha$), 7.15 (d, $J = 2.1$ Hz, H2, H6), 6.79 (m, H3′ and H5′), 6.56 (t, $J = 2.1$ Hz, H4), 3.85 (s, $OCH_3$), 3.10 (s, $-N(CH_3)_2$); $^{13}$C NMR ($(CD_3)_2CO$) 186.8 (C═O), 161.8 (C3, C5), 154.2 (C4′), 142.4 (C$\beta$), 138.1 (C1), 131.4 (C2′, C6′), 126.4 (C1′), 123.5 (C$\alpha$), 111.5 (C3′, C5′), 106.9 (C2, C6), 102.8 (C4), 55.7 ($OCH_3$), 39.9 ($-N(CH_3)_2$). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

**3,5-Dimethoxy-4′-nitrochalcone (25)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (1.0 g, 6.1 mmol) and 4-nitroacetophenone (1.0 g, 6.1 mmol) as starting materials: yellow crystals (1.5 g, 77%); mp 165.5−166.3 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.36 (m, H3′ and H5′), 8.14 (m, H2′ and H6′), 7.75 (d, $J = 15.3$ Hz, H$\beta$), 7.42 (d, $J = 15.3$ Hz, H$\alpha$), 6.78 (d, $J = 2.2$ Hz, H2, H6), 6.56 (t, $J = 2.2$ Hz, H4), 3.84 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 189.4 (C═O), 161.4 (C3, C5), 150.4 (C4′), 143.2 (C1′), 140.7 (C$\beta$), 136.4 (C1), 132.5 (C2′, C6′), 129.7 (C$\alpha$), 127.9 (C3′, C5′), 106.8 (C2, C6), 103.7 (C4), 55.6 ($OCH_3$). Anal. ($C_{17}H_{15}NO_5$) C, H, N.

**4′-Fluorochalcone (26)** was synthesized according to procedure E using benzaldehyde (0.10 mL, 1.0 mmol) and 4-fluoroacetophenone (0.14 g, 1.0 mmol) as starting materials: yellow crystals (0.20 g, 90%); mp 102.1−103.2 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.04 (m, H2′, H6′), 7.80 (d, $J = 15.5$ Hz, H$\beta$), 7.62 (m, H3′, H5′), 7.49 (d, $J = 15.5$ Hz, H$\alpha$), 7.40 (m, H2, H4, H6), 7.15 (m, H3, H5); $^{13}$C NMR 188.1 (C═O), 168.1 (C4′), 145.0 (C$\beta$), 134.7 (C1), 134.4 (C1′), 131.0 (C2′, C6′), 130.6 (C3, C5), 129.0 (C2, C6), 128.5 (C4), 121.4 (C$\alpha$), 115.9 (C3′, C5′). Anal. ($C_{15}H_{11}OF$) C, H.

**2-Butoxy-2′,3′,4′-trimethoxychalcone (27)** was synthesized according to procedure E using 2-butoxybenzaldehyde[40] (1.7 g, 9.5 mmol) and 2,3,4-trimethoxyacetophenone (1.7 mL,

9.5 mmol) as starting materials: yellow crystals (3.0 g, 86%); mp 129.4−130.2 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.04 (d, $J$ = 16.0 Hz, H$\beta$), 7.62 (dd, $J$ = 7.7, 1.5 Hz, H6), 7.55 (d, $J$ = 16.0 Hz, H$\alpha$), 7.46 (d, $J$ = 8.8 Hz, H6′), 7.31 (td, $J$ = 7.7, 1.5 Hz, H4), 6.94 (bt, $J$ = 7.7 Hz, H5), 6.89 (bd, $J$ = 7.7 Hz, H3), 6.74 (d, $J$ = 8.8 Hz, H5′), 4.00 (t, $J$ = 6.4 Hz, H1″), 3.97 (s, $OCH_3$), 1.80 (pent, $J$ = 7.4 Hz, H2″), 1.48 (hext, $J$ = 7.4 Hz, H3″), 0.96 (t, $J$ = 7.3 Hz, H4″); $^{13}$C NMR ($CDCl_3$) 191.4 (C=O), 157.8 (C2), 156.3 (C4′), 153.1 (C2′), 141.6 (C3′), 138.7 (C$\beta$), 131.2 (C4), 128.4 (C6), 126.6 (C1), 126.5 (C$\alpha$), 125.2 (C6′), 123.6 (C1′), 120.1 (C5), 111.7 (C3), 106.8 (C5′), 67.7 (C1″), 61.7 ($OCH_3$), 60.6 ($OCH_3$), 55.7 ($OCH_3$), 30.8 (C2″), 19.0 (C3″), 13.5 (C4″). Anal. ($C_{22}H_{26}O_5$) C, H.

**2-(Dimethylamino)-2′,3′,4′-trimethoxychalcone (28)** was synthesized according to procedure E using 2-(dimethylamino)-benzaldehyde (0.15 g, 1.0 mmol) and 2,3,4-trimethoxyacetophenone (0.18 mL, 1.0 mmol) as starting materials: yellow crystals (0.26 g, 76%); mp 143.2−145.7 °C (ethanol−water); $^1$H NMR ($CO(CD_3)_2$) 8.00 (d, $J$ = 16.0 Hz, H$\beta$), 7.60 (dd, $J$ = 7.7, 1.4 Hz, H6), 7.51 (d, $J$ = 16.0 Hz, H$\alpha$), 7.43 (d, $J$ = 8.8 Hz, H6′), 7.33 (td, $J$ = 7.7, 1.4 Hz, H4), 6.91 (bt, $J$ = 8 Hz, H5), 6.76 (d, $J$ = 8.8 Hz, H5′), 6.71 (bd, $J$ = 8 Hz, H3), 4.01 (s, $OCH_3$), 2.91 (s, $NCH_3$); $^{13}$C NMR 193.2 (C=O), 156.5 (C4′), 153.2 (C2′), 149.8 (C2), 142.0 (C3′), 139.3 (C$\beta$), 133.2 (C4), 128.9 (C6), 129.0 (C1), 126.9 (C$\alpha$), 125.3 (C6′), 123.6 (C1′), 122.2 (C5), 110.5 (C3), 106.9 (C5′), 61.8 ($OCH_3$), 60.9 ($OCH_3$), 55.7 ($OCH_3$), 44.9 ($NCH_3$). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

**2-Nitro-2′,3′,4′-trimethoxychalcone (29)** was synthesized according to procedure F using 2-nitrobenzaldehyde (0.72 g, 4.8 mmol) and 2,3,4-trimethoxyacetophenone (0.8 mL, 4.8 mmol) as starting materials: red-brown crystals (0.22 g, 13%); mp 107.1−108.0 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.04 (d, $J$ = 15.7 Hz, H$\beta$), 8.03 (dd, $J$ = 8.0, 1.2 Hz, H3), 7.76 (dd, $J$ = 7.8, 1.7 Hz, H6), 7.67 (td, $J$ = 7.8, 1.2 Hz, H5), 7.55 (td, $J$ = 8.0, 1.8 Hz, H4), 7.53 (d, $J$ = 8.8 Hz, H6′), 7.37 (d, $J$ = 15.7 Hz, H$\alpha$), 6.79 (d, $J$ = 8.8 Hz, H5′), 3.94 (s, $OCH_3$), 3.92 (s, $OCH_3$), 3.91 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 190.0 (C=O), 157.3 (C4′), 153.9 (C2′), 142.1 (C2), 137.7 (C$\beta$), 136.0 (C3′), 133.3 (C5), 131.3 (C1), 131.2 (C4), 129.9 (C6), 129.0 (C$\alpha$), 126.0 (C3), 125.8 (C1′), 124.8 (C6′), 107.3 (C5′), 62.1 ($OCH_3$), 61.0 ($OCH_3$), 56.0 ($OCH_3$). Anal. ($C_{18}H_{17}NO_6$) C, H, N.

**2-Fluoro-2′,3′,4′-trimethoxychalcone (30)** was synthesized according to procedure E using 2-fluorobenzaldehyde (1.7 mL, 16.1 mmol) and 2,3,4-trimethoxyacetophenone (2.9 mL, 16.1 mmol) as starting materials: white crystals (3.6 g, 81%); mp 75.0−75.8 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.82 (d, $J$ = 16.0 Hz, H$\beta$), 7.64 (td, $J$ = 7.6, 1.4 Hz, H4), 7.62 (d, $J$ = 16.0 Hz, H$\alpha$), 7.52 (d, $J$ = 8.8 Hz, H6′), 7.35 (m, H6), 7.17 (bt, $J$ = ∼8 Hz, H5), 7.10 (bt, $J$ = ∼8 Hz, H3), 6.77 (d, $J$ = 8.8 Hz, H5′), 3.96 (s, $OCH_3$), 3.94 (s, $OCH_3$), 3.91 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 190.4 (C=O), 164.8 (C4′), 157.0 (C2), 154.1 (C2′), 136.0 (C3′), 135.1 (C$\beta$), 131.4 (C4), 129.1 (C6), 128.5 (C$\alpha$), 126.2 (C1), 125.8 (C6′), 124.3 (C5), 123.8 (C1′), 116.2 (C3), 107.1 (C5′), 61.8 ($OCH_3$), 60.8 ($OCH_3$), 55.9 ($OCH_3$). Anal. ($C_{18}H_{17}O_4F$) C, H.

**3-Phenoxy-2′,3′,4′-trimethoxychalcone (31)** was synthesized according to procedure E using 3-phenoxybenzaldehyde (0.82 mL, 4.8 mmol) and 2,3,4-trimethoxyacetophenone (0.87 mL, 4.8 mmol) as starting materials: yellow crystals (1.1 g, 58%); mp 63.3−64.0 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.63 (d, $J$ = 15.8 Hz, H$\beta$), 7.48 (d, $J$ = 8.8 Hz, H6′), 7.45 (d, $J$ = 15.8 Hz, H$\alpha$), 7.4−7.0 (m, H2, H3, H6, H5′, H3″−H5″), 7.12 (t, $J$ = 7.8 Hz, H5), 7.02 (m, H2′, H6″), 3.91 (s, $OCH_3$), 3.87 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 190.2 (C=O), 157.6 (C3, C1″), 157.0 (C4′), 156.4 (C2′), 141.8 (C$\beta$), 137.6 (C3′) 136.7 (C1), 130.0 (C5), 129.6 (C3″), 126.9 (C$\alpha$), 126.2 (C1′), 125.7 (C6′), 123.4 (C4″), 123.1 (C6), 120.1 (C4), 118.9 (C2″), 117.6 (C2), 107.1 (C5′), 61.7 ($OCH_3$), 60.8 ($OCH_3$), 55.9 ($OCH_3$). Anal. ($C_{24}H_{22}O_5$) C, H.

**3-(Dimethylamino)-2′,3′,4′-trimethoxychalcone (32)** was synthesized according to procedure E using 3-(dimethylamino)-benzaldehyde[39] (1.0 g, 6.9 mmol) and 2,3,4-trimethoxyacetophenone (1.3 mL, 6.9 mmol) as starting materials: orange crystals (2.1 g, 90%); mp 87.2−87.9 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.66 (d, $J$ = 15.8 Hz, H$\beta$), 7.48 (d, $J$ = 8.8 Hz, H6′), 7.46 (d, $J$ = 15.8 Hz, H$\alpha$), 7.27 (t, $J$ = 7.9 Hz, H5), 7.02 (bd, $J$ = 7.9 Hz, H6), 6.92 (b, H2), 6.78 (bd, $J$ = 7.9 Hz, H4), 6.75 (d, $J$ = 8.8 Hz, H5′), 3.93 (s, $OCH_3$), 3.92 (s, $OCH_3$), 2.99 (s, $-(N(CH_3)_2$); $^{13}$C NMR ($CDCl_3$) 191.1 (C=O), 156.8 (C4′), 153.6 (C2′), 144.4 (C$\beta$), 141.9 (C3), 135.7 (C1), 136.8 (C3′) 129.4 (C5), 126.8 (C1′), 126.6 (C6′), 126.1 (C$\alpha$), 116.2 (C6), 114.4 (C4), 112.3 (C2), 107.1 (C5′), 62.0 ($OCH_3$), 61.0 ($OCH_3$), 56.0 ($OCH_3$), 40.5 ($-N(CH_3)_2$). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

**3-Nitro-2′,3′,4′-trimethoxychalcone (33)** was synthesized according to procedure E using 3-nitrobenzaldehyde (0.72 g, 4.8 mmol) and 2,3,4-trimethoxyacetophenone (0.87 mL, 4.8 mmol) as starting materials: yellow crystals (1.0 g, 64%); mp 130.1−130.7 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.46 (bt, $J$ = 1.7 Hz, H2), 8.22 (dt, $J$ = 8.1, 1.2 Hz, H6), 7.92 (bd, $J$ = 7.8 Hz, H4), 7.72 (d, $J$ = 15.8 Hz, H$\beta$), 7.66 (d, $J$ = 15.8 Hz, H$\alpha$), 7.61 (t, $J$ = 8.0 Hz, H5), 7.55 (d, $J$ = 8.8 Hz, H6′), 6.80 (d, $J$ = 8.8 Hz, H5′), 3.96 (s, $OCH_3$), 3.95 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 189.6 (C=O), 157.4 (C4′), 153.8 (C2′), 141.9 (C3), 139.2 (C$\beta$), 136.8 (C1), 135.1 (C3′) 133.8 (C6), 129.8 (C5), 129.0 (C$\alpha$), 125.9 (C6), 125.8 (C4), 124.1 (C1′), 122.3 (C2), 107.3 (C5′), 61.9 ($OCH_3$), 60.9 ($OCH_3$), 56.0 ($OCH_3$). Anal. ($C_{18}H_{17}NO_6$) C, H, N.

**3-Fluoro-2′,3′,4′-trimethoxychalcone (34)** was synthesized according to procedure E using 3-fluorobenzaldehyde (1.7 mL, 16.1 mmol) and 2,3,4-trimethoxyacetophenone (2.9 mL, 16.1 mmol) as starting materials: yellow crystals (1.7 g, 34%); mp 79.3−80.2 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.65 (d, $J$ = 15.8 Hz, H$\beta$), 7.52 (d, $J$ = 8.8 Hz, H6′), 7.50 (d, $J$ = 15.8 Hz, H$\alpha$), 7.42−7.28 (m, H4−H6), 7.1 (m, H2), 6.77 (d, $J$ = 8.8 Hz, H5′), 3.94 (s, $OCH_3$), 3.93 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 190.5 (C=O), 165.3 (C4′), 157.9 (C3), 153.8 (C2′), 141.3 (C$\beta$), 138.0 (C1), 136.1 (C3′) 130.5 (C5), 127.7 (C$\alpha$), 126.3 (C1′), 126.0 (C6′), 124.5 (C6), 117.2 (C4), 114.6 (C2), 107.4 (C5′), 62.1 ($OCH_3$), 61.1 ($OCH_3$), 56.2 ($OCH_3$). Anal. ($C_{18}H_{17}O_4F$) C, H.

**4-(Dimethylamino)-2′,3′,4′-trimethoxychalcone (35)** was synthesized according to procedure E using 4-(dimethylamino)-benzaldehyde (0.71 g, 4.8 mmol) and 2,3,4-trimethoxyacetophenone (0.87 mL, 4.8 mmol) as starting materials: yellow crystals (0.86 g, 53%); mp 168.1−169.3 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.64 (d, $J$ = 15.9 Hz, H$\beta$), 7.51 (m, H2 and H6), 7.43 (d, $J$ = 8.8 Hz, H6′), 7.28 (d, 15.9 Hz, H$\alpha$), 6.75 (d, $J$ = 8.8 Hz, H5′), 6.68 (m, H3 and H5), 3.92 (s, $OCH_3$), 3.90 (s, $OCH_3$), 3.03 (s, $-N(CH_3)_2$); $^{13}$C NMR ($CDCl_3$) 190.9 (C=O), 156.2* (C4′), 152.1* (C2′), 144.7 (C$\beta$), 143.8 (C4), 130.3 (C2, C6), 130.2 (C3′), 127.1 (C1), 126.1 (C1′), 125.5 (C$\alpha$), 121.6 (C6′), 111.8 (C3, C5), 107.1 (C5′), 62.1* ($OCH_3$), 61.1* ($OCH_3$), 56.1* ($OCH_3$), 40.2 ($NCH_3$). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

**4-Cyano-2′,3′,4′-trimethoxychalcone (36)** was synthesized according to procedure E using 4-cyanobenzaldehyde (1.3 g, 9.5 mmol) and 2,3,4-trimethoxyacetophenone (1.7 mL, 9.5 mmol) as starting materials: yellow crystals (2.4 g, 81%); mp 131.7−133.0 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.7−7.6 (m, H$\beta$, H$\alpha$, H2, H3, H5, H6), 7.55 (d, $J$ = 8.8 Hz, H6′), 6.78 (d, $J$ = 8.8 Hz, H5′), 3.95 (s, $OCH_3$), 3.92 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 189.6 (C=O), 157.3 (C4′), 154.2 (C2′), 139.6 (C$\beta$), 139.5 (C1), 136.7 (C3′), 132.4 (C2, C6), 129.4 (C$\alpha$), 128.4 (C3, C5), 126.0 (C6′), 125.9 (C1′), 118.9 (CN), 112.8 (C4), 107.3 (C5′), 62.0* ($OCH_3$), 60.9* ($OCH_3$), 56.0* ($OCH_3$). Anal. ($C_{19}H_{17}NO_4$) C, H, N.

**3,5-Dimethoxy-4′-(2-propenyloxy)chalcone** (**38**) was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (16.6 g, 10 mmol) and 4-(2-propenyloxy)acetophenone (17.1 g, 10 mmol) as starting materials: yellow crystals (28.2 g, 91%); mp 89−90 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.07 (m, H2′ and H6′), 7.72 (d, $J$ = 15.9 Hz, H$\beta$), 7.62 (d, $J$ = 15.9 Hz, H$\alpha$), 7.03 (m, H3′ and H5′), 6.90 (d, $J$ = 1.9 Hz, H2 and H6), 6.52 (t, $J$ = 1.9 Hz, H4), 6.03 (ddq, $J$ = 17.3, 10.5, 5.2 Hz, H2″), 5.42 (dd, $J$ = 17.3, 1.3 Hz, H3″trans), 5.32 (dd, $J$ = 10.5, 1.3 Hz, H3″cis); $^{13}$C NMR ($CDCl_3$) 187.4 (C=O), 163.5 (C4′), 162.1 (C3, C5), 144.1 (C$\beta$), 138.0 (C1), 134.1 (C2″), 131.9 (C1′), 131.8 (C2′, C6′), 103.4 (C4), 123.1 (C$\alpha$), 118.3 (C3″), 115.5 (C3′, C5′), 107.3 (C2, C6), 69.7 (C1″), 56.2 ($OCH_3$). Anal. ($C_{20}H_{20}O_4$) C, H.

**4-Butyl-3,5-methoxy-4′-(2-propenyloxy)chalcone (39)** was synthesized according to procedure E using 4-butyl-3,5-dimethoxybenzaldehyde[41] (40 mg, 0.18 mmol) and 4-(2-propenyloxy)acetophenone[42] (32 mg, 0.18 mmol) as starting materials: yellow crystals (44 mg, 64%); mp 74−75 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.03 (m, H2′ and H6′), 7.75 (d, $J$ = 15.9 Hz, H$\beta$), 7.45 (d, $J$ = 15.9 Hz, H$\alpha$), 6.99 (m, H3′ and H5′), 6.80 (s, H2, H6), 6.03 (ddq, $J$ = 17.3, 10.5, 5.2 Hz, H2″), 5.42 (dd, $J$ = 17.3, 1.3 Hz, H3″trans), 5.32 (dd, $J$ = 10.5, 1.3 Hz, H3″cis), 4.58 (bd, $J$ = 5.2, H1″), 3.87 (s, $OCH_3$), 2.65 (t, $J$ = 7.4 Hz, $H_{bu}$1), 1.40 (m, $H_{bu}$2, $H_{bu}$3), 0.92 (t, $J$ = 7.4 Hz, $H_{bu}$4); $^{13}$C NMR ($CDCl_3$) 188.9 (C═O), 162.3 (C4′), 158.4 (C3, C5), 144.9 (C$\beta$), 133.4 (C1), 132.5 (C2″), 131.4 (C1′), 130.8 (C2′, C6′), 123.0 (C4), 121.0 (C$\alpha$), 118.2 (C3″), 114.5 (C3′, C5′), 103.8 (C2, C6), 68.9 (C1″), 55.8 ($OCH_3$), 31.3 ($C_{bu}$1), 23.0 ($C_{bu}$2), 22.9 ($C_{bu}$3), 14.1 ($C_{bu}$4). Anal. ($C_{24}H_{28}O_4$) C, H.

**4-Hexyl-3,5-dimethoxy-4′-(2-propenyloxy)chalcone (40)** was synthesized according to procedure E using 4-hexyl-3,5-dimethoxybenzaldehyde (0.10 g, 0.4 mmol) and 4-(2-propenyloxy)acetophenone[42] (0.07 g, 0.4 mmol) as starting materials: white crystals (0.16 g, 90%); mp 77.9−78.2 °C; $^1$H NMR ($CDCl_3$) 8.03 (m, H2′ and H6′), 7.77 (d, $J$ = 15.4 Hz, H$\beta$), 7.47 (d, $J$ = 15.4 Hz, H$\alpha$), 7.00 (m, H3′ and H5′), 6.80 (s, H2, H6), 6.03 (ddq, $J$ = 17.3, 10.5, 5.2 Hz, H2″), 5.42 (dd, $J$ = 17.3, 1.3 Hz, H3″trans), 5.32 (dd, $J$ = 10.5, 1.3 Hz, H3″cis), 4.58 (bd, $J$ = 5.2, H1″), 3.87 (s, $OCH_3$), 2.65 (t, $J$ = 7.4 Hz, $H_{hex}$1), 1.40 (m, $H_{hex}$2-$H_{hex}$5), 0.89 (t, $J$ = 7 Hz, $H_{hex}$6); $^{13}$C NMR ($CDCl_3$) 188.9 (C═O), 162.3 (C4′), 158.4 (C3, C5), 144.9 (C$\beta$), 133.4 (C1), 132.5 (C2″), 131.3 (C1′), 130.8 (C2′, C6′), 121.0 (C$\alpha$), 118.2 (C3″), 117.3 (C4), 114.5 (C3′, C5′), 103.8 (C2, C6), 68.9 (C1″), 55.8 ($OCH_3$), 31.8 ($C_{hex}$1), 29.5 ($C_{hex}$2), 29.0 ($C_{hex}$3), 23.2 ($C_{hex}$4), 22.7 ($C_{hex}$5), 14.2 ($C_{hex}$6). Anal. ($C_{26}H_{32}O_4$) C, H.

**3,5-Dimethoxy-2′-hydroxychalcone (41)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (0.47 g, 2.8 mmol) and 2-hydroxyacetophenone (0.34 mL, 2.8 mmol) as starting materials: orange crystals (0.27 g, 34%); mp 110.2−110.9 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.91 (dd, $J$ = 8.4, 1.0 Hz, H6′), 7.82 (d, $J$ = 15.6 Hz, H$\beta$), 7.59 (d, $J$ = 15.6 Hz, H$\alpha$), 7.50 (td, $J$ = 8.4, 1.0 Hz, H4′), 7.03 (d, $J$ = 8.4 Hz, H3′), 6.95 (t, $J$ = 8.4 Hz, H5′), 6.79 (d, $J$ = 2.2 Hz, H2, H6), 6.55 (t, $J$ = 2.2 Hz, H4), 3.85 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 193.4 (C═O), 163.4 (C2′), 161.1 (C3, C5), 145.5 (C$\beta$), 136.4 (C1), 136.5 (C4′), 129.7 (C6′), 120.5 (C$\alpha$), 120.0 (C1′), 118.9 (C5′), 118.6 (C3′), 106.5 (C2, C6), 103.0 (C4), 55.5 ($OCH_3$). Anal. ($C_{17}H_{16}O_4$) C, H.

**3,5-Dimethoxy-3′-hydroxychalcone (42)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (0.47 g, 2.8 mmol) and 3-hydroxyacetophenone (0.38 g, 2.8 mmol) as starting materials: yellow crystals (0.25 g, 32%); mp 126.2−126.8 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 9.66 (s, OH), 7.74 (d, $J$ = 16.0 Hz, H$\beta$), 7.66 (d, $J$ = 16.0 Hz, H$\alpha$), 7.59 (bd, $J$ ∼ 8 Hz, H4′), 7.52 (bt, $J$ = 2 Hz, H2′), 7.36 (t, $J$ = 7.8 Hz, H5′), 7.10 (dd, $J$ = 7.8, 2.4 Hz, H6′), 6.95 (d, $J$ = 2.2 Hz, H2, H6), 6.58 (t, $J$ = 2.2 Hz, H4), 3.82 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 188.8 (C═O), 160.3 (C3, C5), 157.3 (C3′), 143.2 (C$\beta$), 138.6 (C1′), 136.1 (C1), 129.1 (C5′), 122.0 (C$\alpha$), 119.5 (C6′), 118.9 (C4′), 114.1 (C2′), 105.8 (C2, C6), 101.9 (C4), 54.5 ($OCH_3$). Anal. ($C_{17}H_{16}O_4$) C, H.

**2-Hydroxy-2′,3′,4′-trimethoxychalcone (43)** was synthesized according to procedure E using 2-hydroxybenzaldehyde (0.25 mL, 2.4 mmol) and 2,3,4-trimethoxyacetophenone (0.43 mL, 2.4 mmol) as starting materials: brown crystals (0.29 g, 39%); mp 122.6−123.0 °C (ethanol−water); $^1$H NMR ($CD_3CN$/DMSO) 7.84 (d, $J$ = 16.0 Hz, H$\beta$), 7.61 (bd, $J$ = 7.7 Hz, H6), 7.47 (d, $J$ = 16.0 Hz, H$\alpha$), 7.35 (d, $J$ = 8.7 Hz, H6′), 7.25 (bt, $J$ ∼ 8, 7.7 Hz, H4), 6.94 (bd, $J$ = 8.2 Hz, H3), 6.85 (m, H5′, H5), 3.88 ($OCH_3$), 3.87 ($OCH_3$), 3.82 ($OCH_3$); $^{13}$C NMR ($CD_3CN$/DMSO) 190.6 (C═O), 156.6 (C2), 156.5 (C4′), 156.0 (C2′), 141.6 (C$\beta$), 138.1 (C4), 136.4 (C3′), 131.0 (C6), 128.1 (C$\alpha$), 126.2 (C1), 125.6 (C6′), 124.4 (C5), 118.9 (C1′), 115.7 (C3), 106.9 (C5′), 60.9 ($OCH_3$), 59.7 ($OCH_3$), 55.2 ($OCH_3$). Anal. ($C_{18}H_{18}O_5$) C, H.

**3,5,2′,3′,4′-Pentamethoxychalcone (44)** was synthesized according to procedure E using 3,5-dimethoxybenzaldehyde (0.79 g, 4.8 mmol) and 2,3,4-trimethoxyacetophenone (0.87 mL, 4.8 mmol) as starting materials: yellow crystals (1.4 g, 83%); mp 111.6−112.5 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.60 (d, $J$ = 15.8 Hz, H$\beta$), 7.49 (d, $J$ = 8.8 Hz, H6′), 7.46 (d, $J$ = 15.8 Hz, H$\alpha$), 6.76 (d, $J$ = 8.8 Hz, H5′), 6.75 (d, $J$ = 2.2 Hz, H2, H6), 6.50 (t, $J$ = 2.2 Hz, H4), 3.92 (s, $OCH_3$), 3.79 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 190.5 (C═O), 160.7 (C3, C5), 156.8 (C4′), 153.5 (C2′), 142.7 (C$\beta$), 141.8 (C1), 136.8 (C3′), 126.8 (C$\alpha$), 126.4 (C1), 125.6 (C6′), 107.1 (C5′), 106.0 (C6), 102.1 (C4), 61.8*($OCH_3$), 60.8*($OCH_3$), 55.8*($OCH_3$), 55.1 (C3/5-$OCH_3$). Anal. ($C_{20}H_{22}O_6$) C, H.

**2,4,3′-Trimethoxychalcone (45)** was synthesized according to procedure E using 2,4-dimethoxybenzaldehyde (0.84 g, 5.0 mmol) and 3-methoxyacetophenone (0.67 mL, 5.0 mL) as starting materials: yellow crystals (1.6 g, 91%); mp 75.6−78.9 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.06 (d, $J$ = 15.8 Hz, H$\beta$), 7.7−7.6 (m, H6, H6′, H2′), 7.55 (d, $J$ = 15.8 Hz, H$\alpha$), 7.43 (t, $J$ = 8.0 Hz, H5′), 7.07 (dt, $J$ = 8.0, 1.0 Hz, H4′), 6.55 (dd, $J$ = 8.4, 2.4 Hz, H5), 6.49 (d, $J$ = 2.4 Hz, H3), 3.90 (s, $OCH_3$), 3.88 (s, $OCH_3$), 3.86 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 191.1 (C═O), 163.2*(C3′), 160.4*(C4), 159.8*(C2), 140.6 (C$\beta$), 140.3 (C1′), 131.0 (C5′), 129.4 (C6), 121.1 (C$\alpha$), 120.4 (C6′), 118.8 (C4′), 112.8 (C2′), 112.2 (C1), 105.4 (C5), 98.4 (C3), 55.5 ($OCH_3$), 55.4 ($OCH_3$). Anal. ($C_{18}H_{18}O_4$) C, H.

**2,4-Dimethoxy-2′-bromochalcone (46)** was synthesized according to procedure E using 2,4-dimethoxybenzaldehyde (0.42 g, 2.5 mmol) and 2-bromoacetophenone (0.33 mL, 2.5 mmol) as starting materials: yellow crystals (0.65 g, 71%); mp 91.3−91.8 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 7.67 (d, $J$ = 16.2 Hz, H$\beta$), 7.61 (dd, $J$ = 7.0, 1.0 Hz, H6′), 7.48 (d, $J$ = 8.6 Hz, H6), 7.5−7.25 (m, H3′−H5′), 7.10 (d, $J$ = 16.2 Hz, H$\alpha$), 6.51 (dd, $J$ = 8.6, 2.3 Hz, H5), 6.43 (d, $J$ = 2.3 Hz, H3), 3.83 (s, $OCH_3$), 3.82 (s, $OCH_3$); $^{13}$C NMR ($CDCl_3$) 195.2 (C═O), 163.4*(C4), 160.3*(C2), 142.6 (C$\beta$), 141.6 (C1′), 133.3 (C4′), 131.0 (C3′), 130.9 (C6′), 129.1 (C6), 127.2 (C$\alpha$), 124.3 (C5′), 119.5 (C2′), 116.5 (C1), 105.5 (C5), 98.3 (C3), 55.5 ($OCH_3$). Anal. ($C_{17}H_{15}O_3Br$) C, H, Br.

**2,4-Dimethoxy-3′-bromochalcone (47)** was synthesized according to procedure E using 2,4-dimethoxybenzaldehyde (0.84 g, 5.0 mmol) and 3-bromoacetophenone (0.65 mL, 5.0 mmol) as starting materials: yellow crystals (1.6 g, 87%); mp 74−75 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.12 (t, $J$ = 1.7 Hz, H2′), 8.06 (d, $J$ = 16.5 Hz, H$\beta$), 7.90 (bd, $J$ = 8 Hz, H4′), 7.68 (bd, $J$ = 8 Hz, H6′), 7.57 (d, $J$ = 8.6 Hz, H6), 7.46 (d, $J$ = 16.5 Hz, H$\alpha$), 7.36 (t, $J$ = 8.0 Hz, H5′), 6.56 (dd, $J$ = 8.6, 2.3 Hz, H5), 6.48 (d, $J$ = 2.3 Hz, H3), 3.90 (s, $OCH_3$), 3.87 (s, $OCH_3$). Anal. ($C_{17}H_{15}O_3Br$) C, H, Br.

**3,4,5-Trimethoxy-4′-(prop-2-enyloxy)chalcone** (**56**) was prepared according to procedure E using 4-(allyloxy)acetophenone[42] (1.76 g, 10 mmol) and 3,4,5-trimethoxybenzaldehyde (1.96 g, 10 mmol) as starting materials: yellow crystals (3.41 g, 96%); mp 92−93 °C (methanol); $^1$H NMR ($CDCl_3$) 8.03 (m, H-2′ and H-6′), 7.71 (d, $J$ = 15 Hz, H-$\beta$), 7.42 (d, $J$ = 15 Hz, H-α), 7.13 (s, H-6), 6.99 (m, H-3′ and H−5′), 6.52 (s, H-3), 6.05 (m, ═CH−), 5.42 (m, ═CH*H*), 5.32 (m, ═C*H*H), 4.60 (m, −$CH_2$−), 3.92 (s, $CH_3O$) 3.90 (s, $CH_3$−O); $^{13}$C NMR ($CDCl_3$) 188.6 (C═O), 162.4 (C-4′), 153.4 (C-5), 144.1 (C-$\beta$), 132.5 (═CH−), 131.2 (C-1′), 130.8 (C-2′ and C-6′), 130.6 (C-1), 121.2 (C-α), 118.2 (═$CH_2$), 114.5 (C-3′ and C-5′), 105.6 (C-6), 68.9 (−$CH_2$−), 61.0 and 56.2 ($CH_3O$). Anal. ($C_{21}H_{22}O_5$) C, H.

**2,5-Dimethoxy-4′-(prop-2-enyloxy)chalcone** (**58**) was prepared according to procedure E using 4-(allyloxy)acetophenone[39] (1.66 g, 10 mmol) and 2,5-dimethoxybenzaldehyde (1.67 g, 10 mmol) as starting materials: yellow crystals (2.50 g, 83%); mp 86−87 °C (methanol); $^1$H NMR ($CDCl_3$) 8.06 (d, $J$ = 15 Hz, H-$\beta$), 8.02 (m, H-2′ and H-6′), 7.59 (d, $J$ = 15 Hz, H-α), 7.16 (d, $J$ = 2 Hz, H-6), 6.97 (m, H-3′ and H-5′), 6.93 (dd, $J$ = 2, 7 Hz, H-4), 6.84 (d, $J$ = 7 Hz, H-3), 6.05 (m, ═CH−), 5.42 (m, ═CH*H*), 5.32 (m, ═C*H*H), 4.60 (m, −$CH_2$−), 3.85 (s, $CH_3$−O), 3.80 (s, $CH_3$−O); $^{13}$C NMR ($CDCl_3$) 122.9 (C-α), 139.3 (C-$\beta$), 189.1 (C═O), 124.6 (C-1), 152.2 (C-2), 112.4 (C-3), 113.8 (C-4), 153.5 (C-5), 116.9 (C-6), 131.4 (C-1′), 130.7 (C-2′ and

C-6′), 114.5 (C-3′ and C-5′), 162.3 (C-4′), 68.9 ($CH_2$), 118.1 (=$CH_2$), 132.7 (=CH-*$CH_2$*), 56.1 and 55.8 ($CH_3$). Anal. ($C_{20}H_{20}O_4$) C, H.

**3,4-Dimethoxy-4′-(prop-2-enyloxy)chalcone** (**59**) was prepared according to procedure E using 4-(allyloxy)acetophenone[42] (1.76 g, 10 mmol) and 3,4-dimethoxybenzaldehyde (1.66 g, 10 mmol) as starting materials: yellow crystals (3.0 g, 99%); mp 74.5−75 °C (ethanol); $^1$H NMR (CDCl3) 8.06 (H-2′ and H-6′), 7.70 (d, $J$ = 15 Hz, H-$\beta$), 7.58 (d, $J$ = 15 Hz, H-α), 7.33 (d, $J$ = 2 Hz, H-2), 7.25 (dd, $J$ = 2, 8 Hz, H-6), 7.00 (m, H-3′ and H-5′), 6.91 (d, $J$ = 8 Hz, H-5), 6.04 (m, =CH−), 5.42 (m, =CH*H*), 5.28 (m, =C*H*H), 4.60 (m, $-CH_2-$), 3.87 and 3.83 (s, $CH_3$); $^{13}$C NMR ($CDCl_3$) 119.2 (C-α), 143.0 (C-$\beta$), 187.9 (C=O), 130.9 (C-1), 109.9 (C-2), 151.0 (C-3), 148.8 (C-4), 110.9 (C-5), 122.7 (C-6), 127.4 (C-1′), 130.1 (C-2′ and C-6′), 113.9 (C-3′ and C-5′), 161.7 (C-4′), 68.2 ($CH_2$), 116.9 (=$CH_2$), 132.6 (=CH-*$CH_2$*), 54.9 and 54.8 ($CH_3$). Anal. ($C_{20}H_{20}O_4$) C, H.

**2,4,2′-Trimethoxychalcone** (**60**) was prepared according to procedure E using 2-methoxyacetophenone (0.46 mL, 3.3 mmol) and 2,4-dimethoxybenzaldehyde (0.55 g, 3.3 mmol) as starting materials: yellow crystals (0.76 g, 73%); mp 84.5−85 °C (ethanol); $^1$H NMR ($CDCl_3$) 7.87 (d, $J$ = 16 Hz, H-$\beta$), 7.57 (dd, $J$ = 8, 2 Hz, H-6′), 7.51 (d, $J$ = 8 Hz, H-6), 7.44 (td, $J$ = 6, 2 Hz, H-4′), 7.31 (d, $J$ = 16 Hz, H-α), 7.05−6.95 (m, H-3′ and H-5′), 6.50 (dd, $J$ = 8, 2 Hz, H-5), 6.43 (d, $J$ = 2 Hz, H-3), 3.84 and 3.79 (s, $CH_3O$). Anal. ($C_{18}H_{18}O_4$) C, H.

**4-(Hexyloxy)acetophenone.** To a solution of 2.76 g (20 mmol) 4-hydroxyacetophenone and 1.46 g (10 mmol) of sodium iodide in 30 mL of acetone was added 8.37 g (60 mmol) of potassium carbonate and 9.77 g (80 mmol) of hexyl chloride. The mixture was stirred at 70 °C for 72 h in a sealed glass vessel. The mixture was then filtered and the precipitate washed twice with 5 mL of acetone. The combined filtrates were concentrated in a vacuum. The residue was dissolved in 30 mL of ether and the solution washed twice with a molar aqueous solution of sodium hydroxide. The ether phase was dried ($MgSO_4$) and concentrated in a vacuum. The residue was distilled in a Kugelrohr to give 2.56 g (72%) of 4-(hexyloxy)acetophenone as a colorless oil.

**2,4-Dimethoxy-4′-(hexyloxy)chalcone** (**61**) was prepared according to procedure E using 4-(hexyloxy)acetophenone (0.73 g, 4 mmol) and 2,4-dimethoxybenzaldehyde (0.68 g, 4 mmol) as starting materials: yellow crystals (0.93 g, 63%); mp 67.5−68 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.04 (d, $J$ = 15.8 Hz, H-$\beta$), 8.02 (m, H-2′ and H-6′), 7.57 (d, $J$ = 8.5 Hz, H-6), 7.56 (d, $J$ = 15.8 Hz, H-α), 6.95 (m, H-3′ and H-5′), 6.52 (dd, $J$ = 8.5, 2.3 Hz, H-5), 6.47 (d, $J$ = 2.3 Hz, H-3) 4.02 (t, $J$ = 7 Hz, $CH_2O$), 3.89 and 3.85 (s, $CH_3O$) 1.81 (pentet, $OCCH_2$) 1.6−1.3 [m, $(CH_2)_3$], 0.91 (t, $J$ = 7 Hz, $CCH_3$); $^{13}$C NMR ($CDCl_3$) 117.3 (C-1), 162.8 (C-2), 98.4 (C-3), 160.3 (C-4), 105.3 (C-5), 130.8 (C-6), 131.4 (C-1′), 130.7 (C-2′, C-6′), 114.1 (C-3′, C-5′), 162.7 (C-4′), 68.2 ($OCH_2$), 31.6, 29.1, 25.7, 22.6 ($CH_2$), 14.1 ($CCH_3$), 189.4 (CO), 120.2 (C-α), 139.5 (C-$\beta$), 55.5, 55.5 ($CH_3O$). Anal. ($C_{23}H_{28}O_4$) C, H.

**4′-(Hexyloxy)chalcone** (**63**) was synthesized according to procedure E using 4-(hexyloxy)acetophenone (1.00 g, 4 mmol) and benzaldehyde (0.46 mL, 4 mmol) as starting materials: yellow crystals (0.69 g, 51.7%); mp 64.5−65 °C (ethanol−water); $^1$H NMR ($CDCl_3$) 8.02 (m, H-2′ and H-6′), 7.80 (d, $J$ = 15 Hz, H-$\beta$), 7.7−7.6 (m, H-3, H-4, and H-5), 7.50 (d, $J$ = 15 Hz, H-α), 7.45−7.35 (m, H-2 and H-6), 6.97 (m, H-3′ and H-5′). Anal. ($C_{21}H_{24}O_2$) C, H.

**2,6-Dimethoxy-4′-butoxychalcone** (**65**) was synthesized according to procedure E using 4-butoxyacetophenone (11.6 g, 60 mmol) and 2,6-dimethoxybenzaldehyde (10.0 g, 60 mmol) as starting materials: yellow crystals (18.77 g, 91%); mp 101−102 °C; $^1$H NMR ($CDCl_3$) 8.26 (d, $J$ = 15 Hz, H-$\beta$), 8.03 (m, H-2′ and H-6′), 7.99 (d, $J$ = 15 Hz, H-α), 7.25 (t, $J$ = 7 Hz, H-4), 6.98 (m, H-3′ and H-5′), 6.57 (d, $J$ = 7 Hz, H-3 and H-5), 6.05 (m, =CH), 4.00 (t, $J$ = 4 Hz, $OCH_2-$), 3.90 (s, $CH_3-O$), 1.75 and 1.49 (m, $-CH_2-$), 0.97 (t, $J$ = 4 Hz, $-CH_3$); $^{13}$C NMR ($CDCl_3$) 131.2 (C-α), 134.6 (C-$\beta$), 190.1 (C=O), 112.9 (C-1), 160.1 (C-2 and C-6), 103.5 (C-3 and C-5), 124.4 (C-4), 131.3 (C-1′), 130.6 (C-2′ and C-6′), 113.9 (C-3′ and C-5′), 160.1 (C-4′), 67.7 ($CH_2O$), 55.6 ($OCH_3$), 31.0 and 19.0 ($CH_2$), 13.7 ($CH_3$). Anal. ($C_{21}H_{24}O_4$) C, H.

**2,6-Dimethoxy-4′-(prop-2-enyloxy)chalcone** (**66**) was synthesized according to procedure E using 4-(allyloxy)-acetophenone[42] (0.59 g, 3.3 mmol) and 2,6-dimethoxybenzaldehyde (0.56 g, 3.3 mmol) as starting materials: yellow crystals (0.56 g, 52%); mp 102−103 °C; $^1$H NMR ($CDCl_3$) 8.26 (d, $J$ = 15 Hz, H-$\beta$), 8.03 (m, H-2′ and H-6′), 7.99 (d, $J$ = 15 Hz, H-α), 7.27 (t, $J$ = 7 Hz, H-4), 6.98 (m, H-3′ and H-5′), 6.57 (d, $J$ = 7 Hz, H-3 and H-5), 6.05 (m, =CH), 5.42 (m, =CH*H*), 5.32 (m, =C*H*H), 4.60 (m, $-CH_2-$), 3.90 (s, $CH_3-O$); $^{13}$C NMR ($CDCl_3$) 132.6 (C-α), 134.9 (C-$\beta$), 190.3 (C=O), 112.9 (C-1), 160.3 (C-2 and C-6), 103.7 (C-3 and C-5), 124.7 (C-4), 132.0 (C-1′), 130.7 (C-2′ and C-6′), 114.3 (C-3′ and C-5′), 161.6 (C-4′), 68.8 ($CH_2$), 118.1 (=$CH_2$), 132.0 (=CH-*$CH_2$*), 55.8 ($CH_3$). Anal. ($C_{20}H_{20}O_4$) C, H.

**2,3-Dimethoxy-4′-(prop-2-enyloxy)chalcone** (**67**) was synthesized according to procedure E using 4-(allyloxy)-acetophenone[42] (1.76 g, 10 mmol) and 2,3-dimethoxybenzaldehyde (1.66 g, 10 mmol) as starting materials: yellow crystals (2.92 g, 90%); mp 98−99 °C (methanol−water); $^1$H NMR ($CDCl_3$) 8.09 (d, $J$ = 15 Hz, H-$\beta$), 8.03 (H-2′ and H-6′), 7.59 (d, $J$ = 15 Hz, H-α), 7.27 (dd, $J$ = 7, 2 Hz, H-6), 7.09 (t, $J$ = 7 Hz, H-5), 6.96 (m, H-3′ and H-5′), 6.95 (dd, $J$ = 2, 7 Hz, H-4), 6.05 (m, =CH−), 5.42 (m, =CH*H*), 5.32 (m, =C*H*H), 4.60 (m, $-CH_2-$), 3.88 and 3.46 (s, $CH_3$); $^{13}$C NMR ($CDCl_3$) 124.2 (C-α), 138.9 (C-$\beta$), 189.1 (C=O), 129.2 (C-1), 153.2 (C-2), 148.8 (C-3), 114.1 (C-4), 119.6 (C-5), 123.4 (C-6), 131.2 (C-1′), 130.8 (C-2′ and C-6′), 114.5 (C-3′ and C-5′), 162.4 (C-4′), 68.9 ($CH_2$), 118.2 (=$CH_2$), 132.5 (=CH-*$CH_2$*), 61.3 and 55.8 ($CH_3$). Anal. ($C_{20}H_{20}O_4$) C, H.

**3,5-Dimethoxy-4′-butoxychalcone** (**68**) was synthesized according to procedure E using 4-butoxyacetophenone (5.00 g, 26 mmol) and 3,5-dimethoxybenzaldehyde (4.32 g, 26 mmol) as starting materials: yellow crystals (7.89 g, 91%); mp 100−101 °C; $^1$H NMR ($CDCl_3$) 8.00 (H-2′ and H-6′), 7.58 (d, $J$ = 15 Hz, H-$\beta$), 7.48 (d, $J$ = 15 Hz, H-α), 6.92 (m, H-3′ and H-5′), 6.49 (d, $J$ = 2 Hz, H-2 and H-5), 6.48 (t, $J$ = 2 Hz), 3.97 (t $J$ = 7 Hz, $-OCH_2-$), 3.79 (s, $OCH_3$) 1.58 and 1.48 (m, $CH_2$), 0.96 (t, $J$ = 8 Hz, $CH_2$); $^{13}$C NMR ($CDCl_3$) 122.0 (C-α), 143.5 (C-$\beta$), 188.2 (C=O), 136.7 (C-1), 106.0 (C-2, C-6), 160.8 (C-3, C-5), 102.2 (C-4), 130.4 (C-1′), 130.6 (C-2′ and C-6′), 114.0 (C-3′ and C-5′), 162.9 (C-4′), 67.7 ($OCH_2$), 55.2 ($OCH_3$), 30.9 and 19.0 ($CH_2$), 13.7 ($CH_3$). Anal. ($C_{21}H_{24}O_4$) C, H.

**2,4-Dimethoxy-2′-(2-propenyloxy)chalcone** (**70**) was synthesized according to procedure E using 2-(2-propenyloxy)-acetophenone[43] (1.7 g, 10 mmol) and 2,4-dimethoxybenzaldehyde (1.66 g, 10 mmol) as starting materials. The reaction mixture was concentrated and the residue partitioned between 1 M hydrochloric acid and ethyl acetate. The residue of the organic phase was purified over silica gel using toluene−ethyl acetate as an eluent to give a yellow oil (3.0 g, 95%): $^1$H NMR ($CDCl_3$) 7.91 (d, $J$ = 16 Hz, H$\beta$), 7.60 (dd, $J$ = 8.4, 1.8 Hz, H-6′), 7.52 (d, $J$ = 8.4 Hz, H-5), 7.42 (dt, $J$ = 7.5, 1.8 Hz, H-5′), 7.39 (d, $J$ = 15 Hz, H$\alpha$), 7.02 (dt, $J$ = 7.5, 1.8 Hz, H-4′), 6.96 (d, $J$ = 8.7 Hz, H-3′), 6.50 (dd, $J$ = 8.4, 2.4 Hz, H-4), 6.44 (d, $J$ = 2.4 Hz, H-3), 6.03 (m, CH=C), 5.41 and 5.22 (m, $CH_2$=C); $^{13}$C NMR ($CDCl_3$) 121.1 (C$\alpha$), 139.0 (C$\beta$), 193.9 (C=O), 117.6 (C-1), 160.4 (C-2), 98.5 (C-3), 163.1 (C-4), 105.5 (C-5), 130.6 (C-6), 125.6 (C-1′), 157.2 (C-2′), 113.1 (C-3′), 132.4 (C-4′), 117.5 (C-5′), 130.6 (C-6′), 69.4 ($OCH_2$), 133.0 (CH=$CH_2$), 117.4 (CH=$CH_2$), 55.5 ($OCH_3$). Anal. ($C_{20}H_{20}O_4$) C, H.

**2,5,4′-Tris(2-propenyloxy)chalcone** (**71**) was synthesized according to procedure E using 2,5-bis(2-propenyloxy)benzaldehyde (2.18 g, 10 mmol) and 4-(2-propenyloxy)acetophenone[42] (1.76 g, 10 mmol) as starting materials. The reaction mixture was concentrated and the residue partitioned between hydrochloric acid and ethyl acetate. The residue of the organic phase was purified over silica gel using toluene−ethyl acetate as eluent to give a yellow oil (3.5 g, 90%): $^1$H NMR ($CDCl_3$) 8.04 (d, $J$ = 15 Hz, H$\beta$), 8.00 (m, H-2′ and H-6′), 7.59 (d, $J$ = 15 Hz, H$\alpha$), 7.55 (d, $J$ = 6.4 Hz, H-6), 6.96 (m, H-3′ and H-5′), 6.53 (dd, $J$ = 2, 7 Hz, H-4), 6.48 (d, $J$ = 2 Hz, H-3), 6.0−6.2 (m, =CH−), 5.2−5.4 (m, =$CH_2$), 4.3−4.5 (m, $-CH_2$); $^{13}$C NMR

($CDCl_3$) 120.6 (Cα), 139.9 (C*β*), 189.6 (C═O), 117.8 (C-1), 159.0 (C-2), 100.4 (C-3), 162.4 (C-4), 106.6 (C-5), 130.8 (C-6), 131.2 (C-1′), 130.8 (C-2′ and C-6′), 114.5 (C-3′ and C-5′), 161.9 (C-4′), 69.0, 69.1, 69.3 ($CH_2$), 118.3 (═$CH_2$), 133.0, 132.9, 132.9 (═CH-$CH_2$). Anal. ($C_{24}H_{24}O_4$) C, H.

**2,6-Dimethoxy-4′-hydroxychalcone** (**73**) was synthesized according to procedure D using 1 g of 4-[(2-tetrahydropyranyl)-oxy]acetophenone (1.00 g, 4.5 mmol) and 2,6-dimethoxybenzaldehyde (754 mg, 4.5 mmol) as starting materials: yellow crystals (733 mg, 57%); mp 172−176 °C; $^1$H NMR ($CDCl_3$) 8.21 (d, $J$ = 15 Hz, H-*β*), 7.92 (d, $J$ = 15 Hz, H-α), 7.92 (m, H-2′ and H-6′), 7.30 (t, $J$ = 7 Hz, H-4), 6.91 (m, H-3′ and H-5′), 6.58 (d, $J$ = 7 Hz, H-3 and H-5), 3.90 (s, $CH_3$−O). Anal. ($C_{17}H_{16}O_4$) C, H.

**3,5-Dimethoxy-4′-hydroxychalcone (75).** 2-Methoxyethoxymethyl chloride (13.6 g, 11 mmol) and 4-hydroxyacetophenone (13.6 g, 10 mmol) were dissolved in dry acetone. After addition of potasium carbonate (40 g), the mixture was refluxed for 1 h. The mixture was filtered and the filtrate concentrated. The residue was dissolved in ether (50 mL). The ether solution was washed with aqueous sodium hydroxide (50 mL, 1 M) and concentrated to give 4-(methoxyethoxymethoxy)-acetophenone. Compound **75** was synthesized according to procedure D using 4-(methoxyethoxymethoxy)acetophenone (2.24 g, 10 mmol) and 3,5-dimethoxybenzaldehyde (1.6 g, 10 mmol) as starting materials: yellow crystals (1.5 g, 50%); mp 123−127 °C (ethanol−water); $^1$H NMR (DMSO-$d_6$) 8.03 (m, H-2′ and H-6′), 7.74 (d, $J$ = 15 Hz, H-*β*), 7.63 (d, $J$ = 15 Hz, H-α), 7.0−6.9 (m, H-3′, H-5′, H-2, and H-6), 6.55 (t, $J$ = 2 Hz, H-4), 3.84 (s, $CH_3$); $^{13}$C NMR (DMSO-$d_6$) 122.1 (C-α), 142.1 (C-*β*), 187.4 (C═O), 138.0 (C-1), 105.7 (C-2 and C-6), 160.6 (C-3 and C-5), 101.7 (C-4), 129.0 (C-1′), 130.5 (C-2′ and C-6′), 114.8 (C-3′ and C-5′), 161.9 (C-4′). Anal. ($C_{17}H_{16}O_4$) C, H.

**2,4,6-Trimethoxy-4′-hydroxychalcone (76). Procedure G.** 2,4,6-Trimethoxy-4′-(prop-2-enyloxy)chalcone (0.89 g, 2.5 mmol), prepared according to procedure D, was dissolved in 10 mL of methanol, and to the solution were added 2 mL of water, 0.12 g of 10% of palladium on carbon, and 0.2 g of *p*-toluenesulfonic acid. The mixture was refluxed for 4.5 h and filtered and the filtrate poured into 10 mL of water. The solution was concentrated in vacuo to one-half volume and poured into 25 mL of ethyl acetate. The organic phase was washed with 10 mL of a saturated aqueous solution of sodium hydrogen carbonate and subsequently with 10 mL of a saturated aqueous solution of sodium chloride and concentrated in vacuo to give 106 mg of a yellow gum. The gum was chromatographed over silica gel 60 (Merck 0.063−0.200, 110 g) using petroleum ether−ethyl acetate (2:1, 500 mL; 1:1, 200 mL; 1:2, 700 mL) with 0.5% acetic acid as eluents to give **76** (54.7 mg, 6.6%), which was recrystallized from methanol to give 28 mg of yellow crystals: mp 200−201 °C; $^1$H NMR ($CDCl_3$−DMSO-$d_6$) 8.15 (d, $J$ = 15 Hz, H-*β*), 7.92 (m, H-2′ and H-6′), 7.90 (d, $J$ = 15 Hz, H-α), 6.91 (m, H-3′ and H-5′), 6.16 (s, H-3 and H-5), 3.92 (s, $CH_3$−O), 3.86 (s, $CH_3$−O); $^{13}$C NMR ($CDCl_3$−DMSO-$d_6$) 189.0 (C═O), 162.1 (C-4′), 160.8 (C-2), 160.7 (C-4), 133.7 (C-*β*), 129.8 (C-2′ and C-6′), 120.7 (C-α), 114.5 (C-3′ and C-5′), 105.5 (C-1), 89.8 (C-3), 55.0 and 54.6 ($CH_3$O). Anal. ($C_{18}H_{18}O_5$) C, H.

**2,4,5-Trimethoxy-4′-hydroxychalcone** (**79**) was prepared according to procedure G using 0.89 g (2.5 mmol) of 2,4,5-trimethoxy-4′-(prop-2-enyloxy)chalcone (0.89 g, 2.5 mmol) synthesized from 4-(allyloxy)acetophenone and 2,4,5-trimethoxybenzaldehyde as starting materials: yellow crystals (130 mg, 17%); mp 184−186 °C; $^1$H NMR ($CDCl_3$-DMSO-$d_6$) 7.88 (d, $J$ = 15 Hz, H-*β*), 7.78 (m, H-2′ and H-6′), 7.32 (d, $J$ = 15 Hz, H-α), 6.99 (s, H-6), 6.75 (m, H-3′ and H-5′), 6.38 (s, H-3), 3.78, 3.74, and 3.74 (3 s, $CH_3$−O), 3.86 (s, $CH_3$−O); $^{13}$C NMR ($CDCl_3$-DMSO-$d_6$) 188.7 (C═O), 153.9 (C-5), 151.8 (C-2), 142.7 (C-4), 138.3 (C-*β*), 130.4 (C-2′ and C-6′), 129.8 (C-1′), 119.4 (C-α), 114.9 (C-1, C-3′, and C-5′), 110.8 (C-6), 96.4 (C-3), 56.1, 55.9 and 55.5 ($CH_3$O). Anal. ($C_{18}H_{18}O_5$) C, H.

**2,4-Dimethoxy-4′-hydroxychalcone** (**80**) was prepared according to procedure G using 2,4-dimethoxy-4′-(allyloxy)-chalcone (326 mg, 1 mmol) prepared according to procedure E as starting material: yellow crystals (70 mg, 25%); mp 165−166 °C (methanol); $^1$H NMR ($CD_3CN$−DMSO-$d_6$) 7.98 (m, H-2′ and H-6′), 7.96 (d, $J$ = 15.8 Hz, H-*β*), 7.72 (d, $J$ = 7 Hz, H-6), 7.65 (d, $J$ = 15 Hz, H-α), 6.91 (m, H-3′ and H-5′), 6.59 (dd, $J$ = 7, 2 Hz, H-5), 6.57 (d, $J$ = 2 Hz, H-3), 3.90 and 3.84 (s, $CH_3$O); $^{13}$C NMR ($CDCl_3$) 122.0 (C-α), 137.3 (C-*β*), 187.5 (CO), 116.0 (C-1), 159.6 (C-2), 97.7 (C-3), 161.4 (C-4), 105.3 (C-5), 129.5 (C-6), 119.0 (C-1′), 130.2 (C-2′, C-6′), 114.7 (C-3′, C-5′), 162.5 (C-4′). Anal. ($C_{17}H_{16}O_4$) C, H.

**2-Methoxy-4-hydroxy-4′-(dimethylamino)chalcone** (**81**) was prepared according to procedure D using 2-methoxy-4-[(tetrahydropyranyl)oxy]benzaldehyde[23] (0.342 g, 1.0 mmol) and 4-(dimethylamino)acetophenone (0.163 g, 1.0 mmol) as starting materials: yellow crystals (0.16 g, 41%); mp 198−199 °C (ethanol); $^1$H NMR [$(CD_3)_2CO$] 8.03 (m, H-2′ and H-6′), 8.04 (d, $J$ = 15.8 Hz, H-*β*), 7.70 (d, $J$ = 7 Hz, H-6), 7.72 (d, $J$ = 15 Hz, H-α), 6.78 (m, H-3′ and H-5′), 6.52 (dd, $J$ = 8, 2 Hz, H-5), 6.56 (d, $J$ = 2 Hz, H-3), 3.91 (s, $CH_3$O), 3.09 (s, $NCH_3$); $^{13}$C NMR [$(CD_3)_2CO$] 118.1 (C-α), 136.5 (C-*β*), 187.1 (CO), 114.6 (C-1), 160.9 (C-2), 98.5 (C-3), 153.1 (C-4), 107.5 (C-5), 129.3 (C-6), 125.8 (C-1′), 129.7 (C-2′, C-6′), 110.2 (C-3′, C-5′), 159.8 (C-4′) 38.7 ($CH_3$N), 58.7 ($CH_3$O). Anal. ($C_{18}H_{19}NO_3$) C, H, N.

**4-(Dimethylamino)-4′-hydroxychalcone** (**82**) was prepared according to procedure D using 4-[(tetrahydropyranyl)-oxy]acetophenone (0.22 g, 1.0 mmol) and 4-(dimethylamino)-benzaldehyde (0.15 g, 1.0 mmol) as starting materials: yellow crystals (67 mg, 25%); mp 206−208 °C (ethanol); $^1$H NMR [$(CD_3)_2CO$] 8.05 (m, H-2′ and H-6′), 7.72 (d, $J$ = 15.8 Hz, H-*β*), 7.67 (m, H-2 and H-6), 7.60 (d, $J$ = 15 Hz, H-α), 6.77 (m, H-3′ and H-5′), 6.93 (m, H-3 and H-5), 3.03 (s, $NCH_3$); $^{13}$C NMR [$(CD_3)_2CO$] 117.2 (C-α), 152.9 (C-*β*), 187.6 (CO), 123.7 (C-1), 131.0 (C-2 and C-6), 112.7 (C-3 and C-5), 157.6 (C-4), 144.6 (C-1′), 131.4 (C-2′ and C-6′), 116.0 (C-3′ and C-5′), 162.4 (C-4′) 38.7 ($CH_3$N). Anal. ($C_{17}H_{17}NO_2$) C, H, N.

**Biological Testing.** The antileishmanial activities were determined in vitro by incubating *L. donovani* promastigotes with increasing concentrations of the chalcones as previously described.[7] The inhibitory effect on proliferation of human lymphocytes was determined as previously described[7] by incubating phytohemmagglutinin A-stimulated lymphocytes with increasing concentrations of the chalcones. In both cases the $IC_{50}$ values were estimated by fitting the data to the equation:

$$E = a/(1 + bS^c) + d \qquad (1)$$

in which $S$ is the concentration of the analogues, $E$ is the percent inhibition compared to control, and $a$, $b$, $c$, and $d$ are constants.[44]

**Statistical Design.** Principal component analysis was performed by using SIMCA P 2.1.[45] The variables were autoscaled to unit variance.

**Molecular Alignments.** Low-energy conformations of the chalcones were generated by using the MM3* force field in MacroModel version 4.5.[46] The chalcones adopt four low-energy conformations reflecting rotations about C1′−C═O and C1−C*β* bonds. The energy differences between the four conformations are calculated to be low (less than 1.5 kcal/mol) for all chalcones. To get consistent molecular alignments for the 3D-QSAR analyses, the conformation in which the lowest-numbered substituent points in the same direction as the carbonyl group was employed. The compounds were aligned using the carbonyl oxygen and the carbon atoms of the α,*β*-unsaturated carbonyl system as fitting points.

**GRID Calculations.** The interaction energies were calculated by using GRID (version 15)[9] with a grid spacing of 1 Å and the grid dimensions (Å): $X_{min}/X_{max}$, −17.5/13.5; $Y_{min}/Y_{max}$, −13.5/15.0; and $Z_{min}/Z_{max}$, −8.5/10.5. Interaction energies were calculated for three probes (OH2, C3, and N4) giving 57 600 variables for each chalcone.

**GOLPE Analyses.** Partial least squares (PLS) models were calculated by using GOLPE 3.02.[12]

**Variable Preselection.** GOLPE rejects variables having a total sum of squares (SS) lower than $10^{-7}$. The number of

variables was further reduced by D-optimal preselection or region selection before applying variable selection. Variables were selected according to their position in the *weight space*, using a D-optimal design criterion. The variables containing the most information and having the least correlation were selected. The number of variables was reduced by no more than 50% each time, until the $R^2$ value starts to decrease.

**Smart Region Definition (SRD).** A number of seeds (1920) were selected using a D-optimal design criterion in the *weight space*. Structural difference between different molecules in the series will be reflected in groups of variables, and therefore groups were generated around each seed in the 3D-space. Variables with a distance of no more than 1 Å to the seeds were included in the groups. If two neighboring groups (with a distance smaller than 2 Å) contained the same information, the groups were collapsed. The groups were used in the variable selection procedure replacing the original variables. The effect of the groups on the predictivity was evaluated, and groups instead of individual variables were removed from the data file.

**Region Selection.** The effect of the grouped variables on the predictivity was evaluated using a fractional factorial design (FFD) procedure. A number of reduced models (twice the number of variables) were build removing some of the variables according to the FFD design. The effect of dummy variables (20%) on the predictivity was calculated, and only if a variable had a positive effect on the predictivity larger than the effect of the average dummy variable was the variable included in the final model.

**Cross-Validation.** The models were validated using random groups. Molecules were assigned in a random way to five groups of equal size. Reduced models were built keeping out one group at a time. The formation of the groups was repeated 10 times.

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**Supporting Information Available:** Observed and predicted log $IC_{50}$ values for antileishmanial and antilymphocytic activity (3 pages). Ordering information is given on any current masthead page.

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