3-Aroyl-5-hydroxyflavones: Synthesis and Transformation into Aroylpyrazoles

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Keywords: Chromones / Flavones / Hydrazine / Natural products / Nitrogen heterocycles

Treatment of 3-aroyl-5-benzyloxyflavones **4a–e** with hydrazine afforded 3,5-diaryl-4-(2-benzyloxy-6-hydroxybenzoyl)-pyrazoles **5a–e**, together with 4-aroyl-5-aryl-3-(2-benzyloxy-6-hydroxyphenyl)pyrazoles **6a–e** as minor products. The structures of all new compounds have been established by extensive NMR studies and the reaction mechanisms are discussed. (© Wiley-VCH Verlag GmbH, 69451 Weinheim, Germany, 2002)

Introduction

Flavones are well known six-membered ring oxygen heterocyclic compounds and constitute one of the most common classes of natural flavonoids.[1] Several natural and synthetic derivatives are responsible for a great variety of biocidal,[2−4] pharmacological,[5−11] and antioxidant[5,12−16] activities. It is worth mentioning that the presence of a 5-hydroxy group in the flavone nucleus seems to be very important for some biological activities, such as pharmacological and antioxidant properties.[16,17−19] Significant antibacterial and antifungal activities for flavones bearing a 3-aroyl group have been reported.[20]

Despite the important biocidal applications of 3-aroylflavones (3-AFs), synthetic strategies affording these compounds have not been widely explored. There are three main synthetic routes: i) Baker−Venkataraman rearrangement of 2′,6′-diaroyloxyacetophenones,[21−24] ii) oxidation of benzylideneflavanones with a number of oxidants,[25−27] and iii) condensation of diaroylmethane derivatives with aromatic aldehydes, followed by oxidation of the formed products.[20,28,29] Only the Baker−Venkataraman route has been used for the synthesis of 3-aroyl-5-hydroxyflavones, which always appear contaminated with the corresponding 5-hydroxyflavones. In this context, it would seem advantageous if more studies were to appear on these topics and if other derivatives were to become available for further structure-activity relationship and reactivity studies. Two Indian groups studied the transformation of 3-AFs into 4-aroyl-5-aryl-3-(2-hydroxyaryl)isoxazoles[28,29] and also into 4-aroyl-3-aryl-5-(2-hydroxyaryl)-1-phenylpyrazoles.[30] These compounds were obtained by treatment of 3-AFs with hydroxylamine hydrochloride and phenylhydrazine, respectively. The authors claimed that each reaction gave only one pure product. However, considering the mechanism of these types of reactions[31,32] − nucleophilic attack at C-2 of the chromone with subsequent heterocyclic ring-opening − and the presence of two carbonyl groups in the structures of the 3-AFs, one could reasonably expect the formation of two isomers of isoxazoles and pyrazoles. In view of this, we decided to revisit the reactions between 3-AFs and hydrazines and to study the effect of B-ring substituents on the yields of the expected aroylpyrazoles.

It is worth mentioning that several promising pharmacological, agrochemical, and analytical applications have been reported for some pyrazole derivatives.[33] Certain hydroxyphenylpyrazoles, for instance, can act as ultraviolet stabilizers,[34] as analytical reagents in the complexation of transition metal ions,[35] and as analgesic agents and platelet aggregation inhibitors.[36] Others, such as 3-benzoylpyrazoles, can act as precursors of other important heterocyclic compounds (e.g., in the preparation of Cizolirtine, a potent analgesic).[37,38] This highlights the potential applications of benzoylpyrazole derivatives and has stimulated the study of their synthesis. With these possible applications and our previous work on the synthesis of pyrazoles from chromone precursors in mind,[31,32] a program aiming at the preparation of novel benzoylpyrazole derivatives from 3-AFs has been set up. As a result we describe here our results on the synthesis and structural characterization of 3- and 4-aroylpyrazoles **5a−e** and **6a−e**.

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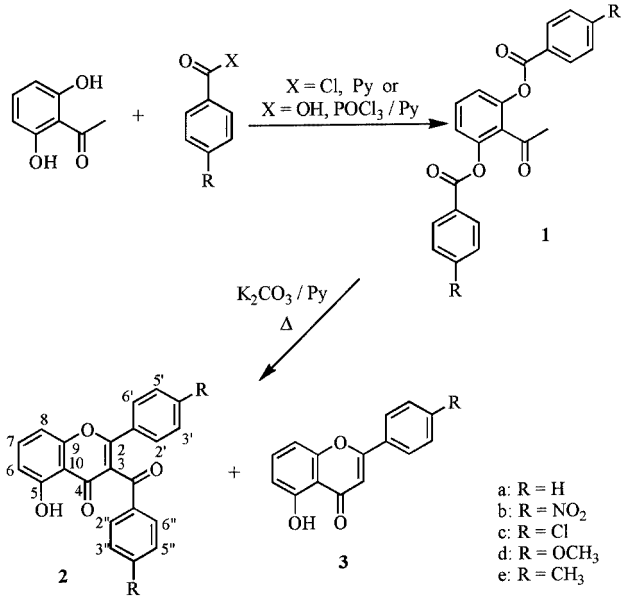
Results and Discussion

Synthesis of 3-Aroyl-5-hydroxyflavones

3-Aroyl-5-hydroxyflavones **2a−e** were synthesized by the Baker−Venkataraman method.[39,40] This approach in-

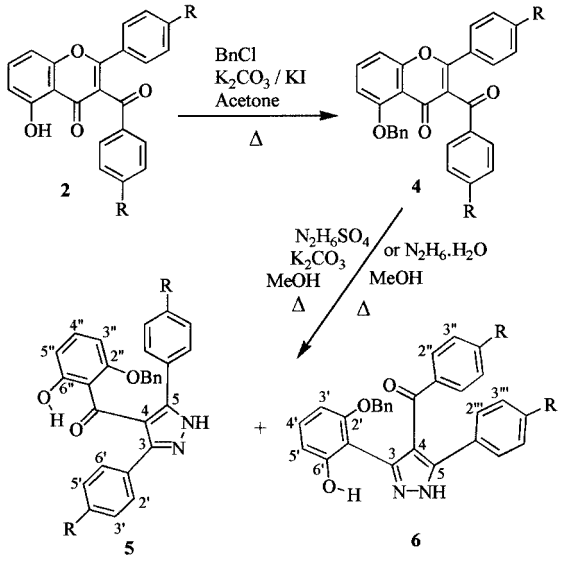
volves the *O*-acylation of 2′,6′-dihydroxyacetophenone with the appropriate benzoyl chlorides, either commercially available or prepared in situ from benzoic acids and phosphoryl oxychloride (Scheme 1). Treatment of these esters **1a**−**e** with potassium carbonate in dry pyridine afforded the target 3-aroyl-5-hydroxyflavones **2a**−**e** as major products (49−82%), with 5-hydroxyflavones **3a**−**e** as by-products (2−20%). The formation of 3-aroylflavones **2a**−**e** involved the base-catalyzed rearrangement of 2′,6′-diaroyloxyacetophenones **1a**−**e** into 2,2-diaroyl-2′,6′-dihydroxyacetophenone and 2-aroyl-2′,6′-dihydroxyacetophenone intermediates, which underwent in situ cyclodehydration to give products **2a**−**e** and **3a**−**e**, respectively.[23] This synthetic route allowed the synthesis of 3-aroyl-5-hydroxyflavones **2a**−**e** in better yields and in fewer steps than previously reported.[21−24] The Baker−Venkataraman rearrangement was carried out under nitrogen atmosphere and the reaction time was carefully controlled, in order to obtain the desired 3-aroyl-5-hydroxyflavones **2a**−**e** in good yields. After a reaction time of one hour, for example, **1b** yielded 4′-nitro-3-(4-nitrobenzoyl)-5-hydroxyflavone (**2b**) (61%) and 4′-nitro-5-hydroxyflavone (**3b**) (15%), but after two hours only **3b** (61%) was obtained. This indicates that after prolonged reaction times there is a cleavage of the 3-aroyl group in the alkaline medium. In order to confirm this cleavage, 4′-chloro-3-(4-chlorobenzoyl)-5-benzyloxyflavone (**2c**) was treated with potassium carbonate for 12 hours, and 4′-chloro-5-hydroxyflavone (**3c**) was obtained as expected.



Scheme 1

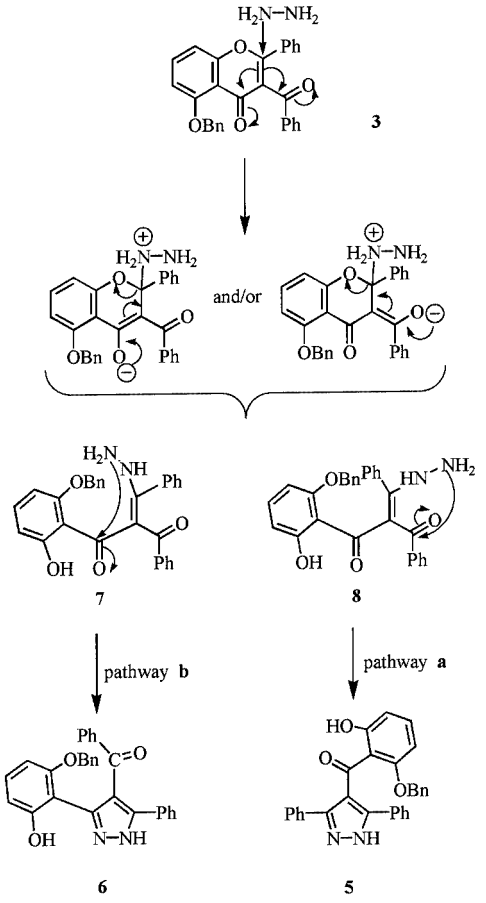
Synthesis of Aroylpyrazoles

Our previous studies on the use of chromone derivatives as starting materials in the synthesis of pyrazoles[31,32] revealed that it was necessary to protect the 5-hydroxyl group before treatment with hydrazine hydrate. This protection was carried out by heating 3-aroyl-5-hydroxyflavones **2a**−**e** with benzyl chloride in the presence of potassium carbonate and potassium iodide under reflux in acetone for 12 h, providing 3-aroyl-5-benzyloxyflavones **4a**−**e** in good yields (82−97%) (Scheme 2). The lability of the 3-aroyl groups to alkaline media (vide supra) made us initiate our study with treatment of compounds **4a**−**e** with hydrazine generated slowly in situ by addition of potassium carbonate to hydrazinium sulfate, and this afforded 3,5-diaryl-4-(2-benzyloxy-6-hydroxybenzoyl)pyrazoles **5a**−**e** (55−69%) together with 4-aroyl-5-aryl-3-(2-benzyloxy-6-hydroxyphenyl-)pyrazoles **6a** and **6c-e** (22−28%) (Scheme 2). The good overall yields of these reactions prompted us to study the treatment of compounds **4a**−**e** with hydrazine hydrate, which also gave **5a**−**e** and **6a**−**e** in better overall yields (72−98%). These results thus indicated that treatment of 3-aroylflavones with hydrazine gave rise to two aroylpyrazoles and not only one as described by Chincholkar and Jamode.[30]



Scheme 2

The mechanism of reactions between chromones and hydrazine has been reported to involve a nucleophilic attack at C-2 of the chromone nucleus, followed by ring-opening.[31,32] In this case the formed intermediates **7** and **8** can cyclise into pyrazoles by two possible pathways, thanks to the presence of two carbonyl groups capable of undergoing intramolecular dehydration reactions with the hydrazino group (Scheme 3). Our results suggest that the carbonyl of the 3-aroyl group is more reactive than the chromone carbonyl group (C-4). This is confirmed by the higher proportion of pyrazoles **5a**−**e** with respect to **6a**−**e** and also by the absence of 3-(2-benzyloxy-6-hydroxyphenyl)-4-(4-nitrobenzoyl)pyrazole (**6b**) after treatment of 5-benzyloxy-3-(4-nitrobenzoyl)flavone (**4b**, bearing a strongly electron-withdrawing substituent in the *para*-position of the 3-aroyl group) with the hydrazine produced in situ.



Scheme 3

NMR Spectroscopy

The main resonances in the ^1H and ^{13}C NMR spectra of 2′,6′-dibenzoyloxyacetophenones **1a**−**e** are: i) the resonances of the 2-CH_3 proton and carbon atoms, which appear at δ = 2.44−2.48 and 31.2−31.4 ppm, respectively, ii) the resonances of the ester and ketone carbonyl groups, which appear at δ = 162.8−164.6 and 197.6−198.6 ppm, respectively, iii) the doublet at δ = 7.20−7.29 ppm, attributable to the resonance of the equivalent 3′-H and 5′-H protons, and iv) the triplet at δ = 7.51−7.62 ppm, attributable to the resonance of 4′-H, which appears at higher frequency than those of 3′,5′-H due to the mesomeric deshielding effect of the ketone carbonyl group.

In the ^1H NMR spectrum of each 5-hydroxyflavone **3a**−**e** it is possible to observe the presence of two singlets at δ = 6.62−6.84 and 12.36−12.69 ppm, attributable to the resonances of the 3-H and the 5-OH proton, respectively. Our previous work on ^{13}C NMR assignments of 5-hydroxyflavones[41,42] and analysis of the HSQC and HMBC spectra of compounds **3a**−**e** enabled all their carbons to be assigned.

The characterization of 3-aroyl-5-hydroxyflavones **2a**−**e** and 3-aroyl-5-benzyloxyflavones **4a**−**e** was based on our previous work.[24] The most noticeable features of the ^1H and ^{13}C NMR spectra of these flavones are: i) the resonances of the 5-OH proton at δ = 11.76−12.24 ppm for **2a**−**e**, ii) the proton and carbon resonances of the methylene group of the benzyloxy substituent, appearing at δ = 5.26−5.29 and 70.9−71.0 ppm, respectively, and iii) the resonances of the aroyl and chromone carbonyl groups, which appear at δ = 190.5−193.9 and 175.5−181.7 ppm, respectively. The carbon resonances of the carbonyl groups of the 3-aroyl substituents were unequivocally assigned after analysis of the HMBC spectra of compounds **2a**−**e** and **4a**−**e**, in which connectivities were observed between 2″,6″-H and these carbonyl groups.

Detailed analysis of the ^1H, ^{13}C, and 2D HSQC and HMBC NMR spectra of aroylpyrazoles **5a**−**e** and **6a**−**e** revealed the presence of the pyrazole ring with an aroyl group at position 4. Important features in the structural characterization of these aroylpyrazoles are the resonances of the carbons atoms of the pyrazole ring, which appear at δ = 143.5−144.8 ppm, 117.1−117.9, and 146.6−147.6 ppm for C-3, C-4 and C-5, respectively, in aroylpyrazoles **6a**−**e**, and at δ = 145.3−148.1 and 119.3−122.1 ppm for C-3/5 and C-4, respectively, for aroylpyrazoles **5a**−**e**. In the structural characterization of aroylpyrazoles **5a**−**e**, it is important to note that, due to the symmetry of the molecule, the carbons C-3 and C-5 and the protons and carbons of the 3- and 5-phenyl rings are equivalent. The most noticeable features to report from their ^1H NMR spectra are therefore a characteristic AB spin system corresponding to the resonances of 2′,6′-H/3′,5′-H of aroylpyrazoles **5b**−**e**, at δ = 7.14−7.51 and 6.66−8.18 ppm, respectively. Other important features are: i) the doublets at δ = 5.92−6.07 and 6.50−6.60 ppm, which correspond to protons 3″-H and 5″-H, respectively, ii) the triplet at δ = 7.08−7.57 ppm, which corresponds to proton 4″-H, and iii) the singlet at δ = 11.77−11.92 ppm, due to the proton resonance of the 6″-OH group, involved in a hydrogen bond with the carbonyl of the aroyl group. These important data confirmed the presence of the 4-(2-benzyloxy-6-hydroxybenzoyl) group, which is only compatible with the structure shown for aroylpyrazoles **5a**−**e** (Scheme 2).

The main characteristics for the structural characterization of aroylpyrazoles **6a**−**e** that can be noted from their ^1H NMR spectra are the proton resonances of 6′-OH and NH at δ = 11.77−11.94 and 9.29−10.47 ppm, respectively, and the two characteristic AB spin systems corresponding to the resonances of 2″,6″-H/3″,5″-H of the phenyl group at carbon C-5 and of 2‴,6‴-H/3‴,5‴-H of the aroyl group at carbon C-4 for **6b**−**e**. Because of the hydrogen bond between the hydroxyl (6′-OH) proton and N-2 there is no prototropy in these aroylpyrazoles **6b**−**e**.

All these data and the connectivities found in the HMBC spectra of aroylpyrazoles **5a**−**e** and **6a**−**e** (Figure 1) provide unequivocal support for the proposed structures for these two isomers.

Conclusion

We have studied the reactions between 3-aroyl-5-benzyloxyflavones **4a**−**e** and either hydrazine, formed in

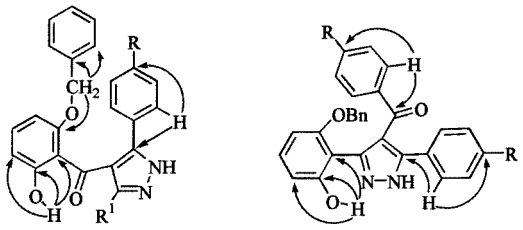


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Figure 1. Important connectivities found in the HMBC spectra of aroylpyrazoles **5a**−**e** and **6a**−**e**

situ from hydrazinium sulfate and sodium carbonate, or hydrazine hydrate. These reactions allowed us to establish new synthetic methods for novel 3,4,5-trisubstituted pyrazoles, 3,5-diaryl-4-(2-benzyloxy-6-hydroxybenzoyl)pyrazoles **5a**−**e** and 4-aroyl-5-aryl-3-(2-benzyloxy-6-hydroxyphenyl)-pyrazoles **6a**−**e**. These last were obtained as minor products, suggesting that the carbonyl group of the 3-aroyl group is more reactive than the chromone carbonyl group (C-4).

Experimental Section

General Remarks: Melting points were measured in a Reichert Thermovar apparatus fitted with a microscope, and are uncorrected. NMR spectra were recorded on Bruker AMX and DRX 300 spectrometers (300.13 for ^{1}H and 75.47 MHz for ^{13}C), in $CDCl_3$ as solvent. Chemical shifts are reported (δ) in ppm and coupling constants (*J*) in Hz; the internal standard was TMS. Unequivocal ^{13}C assignments were made with the aid of 2D *g*HSQC (or HETCOR) and *g*HMBC (delays for one bond and long-range *J* C/H couplings were optimized for 145 and 7 Hz, respectively) experiments. Electron impact (EI, 70 eV) MS were recorded on VG Autospec Q and M spectrometers. Elemental analyses were obtained with a CHNS 932 Leco analyzer (University of Aveiro). Preparative thin layer chromatography was performed with Merck 60 DGF_{254} silica gel. Column chromatography was performed with Merck 60 silica gel, 70−230 mesh.

Synthesis of 2′,6′-Dibenzoyloxyacetophenones 1a−d

Synthesis of 2′,6′-Dibenzoyloxyacetophenone (1a): Benzoyl chloride (4.6 mL, 39.4 mmol) was added to a solution of 2′,6′-dihydroxyacetophenone (2.0 g, 13.3 mmol) in dry pyridine (20 mL). The solution was stirred at room temperature for 12 h; after that period the solution was poured into ice and water, and the pH was adjusted to 4 with hydrochloric acid. The obtained solid was removed by filtration, dissolved in dichloromethane (100 mL), washed with water, and purified by silica gel column chromatography with dichloromethane as eluent. The solvent was evaporated to dryness in each case, and the residue was crystallized from ethanol, yielding **1a** (4.07 g, 85%). **1a:** M.p. 103−104 °C (recrystallization from ethanol). ^{1}H NMR: δ = 2.48 (s, 3 H, 2-CH_3), 7.23 (d, *J* = 8.0 Hz, 2 H, 3′,5′-H), 7.51 (d, *J* = 7.3 Hz, 4 H, 3,5-H of 2′,6′-$OCOC_6H_5$), 7.54 (t, *J* = 8.0 Hz, 1 H, 4′-H), 7.66 (t, *J* = 7.3 Hz, 2 H, 4-H of 2′,6′-$OCOC_6H_5$), 7.82 (d, *J* = 7.3 Hz, 4 H, 2,6-H of 2′,6′-$OCOC_6H_5$) ppm. ^{13}C NMR: δ = 31.4 (2-CH_3), 120.6 (C-3′,5′), 124.4 (C-1′), 128.7 (2 × C-1 of 2′,6′-$OCOC_6H_5$), 128.8 (2 × C-3,5 of 2′,6′-$OCOC_6H_5$), 130.3 (2 × C-2,6 of 2′,6′-$OCOC_6H_5$), 130.9 (C-4′), 134.1 (2 × C-4 of 2′,6′-$OCOC_6H_5$), 148.0 (C-2′,6′), 164.6 (2 × C=O of 2′,6′-$OCOC_6H_5$), 198.4 (C=O) ppm. EI-MS: *m*/*z* (%) = 360 (12) [$M^{+\cdot}$], 342 (1), 239 (4), 238 (5), 213 (4), 132 (3), 106 (33), 105 (100). $C_{22}H_{16}O_5$ (360.10): calcd. C 73.33, H 4.48; found C 73.02, H 4.61.

The 2′,6′-dibenzoyloxyacetophenones **1b**−**d** were obtained in a similar manner, from 2′,6′-dihydroxyacetophenone and appropriate aroyl chlorides.

2′,6′-Bis(4-nitrobenzoyloxy)acetophenone (1b): Yield 98%. M.p. 208−210 °C (recrystallization from ethanol). ^{1}H NMR: δ = 2.47 (s, 3 H, 2-CH_3), 7.29 (d, *J* = 8.3 Hz, 2 H, 3′,5′-H), 7.62 (t, *J* = 8.3 Hz, 1 H, 4′-H), 8.35 (AB, *J* = 9.3 Hz, 4 H, 2,6-H of 2′,6′-$OCOC_6H_5$), 8.38 (AB, *J* = 9.3 Hz, 4 H, 3,5-H of 2′,6′-$OCOC_6H_5$) ppm. ^{13}C NMR: δ = 31.4 (2-CH_3), 120.9 (C-3′,5′), 123.9 (2 × C-3,5 of 2′,6′-$OCOC_6H_5$), 127.8 (C-1′), 131.5 (C-4′ and 2 × C-2,6 of 2′,6′-$OCOC_6H_5$), 133.8 (2 × C-1 of 2′,6′-$OCOC_6H_5$), 147.7 (C-2′,6′), 151.1 (2 × C-4 of 2′,6′-$OCOC_6H_5$), 162.8 (2 × C=O of 2′,6′-$OCOC_6H_5$), 197.6 (C=O) ppm. EI-MS: *m*/*z* (%) = 450 (8) [M^{+}], 301 (1), 150 (100), 120 (9), 104 (19), 92 (7), 76 (7). $C_{22}H_{14}N_2O_9$ (450.07): calcd. C 58.67, H 3.13, N 6.22; found C 58.33, H 3.17, N 6.60.

2′,6′-Bis(4-chlorobenzoyloxy)acetophenone (1c): Yield 92%. M.p. 138−140 °C (recrystallization from ethanol). ^{1}H NMR: δ = 2.45 (s, 3 H, 2-CH_3), 7.23 (d, *J* = 8.3 Hz, 2 H, 3′,5′-H), 7.50 (d, *J* = 8.6 Hz, 4 H, 3,5-H of 2′,6′-$OCOC_6H_5$), 7.55 (t, *J* = 8.3 Hz, 1 H, 4′-H), 8.10 (d, *J* = 8.6 Hz, 4 H, 2,6-H of 2′,6′-$OCOC_6H_5$) ppm. ^{13}C NMR: δ = 31.3 (2-CH_3), 120.7 (C-3′,5′), 127.0 (2 × C-1 of 2′,6′-$OCOC_6H_5$), 128.2 (C-1′), 129.2 (2 × C-3,5 of 2′,6′-$OCOC_6H_5$), 131.0 (C-4′), 131.7 (2 × C-2,6 of 2′,6′-$OCOC_6H_5$), 140.8 (2 × C-4 of 2′,6′-$OCOC_6H_5$), 147.9 (C-2′,6′), 163.7 (2 × C=O of 2′,6′-$OCOC_6H_5$), 198.1 (C=O) ppm. EI-MS: *m*/*z* (%) = 428 (10) [M^{+}], 247 (1), 139 (100), 111 (30), 75 (13). $C_{22}H_{14}Cl_2O_5$ (428.02): calcd. C 61.56, H 3.29; found C 61.51, H 3.56.

2′,6′-Bis(4-methoxybenzoyloxy)acetophenone (1d): Yield 94%. M.p. 141−142 °C (recrystallization from ethanol). ^{1}H NMR: δ = 2.46 (s, 3 H, 2-CH_3), 3.89 (s, 6 H, 2 × 4-OCH_3 of 2′,6′-$OCOC_6H_5$), 6.98 (d, *J* = 9.0 Hz, 4 H, 3,5-H of 2′,6′-$OCOC_6H_5$), 7.20 (d, *J* = 8.2 Hz, 2 H, 3′,5′-H), 7.51 (t, *J* = 8.2 Hz, 1 H, 4′-H), 8.12 (d, *J* = 9.0 Hz, 4 H, 2,6-H of 2′,6′-$OCOC_6H_5$) ppm. ^{13}C NMR: δ = 31.3 (2-CH_3), 55.5 (2 × 4-OCH_3 of 2′,6′-$OCOC_6H_5$), 120.5 (C-3′,5′), 120.9 (C-1′), 114.0 (2 × C-3,5 of 2′,6′-$OCOC_6H_5$), 128.5 (2 × C-1 of 2′,6′-$OCOC_6H_5$), 130.7 (C-4′), 132.5 (2 × C-2,6 of 2′,6′-$OCOC_6H_5$), 148.0 (C-2′,6′), 164.2 (2 × C-4 and 2 × C=O of 2′,6′-$OCOC_6H_5$), 198.6 (C=O) ppm. EI-MS: *m*/*z* (%) = 420 (38) [M^{+}], 402 (13), 373 (5), 243 (17), 152 (8), 135 (100), 107 (5), 92 (6), 77 (10). $C_{24}H_{20}O_7$ (420.12): calcd. C 68.57, H 4.80; found C 68.35, H 4.82.

Synthesis of 2′,6′-Bis(4-methylbenzoyloxy)acetophenone (1e): *p*-Methylbenzoic acid (1.12 g, 8.23 mmol), thionyl chloride (1.8 mL, 24.7 mmol), and one drop of pyridine were heated (60−70 °C) for 4 h. After this period, benzene (50 mL) was added and the reaction solvents were evaporated to dryness. The obtained residue was added to a solution of 2′,6′-dihydroxyacetophenone (0.50 g, 3.29 mmol) in dry pyridine (20 mL). The solution was stirred at room temperature for 12 h; after that period the solution was poured into ice and water, and the pH was adjusted to 4 with hydrochloric acid. The obtained solid was removed by filtration, dissolved in dichloromethane (100 mL), washed with water, and purified by silica gel column chromatography with dichloromethane as eluent. The solvent was evaporated to dryness and the residue was crystallized from ethanol, yielding **1e** (2.12 g, 69%). **1e:** M.p. 100−102 °C (recrystallization from ethanol). ^{1}H NMR: δ = 2.44

(s, 6 H, 2 × 4-CH_3 of 2′,6′-$OCOC_6H_5$), 2.47 (s, 3 H, 2-CH_3), 7.21 (d, J = 8.3 Hz, 2 H, 3′,5′-H), 7.30 (d, J = 8.3 Hz, 4 H, 3,5-H of 2′,6′-$OCOC_6H_5$), 7.52 (t, J = 8.3 Hz, 1 H, 4′-H), 8.05 (d, J = 8.3 Hz, 4 H, 2,6-H of 2′,6′-$OCOC_6H_5$) ppm. ^{13}C NMR: δ = 21.7 (2 × 4-CH_3 of 2′,6′-$OCOC_6H_5$), 31.2 (2-CH_3), 120.5 (C-3′,5′), 125.8 (2 × C-1 of 2′,6′-$OCOC_6H_5$), 128.4 (C-1′), 129.4 (2 × C-3,5 of 2′,6′-$OCOC_6H_5$), 130.3 (2 × C-2,6 of 2′,6′-$OCOC_6H_5$), 130.7 (C-4′), 144.9 (2 × C-4 of 2′,6′-$OCOC_6H_5$), 147.9 (C-2′,6′), 164.5 (2 × C=O of 2′,6′-$OCOC_6H_5$), 198.4 (C=O) ppm. EI-MS: m/z (%) = 388 (5) [M^+], 227 (1), 119 (100), 91 (28), 65 (9). $C_{24}H_{20}O_5$ (388.13): calcd. C 74.21, H 5.19; found C 73.95, H 5.40.

Synthesis of 3-Aroyl-5-hydroxyflavones 2a−e

Synthesis of 3-Benzoyl-5-hydroxyflavone (2a): Anhydrous potassium carbonate (1.355 g, 9.80 mmol) was added to a solution of 2′,6′-dibenzoyloxyacetophenone (**1a**, 2.05 g, 4.90 mmol) in dry pyridine (15 mL). The mixture was heated (120−130 °C) under nitrogen for 2 h; after this period it was poured into a mixture of ice (100 g), water (50 mL), and concentrated hydrochloric acid (pH adjusted to 3−4). The obtained solid was filtered, dissolved in dichloromethane (100 mL), washed with water, and purified on preparative thin layer chromatographic plates, eluting several times with a (1:1) mixture of dichloromethane/light petroleum. Two very close spots were collected; these were, with increasing R_f values, 3-benzoyl-5-hydroxyflavone **2a** (53%) and 5-hydroxyflavones **3a** (16%), which displayed spectroscopic and analytical data identical to those previously reported.[24,42]

3-Aroyl-5-hydroxyflavones **2c−e** and 5-hydroxyflavones **3c−e** were obtained from **1c−e** in a similar manner. In the case of 5-hydroxy-4′-nitro-3-(4-nitrobenzoyl)flavone (**2b**) and 5-hydroxy-4′-nitroflavone **3b**, treatment of 2′,6′-bis(4-nitrobenzoyloxy)acetophenone **1b** with base was carried out only for 1 h.

5-Hydroxy-4′-nitro-3-(4-nitrobenzoyl)flavone (2b): Yield 61%. M.p. 245−247 °C (recrystallization from ethanol). ^{1}H NMR: δ = 6.93 (d, J = 8.4 Hz, 1 H, 6-H), 7.07 (d, J = 8.4 Hz, 1 H, 8-H), 7.68 (t, J = 8.4 Hz, 1 H, 7-H), 7.79 (d, J = 8.8 Hz, 2 H, 2′,6′-H), 8.07 (d, J = 8.8 Hz, 2 H, 2′′,6′′-H), 8.26 (d, J = 8.8 Hz, 2 H, 3′,5′-H), 8.30 (d, J = 8.8 Hz, 2 H, 3′′,5′′-H), 11.76 (s, 1 H, 5-OH) ppm. ^{13}C NMR: δ = 107.3 (C-8), 110.2 (C-10), 112.9 (C-6), 121.8 (C-3), 124.1 (C-3′,5′), 124.3 (C-3′′,5′′), 129.8 (C-2′,6′), 130.2 (C-2′′,6′′), 136.6 (C-1′), 137.0 (C-7), 140.9 (C-1′′), 149.7 (C-4′), 151.0 (C-4′′), 156.1 (C-9), 161.0 (C-5), 162.3 (C-2), 181.1 (C-4), 190.5 (C=O) ppm. EI-MS: m/z (%) = 432 (100) [M^+], 403 (42), 357 (12), 310 (12), 174 (10), 150 (12), 128 (7), 104 (14), 92 (6), 78 (40), 63 (45). $C_{22}H_{12}O_8N_2$ (432.06): calcd. C 61.12, H 2.80, N 6.48; found C 61.32, H 3.01, N 6.53.

5-Hydroxy-4′-nitroflavone (3b): Yield 15%. M.p. 296−298 °C (recrystallization from ethanol). ^{1}H NMR: δ = 6.82 (s, 1 H, 3-H), 6.86 (d, J = 8.4 Hz, 1 H, 6-H), 7.03 (d, J = 8.4 Hz, 1 H, 8-H), 7.60 (t, J = 8.4 Hz, 1H. 7-H), 8.09 (d, J = 8.8 Hz, 2 H, 2′,6′-H), 8.39 (d, J = 8.8 Hz, 2 H, 3′,5′-H), 12.32 (s, 1 H, 5-OH) ppm. ^{13}C NMR: δ = 108.2 (C-3), 107.1 (C-8), 111.0 (C-10), 112.1 (C-6), 127.4 (C-2′,6′), 124.3 (C-3′,5′), 136.0 (C-7), 137.1 (C-1′), 149.8 (C-4′), 156.4 (C-9), 161.0 (C-5), 161.7 (C-2), 183.2 (C-4) ppm. EI-MS: m/z (%) = 283 (100) [M^+], 253 (8), 237 (22), 152 (6), 136 (6), 108 (15), 83 (46), 72 (14), 59 (28). $C_{22}H_{12}O_8N_2$ (283.05): calcd. C 63.61, H 3.20, N 4.95; found C 63.41, H 3.31, N 5.27.

4′-Chloro-3-(4-chlorobenzoyl)-5-hydroxyflavone (**2c**) (58%), **4′-Chloro-5-hydroxyflavone** (**3c**) (18%), **5-Hydroxy-4′-methoxy-3-(4-methoxybenzoyl)flavone** (**2d**) (49%), and **5-Hydroxy-4′-methoxyflavone** (**3d**) (20%) displayed spectroscopic and analytical data identical to those previously reported.[24]

5-Hydroxy-4′-methyl-3-(4-methylbenzoyl)flavone (2e): Yield 82%. M.p. 222−225 °C (recrystallization from ethanol). ^{1}H NMR: δ = 2.34 (s, 3 H, 4′-CH_3), 2.39 (s, 3 H, 4′′-CH_3), 6.85 (dd, J = 8.3, 0.6 *Hz*, 1 H, 6-H), 7.03 (br. d, J = 8.3 Hz, 1 H, 8-H), 7.17 (d, J = 8.2 Hz, 2 H, 3′,5′-H), 7.24 (d, J = 8.2 Hz, 2 H, 3′′,5′′-H), 7.55 (d, J = 8.2 Hz, 2 H, 2′,6′-H), 7.60 (t, J = 8.3 Hz, 1 H, 7-H), 7.85 (d, J = 8.2 Hz, 2 H, 2′′,6′′-H), 12.24 (s, 1 H, 5-OH) ppm. ^{13}C NMR: δ = 21.5 (4′-CH_3), 21.8 (4′′-CH_3), 107.1 (C-8), 110.1 (C-10), 111.8 (C-6), 120.7 (C-3), 128.4 (C-1′), 128.5 (C-2′,6′), 129.6 (6C, C-3′,5′,2′′,3′′,5′′,6′′), 134.5 (C-1′′), 135.9 (C-7), 142.6 (C-4′), 145.2 (C-4′′), 156.2 (C-9), 160.9 (C-5), 163.6 (C-2), 181.7 (C-4), 192.3 (C=O) ppm. EI-MS: m/z (%) = 370 (100) [M^+], 369 (28), 355 (13), 341 (65), 327 (15), 279 (30), 235 (7), 206 (9), 185 (10), 143 (49), 119 (65), 91 (63), 65 (24). $C_{24}H_{18}O_4$ (370.12): calcd. C 77.82, H 4.90; found C 77.62, H 5.27.

5-Hydroxy-4′-methylflavone (3e): Yield 2%. M.p. 183−185 °C (recrystallization from ethanol). ^{1}H NMR: δ = 2.44 (s, 3 H, 4′-CH_3), 6.70 (s, 1 H, 3-H), 6.80 (dd, J = 8.3, 0.8 *Hz*, 1 H, 6-H), 6.99 (dd, J = 8.3, 0.8 *Hz*, 1 H, 8-H), 7.32 (d, J = 8.3 Hz, 2 H, 3′,5′-H), 7.53 (t, J = 8.3 Hz, 1 H, 7-H), 7.80 (d, J = 8.3 Hz, 2 H, 2′,6′-H), 12.61 (s, 1 H, 5-OH) ppm. ^{13}C NMR: δ = 21.6 (4′-CH_3), 105.5 (C-3), 107.0 (C-8), 110.9 (C-10), 111.4 (C-6), 126.4 (C-3′,5′), 128.5 (C-1′), 129.9 (C-2′,6′), 135.3 (C-7), 142.8 (C-4′), 156.5 (C-9), 160.9 (C-5), 164.8 (C-2), 183.6 (C-4) ppm. EI-MS: m/z (%) = 252 (100) [M^+], 251 (26), 237 (20), 224 (32), 195 (12), 181 (13), 137 (15), 136 (59), 115 (42), 108 (56). $C_{16}H_{12}O_3$ (252.26): calcd. C 76.18, H 4.79; found C 76.36, H 4.71.

Synthesis of 3-Aroyl-5-benzyloxyflavones 4a−e

Synthesis of 3-Benzoyl-5-benzyloxyflavone (4a): Anhydrous potassium carbonate (1.113 g, 8.05 mmol), potassium iodide (0.67 g, 4.03 mmol), and benzyl chloride (0.37 mL, 3.22 mmol) were added to a solution of 3-benzoyl-5-hydroxyflavone (**2a**, 0.92 mg, 2.68 mmol) in acetone (150 mL). The mixture was heated under reflux under nitrogen for 12 h. After this period the inorganic salts were filtered and the acetone was evaporated to dryness. The obtained residue was dissolved in dichloromethane (20 mL) and purified by silica gel column chromatography, with dichloromethane as eluent, giving 3-benzoyl-5-benzyloxyflavone (**4a**, 0.95 mg, 82%). M.p. 203−204 °C (recrystallization from ethanol). ^{1}H NMR: δ = 5.27 (s, 2 H, 5-$OCH_2C_6H_5$), 6.88 (d, J = 8.4 Hz, 1 H, 6-H), 7.14 (d, J = 8.4 Hz, 1 H, 8-H), 7.24−7.56 (m, 11 H, 3′,4′,5′,2′′,3′′,4′′,5′′,6′′-H and 3,4,5-H of 5-$OCH_2C_6H_5$), 7.57 (t, J = 8.4 Hz, 1 H, 7-H), 7.64 (d, J = 7.4 Hz, 2 H, 2,6-H of 5-$OCH_2C_6H_5$), 7.95 (d, J = 7.6 Hz, 2 H, 2′,6′-H) ppm. ^{13}C NMR: δ = 70.9 (5-$OCH_2C_6H_5$), 108.8 (C-6), 110.3 (C-8), 114.4 (C-10), 123.7 (C-3), 126.7 (C-2,6 of 5-$OCH_2C_6H_5$), 127.7 (C-4 of 5-$OCH_2C_6H_5$), 128.4 (C-2′,6′), 128.6 (C-2′′,6′′), 128.7 (C-3′′,5′′ and C-3,5 of 5-$OCH_2C_6H_5$), 129.5 (C-3′,5′), 131.2 (C-4′), 131.5 (C-4′′), 133.6 (C-1′′), 134.2 (C-1′), 136.3 (C-1 of 5-$OCH_2C_6H_5$), 137.0 (C-7), 158.1 (C-9), 158.9 (C-5), 159.9 (C-2), 176.0 (C-4), 193.9 (C=O) ppm. EI-MS: m/z (%) = 432 (50) [M^+], 431 (14), 342 (30), 326 (22), 313 (26), 297 (33), 129 (27), 105 (29), 91 (100), 77 (41), 65 (14), 51 (11). $C_{29}H_{20}O_4 \cdot H_2O$ (450.16): calcd. C 77.32, H 4.92; found C 77.28, H 4.81.

The 3-aroyl-5-benzyloxyflavones **4b−d** were obtained from 3-aroyl-5-hydroxyflavones **2b−d** in a similar manner.

5-Benzyloxy-4′-nitro-3-(4-nitrobenzoyl)flavone (4b): Yield 97%. M.p. 244−246 °C (recrystallization from ethanol). ^{1}H NMR: δ =

5.29 (s, 2 H, 5-$OCH_2C_6H_5$), 6.95 (d, J = 8.4 Hz, 1 H, 6-H), 7.16 (d, J = 8.4 Hz, 1 H, 8-H), 7.30 (t, J = 7.4 Hz, 1 H, 4-H of 5-$OCH_2C_6H_5$), 7.36 (t, J = 7.4 Hz, 2 H, 3,5-H of 5-$OCH_2C_6H_5$), 7.51 (d, J = 7.4 Hz, 2 H, 2,6-H of 5-$OCH_2C_6H_5$), 7.65 (t, J = 8.4 Hz, 1 H, 7-H), 7.79 (d, J = 8.9 Hz, 2 H, 2′,6′-H), 8.10 (d, J = 8.9 Hz, 2 H, 2′′,6′′-H), 8.24 (d, J = 8.9 Hz, 2 H, 3′,5′-H), 8.28 (d, J = 8.9 Hz, 2 H, 3′′,5′′-H) ppm. ^{13}C NMR: δ = 70.9 (5-$OCH_2C_6H_5$), 109.3 (C-6), 110.2 (C-8), 114.2 (C-10), 124.2 (C-3), 124.0 (C-3′,5′), 124.2 (C-3′′,5′′), 126.6 (C-2,6 of 5-$OCH_2C_6H_5$), 127.9 (C-4 of 5-$OCH_2C_6H_5$), 128.7 (C-3,5 of 5-$OCH_2C_6H_5$), 129.6 (C-2′,6′), 130.3 (C-2′′,6′′), 135.2 (C-7), 135.8 (C-1 of 5-$OCH_2C_6H_5$), 136.8 (C-1′), 141.0 (C-1′′), 149.3 (C-4′), 150.7 (C-4′′), 157.9 (C-9), 158.7 (C-5), 158.9 (C-2), 175.5 (C-4), 192.0 (C=O) ppm. EI-MS: m/z (%) = 523 (12) [$M^{+\cdot}$], 460 (5), 307 (30), 289 (15), 212 (7), 180 (5), 154 (100), 137 (67), 136 (65), 120 (12), 107 (20), 91 (30), 77 (17), 65 (7). $C_{29}H_{18}N_2O_8$ (540.13): calcd. C 64.44, H 3.73, N 5.18; found C 64.68, H 3.82, N 5.50.

5-Benzyloxy-4′-chloro-3-(4-chlorobenzoyl)flavone (4c): Yield 85%. M.p. 231−233 °C (recrystallization from ethanol). ^{1}H NMR: δ = 5.27 (s, 2 H, 5-$OCH_2C_6H_5$), 6.90 (dd, J = 8.4, 0.8 *Hz*, 1 H, 6-H), 7.12 (dd, J = 8.4, 0.8 Hz, 1 H, 8-H), 7.27−7.34 (m, 3 H, 3,4,5-H of 5-$OCH_2C_6H_5$), 7.34 (d, J = 6.7 Hz, 2 H, 3′,5′-H), 7.38 (d, J = 6.7 Hz, 2 H, 3′′,5′′-H), 7.53 (d, J = 7.1 Hz, 2 H, 2,6-H of 5-$OCH_2C_6H_5$), 7.56 (d, J = 6.7 Hz, 2 H, 2′,6′-H), 7.59 (t, J = 8.4 Hz, 1 H, 7-H), 7.87 (d, J = 6.7 Hz, 2 H, 2′′,6′′-H) ppm. ^{13}C NMR: δ = 71.0 (5-$OCH_2C_6H_5$), 108.9 (C-6), 110.2 (C-8), 114.3 (C-10), 123.4 (C-3), 126.7 (C-2,6 of 5-$OCH_2C_6H_5$), 127.8 (C-4 of 5-$OCH_2C_6H_5$), 128.6 (C-3′,5′), 129.2 (C-3′′,5′′ and C-3,5 of 5-$OCH_2C_6H_5$), 129.6 (C-2′,6′), 129.7 (C-1′), 130.8 (C-2′′,6′′), 134.5 (C-7), 135.3 (C-1′′), 136.1 (C-1 of 5-$OCH_2C_6H_5$), 137.8 (C-4′), 140.3 (C-4′′), 157.9 (C-9), 158.9 (C-2 and C-5), 175.7 (C-4), 192.6 (C=O) ppm. EI-MS: m/z (%) = 500 (18) [$M^{+\cdot}$], 482 (5), 410 (5), 394 (5), 365 (8), 163 (10), 139 (16), 111 (17), 91 (100), 75 (8), 65 (11). $C_{29}H_{18}Cl_2O_4$ (518.08): calcd. C 67.06, H 3.88; found C 67.03, H 3.81.

5-Benzyloxy-4′-methoxy-3-(4-methoxybenzoyl)flavone (4d): Yield 90%. M.p. 155−157 °C (recrystallization from ethanol). ^{1}H NMR: δ = 3.78 (s, 3 H, 4′-OCH_3), 3.82 (s, 3 H, 4′′-OCH_3), 5.26 (s, 2 H, 5-$OCH_2C_6H_5$), 6.84 (d, J = 6.0 Hz, 2 H, 3′′,5′′-H), 6.85 (d, J = 6.5 Hz, 2 H, 3′,5′-H), 6.86 (d, J = 8.5 Hz, 1 H, 6-H), 7.12 (dd, J = 8.5, 0.9 *Hz*, 1 H, 8-H), 7.26 (t, J = 7.2 Hz, 1 H, 4-H of 5-$OCH_2C_6H_5$), 7.35 (t, J = 7.2 Hz, 2 H, 3,5-H of 5-$OCH_2C_6H_5$), 7.55 (d, J = 7.2 Hz, 2 H, 2,6-H of 5-$OCH_2C_6H_5$), 7.55 (t, J = 8.5 Hz, 1 H, 7-H), 7.63 (d, J = 6.5 Hz, 2 H, 2′,6′-H), 7.93 (d, J = 6.0 Hz, 2 H, 2′′,6′′-H) ppm. ^{13}C NMR: δ = 55.3 (4′-OCH_3), 55.4 (4′′-OCH_3), 70.9 (5-$OCH_2C_6H_5$), 108.6 (C-6), 110.3 (C-8), 113.9 (C-3′,5′), 114.1 (C-3′′,5′′), 114.4 (C-10), 122.7 (C-3), 123.7 (C-1′), 126.7 (C-2,6 of 5-$OCH_2C_6H_5$), 127.6 (C-4 of 5-$OCH_2C_6H_5$), 128.6 (C-3,5 of 5-$OCH_2C_6H_5$), 130.1 (C-2′,6′), 130.4 (C-1′′), 131.9 (C-2′′,6′′), 133.9 (C-7), 136.3 (C-1 of 5-$OCH_2C_6H_5$), 158.0 (C-9), 158.8 (C-5), 159.3 (C-2), 161.8 (C-4′), 163.9 (C-4′′), 176.0 (C-4), 192.8 (C=O) ppm. EI-MS: m/z (%) = 492 (96) [$M^{+\cdot}$], 474 (12), 402 (46), 386 (28), 373 (22), 357 (40), 295 (10), 278 (15), 159 (24), 135 (93), 107 (7), 91 (94), 78 (91), 63 (100). $C_{31}H_{24}O_6$ (510.18): calcd. C 72.93, H 5.13; found C 72.83, H 5.34.

5-Benzyloxy-4′-methyl-3-(4-methylbenzoyl)flavone (4e): Yield 94%. M.p. 174−177 °C (recrystallization from ethanol). ^{1}H NMR: δ = 2.32 (s, 3 H, 4′-CH_3), 2.36 (s, 3 H, 4′′-CH_3), 5.27 (s, 2 H, 5-$OCH_2C_6H_5$), 6.87 (d, J = 8.3 Hz, 1 H, 6-H), 7.13 (d, J = 8.3 Hz, 1 H, 8-H), 7.14 (d, J = 8.1 Hz, 2 H, 3′,5′-H), 7.18 (d, J = 8.1 Hz, 2 H, 3′′,5′′-H), 7.26−7.29 (m, 1 H, 4-H of 5-$OCH_2C_6H_5$), 7.35 (t, J = 7.6 Hz, 2 H, 3,5-H of 5-$OCH_2C_6H_5$), 7.54 (d, J = 7.6 Hz, 2 H, 2,6-H of 5-$OCH_2C_6H_5$), 7.55 (t, J = 8.3 Hz, 1 H, 7-H), 7.55 (d, J = 8.1 Hz, 2 H, 2′,6′-H), 7.85 (d, J = 8.1 Hz, 2 H, 2′′,6′′-H) ppm. ^{13}C NMR: δ = 21.5 (4′-CH_3), 21.8 (4′′-CH_3), 70.9 (5-$OCH_2C_6H_5$), 108.6 (C-6), 110.3 (C-8), 114.4 (C-10), 123.3 (C-3), 126.7 (C-2,6 of 5-$OCH_2C_6H_5$), 127.6 (C-4 of 5-$OCH_2C_6H_5$), 128.3 (C-2′,6′), 128.6 (C-1′ and C-3,5 of 5-$OCH_2C_6H_5$), 129.4 (C-3′,5′ and C-3′′,5′′), 129.7 (C-2′′,6′′), 134.0 (C-7), 134.7 (C-1′′), 136.3 (C-1 of 5-$OCH_2C_6H_5$), 141.7 (C-4′), 144.5 (C-4′′), 158.1 (C-9), 158.8 (C-5), 159.7 (C-2), 176.0 (C-4), 193.8 (C=O) ppm. EI-MS: m/z (%) = 460 (41) [$M^{+\cdot}$], 442 (9), 370 (15), 356 (20), 341 (18), 325 (22), 311 (6), 279 (5), 143 (16), 119 (29), 91 (100), 65 (17). $C_{31}H_{24}O_4$ (478.19): calcd. C 77.81, H 5.48; found C 77.48, H 5.58.

Synthesis of 3,5-Diaryl-4-(2-benzyloxy-6-hydroxybenzoyl)pyrazoles 5a−e and 4-Aroyl-5-aryl-3-(2-benzyloxy-6-hydroxyphenyl)pyrazoles 6a−e

Synthesis of 4-(2-Benzyloxy-6-hydroxybenzoyl)-3,5-diphenylpyrazole (5a) and 4-Benzoyl-3-(2-benzyloxy-6-hydroxyphenyl)-5-phenylpyrazole (6a):

Method A: Hydrazinium sulfate (0.997 g, 7.67 mmol) was added to a solution of 3-benzoyl-5-benzyloxyflavone (**4a**, 550 mg, 1.28 mmol) in methanol (50 mL). The mixture was heated (80 °C) under nitrogen, and a saturated solution of potassium carbonate in methanol (100 mL) was slowly added, then the mixture was heated for 20 h. After this period the reaction mixture was poured into water and extracted with chloroform (3 × 100 mL). The solvent was evaporated to dryness and the residue was dissolved in dichloromethane and chromatographed on preparative thin layer chromatographic plates, eluting several times with dichloromethane. Two very close spots were collected, representing, with increasing R_f values, 4-(2-benzyloxy-6-hydroxybenzoyl)-3,5-diphenylpyrazole (**5a**, 320 mg, 56%) and 4-benzoyl-3-(2-benzyloxy-6-hydroxyphenyl)-5-phenylpyrazole (**6a**, 160 mg, 28%).

Method B: Hydrazine hydrate (0.37 mL, 7.67 mmol) was added to a solution of 3-benzoyl-5-benzyloxyflavone (**4a**, 550 mg, 1.28 mmol) in methanol (50 mL). The mixture was heated (80 °C) under nitrogen for 20 h. After this period the reaction mixture was poured into water and extracted with chloroform (3 × 100 mL). The solvent was evaporated to dryness and the residue was dissolved in dichloromethane and chromatographed on preparative thin layer chromatographic plates, eluting several times with dichloromethane. Two very close spots were collected, representing, with increasing R_f values, 4-(2-benzyloxy-6-hydroxybenzoyl)-3,5-diphenylpyrazole (**5a**, 297 mg, 52%) and 4-benzoyl-3-(2-benzyloxy-6-hydroxyphenyl)-5-phenylpyrazole (**6a**, 171 mg, 30%).

4-(2-Benzyloxy-6-hydroxybenzoyl)-3,5-diphenylpyrazole (5a): Yield 56%. M.p. 150−152 °C (recrystallization from methanol). ^{1}H NMR: δ = 4.51 (s, 2 H, 2′′-$OCH_2C_6H_5$), 5.94 (br. d, J = 8.3 Hz, 1 H, 3′′-H), 6.52 (dd, J = 8.3, 0.6 *Hz*, 1 H, 5′′-H), 6.89−6.92 (m, 2 H, 2,6-H of 2′′-$OCH_2C_6H_5$), 7.14−7.33 (m, 8 H, 2′,3′,4′,5′,6′-H and 3,4,5-H of 2′′-$OCH_2C_6H_5$), 7.57 (t, J = 8.3 Hz, 1 H, 4′′-H), 11.90 (s, 1 H, 2′′-OH) ppm. ^{13}C NMR: δ = 70.0 (2′′-$OCH_2C_6H_5$), 101.8 (C-3′′), 110.0 (C-5′′), 113.0 (C-1′′), 120.0 (C-4), 126.6 (C-2,6 of 2′′-$OCH_2C_6H_5$), 127.8 (C-4 of 2′′-$OCH_2C_6H_5$), 127.9 (2 × C-2′,6′), 128.2 (C-3,5 of 2′′-$OCH_2C_6H_5$), 128.3 (2 × C-3′,5′), 128.6 (2 × C-4′), 130.3 (2 × C-1′), 135.7 (C-1 of 2′′-$OCH_2C_6H_5$), 136.2 (C-4′′), 148.0 (C-3,5), 159.2 (C-2′′), 163.0 (C-6′′), 195.2 (C=O) ppm. EI-MS: m/z (%) = 446 (98) [$M^{+\cdot}$], 428 (22), 311 (53), 247 (16), 233 (9), 221 (33), 104 (9), 91 (100), 77 (12), 65 (14). $C_{29}H_{22}N_2O_3$ (446.16): calcd. C 78.01, H 4.97, N 6.27; found C 78.12, H 4.99, N 6.23.

4-Benzoyl-3-(2-benzyloxy-6-hydroxyphenyl)-5-phenylpyrazole (6a): Yield 28%. Yellow oil − ^{1}H NMR: δ = 4.71 (s, 2 H, 2′-$OCH_2C_6H_5$), 6.20 (d, *J* = 8.1 Hz, 1 H, 3′-H), 6.62 (d, *J* = 8.1 Hz, 1 H, 5′-H), 6.99 (t, *J* = 8.1 Hz, 1 H, 4′-H), 7.09−7.14 (m, 5 H, 2,3,4,5,6-H of 2′-$OCH_2C_6H_5$), 7.16−7.25 (m, 5 H, 3′′,4′′,5′′,3′′′,5′′′-H), 7.30 (t, *J* = 7.6 Hz, 1 H, 4′′′-H), 7.38−7.41 (m, 2 H, 2′′,6′′-H), 7.65 (d, *J* = 7.6 Hz, 2 H, 2′′′,6′′′-H), 9.29 (br. s, 1 H, NH), 11.87 (br. s, 1 H, 6′-OH) ppm. ^{13}C NMR: δ = 69.8 (2′-$OCH_2C_6H_5$), 104.4 (C-3′), 107.3 (C-1′), 110.4 (C-5′), 117.9 (C-4), 126.7 (C-2,6 of 2′-$OCH_2C_6H_5$), 127.6 (C-4 of 2′-$OCH_2C_6H_5$), 127.8 (C-3,5 of 2′-$OCH_2C_6H_5$), 128.4 (C-3′′,5′′), 128.5 (C-2′′,6′′ and C-3′′′,5′′′), 128.9 (C-4′′), 129.4 (C-1′′′), 129.7 (C-2′′′,6′′′), 130.6 (C-4′), 132.7 (C-4′′′), 136.7 (C-1 of 2′-$OCH_2C_6H_5$), 137.3 (C-1′′), 144.8 (C-3), 147.6 (C-5), 156.1 (C-6′), 156.3 (C-2′), 192.5 (C=O) ppm. EI-MS: *m/z* (%) = 446 (85) [$M^{+\cdot}$], 429 (7), 369 (8), 341 (61), 311 (5), 193 (5), 105 (85), 91 (100), 77 (17), 65 (6). EI-HRMS: calcd. for $C_{29}H_{22}N_2O_3$ ($M^{+\cdot}$) 446.1630, found 446.1631.

3,5-Diaryl-4-(2-benzyloxy-6-hydroxybenzoyl)pyrazoles **5c−e** and 4-aroyl-5-aryl-3-(2-benzyloxy-6-hydroxyphenyl)pyrazoles **6c−e** were obtained from 3-aroyl-5-benzyloxyflavone **2b−e** in a similar manner. The yields obtained were listed in Table 1

Table 1. Yields of **5b−e** and **6b−e**

Compounds	**5b**	**6b**	**5c**	**6c**	**5d**	**6d**	**5e**	**6e**
Method A (%)	64	−	55	22	69	25	61	24
Method B (%)	48	24	57	40	51	37	58	40

4-(2-Benzyloxy-6-hydroxybenzoyl)-3,5-bis(4-nitrophenyl)-pyrazole (5b): M.p. 202−204 °C (recrystallization from methanol). ^{1}H NMR: δ = 4.55 (s, 2 H, 2′′-$OCH_2C_6H_5$), 6.07 (d, *J* = 8.3 Hz, 1 H, 3′′-H), 6.60 (d, *J* = 8.3 Hz, 1 H, 5′′-H), 6.95 (d, *J* = 7.6 Hz, 2 H, 2,6-H of 2′′-$OCH_2C_6H_5$), 7.23 (t, *J* = 8.3 Hz, 1 H, 4′′-H), 7.29−7.35 (m, 3 H, 3,4,5-H of 2′′-$OCH_2C_6H_5$), 7.51 (d, *J* = 7.7 Hz, 2 H, 2′,6′-H), 8.18 (d, *J* = 7.7 Hz, 2 H, -3′,5′-H), 11.85 (s, 1 H, 2′′-OH) ppm. ^{13}C NMR: δ = 70.6 (2′′-$OCH_2C_6H_5$), 102.0 (C-3′′), 110.8 (C-5′′), 112.7 (C-1′′), 122.1 (C-4), 123.8 (2 × C-3′,5′), 127.5 (C-2,6 of 2′′-$OCH_2C_6H_5$), 128.4 (2 × C-2′,6′ and C-3,4,5 of 2′′-$OCH_2C_6H_5$), 135.1 (C-1 of 2′′-$OCH_2C_6H_5$), 137.6 (2 × C-1′ and C-4′′), 145.3 (C-3,5), 147.8 (2 × C-4′), 159.2 (C-2′′), 163.6 (C-6′′), 194.5 (C=O) ppm. EI-MS: *m/z* (%) = 536 (44) [$M^{+\cdot}$], 506 (12), 416 (5), 352 (8), 310 (29), 296 (9), 280 (30), 176 (7), 160 (10), 91 (100), 78 (7), 69 (13). $C_{29}H_{20}N_4O_7$ (536.13): calcd. C 64.92, H 3.76, N 10.44; found C 64.87, H 4.00, N 10.67.

3-(2-Benzyloxy-6-hydroxyphenyl)-4-(4-nitrobenzoyl)-5-(4-nitrophenyl)pyrazole (6b): Yellow oil. ^{1}H NMR (DMSO): δ = 4.96 (s, 2 H, 2′-$OCH_2C_6H_5$), 6.30 (d, *J* = 8.3 Hz, 1 H, 5′-H), 6.38 (d, *J* = 8.3 Hz, 1 H, 3′-H), 6.98 (t, *J* = 8.3 Hz, 1H. 4′-H), 7.27−7.33 (m, 5 H, 2,3,4,5,6-H of 2′-$OCH_2C_6H_5$), 7.68 (d, *J* = 8.6 Hz, 2 H, 2′′,6′′-H), 7.88 (d, *J* = 8.7 Hz, 2 H, 2′′′,6′′′-H), 7.94 (d, *J* = 8.6 Hz, 2 H, 3′′,5′′-H), 8.22 (d, *J* = 8.7 Hz, 2 H, 3′′′,5′′′-H), 9.95 (NH), 13.75 (OH) ppm. ^{13}C NMR (DMSO): δ = 69.5 (2′-$OCH_2C_6H_5$), 102.9 (C-3′), 105.0 (C-1′), 108.2 (C-5′), 117.1 (C-4), 122.7 (C-3′′,5′′), 123.4 (C-3′′′,5′′′), 127.2 (C-2,6 of 2′-$OCH_2C_6H_5$), 127.7 (C-4 of 2′-$OCH_2C_6H_5$), 128.4 (C-3,5 of 2′-$OCH_2C_6H_5$), 129.4 (C-2′′′,6′′′), 129.9 (C-2′′,6′′), 131.1 (C-4′), 136.9 (C-1 of 2′-$OCH_2C_6H_5$), 139.6 (C-1′′′), 140.5 (C-3), 143.4 (C-1′′), 146.8 (C-4′′′), 148.8 (C-4′′), 149.6 (C-5), 156.1 (C-6′), 156.7 (C-2′), 189.6 (C=O) ppm. FAB+-MS: *m/z* (%) = 537 (20) [[M + H]$^{+\cdot}$], 536 (7), 307 (23), 289 (13), 154 (100), 136 (70), 120 (13), 107 (23), 91 (51), 77 (20). EI-HRMS: calcd. for $C_{29}H_{20}O_3N_2Cl_2$ ($M^{+\cdot}$) 536.1332, found 536.1334.

4-(2-Benzyloxy-6-hydroxybenzoyl)-3,5-bis(4-chlorophenyl)-pyrazole (5c): M.p. 108−110 °C (recrystallization from methanol). ^{1}H NMR: δ = 4.51 (s, 2 H, 2′′-$OCH_2C_6H_5$), 5.99 (br. d, *J* = 8.2 Hz, 1 H, 3′′-H), 6.54 (dd, *J* = 8.2, 0.6 *Hz*, 1 H, 5′′-H), 6.89 (m, 2 H, 2,6-H of 2′′-$OCH_2C_6H_5$), 7.13 (AB, *J* = 8.3 Hz, 4 H, 2 × 3′,5′-H), 7.16 (AB, *J* = 8.3 Hz, 4 H, 2 × 2′,6′-H), 7.10−7.20 (m, 4 H, 4′′-H and 3,4,5-H of 2′′-$OCH_2C_6H_5$), 11.77 (s, 1 H, 2′′-OH) ppm. ^{13}C NMR: δ = 70.0 (2′′-$OCH_2C_6H_5$), 101.9 (C-3′′), 110.3 (C-5′′), 112.8 (C-1′′), 120.4 (C-4), 126.7 (C-2,6 of 2′′-$OCH_2C_6H_5$), 127.9 (C-4 of 2′′-$OCH_2C_6H_5$), 128.3 (C-3,5 of 2′′-$OCH_2C_6H_5$), 128.4 (2 × C-1′), 128.5 (2 × C-3′,5′), 129.0 (2 × C-2′,6′), 134.8 (2 × C-4′), 135.5 (C-1 of 2′′-$OCH_2C_6H_5$), 136.7 (C-4′′), 147.0 (C-3,5), 159.0 (C-2′′), 163.0 (C-6′′), 194.6 (C=O) ppm. EI-MS: *m/z* (%) = 514 (32) [$M^{+\cdot}$], 379 (6), 289 (5), 91 (100), 65 (6). $C_{29}H_{20}Cl_2N_2O_3$ (514.09): calcd. C 67.58, H 3.91, N 5.44; found C 67.23, H 4.11, N 5.26.

3-(2-Benzyloxy-6-hydroxyphenyl)-4-(4-chlorobenzoyl)-5-(4-chlorophenyl)pyrazole (6c): Yellow oil. ^{1}H NMR: δ = 4.63 (s, 2 H, 2′-$OCH_2C_6H_5$), 6.16 (d, *J* = 8.3 Hz, 1 H, 3′-H), 6.40 (d, *J* = 8.3 Hz, 1 H, 5′-H), 6.86 (t, *J* = 8.3 Hz, 1 H, 4′-H), 7.01−7.05 (m, 6 H, 3′′,5′′,3′′′,5′′′-H and 2,6-H of 2′-$OCH_2C_6H_5$), 7.09−7.18 (m, 5 H, 2′′,6′′-H and 3,4,5-H of 2′-$OCH_2C_6H_5$), 7.49 (d, *J* = 8.5 Hz, 2 H, 2′′′,6′′′-H), 10.36 (br. s, 1 H, NH), 11.77 (br. s, 1 H, 6′-OH) ppm. ^{13}C NMR: δ = 69.9 (2′-$OCH_2C_6H_5$), 104.1 (C-3′), 106.3 (C-1′), 109.7 (C-5′), 117.1 (C-4), 126.9 (C-2,6 of 2′-$OCH_2C_6H_5$), 127.6 (C-4 of 2′-$OCH_2C_6H_5$), 128.1 (C-3′′,5′′), 128.3 (C-3,5 of 2′-$OCH_2C_6H_5$), 128.5 (C-3′′′,5′′′), 129.6 (C-2′′,6′′), 130.7 (C-4′), 130.9 (C-2′′′,6′′′), 134.7 (C-4′′), 135.4 (C-1′′′), 136.3 (2 × C-1′′ and C-1 of 2′-$OCH_2C_6H_5$), 139.1 (C-4′′′), 143.5 (C-3), 147.3 (C-5), 155.4 (C-6′), 156.0 (C-2′), 191.7 (C=O) ppm. EI-MS: *m/z* (%) = 514 (20) [$M^{+\cdot}$], 375 (11), 139 (36), 111 (7), 91 (100), 65 (7). EI-HRMS: calcd. for $C_{29}H_{20}{}^{35}Cl_2N_2O_3$ ($M^{+\cdot}$) 514.0851, found 514.0858.

4-(2-Benzyloxy-6-hydroxybenzoyl)-3,5-bis(4-methoxyphenyl)-pyrazole (5d): M.p. 94−97 °C (recrystallization from methanol). ^{1}H NMR: δ = 3.74 (s, 6 H, 2 × 4′-OCH_3), 4.51 (s, 2 H, 2′′-$OCH_2C_6H_5$), 5.94 (dd, *J* = 8.4, 0.7 *Hz*, 1 H, 3′′-H), 6.51 (dd, *J* = 8.4, 0.7 *Hz*, 1 H, 5′′-H), 6.66 (d, *J* = 8.8 Hz, 4 H, 2 × 3′,5′-H), 6.89 (m, 2 H, 2,6-H of 2′′-$OCH_2C_6H_5$), 7.09 (t, *J* = 8.4 Hz, 1 H, 4′′-H), 7.13−7.17 (m, 3 H, 3,4,5-H of 2′′-$OCH_2C_6H_5$), 7.20 (d, *J* = 8.8 Hz, 4 H, 2 × 2′,6′-H), 11.81 (s, 1 H, 2′′-OH) ppm. ^{13}C NMR: δ = 54.9 (2 × 4′-OCH_3), 69.7 (2′′-$OCH_2C_6H_5$), 101.9 (C-3′′), 109.8 (C-5′′), 113.0 (C-1′′), 113.5 (2 × C-3′,5′), 119.3 (C-4), 122.7 (2 × C-1′), 126.3 (C-2,6 of 2′′-$OCH_2C_6H_5$), 127.6 (C-4 of 2′′-$OCH_2C_6H_5$), 128.1 (C-3,5 of 2′′-$OCH_2C_6H_5$), 129.2 (2 × C-2′,6′), 135.8 (C-1 of 2′′-$OCH_2C_6H_5$), 135.9 (C-4′′), 148.1 (C-3,5), 159.0 (C-2′′), 159.5 (2 × C-4′), 162.6 (C-6′′), 195.1 (C=O) ppm. EI-MS: *m/z* (%) = 506 (100) [$M^{+\cdot}$], 488 (14), 415 (13), 370 (38), 307 (6), 280 (66), 265 (6), 91 (62). $C_{31}H_{26}N_2O_5$ (506.18): calcd. C 73.50, H 5.17, N 5.53; found C 73.23, H 4.91, N 5.31.

3-(2-Benzyloxy-6-hydroxyphenyl)-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)pyrazole (6d): Yellow oil. ^{1}H NMR: δ = 3.66 (s, 3 H, 4′′′-OCH_3), 3.71 (s, 3 H, 4′′′-OCH_3), 4.67 (s, 2 H, 2′-$OCH_2C_6H_5$), 6.15 (d, *J* = 8.2 Hz, 1 H, 3′-H), 6.56 (d, *J* = 8.2 Hz, 1 H, 5′-H), 6.61 (d, *J* = 7.1 Hz, 2 H, 3′′′,5′′′-H), 6.66 (d, *J* = 8.8 Hz, 2 H, 3′′,5′′-H), 6.91 (t, *J* = 8.2 Hz, 1 H, 4′-H), 7.06−7.10 (m, 2 H, 2,6-H of 2′-$OCH_2C_6H_5$), 7.14−7.19 (m, 3 H, 3,4,5-H of 2′-$OCH_2C_6H_5$), 7.26 (d, *J* = 8.8 Hz, 2 H, 2′′,6′′-H), 7.66 (d, *J* = 7.1 Hz, 2 H, 2′′′,6′′′-H), 10.26 (br. s, 1 H, NH), 11.84 (br. s, 1 H, 6′-OH) ppm. ^{13}C NMR: δ = 55.1 (4′′-OCH_3), 55.2 (4′′′-OCH_3),

69.6 (2′-$OCH_2C_6H_5$), 104.2 (C-3′), 107.4 (C-1′), 109.9 (C-5′), 113.1 (C-3‴,5‴), 113.7 (C-3″,5″), 117.2 (C-4), 121.7 (C-1″), 126.6 (C-2,6 of 2′-$OCH_2C_6H_5$), 127.3 (C-4 of 2′-$OCH_2C_6H_5$), 128.2 (C-3,5 of 2′-$OCH_2C_6H_5$), 129.6 (C-2″,6″), 130.1 (C-1‴), 130.3 (C-4′), 132.0 (C-2‴,6‴), 136.9 (C-1 of 2′-$OCH_2C_6H_5$), 144.5 (C-3), 146.6 (C-5), 155.9 (C-6′), 156.2 (C-2′), 159.7 (C-4″), 163.1 (C-4‴), 191.7 (C=O) ppm. EI-MS: *m/z* (%) = 506 (58) [$M^{+\cdot}$], 489 (6), 415 (10), 399 (18), 371 (29), 308 (10), 280 (8), 225 (5), 152 (5), 135 (100), 112 (22), 91 (70), 77 (16), 65 (16), 56 (42). EI-HRMS: calcd. for $C_{31}H_{26}N_2O_5$ ($M^{+\cdot}$) 506.1842, found 506.1845.

4-(2-Benzyloxy-6-hydroxybenzoyl)-3,5-bis(4-methylphenyl)-pyrazole (5e): M.p. 143−144 °C (recrystallization from methanol). ^{1}H NMR: δ = 2.26 (s, 6 H, 2 × 4′-CH_3), 4.49 (s, 2 H, 2″-$OCH_2C_6H_5$), 5.92 (d, *J* = 8.2 Hz, 1 H, 3″-H), 6.50 (d, *J* = 8.2 Hz, 1 H, 5″-H), 6.85 (m, 2 H, 2,6-H of 2″-$OCH_2C_6H_5$), 6.93 (d, *J* = 8.0 Hz, 4 H, 2 × 3′,5′-H), 7.08 (t, *J* = 8.2 Hz, 1 H, 4″-H), 7.10−7.15 (m, 3 H, 3,4,5-H of 2″-$OCH_2C_6H_5$), 7.14 (d, *J* = 8.8 Hz, 4 H, 2 × 2′,6′-H), 11.92 (s, 1 H, 2″-OH) ppm. ^{13}C NMR: δ = 21.2 (2 × 4′-CH_3), 69.8 (2″-$OCH_2C_6H_5$), 101.8 (C-3″), 109.9 (C-5″), 113.0 (C-1″), 119.7 (C-4), 126.4 (C-2,6 of 2″-$OCH_2C_6H_5$), 127.7 (2 × C-1′,2′,6′and C-4 of 2″-$OCH_2C_6H_5$), 128.2 (C-3,5 of 2″-$OCH_2C_6H_5$), 128.8 (2 × C-3′,5′), 135.7 (C-1 of 2″-$OCH_2C_6H_5$), 135.9 (C-4″), 138.2 (2 × C-4′), 148.1 (C-3,5), 159.2 (C-2″), 162.9 (C-6″), 195.3 (C=O) ppm. EI-MS: *m/z* (%) = 474 (65) [$M^{+\cdot}$], 456 (15), 384 (9), 338 (24), 275 (8), 248 (60), 202 (5), 121 (9), 91 (100), 65 (13). $C_{31}H_{26}N_2O_3$ (474.19): calcd. C 78.46, H 5.52, N 5.90; found C 78.42, H 5.63, N 5.92.

3-(2-Benzyloxy-6-hydroxyphenyl)-4-(4-methylbenzoyl)-5-(4-methylphenyl)pyrazole (6e): Yellow oil. ^{1}H NMR: δ = 2.17 (s, 3 H, 4″-CH_3), 2.21 (s, 3 H, 4‴-CH_3), 4.62 (s, 2 H, 2′-$OCH_2C_6H_5$), 6.10 (d, *J* = 8.2 Hz, 1 H, 3′-H), 6.52 (d, *J* = 8.2 Hz, 1 H, 5′-H), 6.86 (t, *J* = 8.2 Hz, 1 H, 4′-H), 6.89 (d, *J* = 7.0 Hz, 2 H, 3″,5″-H), 6.91 (d, *J* = 8.1 Hz, 2 H, 3‴,5‴-H), 7.04−7.07 (m, 2 H, 2,6-H of 2′-$OCH_2C_6H_5$), 7.11−7.22 (m, 5 H, 2″,6″-H and 3,4,5-H of 2′-$OCH_2C_6H_5$), 7.58 (d, *J* = 8.1 Hz, 2 H, 2‴,6‴-H), 10.47 (br. s, 1 H, NH), 11.94 (br. s, 1 H, 6′-OH) ppm. ^{13}C NMR: δ = 21.1 (4″-CH_3), 21.5 (4‴-CH_3), 69.5 (2′-$OCH_2C_6H_5$), 104.0 (C-3′), 107.2 (C-1′), 109.8 (C-5′), 117.3 (C-4), 126.5 (C-2,6 of 2′-$OCH_2C_6H_5$), 127.2 (C-4 of 2′-$OCH_2C_6H_5$), 127.7 (C-1″), 128.1 (C-2″,6″), 128.2 (C-3,5 of 2′-$OCH_2C_6H_5$), 128.5 (C-3‴,5‴), 128.9 (C-3″,5″), 129.7 (C-2‴,6‴), 130.0 (C-4′), 134.8 (C-1‴), 136.8 (C-1 of 2′-$OCH_2C_6H_5$), 138.4 (C-4″), 143.2 (C-4‴), 144.4 (C-3), 147.0 (C-5), 155.9 (C-6′), 156.0 (C-2′), 192.6 (C=O) ppm. EI-MS: *m/z* (%) = 474 (45) [$M^{+\cdot}$], 384 (6), 367 (8), 355 (30), 248 (5), 207 (5), 119 (100), 91 (85), 65 (14). EI-HRMS: calcd. for $C_{31}H_{26}N_2O_3$ ($M^{+\cdot}$) 474.1943, found 474.1946.

Acknowledgments

Sincere thanks are expressed to the University of Aveiro and the "Fundação para a Ciência e Tecnologia", Portugal, for funding the Organic Chemistry Research Unit.

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Received May 8, 2002
[O02250]