Improved Solvent-Free Synthesis and Structure Elucidation of (*E*)- and (*Z*)-4-(Arylmethylene)-3-isochromanones

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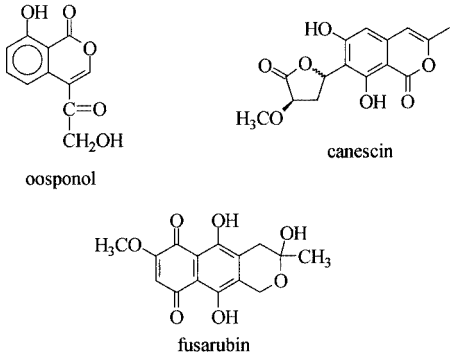
A series of new 4-(arylmethylene)-3-isochromanones **1**–**17** has been prepared by base-catalyzed Knoevenagel condensations. Stereochemical and conformational analyses were performed by ^{1}H and ^{13}C NMR methods, and X-ray crystallography was used to complement the configurational assignment for a representative product. The reaction generally yields the (*E*) isomer, but the isomeric composition of the products was influenced by the aromatic aldehyde and usually governed by the stability of the products. Several aldehydes exclusively afforded the (*Z*) isomer, due to intramolecular steric/electronic interactions reflected in the increased stability of the product. The condensation performed with *ortho*-hydroxyarenecarbaldehydes furnished the unexpected 3-arylcoumarins or 3-arylbenzocoumarins.

Introduction

1-Isochromanone derivatives (isocoumarins) are known to possess a variety of important biological activities. Oosponol, a fungal metabolite, displayed antifungal effects against phytopathogenic fungi[1,2] (Scheme 1). Fusarubine,[3] an antibiotic of isochromane isolated from *Nectria haematococca* strains of *Fusarium solani*, exhibited antibacterial, antifungal, insecticide and phytotoxic effects.[4,5] 3-Isochromanone also plays an important role in the utilization of all fluorene carbon atoms in fluorene metabolism by *Arthrobacter sp.* strain F101.[6] Some α,β-unsaturated ketones are also known to possess antimicrobial effects.[7] 3-(Arylmethylene)-4-chromanones (homoisoflavones) have been isolated from plants (*Liliaceae* family),[8] and both naturally occurring and synthetic homoisoflavones have been investigated for antifungal effects.[5,9] We have also screened some homoisoflavones, such as (*E*)-2-(arylmethylene)-1-tetralones, (*E*)-3-(arylmethylene)-4-chromanones and (*E*)-3-(arylmethylene)-1-thiochroman-4-ones,[10,11] against human pathogenic yeasts (*Cryptococcus neoformans*, *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Trichosporon cutaneum* and *Torulopsis glabrata*). In in vitro tests, some of these showed activities (MIC values) as high as 1.5−6 μg/mL.[12] As an extension of these studies, we set out to study the isomeric 4-(arylmethylene)-3-isochromanones in order to gain a better understanding of the structure-activity relationships.



Scheme 1. Biologically important isochromane derivatives

4-Subsutituted isochromanones have been prepared as fusarubine-type models by pH-controlled Knoevenagel condensations of 3-isochromanone and selected aldehydes such as benzaldehyde and 4-hydroxybenzaldehyde.[13] These reactions resulted in mixtures of the appropriate (*E*) and

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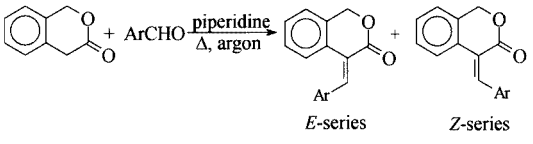
(*Z*) isomers with yields of 8−30%, but the majority of the starting 3-isochromanone hydrolysed under the basic conditions to give the corresponding hydroxycarboxylic acids. Prolonged reaction times only give improved yields (46−60%) with long-chain aliphatic aldehydes,[14] and so this synthetic procedure does not allow for efficient or high-throughput preparation of combinatorial libraries involving reagents with multiple points of diversification (i.e., substituted isochromanones and substituted aromatic aldehydes). In addition, it cannot easily be scaled up for the preparation of gram quantities of 4-(arylmethylene)-3-isochomanones. We now report a new, one-step method for the preparation of this class of compounds that satisfies the above requirements, along with the structural verification of the products. The selection of the aromatic aldehydes in our study was guided by previous knowledge of the structure-(antimicrobial) activity relationships.[10,11] The Knoevenagel condensation involving 3-isochromanones generally yields an excess of the (*E*) isomer of the product. On the other hand, the choice of aromatic aldehyde may under specific circumstances bring about the predominant formation of (*Z*) isomers. With aliphatic aldehydes as reactants, the steric strain of the product formed was a governing factor.[14] Our experimental efforts were therefore supported by theoretical studies to address the selectivity observed in the reaction.

Results and Discussion

If the Knoevenagel condensation is conducted in alcohols, the opening of the lactone ring of the isochromanone consumes a large portion of the starting material. A method in which the title compounds were synthesized under solvent-free conditions was therefore developed. Typically, a few drops of piperidine would be added as a catalyst to a mixture of 3-isochromanone and an appropriate aromatic aldehyde, and the molten reaction mixture would then be stirred at 140 °C for 1 h. After the reaction mixture had cooled to room temperature, compounds **1**−**17** (Scheme 2 and Table 1) were obtained in better yields (50−97%) than reported in the literature by traditional methods. The degree of conversion was found to be 100% under the conditions applied.



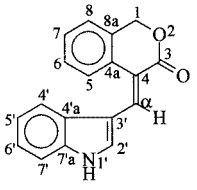
Scheme 2. Preparation of 4-(arylmethylene)-3-isochromanones **1**−**17**

In order to examine the possibility of (*E*)/(*Z*) isomerization of the products during the Knoevenagel condensation, pure isomers were heated under Ar at 140 °C in the presence of piperidine for 1 h. Neither the (*E*) nor the (*Z*) isomers changed. This finding ruled out the isomerization of the product 4-(arylmethylene)-3-isochromanones during their preparation and indicated that they were formed in thermodynamically controlled reactions.

Table 1. Isomeric composition of **1**−**17**

Compound	Ar	Isomeric composition
1	Ph	60% (*E*), 40% (*Z*)
2	4′-$HO_2CC_6H_4$	100% (*E*)
3	3′-pyridyl	100% (*E*)
4	1′-methyl-2′-pyrrolyl	66% (*E*), 33% *Z*)
5	2′-pyrrolyl	100% (*Z*)
6	2′,6′-$Cl_2C_6H_3$	100% (*Z*)
7	2′-$CH_3OC_6H_4$	100% (*E*)
8	2′-ClC_6H_4	70% (*E*), 30% (*Z*)
9	2′,3′-$(CH_3O)_2C_6H_3$	100% (*E*)
10	2′,4′-$(CH_3O)_2C_6H_3$	100% (*E*)
11	2′-$O_2NC_6H_4$	33% (*E*), 66% (*Z*)
12	2′-hydroxy-1′-naphthyl	coumarin
13	2′-furyl	66% (*E*), 33% (*Z*)
14	3′-indolyl	20% (*E*), 80% (*Z*)
15	2′-BrC_6H_4	100% (*E*)
16	2′-HOC_6H_4	coumarin
17	3′-HOC_6H_4	100% (*E*)

The generally accepted method used to determine which isomer is present is based solely on the ^1H chemical shift of the methine proton (Scheme 3).[13,14] The overlap in the observed chemical shift ranges for this proton [δ = 8.14−7.55 ppm for the (*E*) series versus δ = 7.74−7.11 ppm for the (*Z*) series], however, indicates that this way to assign the configuration is in fact unreliable when one single isomer is formed. In the NOESY or ROESY spectra of the compounds studied here, the presence of a cross-peak between α-H and 5-H clearly attests to the steric proximity of these protons [i.e., the (*Z*) configuration in the case of compounds **1*Z***, **4*Z***−**6*Z***, **8*Z***, **13*Z*** and **14*Z***], but spectral crowding can prevent the use of these techniques (such as for derivative **11*Z***, in which α-H and 5-H are isochronous). In the same way, the (*E*) configuration is indicated by strong NOE correlations between aromatic protons 5-H and 6′-H (for **1*E***, **2*E***, **7*E***−**11*E***, **15*E*** and **17*E***), 5-H and 2′-H (for **1*E***−**3*E***, **14*E*** and **17*E***), 5-H and 4′-H (for **3*E***) or 5-H and 3′-H (for **4*E*** and **13*E***).



Scheme 3. Numbering of heavy atoms for NMR assignment of **14*E***

On the other hand, little is known about the usefulness of ^{13}C NMR spectroscopy for the assignment of the configurations of these ene-lactones, in spite of the apparent differences in the carbon spectra of the two stereoisomers. It is worth mentioning here that, for the compounds in this study, the use of [D_6]DMSO as NMR solvent results in

better ^{1}H chemical shift separation than with $CDCl_3$, as exemplified for compound **9*E***, facilitating the assignment of the carbon signals. One characteristic difference is the chemical shift order: δ(C-7) > δ(C-6) > δ(C-5) > δ(C-8) for the (*E*) series versus δ(C-6) > δ(C-7) > δ(C-8) > δ(C-5) for the (*Z*) series. Similarly, δ(C-8a) > δ(C-4a) holds for compounds with the (*E*) configuration, whereas δ(C-4a) > δ(C-8a) applies for the (*Z*) family. The C-3 signal is more shielded in the (*Z*) series (Δδ ≈ 3−4 ppm), most probably due to steric crowding. Another straightforward way to corroborate the configuration across the double bond is by inspection of the well-resolved ^{13}C signal of C-3, which has a double triplet multiplicity in the proton-coupled experiment. The magnitude of the $^3J_{\alpha\text{-H,C-3}}$ coupling constants unequivocally proves the configuration of the double bond [ca. 13 Hz for (*Z*) isomers, and ca. 7 Hz for (*E*)]. The UV spectra of the different isomers generally show two absorption maxima. For compounds **1**, **4**, **8** and **11**, the molar absorption of higher wavelength maxima is greater for the (*E*) isomers. Other than this, there are no characteristic differences between the spectral properties of the (*E*) and (*Z*) isomers. Probably, no extended conjugation exists between the isochromanone ring and the aryl group; this would explain the similarities in the UV spectra of the isomers. However, the tendency described above is not valid for the furyl derivatives **13*E*** and **13*Z***, in which the (*Z*) isomer has a greater molar absorption at the higher wavelength maxima. Certainly, in this compound, perfect conjugation can be attained between the isochromanone and the furan ring, and possibly the most stable conformation is when the furyl ring is in the plane of the isochromanone ring. It is possible for this compound to adopt a conformation in which the six atoms are in plane. In the cases of the five-membered aryl derivatives (**4**, **5** and **13**) there is generally greater absorbance at higher wavelength maxima than in the phenyl derivatives. This may relate to a greater degree of conjugation due to a more planar conformation for these five-membered compounds, which suffer less steric repulsion than the phenyl analogs.

Another possible isomer type for several compounds synthesized in this study was found on confirmation of our spectroscopy-based structure assignment by X-ray crystallography. The unit cell of single crystals grown from **13*E*** contained an isomer pair obtainable by rotation of the heteroaromatic ring (rotamers), as shown in Figure 1. The rotamers are designated as **13*E*1** and **13*E*2**, respectively, depending on whether the oxygen atom of the furyl ring is on the opposite side to, or on the same side as, the CO group. A similar convention is used for compounds **4**, **5** and **14**. We therefore included these possible rotamers of the compounds in the attempted theoretical interpretation of the stereoselectivity observed for their formation. This could be predicted fairly accurately by considering the calculated stability (indicated by the heats of formation, $\Delta H_f°$) of the isomeric reaction products. Table 2 summarizes the $\Delta H_f°$ values for the isomers and, if they exist, rotamers calculated by a semiempirical quantum-chemical method (PM3) for compounds **1**−**17**.

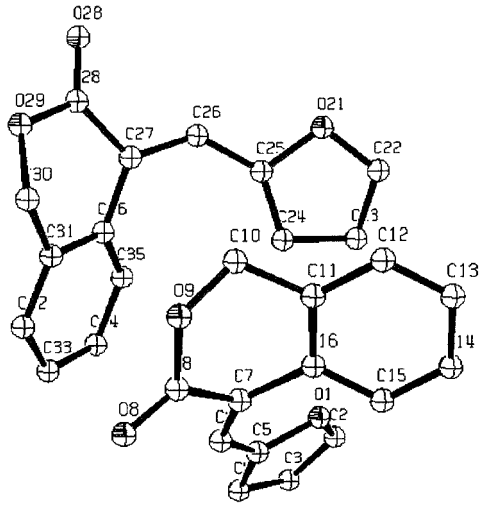


Figure 1. X-ray crystallography ORTEP diagram (30% thermal ellipsoids) showing the two rotamers in the unit cell of **13*E***

Table 2. Heats of formation [kcal/mol] of the condensation products **1**−**17**; parentheses indicate that the isochromanones are not obtained

Compound	(*E*) isomer(s)	(*Z*) isomer(s)
1	−12.9	−12.0
2	−102.0	−101.5
3	−5.5	−5.2
4	−10.8 (*E1*)	−10.4 (*Z1*)
	−11.8 (*E2*)	−10.5 (*Z2*)
5	−11.1 (*E1*)	−9.8 (*Z1*)
	−11.0 (*E2*)	−16.6 (*Z2*)
6	−25.4	−26.7
7	−49.2	−48.7
8	−18.2	−17.8
9	−82.3	−83.2
10	−87.5	−86.9
11	−16.9	−18.4
12[a]	(−37.4)	(−37.8)
13	−38.3 (*E1*)	−38.1 (*Z1*)
	−39.2 (*E2*)	−38.1 (*Z2*)
14	4.8 (*E1*)	5.9 (*Z1*)
	5.9 (*E2*)	1.8 (*Z2*)
15	−3.7	−3.6
16[b]	(−56.4)	(−56.0)
17	−57.9	−57.0

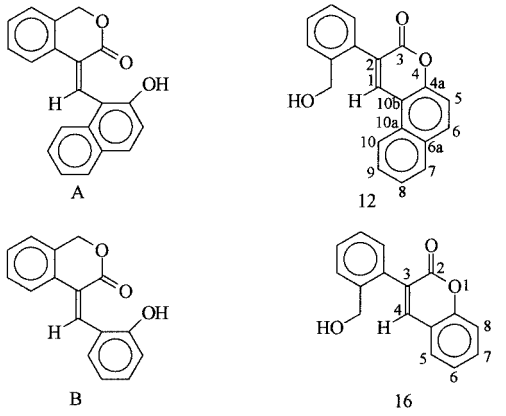
[a] Benzocoumarin: ΔH_f = (1−42.0 kcal/mol. [b] Coumarin: ΔH_f = (1−58.7 kcal/mol.

The synthetic procedure was in most cases expected to provide the (*E*) isomer with exclusive stereoselectivity, because aldol condensations are known usually to afford (*E*) isomers, except when a high degree of steric overcrowding renders the (*E*) isomers less stable than the (*Z*) isomers.[15,16] For example, the condensation of the 2,2-diphenylchromanone with benzaldehyde furnishes the (*Z*) isomer.[17] The generally used method to prepare (*Z*) isomers of the exocyclic α,β-unsaturated cyclic ketones is the photochemical isomerization of the (*E*) isomers.[15,16] Nevertheless, the piperidine-catalyzed condensation of 3-isochromanone with

benzaldehyde, 2-nitrobenzaldehyde, 2-chlorobenzaldehyde, 2-furaldehyde, *N*-methylpyrrole-2-carbaldehyde and indole-3-carbaldehyde furnished mixtures of the (*E*) and (*Z*) isomers, whereas 2,6-dichlorobenzaldehyde and pyrrole-2-carbaldehyde gave exclusively the (*Z*) isomers. The mixtures of isomers were separated by column chromatography, except for the **14*E*** and **14*Z*** isomeric pair, which readily interconvert.

In the case of **5*Z*** (obtained from pyrrole-2-carbaldehyde), the hydrogen-bonded chelate ring stabilizes the (*Z*) configuration, according to the IR and NMR spectroscopic data.[18] This stabilization is also reflected by the decrease in the PM3-calculated heat of formation (i.e., higher stability than the other isomeric forms) for the appropriate rotamer, as given in Table 2. The significance of hydrogen bonding is apparent, since the same conformation does not show such a distinct increase in the stability of the corresponding isomer when *N*-methylpyrrole-2-carbaldehyde is involved as a reactant during condensation (compounds **4*El Z***), the reaction indeed furnishing a mixture rich in the **4*E*** isomer, which is the preferred isomer by the underlying mechanism. The observed selectivity (or lack thereof) can be explained by considering heats of formation for most of the compounds studied, except for 2,6-dichlorobenzaldehyde, which requires further scrutiny.

Knoevenagel condensations of 3-isochromanone with 2-hydroxybenzaldehyde and 2-hydroxy-1-naphthaldehyde did not yield (arylmethylene)-3-isochromanones. In the ^{1}H NMR spectra of the products the methylene signal appears as a doublet and is coupled to a triplet that disappears upon addition of D_2O, indicating the presence of an opened lactone ring of the 3-isochromanone moiety, whereas atmospheric pressure chemical ionization (APCI) mass spectra showed the expected molecular ions. These observations could be resolved by invoking a putative internal attack of the *ortho*-hydroxy group on the carbonyl center, well situated for such an attack in the intermediate (*Z*) isomer (**A** and **B**), which results in the formation of benzocoumarin derivative **12** or coumarin **16** (Scheme 4) in a way similar to that found in the reaction between a (triphenylphosphoranylidene)benzofuran-2(3*H*)-one derivative and salicylaldehydes.[18] The observed ^{1}H and ^{13}C NMR spectra are consistent with the presence of these skeletons[19−21] (especially when compared to the product formed from 3-hydroxybenzaldehyde). In particular, the ca. 4−7 ppm shielding of the carbonyl signals in the ^{13}C data showed increased conjugation, and the measured (ca. 10 Hz) $^3J_{4\text{-H,C-2}}$ and $^3J_{1\text{-H,C-3}}$ coupling values for **16** and **12**, respectively, were clearly in good agreement with the presence of the C-3 (for **16**) or C-2 (for **12**) phenyl-substituted endocyclic double bond.[22] In order to rule out the possible nucleophilic effect of the basic catalyst, used in excess because of the acidic character of the reagent, the reaction between 3-isochromanone and salicylaldehyde was reexamined with smaller amounts of catalyst. In a separate experiment, acidification of the reaction mixture was also performed at the end of the reaction. In both cases, the products were identical to **16** in every respect. Again, the formation of the coumarin and benzocoumarin from these reactants can be explained by the significant decrease in the ΔH_f° relative to the corresponding (arylmethylene)-3-isochromanones, as shown in Table 2.



Scheme 4. Structures of coumarins (**12**, **16**) and the possible precursor isochromanones (**A**, **B**)

Conclusion

In conclusion, we have synthesized a series of 4-(arylmethylene)-3-isochromanones with improved yields in a solvent-free, one-step reaction. These reactions probably proceed as tandem Knoevenagel condensations followed by dehydration steps. In several instances these condensations unexpectedly furnished the (*Z*) isomers as sole products, and the selectivity (or the lack thereof) could be explained by considering the relative stability of the isomeric forms. ^{13}C NMR spectroscopic data have been collected for these compounds, and it has been established that the ^{13}C chemical shift of C-3, the chemical shift order of C-6, C-7, C-8 and C-5, and also the $^3J_{\alpha\text{-H,C-3}}$ coupling constant can be used to differentiate between the (*E*) and (*Z*) isomers, which might be especially important when only one stereoisomer is formed in the reaction. The condensation performed with *ortho*-hydroxyarenecarbaldehydes furnished the unexpected 3-arylcoumarins or 3-arylbenzocoumarins. Members of the latter class of compounds have been reported to have several biological effects, such as regulation of plant growth and antagonistic action on sex hormones.[23] The preparation of the 3-arylcoumarins and 3-arylbenzocoumarins usually employs phenylacetic acid and salicylaldehyde as reactants or starts from acrylonitrile derivatives.[23,24] However, our methods could be considered to be a simple procedure for the one-pot synthesis of several functionalized 3-arylcoumarins (e.g., 2′-hydroxymethyl derivatives) or 3-arylbenzocoumarins.

Experimental Section

General Remarks: The reagents used were purchased from Aldrich Chemical Co. and Fluka and were not further purified. Column

chromatography was performed on Merck silica gel (60, particle size 0.040−0.063 mm). Thin layer chromatography (TLC) was performed on Merck silica gel plates (60 F_{254}), the eluents are mentioned in the description of the new compounds. NMR spectra were recorded with Varian Unity+ 300 (300/75 MHz for $^1H/^{13}C$) and Varian ^{UNITY}INOVA 400 WB (400/100 MHz for $^1H/^{13}C$) spectrometers. Chemical shift (δ) data are given in ppm with reference to TMS (^1H NMR), or measured relative to the central peak of the solvents at δ = 76.9 ppm ($CDCl_3$) or δ = 39.6 ppm [D_6]DMSO in ^{13}C NMR experiments. Signal assignments for each compound were achieved by double resonance, 1D difference NOE, and 2D NMR experiments (^1H-^1H COSY, ^1H-^{13}C HETCOR, COLOC, NOESY, ROESY) using standard software. Carbon multiplicities and overlapping quaternary signals were identified by APT experiments. Assignments were corroborated by spectral simulation (g NMR, Cherwell Scientific Publishing) and by comparison with literature data.[18−22,25−27] UV/Vis spectra were recorded with a Beckman DU 65 spectrophotometer in ethanol. Atmospheric pressure chemical ionization (APCI) mass spectra were recorded with an ion-trap instrument (LCQ, ThermoFinnigan, San Jose, CA). Melting points were determined with a Boetius hot plate apparatus and are uncorrected. Molecular modeling was performed with Chem3D Ultra (version 5.0, CambridgeSoft, Cambridge, MA) incorporating the MOPAC97 semiempirical quantum-chemical package. The PM3 parametrization[29] and in vacuo conditions were used. Geometries were optimized to a gradient norm of < 0.1 kcal/mol.

General Procedure for the Synthesis of 4-(Arylmethylene)-3-isochromanones: A mixture of 3-isochromanone (6.75 mmol), the appropriate aldehyde (6.75 mmol) and five drops of piperidine was stirred at 140 °C under argon for 1 h. The mixture was allowed to cool to room temperature, and the oily residue was crystallized from ethanol. A second recrystallisation from methanol gave pure products. In some cases the products were purified by column chromatography.

(*E*)-4-(Phenylmethylene)-3-isochromanone (1*E*) and (*Z*)-4-(Phenylmethylene)-3-isochromanone (1*Z*): These compounds were obtained from 3-isochromanone (0.56 g, 3.75 mmol) and benzaldehyde (0.40 g, 3.75 mmol) as a 3:2 mixture of (*E*)/(*Z*) diastereoisomers (based on separation). Recrystallization from methanol gave **1*E*** and **1*Z*** (0.51 g, 57% yield). The isomeric mixture was separated by column chromatography (silica gel) with dichloromethane as eluent. **1*E*:** UV (ethanol): λ_{max} (log ε) = 230 nm (4.49), 321 (4.40). ^1H NMR ([D_6]DMSO): δ = 5.53 (s, 1-H_2), 7.30 (t, 6-H), 7.35 (d, 5-H), 7.46 (m, 7-H), 7.53−7.41 (m, 3′-H, 4′-H, 5′-H), 7.56 (d, 8-H), 7.61 (m, 2′-H, 6′-H), 7.84 (s, α-H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 68.8 (C-1), 125.4 (C-4), 125.8 (C-8), 126.7 (C-5), 127.8 (C-6), 128.6 (C-7), 128.7 (C-3′, C-5′), 129.3 (C-2′, C-6′), 129.6 (C-4′), 130.0 (C-4a), 133.2 (C-8a), 134.2 (C-1′), 137.7 (C-α), 167.8 (dt, $^3J_{α\text{-H,C-3}}$ = 7.4, $^3J_{1\text{-H,C-3}}$ = 5.2 Hz, C-3). **1*Z*:** UV (ethanol) λ_{max} (log ε) 229 nm (3.94), 316 (4.11). ^1H NMR ([D_6]DMSO): δ = 5.50 (s, 1-H_2), 7.54−7.45 (m, 3′-H, 5′-H, 8-H, 4′-H), 7.54 (m, 7-H), 7.59 (m, 6-H), 7.60 (s, α-H), 7.81 (m, 2′-H, 6′-H), 7.89 (d, 5-H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 68.9 (C-1), 124.0 (C-5), 125.0 (C-8), 125.4 (C-4), 128.3 (C-3′, C-5′), 128.5 (C-7), 129.3 (C-6), 129.5 (C-4′), 130.3 (C-2′, C-6′), 132.1 (C-8a), 134.4 (C-4a), 134.8 (C-1′), 139.8 (C-α), 165.9 (dt, $^3J_{α\text{-H,C-3}}$ = 13.1, $^3J_{1\text{-H,C-3}}$ = 5.0 Hz, C-3) ppm. All the physical data for **1*E*** and **1*Z*** are in accordance with those published by Barbier.[13]

4-[(*E*)-3-Oxoisochroman-4-ylidene]benzoic Acid (2*E*): This compound was obtained from 3-isochromanone (1.00 g, 6.75 mmol) and 4-formylbenzoic acid (1.01 g, 6.75 mmol). Recrystallization from methanol gave **2*E*** as white crystals (1.10 g, 57% yield). M.p. 201 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 235 nm (4.88), 327 (4.80). ^1H NMR ([D_6]DMSO): δ = 5.56 (s, 1-H_2), 7.4−7.3 (m, 6-H, 5-H), 7.48 (dt, 7-H), 7.56 (d, 8-H), 7.71 (d, 2′-H, 6′-H), 7.87 (s, H-α), 8.02 (d, 3′-H, 5-H′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 68.9 (C-1), 125.9 (C-8), 126.96 (C-5), 127.0 (C-4), 128.0 (C-6), 128.9 (C-7), 129.4 (C-2′, C-6′), 129.56 (C-4a), 129.6 (C-3′, C-5′), 131.2 (C-4′), 133.4 (C-8a), 136.5 (C-α),138.8 (C-1′), 166.8 (dt, $^3J_{α\text{-H,C-3}}$ = 7.5, $^3J_{1\text{-H,C-3}}$ = 5.2 Hz, C-3), 167.5 (*C*OOH) ppm. $C_{17}H_{12}O_4$ (280.28) calcd. C 72.85, H 4.32; found C 72.76, H 4.51.

(*E*)-4-(Pyridin-3′-ylmethylene)-3-isochromanone (3*E*): This compound was obtained from 3-isochromanone (1.00 g, 6.75 mmol) and pyridine-3-carbaldehyde (0.72 g, 6.75 mmol). Recrystallization from methanol gave **3*E*** as faint yellow crystals (1.00 g, 62% yield). M.p. 131 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 228 nm sh (4.31) 317 (4.18). ^1H NMR ([D_6]DMSO): δ = 5.56 (s, 1-H_2), 7.30 (m, 5-H), 7.33 (m, 6-H), 7.48 (m, 7-H), 7.51 (m, 5′-H), 7.58 (d, 8-H), 7.84 (s, α-H), 8.00 (dt, 4′-H), 8.64 (dd, 6′-H), 8.76 (m, 2′-H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 68.9 (C-1), 123.6 (C-5′), 125.9 (C-8), 126.6 (C-5), 127.3 (C-4), 128.1 (C-6), 128.9 (C-7), 129.5 (C-4a), 130.5 (C-3′), 133.5 (C-8a), 134.2 (C-α), 136.3 (C-4′), 149.9 (C-6′), 150.0 (C-2′), 167.4 (dt, $^3J_{α\text{-H,C-3}}$ = 7.3, $^3J_{1\text{-H,C-3}}$ = 5.3 Hz, C-3) ppm. $C_{15}H_{11}NO_2$ (237.26): calcd. C 75.94, H 4.67, N 5.90; found C 76.07; H 4.76, N 5.81.

(*E*)-4-[(1′-Methyl-1*H*-pyrrol-2′-yl)methylene]-3-isochromanone (4*E*) and (*Z*)-4-[(1′-Methyl-1*H*-pyrrol-2′-yl)methylene]-3-isochromanone (4*Z*): These compounds were obtained as a 2:1 mixture of (*E*)/(*Z*) diastereoisomers (based on separation) from 3-isochromanone (1.00 g, 6.75 mmol) and 1-methylpyrrole-2-carbaldehyde (0.74 g, 6.75 mmol) by the above procedure (0.80 g, 50% yield). The isomeric mixture was separated by column chromatography (silica gel) and eluted with petroleum ether/dichloromethane (30:70). **4*E*:** Orange crystals from methanol; m.p. 127 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 251 nm (4.56), 389 (4.79). ^1H NMR ([D_6]DMSO): δ = 3.85 (s, N−CH_3), 5.38 (s, 1-H_2), 6.19 (dd, 4′-H), 6.91 (dd, 3′-H), 7.20 (t, 5′-H), 7.5−7.4 (m, 6-H, 7-H), 7.53 (m, 8-H), 7.68 (s, α-H), 8.06 (m, 5-H) ppm. ^{13}C NMR ([D_6]DMSO). δ = 34.0 (N−*C*H_3), 68.4 (C-1), 108.9 (C-4′), 112.6 (C-3′), 117.7 (C-4), 125.4 (C-α), 125.7 (C-5, C-8), 127.0 (C-2′), 127.7 (C-6), 128.0 (C-7), 128.2 (C-5′), 131.0 (C-4a), 132.7 (C-8a), 168.8 (dt, $^3J_{α\text{-H,C-3}}$ = 7.5, $^3J_{1\text{-H,C-3}}$ = 5.3 Hz, C-3) ppm. $C_{15}H_{13}NO_2$ (239.27): calcd. C 75.30, H 5.48, N 5.85; found C 75.21, H 5.32, N 5.99. **4*Z*:** Orange crystals from methanol; m.p. 116 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 251 nm (4.30), 385 (4.75). ^1H NMR ($CDCl_3$): δ = 3.75 (s, N−CH_3), 5.21 (s, 1-H_2), 6.27 (dd, 4′-H), 6.84 (t, 5′-H), 7.11 (s, α-H),7.20 (d, 8-H), 7.29 (dt, 7-H), 7.39 (dt, 6-H), 7.47 (d, 5-H), 7.76 (dd, 3′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.3 (N−*C*H_3), 68.8 (C-1), 109.5 (C-4′), 116.7 (C-4), 118.2 (C-3′), 122.9 (C-5), 124.1 (C-8), 126.4 (C-α),126.9 (C-7), 127.9 (C-5′), 128.3 (C-2′), 128.9 (C-6), 131.1 (C-8a), 136.0 (C-4a), 165.8 (dt, $^3J_{α\text{-H,C-3}}$ = 12.5, $^3J_{1\text{-H,C-3}}$ = 5.1 Hz, C-3) ppm. $C_{15}H_{13}NO_2$ (239.27): calcd. C 75.30, H 5.48, N 5.85; found C 75.42, H 5.59, N 5.90.

(*Z*)-4-[(Pyrrol-2′-yl)methylene]-3-isochromanone (5*Z*): This compound was obtained from 3-isochromanone (1.00 g, 6.75 mmol) and pyrrole-2-carbaldehyde (0.64 g, 6.75 mmol). Recrystallization from methanol gave **5*Z*** as dark red crystals (1.13 g, 74% yield). M.p. 85−86 °C. UV (ethanol): λ_{max} (log ε) 256 nm (4.36), 384 (4.80). ^1H NMR ($CDCl_3$): δ = 5.27 (s, 1-H_2), 6.36 (m, 4′-H), 6.72 (m, 3′-H), 7.10 (m, 5′-H), 7.19 (d, 8-H), 7.28 (m, 7-H), 7.30 (s, H-α),7.39 (dt, 6-H), 7.52 (d, 5-H), 12.03 (NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.5 (C-1), 111.1 (C-4′), 113.1 (C-4), 121.5 (C-3′), 122.9 (C-5), 124.1 (C-8), 124.3 (C-5′), 126.8 (C-7), 128.7 (C-2′),

129.0 (C-6), 129.8 (C-8a), 130.5 (C-α), 135.0 (C-4a), 169.0 (C-3) ppm. $C_{14}H_{11}NO_2$ (225.25): calcd. C 74.65, H 4.92, N 6.22; found C 74.79, H 5.01, N 6.29.

(*Z*)-4-[(2′,6′-Dichlorophenyl)methylene]-3-isochromanone (6*Z*): This compound was obtained from 3-isochromanone (1.00 g, 6.75 mmol) and 2,6-dichlorobenzaldehyde (1.18 g, 6.75 mmol). Recrystallization from methanol gave **6*Z*** as faint yellow crystals (1.22 g, 59% yield). M.p. 158 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 288 nm (3.98). ^{1}H NMR ($CDCl_3$): δ = 5.35 (s, 1-H_2), 7.17 (s, α-H), 7.21 (m, 4′-H), 7.26 (d, 8-H), 7.37 (m, 3′-H, 5′-H), 7.41 (dt, 7-H), 7.47 (dt, 6-H), 7.73 (d, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.2 (C-1), 124.0 (C-5), 124.4 (C-8), 127.8 (C-5′, C-3′), 129.0 (C-7), 129.2 (C-6), 129.3 (C-4′), 130.0 (C-4), 131.5 (C-8a), 131.8 (C-α), 132.5 (C-4a), 133.4 (C-2′, C-6′), 133.8 (C-1′), 164.5 (dt, $^3J_{H\alpha,C3}$ = 12.7, $^3J_{1H,C3}$ = 5.0 Hz, C-3) ppm. $C_{16}H_{10}Cl_2O_2$ (305.16): calcd. C 62.98, H 3.30; found C 62.82, H 3.44.

(*E*)-4-[(2′-Methoxyphenyl)methylene]-3-isochromanone (7*E*): This compound was prepared from 3-isochromanone (1.00 g, 6.75 mmol) and 2-methoxybenzaldehyde (0.92 g, 6.75 mmol). Recrystallization from methanol gave **7*E*** as faint yellow crystals (1.41 g, 78% yield). M.p. 113 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 234 nm (4.33), 341 (4.20). ^{1}H NMR ($CDCl_3$): δ = 3.79 (2′-OCH_3), 5.29 (s, 1-H_2), 6.77 (t, 5′-H), 6.91 (d, 3′-H), 7.10 (m, 6-H), 7.22 (m, 8-H), 7.23 (m, 7-H), 7.30 (m, 4′-H), 7.32 (2 × d, 5-H, 6′-H), 8.03 (s, α-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.3 (2′-O*C*H_3), 69.1 (C-1), 111.0 (C-3′), 120.0 (C-5′), 123.3 (C-1′), 124.6 (C-4), 124.8 (C-8), 127.1 (C-5), 127.7 (C-6), 127.9 (C-7), 129.4 (C-6′), 130.9 (C-4a, C-6′), 132.0 (C-8a), 135.0 (C-α),158.0 (C-2′), 168.4 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 7.3, $^3J_{1\text{-H,C-3}}$ = 5.0 Hz, C-3) ppm. $C_{17}H_{14}O_3$ (266.29): calcd. C 76.68, H 5.30; found C 76.79, H 5.44.

(*E*)-4-[(2′-Chlorophenyl)methylene]-3-isochromanone (8*E*) and (*Z*)-4-[(2′-Chlorophenyl)methylene]-3-isochromanone (8*Z*): These compounds were obtained as a 7:3 mixture of (*E*)/(*Z*) diastereoisomers (based on separation) prepared from 3-isochromanone (1.00 g, 6.75 mmol) and 2-chlorobenzaldehyde (0.95 g, 6.75 mmol) by the above procedure (1.24 g, 68% yield). The isomeric mixture was separated by column chromatography (silica gel) and eluted with dichloromethane. **8*E*:** Faint yellow crystals from methanol; m.p. 103 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 228 nm (4.18), 310 (4.06). ^{1}H NMR ([D_6]DMSO): δ = 5.57 (s, 1-H_2), 7.06 (d, 5-H), 7.25 (t, 6-H), 7.36 (t, 5′-H), 7.44 (m, 7-H), 7.45 (d, 6′-H), 7.52 (m, 4′-H), 7.54 (d, 8-H), 7.70 (d, 3′-H), 7.87 (s, α-H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 68.9 (C-1), 125.7 (C-8), 126.6 (C-5), 127.3 (C-5′), 127.5 (C-4), 128.0 (C-6), 128.8 (C-7), 129.4 (C-4a), 129.9 (C-3′), 130.2 (C-6′), 130.9 (C-4′), 133.1 (C-8a, C-2′), 133.3 (C-1′), 134.2 (C-α), 167.1 (dt, $^3J_{H\alpha,C3}$ = 7.3, $^3J_{1H,C3}$ = 5.1 Hz, C-3) ppm. $C_{16}H_{11}ClO_2$ (270.72): calcd. C 70.99, H 4.10; found C 70.81, H 4.33. **8*Z*:** Faint yellow crystals from methanol; m.p. 122 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 229 nm (4.17) 304 (4.26). ^{1}H NMR ([D_6]DMSO): δ = 5.56 (s, 1-H_2) 7.47 (m, 5′-H), 7.48 (m, 4′-H), 7.53 (m, 8-H), 7.57 (m, 7-H), 7.62 (m, 6-H), 7.63 (m, 3′-H), 7.68 (s, α-H), 7.74 (m, 6′-H), 7.88 (d, 5-H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 68.7 (C-1), 123.9 (C-5), 124.9 (C-8), 126.7 (C-5′), 127.6 (C-4), 128.8 (C-7), 129.0 (C-3′), 129.1 (C-6), 130.1 (C-4′), 131.1 (C-6′), 131.9 (C-8a), 132.1 (C-2′), 132.7 (C-4a), 134.2 (C-1′), 135.6 (C-α), 164.7 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 12.7, $^3J_{1\text{-H,C-3}}$ = 5.0 Hz, C-3) ppm. $C_{16}H_{11}ClO_2$ (270.72): calcd. C 70.99, H 4.10; found C 71.11, H 4.20.

(*E*)-4-[(2′,3′-Dimethoxyphenyl)methylene]-3-isochromanone (9*E*): This compound was prepared from 3-isochromanone (1.00 g, 6.75 mmol) and 2,3-dimethoxybenzaldehyde (1.12 g, 6.75 mmol). Recrystallization from methanol gave **9*E*** as faint yellow crystals (1.66 g, 83% yield). M.p. 136 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 250 nm, shoulder (3.66), 323 (3.63). ^{1}H NMR ([D_6]DMSO): δ = 3.89 (2′-OCH_3), 3.94 (3′-OCH_3), 5.50 (s, 1-H_2), 6.90 (m, 6′-H), 7.04 (t, 5′-H), 7.13 (dd, 4′-H), 7.25 (m, 5-H), 7.27 (m, 6-H), 7.43 (m, 7-H), 7.52 (d, 8-H), 7.87 (s, α-H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 56.1 (3′-O*C*H_3), 61.0 (2′-O*C*H_3), 69.1 (C-1), 114.4 (C-4′), 120.9 (C-6′), 124.3 (C-5′), 125.9 (C-8), 126.2 (C-4), 127.0 (C-5), 128.1 (C-6), 128.6 (C-1′), 128.8 (C-7), 130.2 (C-4a), 133.1 (C-8a), 134.0 (C-α),147.9 (C-2′), 152.9 (C-3′), 168.1 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 7.3, $^3J_{1\text{-H,C-3}}$ = 4.9 Hz, C-3). ^{1}H NMR ($CDCl_3$): δ = 3.88 (2′-O*C*H_3), 3.89 (3′-O*C*H_3), 5.32 (s, 1-H_2), 6.87 (m, 5′-H, 6′-H), 6.91 (m, 4′-H), 7.11 (m, 6-H), 7.24 (m, 8-H), 7.26 (m, 7-H), 7.30 (d, 5-H), 8.02 (s, α-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.7 (3′-O*C*H_3), 61.2 (2′-O*C*H_3), 69.1 (C-1), 113.3 (C-4′), 121.0 (C-6′), 123.5 (C-5′), 124.8 (C-8), 125.6 (C-4), 127.4 (C-5), 127.8 (C-6), 128.2 (C-7), 128.8 (C-1′), 130.6 (C-4a), 132.1 (C-8a), 134.8 (C-α), 148.3 (C-2′), 152.9 (C-3′), 168.1 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 7.2, $^3J_{1\text{-H,C-3}}$ = 5.2 Hz, C-3) ppm. $C_{18}H_{16}O_4$ (296.32): calcd. C 72.96, H 5.44; found C 73.11, H 5.56.

(*E*)-4-[(2′,4′-Dimethoxyphenyl)methylene]-3-isochromanone (10*E*): This compound was prepared from 3-isochromanone (1.00 g, 6.75 mmol) and 2,4-dimethoxybenzaldehyde (1.12 g, 6.75 mmol). Recrystallization from methanol gave **10*E*** as faint yellow crystals (1.40 g, 70% yield). M.p. 91 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 244 nm (4.19), 359 (4.20). ^{1}H NMR ($CDCl_3$): δ = 3.76 (2′-OCH_3), 3.78 (4′-OCH_3), 5.24 (s, 1-H_2), 6.29 (dd, 5′-H), 6.43 (d, 3′-H), 7.10 (m, 6-H), 7.20 (m, 7-H, 8-H), 7.32 (d, 6′-H), 7.42 (d, 5-H), 7.99 (s, α-H), ppm. ^{13}C NMR ($CDCl_3$): δ = 55.2 (2 × O*C*H_3), 68.9 (C-1), 98.0 (C-3′), 104.8 (C-5′), 115.7 (C-1′), 122.2 (C-4), 124.8 (C-8), 126.7 (C-5), 127.6 (C-7, C-6), 130.3 (C-6′), 131.3 (C-4a), 131.9 (C-8a), 134.5 (C-α), 159.5 (C-4′), 162.4 (C-2′), 168.8 (C-3) ppm. $C_{18}H_{16}O_4$ (296.32): calcd. C 72.96, H 5.44; found C 72.82, H 5.61.

(*E*)-4-[(2′-Nitrophenyl)methylene]-3-isochromanone (11*E*) and (*Z*)-4-[(2′-(Nitrophenyl)methylene]-3-isochromanone (11*Z*): These compounds were obtained as a 1:2 mixture of (*E*)/(*Z*) diastereoisomers (based on separation) from 3-isochromanone (1.00 g, 6.75 mmol) and 2-nitrobenzaldehyde (1.02 g, 6.75 mmol) by the above procedure (1.05 g, 55% yield). The isomeric mixture was separated by column chromatography (silica gel) and eluted with dichloromethane/MeOH (10:0.01). **11*E*:** Yellow crystals from methanol; m.p. 151 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 224 nm (4.21), 274 (3.93). ^{1}H NMR ($CDCl_3$): δ = 5.36 (s, 1-H_2), 6.81 (d, 5-H), 7.04 (m, 6-H), 7.25 (m, 8-H), 7.26 (m, 7-H), 7.32 (m, 4′-H), 7.54 (m, 5′-H, 6′-H), 8.11 (s, α-H), 8.19 (m, 3′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.3 (C-1), 125.1 (C-8, C-3′), 126.9 (C-4), 127.4 (C-5), 128.1 (C-6), 128.7 (C-7), 129.3 (C-4a), 129.7 (C-6′), 131.0 (C-4′), 131.5 (C-1′), 132.3 (C-8a), 133.7 (C-5′), 135.4 (C-α), 147.7 (C-2′), 167.2 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 7.2, $^3J_{1\text{-H,C-3}}$ = 5.1 Hz, C-3) ppm. $C_{16}H_{11}NO_4$ (281.27): calcd. C 68.32, H 3.94, N 4.98; found C 68.28, H 4.09, N 4.82. **11*Z*:** Yellow crystals from methanol; m.p. 154 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 226 nm, shoulder (4.09) 269 (4.00). ^{1}H NMR ($CDCl_3$): δ = 5.35 (s, 1-H_2) 7.25 (dd, 8-H), 7.40 (dt, 7-H), 7.47 (m, 6-H), 7.49 (m, 6′-H), 7.52 (m, 4′-H), 7.64 (dt, 5′-H), 7.74 (m, 5-H), 7.74 (s, α-H), 8.22 (dd, 3′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.3 (C-1), 124.2 (C-5), 124.4 (C-8), 124.7 (C-3′), 126.0 (C-4), 128.8 (C-7), 129.1 (C-4′), 129.3 (C-6), 131.0 (C-8a), 131.3 (C-6′), 132.3 (C-1′), 132.7 (C-4a), 133.4 (C-5′), 136.4 (C-α), 147.0 (C-2′), 164.6 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 12.7, $^3J_{1\text{-H,C-3}}$ = 4.7 Hz, C-3) ppm. $C_{16}H_{11}NO_4$ (281.27): calcd. C 68.32, H 3.94, N 4.98; found C 68.21, H 4.09, N 4.87.

2-[(2′-Hydroxymethyl)phenyl]-3*H*-naphtho[2,1*b*]pyran-3-one (12): This compound was prepared from 3-isochromanone (1.00 g, 6.75 mmol) and 2-hydroxy-1-naphthaldehyde (1.16 g, 6.75 mmol), with addition of ten drops of piperidine. Recrystallization from methanol gave **12** as white crystals (1.33 g, 65% yield). M.p. 141 °C (decomposition). UV (ethanol): λ_{max} (log ε) = (log ε) 233 nm (4.84), 325 (4.19), 357 (4.32). ^{1}H NMR ($CDCl_3$): δ = 3.00 (t, OH), 4.58 (d, CH_2), 7.39 (dt, 6′-H), 7.43 (dt, 5′-H), 7.50 (dt, 4′-H), 7.53 (d, 5-H), 7.59 (m, 8-H), 7.61 (d, 3′-H), 7.68 (t, 9-H), 7.94 (d, 7-H), 8.03 (d, 6-H), 8.25 (d, 10-H), 8.57 (s, 1-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 63.4 (*C*H_2), 113.5 (C-10b), 116.6 (C-5), 121.4 (C-10), 126.1 (C-8), 127.7 (C-2), 128.2 (C-5′), 128.3 (C-9), 129.0 (C-7, C-10a), 129.5 (C-4′), 130.1 (C-3′), 130.2 (C-6′), 130.3 (C-6a), 133.1 (C-6), 134.2 (C-1′), 138.3 (C-1), 139.6 (C-2′), 153.3 (C-4a), 161.8 (d, $^3J_{1\text{-H,C-3}}$ = 9.9 Hz, C-3) ppm. $C_{20}H_{14}O_3$ (302.33): calcd. C 79.46, H 4.67; found C 79.58, H 4.70.

(*E*)-4-[(2′-Furanyl)methylene]-3-isochromanone (13*E*) and (*Z*)-4-[(2′-Furanyl)methylene]-3-isochromanone (13*Z*): These compounds were obtained as a 2:1 mixture of (*E*)/(*Z*) diastereoisomers (based on separation) from 3-isochromanone (1.00 g, 6.75 mmol) and 2-furaldehyde (0.65 g, 6.75 mmol) by the above procedure (1.23 g, 81% yield). The isomeric mixture was separated by column chromatography (silica gel) and eluted with benzene/ethyl acetate (10:1). **13*E*:** Yellow crystals from ether; m.p. 85 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 236 nm (4.08), 346 (4.27). ^{1}H NMR ($CDCl_3$): δ = 5.25 (s, 1-H_2), 6.51 (dd, 4′-H), 6.86 (d, 3′-H), 7.25 (m, 8-H), 7.35 (m, 7-H), 7.37 (m, 6-H), 7.43 (d, 5′-H), 7.55 (s, α-H), 7.84 (m, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.2 (C-1), 112.4 (C-4′), 117.9 (C-3′), 120.9 (C-4), 123.7 (C-α),124.5 (C-8), 127.7 (C-6), 127.8 (C-5), 128.3 (C-7), 130.6 (C-4a), 132.0 (C-8a), 144.7 (C-5′), 150.2 (C-2′), 169.2 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 7.5, $^3J_{1\text{-H,C-3}}$ = 5.1 Hz, C-3) ppm. $C_{14}H_{10}O_3$ (226.23): calcd. C 74.33, H 4.46; found C 74.48, H 4.46. **13*Z*:** Yellow crystals from ether; m.p. 51 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 236 nm (3.99), 351 (4.44). ^{1}H NMR ($CDCl_3$): δ = 5.26 (s, 1-H_2), 6.56 (m, 4′-H), 7.19 (m, 8-H), 7.23 (s, α-H), 7.31 (dt, 7-H), 7.39 (dt, 6-H), 7.51 (d, 5-H), 7.55 (m, 5′-H), 7.81 (d, 3′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.1 (C-1), 113.1 (C-4′), 117.7 (C-3′), 119.5 (C-4), 123.4 (C-5), 124.2 (C-8), 127.8 (C-7), 129.0 (C-6), 129.1 (C-α), 131.1 (C-8a), 134.2 (C-4a), 144.8 (C-5′), 150.8 (C-2′), 165.3 (C-3) ppm. $C_{14}H_{10}O_3$ (226.23): calcd. C 74.33, H 4.46; found C 74.25, H 4.59.

(*Z*)-4-[(1*H*-Indol-3-yl)methylene]-3-isochromanone (14): This compound was obtained as a 1:4 mixture of (*E*)/(*Z*) diastereoisomers (based on NMR spectroscopic data) from 3-isochromanone (1.00 g, 6.75 mmol) and indole-2-carbaldehyde (96%, 1.02 g, 6.75 mmol). Recrystallization from methanol gave orange crystals (1.27 g, 68% yield). It was not possible to separate the (*E*) and (*Z*) isomers completely, due to isomerization. **14*E*:** ^{1}H NMR ([D_6]DMSO): δ = 5.45 (s, 1-H_2), 7.07 (m, 5′-H), 7.16 (d, 4′-H), 7.27 (m, 6′-H), 7.31 (dt, 6-H), 7.41 (dt, 7-H), 7.54 (d, 8-H), 7.59 (d, 7′-H), 7.62 (d, 5-H), 8.14 (2 × s, 2′-H, α-H), 12.03 (br. s, NH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 68.4 (C-1), 110.3 (C-3′), 112.4 (C-7′), 117.9 (C-4), 120.3 (C-5′), 120.5 (C-4′), 122.3 (C-6′), 125.3 (C-8, C-4′a), 126.1 (C-5), 127.8 (C-6), 128.4 (C-7), 130.6 (C-2′), 131.4 (C-α), 132.1 (C-4a), 132.4 (C-8a), 136.7 (C-7′a), 168.9 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 7.3, $^3J_{1\text{-H,C-3}}$ = 5.2 Hz, C-3). **14*Z*:** ^{1}H NMR ($CDCl_3$/[D_6]DMSO): δ = 5.23 (s, 1-H), 7.14 (dt, 5′-H), 7.17 (dt, 6′-H), 7.24 (d, 8-H), 7.26 (dt, 7-H), 7.40 (dt, 6-H), 7.44 (dd, 7′-H), 7.65 (d, 5-H), 7.72 (s, α-H), 7.80 (dd, 4′-H), 8.75 (d, $^3J_{2'\text{-H,N-H}}$ = 2.9 Hz, 2′-H), 11.43 (br. s, NH) ppm. ^{13}C NMR ($CDCl_3$/[D_6]DMSO): δ = 68.3 (C-1), 110.3 (C-3′), 111.9 (C-7′), 116.1 (C-4), 117.5 (C-4′), 120.3 (C-5′), 122.0 (C-6′), 122.8 (C-5), 123.9 (C-8), 126.3 (C-7), 128.4 (C-4′a), 128.6 (C-6), 130.4 (C-8a), 131.2 (C-2′), 131.3 (C-α), 135.4 (C-4a), 135.6 (C-7′a), 166.2 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 12.7, $^3J_{1\text{-H,C-3}}$ = 5.0 Hz, C-3).

(*E*)-4-[(2′-Bromophenyl)methylene]-3-isochromanone (15E): This compound was prepared from 3-isochromanone (1.00 g, 6.75 mmol) and 2-bromobenzaldehyde (98%, 1.10 g, 6.75 mmol). Recrystallization from methanol gave **15*E*** as faint yellow crystals (1.57 g, 74% yield). M.p. 133 °C (decomposition). UV (ethanol): λ_{max} (log ε) = 310 nm (4.04). ^{1}H NMR ([D_6]DMSO): δ = 5.55 (s, 1-H_2), 6.99 (d, 5-H), 7.23 (t, 6-H), 7.40 (d, 5′-H, 6′-H), 7.42 (m, 4′-H), 7.43 (m, 7-H), 7.53 (d, 8-H), 7.80 (s, α-H), 7.86 (d, 3′-H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 69.2 (C-1), 123.6 (C-2′), 126.0 (C-8), 126.9 (C-5), 127.4 (C-4), 128.1 (C-5′), 128.3 (C-6), 129.1 (C-7), 129.5 (C-4a), 130.6 (C-6′), 131.3 (C-4′), 133.3 (C-8a, C-3′), 135.5 (C-1′), 136.8 (C-α), 167.5 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 7.3, $^3J_{1\text{-H,C-3}}$ = 5.1 Hz, C-3) ppm. $C_{16}H_{11}BrO_2$ (315.17): calcd. C 60.98, H 3.52; found C 61.12, H 3.66.

3-[(2′-Hydroxymethyl)phenyl]coumarin (16). Method A: This compound was prepared from 3-isochromanone (0.50 g, 3.38 mmol) and salicylaldehyde (0.41 g, 3.38 mmol), with addition of ten drops of piperidine. Recrystallization from ether gave **16** as white crystals. The product was purified by column chromatography (silica gel) and eluted with benzene/ethyl acetate (10:1) and recrystallized from methanol, yielding **16** (0.83 g, 97% yield). M.p. 73−74 °C. UV (ethanol): λ_{max} (log ε) = 290 nm (3.96), 313 (3.92). ^{1}H NMR ($CDCl_3$): δ = 2.84 (t, OH), 4.54 (d, CH_2), 7.29 (dt, 6′-H), 7.34 (t, 6-H), 7.39 (dt, 5′-H), 7.41 (d, 8-H), 7.47 (dt, 4′-H), 7.55 (d, 5-H), 7.58 (d, 3′-H), 7.58 (dt, 7-H), 7.77 (s, 4-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 63.3 (*C*H_2), 116.6 (C-8), 119.2 (C-4a), 124.7 (C-6), 127.9 (C-5), 128.1 (C-5′), 128.8 (C-3), 129.4 (C-4′), 129.9 (C-3′), 130.0 (C-6′), 131.7 (C-7), 133.8 (C-1′), 139.6 (C-2′), 142.2 (C-4), 153.6 (C-8a), 161.7 (d, $^3J_{4\text{-H,C-2}}$ = 9.9 Hz, C-2) ppm. MS (APCI): *m*/*z* = 253 [M + H]$^+$, 235 [MH − H_2O]$^+$. $C_{16}H_{12}O_3$ (252.27): calcd. C 76.18, H 4.79; found C 76.06, H 4.83. **Method B:** A modified preparation by the general procedure was applied, yielding a product identical to **16** in every respect. **Method C:** In a third method, the conditions above were used, but the mixture was dissolved in ethanol (10 mL) and the pH was adjusted to 5 with acetic acid at the end of the reaction. The ethanolic solution was concentrated and the residue was worked up as in Method A. The product was identical to **16** in every respect.

(*E*)-4-[(3′-Hydroxyphenyl)methylene]-3-isochromanone (17*E*): This compound was prepared from 3-isochromanone (0.50 g, 3.38 mmol) and 3-hydroxybenzaldehyde (0.41 g, 3.38 mmol). Recrystallization from methanol gave **17*E*** as faint yellow crystals (0.55 g, 65% yield). M.p. 228−230 °C. UV (ethanol): λ_{max} (log ε) = 321 nm (4.42). ^{1}H NMR ([D_6]DMSO): δ = 5.51 (s, 1-H_2), 6.89 (d, 4′-H), 7.01 (s, 2′-H), 7.02 (d, 6′-H), 7.28 (t, 5′-H), 7.32 (t, 6-H), 7.41 (d, 5-H), 7.45 (t, 7-H), 7.54 (d, 8-H), 7.75 (s, α-H), 9.68 (br. s, OH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 68.7 (C-1), 115.5 (C-2′), 116.8 (C-4′), 120.2 (C-6′), 125.2 (C-4), 125.7 (C-8), 126.9 (C-5), 127.9 (C-6), 128.6 (C-7), 129.9 (C-5′), 130.0 (C-4a), 133.1 (C-8a), 135.4 (C-1′), 138.0 (C-α), 157.5 (C-3′), 167.9 (dt, $^3J_{\alpha\text{-H,C-3}}$ = 7.3, $^3J_{1\text{-H,C-3}}$ = 5.4 Hz, C-3) ppm. MS (APCI): *m*/*z* = 253 [M + H]$^+$. $C_{16}H_{12}O_3$ (252.27): calcd. C 76.18, H 4.79; found C 76.06, H 4.83.

General Method for the Examination of the Thermal Stability of 4-(Arylmethylene)-3-isochromanones: A mixture of the corresponding isochromanone (0.2 mmol) and five drops of piperidine was stirred at 140 °C under argon for 1 h. The reaction was monitored by TLC. The mixture was allowed to cool to room temperature, and the oily residue was concentrated in vacuo to remove the traces

of piperidine and was checked by NMR spectroscopic methods. According to the results of the TLC and the NMR method neither the (*E*) nor the (*Z*) isomers showed any change.

X-ray Crystallographic Study: Crystal data for compound **13** are as follows. Empirical formula: $C_{14}H_{18}O_3$; formula mass: 226.22; crystal system: triclinic; space group: $P\bar{1}$; unit cell dimensions: a = 7.3563(5) Å, α = 82.485(1)°, b = 10.0159(6) Å, β = 80.082(1)°, c = 15.448(1) Å, γ = 75.395(1)°; V = 1080.4(1) Å^3; Z = 4; density: 1.391 mg/m^3; crystal size: 0.09 × 0.16 × 0.35 mm. X-ray crystallography data were collected at 173 K with a Siemens SMART PLATFORM equipped with a CCD area detector and a graphite monochromator with Mo-K_α radiation (λ = 0.71073 Å). The Θ range for data collection was 2.11−27.50°, the number of reflections collected was 7514 and the number of symmetry-independent reflections was 4786. The absorption coefficient was 0.098 mm^{-1}. Cell parameters for each structure were refined by use of up to 8192 reflections and a hemisphere of data (1381 frames) was collected by the ω-scan method (0.3° frame width). Absorption corrections by integration based on measured indexed crystal faces were applied. The maximal and minimal transmissions were between 0.992 and 0.963. Both structures were solved by direct methods in SHELXTL5[27] and refined by full-matrix, least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were placed in calculated ideal positions on their respective heavy atoms. CCDC-178573 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[1] Y. Yamamoto, *Agr. Biol. Chem.* **1961**, *25*, 400−404.
[2] J. Sonnenbichler, J. Dietrich, H. Peipp, *Biol. Chem. Hoppe-Seyler* **1994**, *375*, 71−79.
[3] H. W. Ruelius, A. Gauhe, *Justus Liebigs Ann. Chem.* **1950**, *569*, 38−59.
[4] H. Kern, *Ann. Phytopathol.* **1978**, *10*, 327−345.
[5] M. S. Ammar, N. N. Gerber, L. E. Mc Daniel, *J. Antibiot.* **1979**, *32*, 679−684.
[6] M. Casellas, M. Grifoll, J. M. Bayona, A. M. Solanas, *Appl. Environment. Microbiol.* **1997**, *63*, 819−826.
[7] J. R. Dimmock, M. L. C. Wong, *Can. J. Pharm. Sci.* **1976**, *11*, 35−53.
[8] H. Geiger, *The Flavonoids* (Ed.: J. B. Harborne), Chapman & Hall, Ltd., London, **1988**, pp. 389−397.
[9] A. Ravisé, B. S. Kirkiacharian, *Phytopath. Z.* **1978**, *92*, 36−50.
[10] T. M. Al-Nakib, V. Bezjak, M. J. Meegan, R. Chandy, *Eur. J. Med. Chem.* **1990**, *25*, 455−462.
[11] T. Lóránd, T. M. Al-Nakib, L. Prókai, *Synthesis, antimycotic activity and QSAR studies of homoisoflavanone analogs*, 212th National Meeting of the American Chemical Society, Orlando, FL, USA, August 24−29, **1996**.
[12] T. M. AL-Nakib, T. Lóránd, A. Földesi, R. Varghese, *Med. Principles Pract.* **2001**, *10*, 191−196.
[13] M. Barbier, *Heterocycles* **1987**, *26*, 421−425.
[14] M. Barbier, *Synth. Commun.* **1989**, *19*, 1661−1667.
[15] B. Benett, J. A. Donally, D. C. Meaney, P. O'Boyle, *J. Chem. Soc., Perkin Trans. 1* **1972**, 1554−1559.
[16] D. D. Keane, K. G. Marathe, W. I. O'Sulivan, E. M. Philbin, R. M. Simons, P. C. Teague, *J. Org. Chem.* **1970**, *35*, 2286−2290.
[17] B. A. Brady, J. A. Kennedy, W. I. O'Sullivan, *Tetrahedron* **1973**, *29*, 359−362.
[18] K. E. Litinas, X. N. Stampelos, *J. Chem. Soc., Perkin Trans. 1* **1992**, 2981−2984.
[19] A. Patra, S. K. Misra, *Magn. Reson. Chem.* **1991**, *29*, 749−752.
[20] E. Breitmaier, W. Voelter, *Carbon-13 NMR Spectroscopy*, VHC Publishers, Weinheim, **1987**, pp. 278.
[21] M. S. Phansalkar, K. K. Deshmukh, S. L. Kelkar, M. S. Wadia, *Indian J. Chem. B* **1987**, *26*, 562−563.
[22] E. Breitmaier, *Structure Elucidation by NMR in Organic Chemistry*, John Wiley & Sons, Chichester, **1993**, pp. 213.
[23] N. G. P. H. Buu-Hoi, N. G. Hoán, M. R. Khenissi, *J. Chem. Soc.* **1949**, 2307−2309.
[24] T. Kinoshita, *Tetrahedron Lett.* **1997**, *38*, 259−262.
[25] E. Yoneda, T. Kaneko, S.-W. Zhang, S. Takahashi, *Tetrahedron Lett.* **1998**, *39*, 5061−5064.
[26] S. Okamoto, A. Kasatkin, P. K. Zubaidha, F. Sato, *J. Am. Chem. Soc.* **1996**, *118*, 2208−2216.
[27] G. A. Cartwright, H. McNab, *J. Chem. Research (S)* **1997**, 296−297.
[28] G. M. Sheldrick, *SHELXTL5*, Bruker-AXS, Madison, Wisconsin, USA, **1998**.
[29] J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209−220.

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