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One-pot syntheses of 5-hydroxy-2-(phenyl or styryl)chromones and the corresponding 6- and 8-monoiodo- and 6,8-diiodochromones have been developed. The procedures involve oxidative cyclization of 2'-benzyloxy-6'-hydroxychalcones and 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenones and electrophilic substitution processes on the chromone moieties; such procedures were also applied to the syntheses of 6,8-dibromochromone derivatives.

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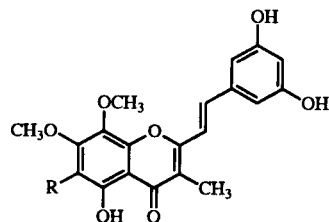
Introduction.

2-Phenylchromones, also known as flavones, constitute one of the major classes of natural compounds occurring in all plants. Due to the significance of plant components to human life as food products, biocides and pharmaceutical drugs [1], chromones have been investigated ever since their discovery aiming to find new compounds with significant biological activity. Natural chromones, together with a number of synthetic analogues, are biologically active in a variety of ways: (1) they exhibit biocidal activity, especially as fungicides or bactericides [2]; (2) they can act as antioxidants [3], due to their capacities to chelate metal ions or scavenge free radicals; (3) they demonstrate a broad spectrum of biological activity in mammalian cell systems, particularly by inhibiting the growth of carcinoma cells and the proliferation of some tumours [4].

In the last decade, two new natural 2-styrylchromones, hormothamnione **1a** and 6-demethoxyhormothamnione **1b**, were found in the marine Cryptophyceean alga *Chrysophaeum taylori* [5]; potent *in vitro* cytotoxic activities against P388 lymphocytic and HL-60 human promyelocytic leukemia cells were demonstrated by these natural compounds [5]. This biological behaviour has stimulated the search for synthetic routes leading to several analogues of these natural compounds. As a result, several 2-styrylchromones were synthesized and some of their derivatives were shown to display good anti-allergic or anti-tumour activities [6].

The biological behaviour of 2-phenyl- and 2-styrylchromone derivatives clearly points out the potential uses of such compounds as new drugs and biocides. Hence it would be advantageous if they were available by simple and easy synthetic transformations. Since halogenation of an active molecule quite often increases its biological activity, and considering that many pharmaceutical drugs [7], fungicides, herbicides and insecticides are halo-substituted compounds [8], the syntheses of 2-phenyl- or 2-styrylchromones and some iodinated and brominated derivatives were undertaken. As a result of this work,

routes to the new 6-iodo-, 8-iodo-, 6,8-diiodo- and 6,8-dibromo- derivatives of 2-phenyl- and 2-styrylchromones have been developed.



1a R = OCH₃ Hormothamnione

1b R = H 6-Demethoxyhormothamnione

Results and Discussion.

2'-Benzyloxy-6'-hydroxychalcone **2a** and 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b** were obtained in good yields by base-catalysed aldol condensation of 2'-benzyloxy-6'-hydroxyacetophenone, prepared by monobenylation of 2',6'-dihydroxyacetophenone, and benzaldehyde or cinnamaldehyde, respectively.

The most noticeable features in the ¹H nmr spectrum of compound **2a** were the signals corresponding to resonances of H-α and H-β protons, which appear as doublets at δ 7.74 and 7.88 ppm, respectively. The coupling constant (J = 15.5 Hz) indicates the *trans* configuration of the vinylic system. In the ¹³C nmr spectrum the chemical shifts of C-α and C-β appear at δ 127.6 and 143.4 ppm, respectively. The higher frequency value of the C-β resonance is due to the deshielding mesomeric effect of the carbonyl group.

Based on our previous work [9], the assignment of the ABCD system corresponding to the resonance of H-α, H-β, H-γ and H-δ protons in the ¹H nmr spectrum of compound **2b** was carried out through a 2D COSY experiment. Also with an HETCOR experiment of compound **2b**, which correlates the ¹H and ¹³C (protonated carbon atoms) nmr spectra, it was possible to assign all of the protonated carbon atoms, including those of the α:β:γ:δ unsaturated system (Table 1).

Table 1

¹H and ¹³C Assignments Made Through 2D COSY and HETCOR Experiments and Some Coupling Constants

		α	β	γ	δ
δ, ppm	¹ H	7.42	7.53	6.63	6.94
	¹³ C	131.7	143.0	127.4	141.1
³ J, Hz	³ J _{α-β}	= 15.4		³ J _{γ-β}	= 10.5
	³ J _{β-γ}	=		³ J _{γ-δ}	
				³ J _{δ-γ}	= 15.6

The ³J (H/H) coupling constant values seem to indicate a *trans*-(*s-trans*)-*trans* configuration of the α:β:γ:δ unsaturated system.

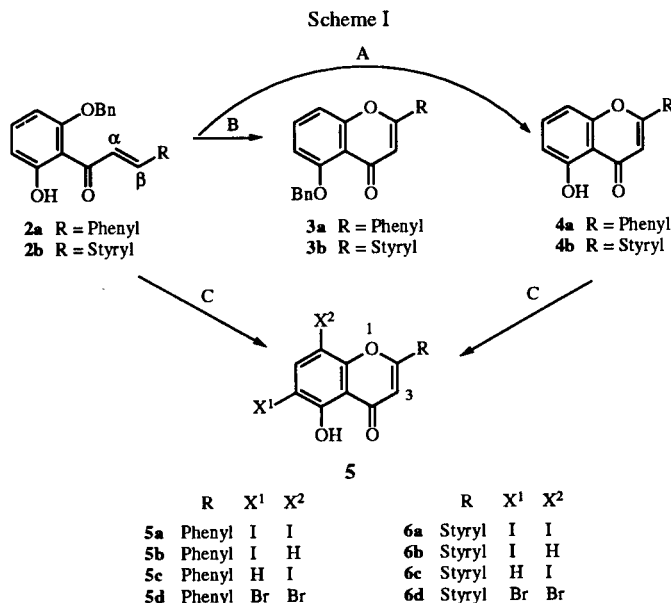
It is known that catalytic amounts of iodine in DMSO will accomplish the oxidative cyclizations of 2'-hydroxychalcones and 2'-hydroxy-2-cinnamylideneacetophenones into 2-phenyl- and 2-styrylchromones [9-11], respectively. Therefore in the oxidative cyclizations of 2'-benzyloxy-6'-hydroxychalcones **2a** and 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenones **2b**, and depending on the reflux periods (Scheme I), the formation of chromones **3a,b** and **4a,b** takes place [12]. The formation of chromones **3a,b** involves only the oxidative cyclization of the starting compounds **2a,b** by the DMSO/iodine mixture (heating at reflux during 30 minutes). However chromones **4a,b** were obtained after a longer reflux period (two hours); in each case the initial reaction mixture leads, in one step, to the oxidative cyclization of reagents **2a,b** and also to the debenzoylation of the 5-substituent.

The 5-debenzoylation is probably due to the catalytic action of hydrogen iodide which is formed during the cyclization step [13]. Hydrogen iodide can form benzyl iodide, which, after being oxidized by DMSO to benzaldehyde, generates another hydrogen iodide molecule to continue the debenzoylation process.

This proposal was corroborated by the results obtained in the following experiments: a) ¹H nmr analysis of a product mixture obtained by submitting chalcone **2a** to reflux with the reagent system DMSO/iodine during two hours, revealed signals due not only to **4a** but also to benzaldehyde; b) refluxing benzyl chloride in DMSO during two hours, followed by work-up and ¹H nmr analysis, gave rise to the formation of benzaldehyde [12,14].

However when 2'-benzyloxy-6'-hydroxychalcone **2a** and 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b** were submitted to the DMSO/iodine reagent system but using iodine in equivalent quantities, the diiodo derivatives **5a** and **6a** were obtained [15]. Analogous brominated products **5d** and **6d** were also obtained by simply replacing iodine with bromine. These dihalochromones can also be obtained by treatment of chromones **4a** and **4b** with one equivalent of bromine or iodine [15]. Under these conditions, the transformations

of compounds **4a** and **4b** into **5a,5d** and **6a,6d** are consistent with electrophilic substitution processes at the most activated aromatic positions. However in the former case, when using 2'-benzyloxy-6'-hydroxychalcone **2a** or 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b**, the formation of each product involves a cyclization and the cleavage of the benzylic protecting group, catalysed by the iodine-DMSO mixture, as well as an electrophilic substitution process [12,15] (Scheme I).

Bn = CH₂C₆H₅A - DMSO/I₂ (catalytic amount), reflux 2 hoursB - DMSO/I₂ (catalytic amount), reflux 30 minutesC - DMSO/I₂ or Br₂ (1 or 0.5 equivalents), reflux 30 minutes

The next step in the synthesis of halogenated chromones was to accomplish the preparation of monoiodinated compounds. Under the conditions referred to above but using only half equivalent of iodine not only the expected monoiodochromones, but also the diiodinated and non-iodinated chromones were observed. These findings suggest that, under these reaction conditions, the monoiodo-5-hydroxychromones are not significantly less reactive than the corresponding 5-hydroxychromones towards iodine and so diiodination occurred even with 5-hydroxychromones in excess. This situation is similar to that observed by Tee *et al.* [16] on the halogenation of phenolic compounds.

In the ¹H nmr spectra of all synthesized 2-styrylchromones **3b**, **4b** and **6a-d** the signals corresponding to the resonances of H-α and H-β appear as doublets at δ 6.74-6.79 and 7.59-7.87, respectively; the coupling constant value (~ 16 Hz) indicates a *trans* configuration of the vinylic group in this type of compounds.

The ¹H nmr spectra of all compounds **3** and **4** show singlets at δ 6.24-6.76 ppm corresponding to the resonances

of H-3 protons. However the signals due to H-3 protons of 2-phenylchromones **3a** and **4a** were downfield (~ 0.5 ppm) in comparison with those of the same protons of the 2-styrylchromones **3b** and **4b**, respectively. This effect can be rationalized by considering the anisotropic deshielding effect of the B ring on H-3 proton in the case of 2-phenylchromones, due to the almost coplanarity of this ring with chromone nucleus.

In the ^{13}C nmr spectra of all compounds **3** and **4**, the signals corresponding to the resonances of C-3 carbons appear at δ 106.1-112.3 ppm. The signals of C-3 carbons of 5-hydroxy-2-(phenyl or styryl)chromones **4a,b** are upfield (2.8-3.3 ppm) relative to those of the 5-benzyloxy-2-(phenyl or styryl)chromones **3a,b**. This observation can be explained by taking into account a strong hydrogen bond involving the carbonyl and the proton of the 5-hydroxyl groups of the former, inducing a delocalization along the $\alpha:\beta$ unsaturated system, in the case of 2-phenylchromone **4a**, or the $\alpha:\beta:\gamma:\delta$ unsaturated system,

For the halochromones **5a-d** and **6a-d** the ^1H and ^{13}C nmr resonances of the H-3 and H-7 protons appear at δ 6.30-6.88 and 7.91-8.37 ppm, respectively; those due to C-3 and C-7 carbons appear at δ 105.6-108.9 and 140.4-151.3 ppm, respectively. In comparison with the nmr results obtained for the non-halogenated chromones **4a,b**, a shift to higher frequency was observed for the H-7 and C-7 atoms (Table 2) which is due to the deshielding effect of the adjacent halogen substituents.

In chromones **5a-c** and **6a-c** the resonances due to the C-6 and C-8 carbon atoms which are bonded to iodo or bromo substituents appear at δ 76.8-78.5 and 68.8-70.3 ppm, respectively; for **5d** and **6d** the C-6 and C-8 carbons resonate at δ 104.3-104.5 and 98.7-99.0 ppm, respectively. Comparing the ^1H and ^{13}C chemical shifts of these compounds with those of the non-halogenated chromones **4a,b**, several shifts to lower frequencies have been observed (Table 2) and these are due to different shielding effects of the halogen substituents.

Table 2
Difference Between Chemical Shifts of Some ^1H and ^{13}C Atoms of Halo- and Non-halo-5-hydroxychromones

	$\Delta\text{C-6}$	$\Delta\text{C-7}$	$\Delta\text{C-8}$	$\Delta\text{H-7}$		$\Delta\text{C-6}$	$\Delta\text{C-7}$	$\Delta\text{C-8}$	$\Delta\text{H-7}$
5a	- 33.0	+ 15.9	- 36.8	+ 0.82	6a	- 33.1	+ 14.8	- 36.7	+ 0.81
5b	- 34.0	+ 8.5	+ 2.2	+ 0.43	6b	- 34.6	+ 7.4	+ 2.2	+ 0.42
5c	+ 2.4	+ 8.9	- 38.2	+ 0.39	6c	+ 2.3	+ 7.7	- 38.1	+ 0.37
5d	- 7.0	+ 5.1	- 8.1	+ 0.48	6d	- 7.1	+ 4.0	- 8.2	+ 0.46

in the case of 2-styrylchromone **4b**; consequently the C-3 carbon is shielded. An analogous situation is observed for C- α carbon of 2-styrylchromone **4b**.

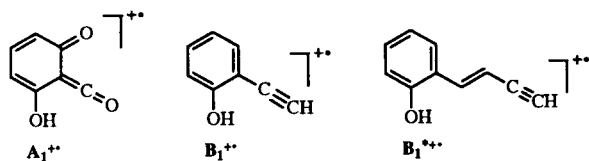
The assignments of all remaining protons and protonated carbon atoms of the chromones **3a,b** and **4a,b** were carried out through 2D COSY and HETCOR experiments.

As shown earlier [12], the resonance of the C-6 carbon of 5-hydroxy-2-(phenyl or styryl)chromones **4a,b** occurs at higher frequency than the one due to C-8. However in the case of 5-benzyloxy-2-(phenyl or styryl)chromones **3a,b** the opposite is concluded in the present work by using one-dimensional selective INEPT measurements [17]. These measurements give the connectivity of a selected proton, by irradiation of the corresponding resonance, to the carbon atoms to which they are coupled, and can be optimized for different long-range J (C/H) coupling. In the case of compounds **3a,b** on irradiation of the signal of the benzylic CH_2 , optimized for 7 Hz long-range J (C/H) coupling, enhancements on the signals of C-1 and C-2,6 of the benzyl group and also of C-5 were observed. Subsequently with the irradiation of the same signal, optimized for 1 Hz long-range J (C/H) coupling, enhancements of the signals of C-3,5 and C-4 of the benzyl groups, and also of C-10, were observed with minor enhancements of the signal at δ 108.3 ppm. This signal was thus assigned to the C-6 carbon resonance.

For the monoiodochromones **5b-c** and **6b-c**, the proton-coupled ^{13}C nmr spectra enable assignments of the resonances of all carbon atoms. In particular, the C-6 carbons of chromones **5c** and **6c** exhibit spin-spin coupling not only with the H-6 protons, but also with the 5-OH proton and a double doublet is assigned to this carbon atom. On the other hand, for the chromones **5b** and **6b** only the H-8 protons are coupled with the C-8 carbons and a doublet is observed in each case. The assignments of these carbon atoms were also very helpful in the identification and distinction between the 6- and 8-mono-iodochromones.

The EI mass spectra were recorded for all the chromones reported here. The important peaks in the structural characterization are the molecular ions, $\text{M}^{+\bullet}$ (the base peak in all cases) and those ions with rings A or B intact, derived from retro Diels-Alder fragmentations [18]. For example, in the case of 5-hydroxy-2-(phenyl or 2-styryl)chromone, the peak at m/z 136 corresponds to fragment $\text{A}_1^{+\bullet}$; with a mono- or diiodinated ring A the corresponding m/z values are 262 and 388, respectively.

All 2-phenylchromones reported give fragment $\text{B}_1^{+\bullet}$, which appears at m/z 102, since there are no substituents in ring B. A similar situation is observed for all 2-styrylchromone derivatives, with a fragment $\text{B}_1^{+\bullet}$ at m/z 128.



EXPERIMENTAL

Measurements.

Melting points are uncorrected and were determined on a Reichert Thermovar apparatus fitted with a microscope. The ^1H and ^{13}C nmr spectra were taken in deuteriochloroform solutions on a Bruker AMX 300, at 300.13 and 75.47 MHz, respectively; the chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference. Preparative thin layer chromatography was carried out on silica gel plates (Riedel silica gel 60 DGF₂₅₄). Column chromatography was also performed on silica gel (Merck silica gel 60, 70-230 mesh). Mass spectra were obtained at 70 eV electron impact ionization using a VG Autospec Q mass spectrometer. Elemental analyses were performed by the microanalytical laboratory of the University of Liverpool.

All other chemicals and solvents used herein were obtained from commercial sources and used as received.

Synthesis.

Synthesis of 2'-Benzyloxy-6'-hydroxychalcone **2a** and 2'-Benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b**.

To a methanolic solution (25 ml) of 2'-benzyloxy-6'-hydroxyacetophenone (1.2 g, 5 mmol), was slowly added an aqueous solution of sodium hydroxide (60%, 25 ml). After cooling the solution to room temperature, the appropriate aldehyde (7.5 mmol) was added. The reaction mixture was stirred, at room temperature, during 20 hours, and after this period it was poured into a mixture of ice (150 g) and commercial hydrochloric acid (pH was adjusted to ~ 2). The solid which was formed was filtered, dissolved in chloroform (200 ml), and washed with a 5% aqueous solution of sodium hydrogen carbonate (2 x 200 ml). The organic layer was collected, dried through anhydrous sodium sulfate and the solvent evaporated to dryness. The residue was purified by column chromatography, using dichloromethane as eluent. Finally the compound, in each case, was crystallized from ethanol. With benzaldehyde as starting material, 2'-benzyloxy-6'-hydroxychalcone **2a** was obtained (1.40 g, 85%); starting with cinnamaldehyde, the 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b** was also obtained (1.48 g, 83%).

2'-Benzyloxy-6'-hydroxychalcone **2a**.

This compound was obtained as orange needles, mp 130-131°C. ^1H nmr δ 5.13 (s, 2H, 2'-OCH₂C₆H₅), 6.55 (d, 1H, H-3', J = 8.2 Hz), 6.65 (d, 1H, H-5', J = 8.4 Hz), 7.10-7.51 (m, 11 H, H-2,3,4,4',5,6 and 2'-OCH₂C₆H₅), 7.74 (d, 1H, H- α , J = 15.5 Hz), 7.88 (d, 1H, H- β , J = 15.5 Hz), 13.54 (s, 1H, OH-2'); ^{13}C nmr: δ 71.4 (2'-OCH₂C₆H₅), 102.3 (C-3'), 111.4 (C-5'), 111.9 (C-1'), 127.6 (C- α), 128.5-128.9 (C-2,3,5,6, and C-2,3,4,5,6 of 2'-OCH₂C₆H₅), 130.1 (C-4), 135.1 (C-1), 135.6 (C-1 of 2'-OCH₂C₆H₅), 136.0 (C-4'), 143.4 (C- β), 160.3 (C-6'), 165.5 (C-2'), 194.5 (C=O); ms: (EI) m/z (relative intensity) 330 (M⁺,

53), 329 (8), 312 (7), 253 (17), 239 (73), 211 (21), 194 (10), 181 (12), 180 (15), 165 (13), 137 (26), 136 (13), 131 (41), 115 (10), 108 (10), 103 (22), 91 (100), 77 (25).

Anal. Calcd. for C₂₂H₁₈O₃: C, 79.98; H, 5.49. Found: C, 80.08; H, 5.57.

2'-Benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b**.

This compound was obtained as orange needles, mp 134-137°C; ^1H nmr: δ 5.17 (s, 2H, 2'-OCH₂C₆H₅), 6.50 (dd, 1H, H-3', J = 8.2 and 0.9 Hz), 6.63 (dd, 1H, H-5', J = 8.4 and 0.9 Hz), 6.63 (dd, 1H, H- γ , J = 15.6 and 10.5 Hz), 6.94 (d, 1H, H- δ , J = 15.6 Hz), 7.30-7.58 (m, 10 H, H-2,3,4,5,6 and 2'-OCH₂C₆H₅), 7.36 (dd, 1H, H-4', J = 8.4 and 8.2 Hz), 7.42 (d, 1H, H- α , J = 15.4 Hz), 7.53 (dd, 1H, H- β , J = 15.4 and 10.5 Hz), 13.29 (s, 1H, OH-2'); ^{13}C nmr: δ 71.2 (2'-OCH₂C₆H₅), 102.6 (C-3'), 111.2 (C-5'), 112.0 (C-1'), 127.2 (C-2,6), 127.4 (C- γ), 127.9 (C-2,6 of 2'-OCH₂C₆H₅), 128.3 (C-4 of 2'-OCH₂C₆H₅), 128.7 (C-3,5), 128.8 (C-3,5 of 2'-OCH₂C₆H₅), 129.1 (C-4), 131.7 (C- α), 135.9 (C-4'), 136.0 (C-1), 136.3 (C-1 of 2'-OCH₂C₆H₅), 141.1 (C- δ), 143.0 (C- β), 160.1 (C-6'), 165.1 (C-2'), 194.5 (C=O); ms: (EI) m/z (relative intensity) 356 (M⁺, 23), 265 (46), 236 (9), 157 (7), 137 (28), 129 (10), 128 (17), 127 (6), 115 (34), 91 (100), 77 (6).

Anal. Calcd. for C₂₄H₂₀O₃: C, 80.88; H, 5.66. Found: C, 80.89; H, 5.64.

Synthesis of 5-Benzyloxy-2-(phenyl or 2-styryl)chromones **3a** or **3b**.

To a 2 mmol solution of 2'-benzyloxy-6'-hydroxychalcone **2a** or 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b**, in DMSO, (6 ml), was added iodine (20 mg, 0.079 mmol). The mixture was heated at reflux for 2 hours, then was poured into ice (150 g) and water (150 ml) to precipitate the product. The solid was removed by filtration, dissolved in chloroform (150 ml), and washed with a 20% aqueous solution of sodium thiosulfate (2 x 150 ml). The organic layer was passed through anhydrous sodium sulfate and the solvent evaporated to dryness. The residue was purified by column chromatography, using dichloromethane as eluent. Finally the compound, in each case, was crystallized from ethanol. With 2'-benzyloxy-6'-hydroxychalcone **2a** as starting material, 5-benzyloxy-2-phenylchromone **3a** was obtained (61 mg, 93%); starting with 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b** the 5-benzyloxy-2-styrylchromone **3b** was also obtained (65.9 mg, 93%).

5-Benzyloxy-2-phenylchromone **3a**.

This compound was obtained as colorless needles, mp 151-152°C; ^1H nmr: δ 5.26 (s, 2H, 5-OCH₂C₆H₅), 6.71 (s, 1H, H-3), 6.82 (dd, 1H, H-6, J = 8.3 and 0.8 Hz), 7.13 (dd, 1H, H-8, J = 8.4 and 0.8 Hz), 7.29 (t, 1H, H-4 of 5-OCH₂C₆H₅, J = 7.2 Hz), 7.39 (dd, 2H, H-3,5 of 5-OCH₂C₆H₅, J = 7.8 and 7.2 Hz), 7.45-7.50 (m, 3H, H-3',4',5'), 7.48 (dd, 1H, H-7, J = 8.3 and 8.4 Hz), 7.63 (d, 2H, H-2,6 of 5-OCH₂C₆H₅, J = 7.8 Hz), 7.84-7.89 (m, 2H, H-2',6'); ^{13}C nmr: δ 70.7 (5-CH₂C₆H₅), 108.3 (C-6), 108.9 (C-3), 110.3 (C-8), 114.9 (C-10), 125.9 (C-2',6'), 126.4 (C-2,6 of 5-OCH₂C₆H₅), 127.5 (C-4 of 5-OCH₂C₆H₅), 128.4 (C-3,5 of 5-OCH₂C₆H₅), 128.8 (C-3',5'), 131.2 (C-4'), 131.3 (C-1'), 133.5 (C-7), 136.4 (C-1 of 5-OCH₂C₆H₅), 158.1 (C-9), 158.4 (C-5), 160.9 (C-2), 177.9 (C=O); ms: (EI) m/z (relative intensity) 328 (M⁺, 70), 327 (11), 251 (9), 238 (9), 222 (63), 221 (11), 209 (9), 194 (20), 120 (13), 105 (8), 102 (8), 91 (100), 77 (11).

Anal. Calcd. for C₂₂H₁₆O₃: C, 80.47; H, 4.91. Found: C, 80.37; H, 4.89.

5-Benzyloxy-2-styrylchromone **3b**.

This compound was obtained as colorless needles, mp 179–181°C; ^1H nmr: δ 5.28 (s, 2H, 5-OCH₂C₆H₅), 6.24 (s, 1H, H-3), 6.74 (d, 1H, H- α , J = 16.0 Hz), 6.83 (d, 1H, H-6, J = 8.3 Hz), 7.11 (d, 1H, H-8, J = 8.4 Hz), 7.30 (t, 1H, H-4 of 5-OCH₂C₆H₅, J = 7.3 Hz), 7.37–7.44 (m, 5H, H-3',4',5' and H-3,5 of 5-OCH₂C₆H₅), 7.51 (dd, 1H, H-7, J = 8.3 and 8.4 Hz), 7.54 (d, 1H, H- β , J = 16.0 Hz), 7.57 (dd, 2H, H-2',6', J = 1.6 and 7.6 Hz), 7.63 (d, 2H, H-2,6 of 5-OCH₂C₆H₅, J = 7.2 Hz); ^{13}C nmr: δ 70.8 (5-OCH₂C₆H₅), 108.3 (C-6), 110.3 (C-8), 112.3 (C-3), 115.2 (C-10), 119.9 (C- α), 126.6 (C-2,6 of 5-OCH₂C₆H₅), 127.5 (C-2',6'), 127.6 (C-4 of 5-OCH₂C₆H₅), 128.5 (C-3,5 of 5-OCH₂C₆H₅), 128.9 (C-3',5'), 129.6 (C-4'), 133.6 (H-7), 135.1 (C-1'), 136.2 (C- β), 136.6 (C-1 of 5-OCH₂C₆H₅), 158.0 (C-9), 158.5 (C-5), 159.5 (C-2), 178.1 (C=O); ms: (EI) m/z (relative intensity) 354 (M^+ , 92), 353 (17), 277 (13), 264 (10), 248 (54), 247 (49), 231 (21), 128 (25), 91 (100).

Anal. Calcd. for C₂₄H₁₈O₃: C, 81.34; H, 5.12. Found: C, 81.54; H, 5.02.

Synthesis of 5-Hydroxy-2-(phenyl or 2-styryl)chromones **4a** or **4b**.

To a 2 mmole solution of 2'-benzyloxy-6'-hydroxychalcone **2a** or 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b** in DMSO, (6 ml), was added iodine (20 mg, 0.079 mmole). The mixture was heated at reflux for 2 hours, then was poured into ice (150 g) and water (150 ml) to precipitate the product. The solid was removed by filtration, dissolved in chloroform (150 ml), and washed with a 20% aqueous solution of sodium thiosulfate (2 x 150 ml). The organic layer was passed through anhydrous sodium sulfate and the solvent evaporated to dryness. The residue was purified by column chromatography, using a mixture of petroleum ether:dichloromethane (3:7) as eluent. Finally the compound, in each case, was crystallized from ethanol. With 2'-benzyloxy-6'-hydroxychalcone **2a** as starting material, 5-hydroxy-2-phenylchromone **4a** was obtained (424 mg, 89%); starting with 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b** the 5-hydroxy-2-styrylchromone **4b** was also obtained (428 mg, 81%).

5-Hydroxy-2-phenylchromone **4a**.

This compound was obtained as yellow needles, mp 153–154°C (lit [19] 158–159°C); ^1H nmr: δ 6.76 (s, 1H, H-3), 6.83 (d, 1H, H-6, J = 8.2 Hz), 7.02 (d, 1H, H-8, J = 8.4 Hz), 7.51–7.59 (m, 4H, H-3',4',5',7), 7.93 (dd, 2H, H-2',6', J = 7.8 and 1.8 Hz), 12.59 (s, 1H, OH-5); ^{13}C nmr: δ 106.1 (C-3), 107.1 (C-8), 110.9 (C-10), 111.5 (C-6), 126.5 (C-2',6'), 129.2 (C-3',5'), 131.3 (C-1'), 132.1 (C-4'), 135.4 (C-7), 156.5 (C-9), 160.8 (C-5), 164.6 (C-2), 183.6 (C-4); ms: (EI) m/z (relative intensity) 238 (M^+ , 100), 237 (8), 210 (6), 136 (17), 108 (26), 102 (7), 77 (9).

5-Hydroxy-2-styrylchromone **4b**.

This compound was obtained as yellow needles, mp 171–173°C; ^1H nmr: δ 6.26 (s, 1H, H-3), 6.78 (d, 1H, H- α , J = 16.1 Hz), 6.80 (d, 1H, H-6, J = 8.1 Hz), 6.98 (d, 1H, H-8, J = 8.4 Hz), 7.42–7.44 (m, 2H, H-2',6'), 7.54 (t, 1H, H-7, J = 8.4 Hz), 7.57–7.61 (m, 3H, H-3',4',5'), 7.64 (d, 1H, H- β , J = 16.1 Hz), 12.61 (s, 1H, OH-5); ^{13}C nmr: δ 106.9 (C-8), 109.0 (C-3), 111.0 (C-10), 111.4 (C-6), 119.6 (C- α), 127.8 (C-2',6'), 129.1 (C-3',5'), 130.2 (C-4'), 134.8 (C-1'), 136.4 (C-7), 138.1 (C- β), 156.2 (C-9), 160.9 (C-5), 162.9 (C-2), 183.6 (C-4); ms: (EI) m/z (relative intensity)

264 (M^+ , 100), 263 (84), 247 (25), 246 (32), 235 (7), 218 (9), 189 (8), 155 (8), 137 (16), 136 (22), 128 (35), 127 (9), 108 (24), 102 (7), 91 (6), 77 (7).

Anal. Calcd. for C₁₇H₁₂O₃: C, 77.26; H, 4.58. Found: C, 76.99; H, 4.55.

General Procedure for the Synthesis of 5-Hydroxy-6,8-dihalo-2-(phenyl or 2-styryl)chromones **5a,d** or **6a,d**.

To a 0.2 mmole solution of 2'-benzyloxy-6'-hydroxychalcone **2a** or 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b** or 5-hydroxy-2-phenylchromone **4a** or 5-hydroxy-2-styrylchromone **4b** in DMSO (0.6 ml) was added iodine or bromine (0.2 mmole). The mixture was heated at reflux for 30 minutes, then was poured into ice (50 g) and water (50 ml) to precipitate the product. The solid was removed by filtration, dissolved in chloroform (50 ml), and washed with a 20% aqueous solution of sodium thiosulfate (2 x 50 ml). The organic layer was passed through anhydrous sodium sulfate and evaporated to dryness. The residue was purified by column chromatography, using dichloromethane as eluent. Finally the product, in each case, was crystallized from acetone. The yields obtained were as follows: **5a**, 86 mg, 88%, and **5d**, 64 mg, 81%, from, respectively **2a** or **4a**; **6a**, 79–84 mg, 77–82%, and **6d**, 66 mg, 78%, from **2b** or **4b**.

5-Hydroxy-6,8-diiodo-2-phenylchromone **5a**.

This compound was obtained as a yellow powder, mp 262–263°C; ^1H nmr: δ 6.88 (s, 1H, H-3), 7.56–7.60 (m, 3H, H-3',4',5'), 8.05 (d, 2H, H-2',6', J = 6.5 Hz), 8.37 (s, 1H, H-7), 13.70 (s, 1H, OH-5); ^{13}C nmr: δ 70.3 (C-8), 78.5 (C-6), 105.6 (C-3), 111.2 (C-10), 126.8 (C-2',6'), 129.4 (C-3',5'), 130.3 (C-1'), 132.7 (C-4'), 151.3 (C-7), 155.1 (C-9), 160.4 (C-5), 165.2 (C-2), 182.4 (C-4); ms: (EI) m/z (relative intensity) 490 (M^+ , 100), 388 (31), 364 (17), 261 (17), 245 (7), 233 (15), 205 (7), 181 (7), 152 (7), 102 (8), 77 (18).

Anal. Calcd. for C₁₅H₈O₃I₂: C, 36.77; H, 1.65. Found: C, 37.00; H, 1.65.

6,8-Dibromo-5-hydroxy-2-phenylchromone **5d**.

This compound was obtained as yellow needles, mp 252–254°C; ^1H nmr: δ 6.86 (s, 1H, H-3), 7.55–7.62 (m, 3H, H-3',4',5'), 8.00–8.03 (m, 2H, H-2',6'), 8.03 (s, 1H, H-7), 13.41 (s, 1H, OH-5); ^{13}C nmr: δ 99.0 (C-8), 104.5 (C-6), 105.7 (C-3), 111.9 (C-10), 126.7 (C-2',6'), 129.4 (C-3',5'), 130.3 (C-1'), 132.8 (C-4'), 140.5 (C-7), 151.7 (C-9), 156.8 (C-5), 165.1 (C-2), 182.6 (C-4); ms: (EI) m/z (relative intensity) 396 (M^+ , 100), 316 (17); 294 (39), 266 (8), 215 (8), 185 (6), 102 (11), 77 (19).

Anal. Calcd. for C₁₅H₈O₃Br₂: C, 45.49; H, 2.04. Found: C, 45.51; H, 2.02.

5-Hydroxy-6,8-diiodo-2-styrylchromone **6a**.

This compound was obtained as a yellow powder, mp 252–254°C; ^1H nmr: δ 6.35 (s, 1H, H-3), 6.77 (d, 1H, H- α , J = 15.9 Hz), 7.43–7.47 (m, 3H, H-3',4',5'), 7.60–7.64 (m, 2H, H-2',6'), 7.86 (d, 1H, H- β , J = 15.9 Hz), 8.35 (s, 1H, H-7), 13.74 (s, 1H, OH-5); ^{13}C nmr: δ 70.2 (C-8), 78.3 (C-6), 108.6 (C-3), 111.3 (C-10), 118.7 (C- α), 128.2 (C-2',6'), 129.1 (C-3',5'), 130.6 (C-4'), 134.5 (C-1'), 140.3 (C- β), 151.2 (C-7), 154.8 (C-9), 160.5 (C-5), 163.6 (C-2), 182.4 (C-4); ms: (EI) m/z (relative intensity) 516 (M^+ , 100), 515 (17), 498 (5), 490 (5), 388 (28), 360 (6), 261 (12), 205 (5), 128 (38), 115 (6), 102 (12), 77 (23).

Anal. Calcd. for C₁₇H₁₀O₃I₂: C, 39.57; H, 1.95. Found: C, 39.45; H, 1.90.

6,8-Dibromo-5-hydroxy-2-styrylchromone **6d**.

This compound was obtained as yellow needles, mp 241–243°C; ^1H nmr: δ 6.34 (s, 1H, H-3), 6.79 (d, 1H, H- α , J = 16.0 Hz), 7.43–7.45 (m, 3H, H-3',4',5'), 7.60–7.63 (m, 2H, H-2',6'), 7.78 (d, 1H, H- β , J = 16.0 Hz), 8.00 (s, 1H, H-7), 13.45 (s, 1H, OH-5); ^{13}C nmr: δ 98.7 (C-8), 104.3 (C-6), 108.8 (C-3), 111.9 (C-10), 118.7 (C- α), 128.1 (C-2',6'), 129.1 (C-3',5'), 130.6 (C-4'), 134.5 (C-1'), 140.0 (C- β), 140.4 (C-7), 151.4 (C-9), 156.9 (C-5), 163.5 (C-2), 182.5 (C-4); ms: (EI) m/z (relative intensity) 422 (M^{+} , 100), 421 (49), 404 (15), 342 (14), 294 (32), 266 (9), 215 (9), 176 (8), 155 (12), 128 (69), 102 (13), 77 (22).

Anal. Calcd. for $\text{C}_{17}\text{H}_{10}\text{O}_3\text{Br}_2$: C, 48.37; H, 2.39. Found: C, 48.31; H, 2.38.

Synthesis of 5-Hydroxy-6-iodo- or 5-Hydroxy-8-iodo-2-phenylchromones **5b** or **5c**.

To a 0.2 mmole solution of 2'-benzyloxy-6'-hydroxychalcone **2a** or 5-hydroxy-2-phenylchromone **4a** in DMSO (0.6 ml) was added iodine (0.1 mmole). The mixture was heated at reflux for 30 minutes, then was poured into ice (50 g) and water (50 ml) to precipitate the product. The solid was removed by filtration and dissolved in chloroform (50 ml), and washed with a 20% aqueous solution of sodium thiosulfate (2 x 50 ml). The organic layer was passed through anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on several preparative layer chromatography plates, eluting with petroleum ether:dichloromethane and petroleum ether:ethyl acetate mixtures. The yields obtained were as follows:

Starting with chalcone **2a** the following products, in an increasing R_f order, have been obtained **4a**, 13 mg, 27%, **5a**, 27 mg, 28%, **5b**, 4 mg, 5%, all crystallized from ethanol, and **5c**, 10 mg, 14%, from acetone.

When using **4a** as a reagent, 34% of unreacted compound was recovered and **5b**, 21 mg, 29% and **5c**, 6 mg, 8%, have been obtained.

5-Hydroxy-6-iodo-2-phenylchromone **5b**.

This compound was obtained as a yellow powder, mp 153–156°C; ^1H nmr: δ 6.82 (s, 1H, H-3), 6.91 (d, 1H, H-8, J = 8.8 Hz), 7.51–7.61 (m, 3H, H-3',4',5'), 7.92 (dd, 2H, H-2',6', J = 8.0 and 1.7 Hz), 7.98 (d, 1H, H-7, J = 8.8 Hz), 13.61 (s, 1H, OH-5); ^{13}C nmr: δ 77.5 (C-6), 105.9 (C-3), 109.3 (C-8), 110.9 (C-10), 126.5 (C-2',6'), 129.2 (C-3',5'), 130.9 (C-1'), 132.4 (C-4'), 143.9 (C-7), 156.5 (C-9), 159.8 (C-5), 165.0 (C-2), 182.6 (C-4); ms: (EI) m/z (relative intensity) 364 (M^{+} , 100), 262 (26), 238 (10), 234 (11), 152 (6), 107 (12), 77 (6).

Anal. Calcd. for $\text{C}_{15}\text{H}_9\text{O}_3\text{I}$: C, 49.48; H, 2.49. Found: C, 49.53; H, 2.47.

5-Hydroxy-8-iodo-2-phenylchromone **5c**.

This compound was obtained as a yellow powder, mp 168–171°C; ^1H nmr: δ 6.70 (d, 1H, H-6, J = 8.7 Hz), 6.82 (s, 1H, H-3), 7.55–7.60 (m, 3H, H-3',4',5'), 7.94 (d, 1H, H-7, J = 8.7 Hz), 8.07 (dd, 2H, H-2',6', J = 7.8 and 2.0 Hz), 12.70 (s, 1H, OH-5); ^{13}C nmr: δ 68.9 (C-8), 105.8 (C-3), 111.8 (C-10), 113.9 (C-6), 126.8 (C-2',6'), 129.3 (C-3',5'), 130.7 (C-1'), 132.5 (C-4'), 144.3 (C-7), 154.9 (C-9), 161.4 (C-5), 164.9 (C-2), 183.4 (C-4); ms: (EI) m/z (relative intensity) 364 (M^{+} , 100), 262 (30), 234 (8), 168 (6), 152 (6), 135 (21), 102 (7), 79 (8).

Anal. Calcd. for $\text{C}_{15}\text{H}_9\text{O}_3\text{I}$: C, 49.48; H, 2.49. Found: C, 49.30; H, 2.50.

Synthesis of 5-Hydroxy-6-iodo- or 5-Hydroxy-8-iodo-2-styrylchromones **6b** or **6c**.

Using the 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **2b** or 5-hydroxy-2-styrylchromone **4b** and the same experimental procedure described for the synthesis of **5b** and **5c**, the following monoiodo-compounds were obtained: **6b**, 8 mg, 10%, **6c**, 11 mg, 14%, from **2b**; **6b**, 10 mg, 13% and **6c**, 7 mg, 9%, from **4b**.

5-Hydroxy-6-iodo-2-styrylchromone **6b**.

This compound was obtained as a yellow powder mp 183–186°C; ^1H nmr: δ 6.33 (s, 1H, H-3), 6.78 (d, 1H, H- α , J = 16.2 Hz), 6.87 (d, 1H, H-8, J = 8.9 Hz), 7.42–7.48 (m, 3H, H-3',4',5'), 7.58–7.61 (m, 2H, H-2',6'), 7.64 (d, 1H, H- β , J = 16.2 Hz), 7.96 (d, 1H, H-7, J = 8.9 Hz), 13.64 (s, 1H, OH-5); ^{13}C nmr: δ 76.8 (C-6), 108.8 (C-3), 109.1 (C-8), 111.0 (C-10), 119.3 (C- α), 127.9 (C-2',6'), 129.1 (C-3',5'), 130.4 (C-4'), 134.6 (C-1'), 138.7 (C- β), 143.8 (C-7), 156.3 (C-9), 159.9 (C-5), 163.2 (C-2), 182.6 (C-4); ms: (EI) m/z (relative intensity) 390 (M^{+} , 100), 389 (29), 372 (13), 263 (13), 262 (34), 234 (18), 189 (6), 181 (22), 178 (7), 155 (8), 135 (22), 131 (21), 129 (7), 128 (26), 127 (13), 114 (7), 107 (14), 103 (7), 102 (11), 100 (12), 93 (9), 91 (28), 79 (18).

Anal. Calcd. for $\text{C}_{17}\text{H}_{11}\text{O}_3\text{I}$: C, 52.33; H, 2.84. Found: C, 52.37; H, 2.84.

5-Hydroxy-8-iodo-2-styrylchromone **6c**.

This compound was obtained as a yellow powder, mp 186–188°C; ^1H nmr: δ 6.30 (s, 1H, H-3), 6.68 (d, 1H, H-6, J = 8.7 Hz), 6.78 (d, 1H, H- α , J = 15.5 Hz), 7.42–7.45 (m, 3H, H-3',4',5'), 7.61–7.64 (m, 2H, H-2',6'), 7.87 (d, 1H, H- β , J = 15.5 Hz), 7.91 (d, 1H, H-7, J = 8.7 Hz), 12.72 (s, 1H, OH-5); ^{13}C nmr: δ 68.8 (C-8), 108.9 (C-3), 111.8 (C-10), 113.7 (C-6), 119.0 (C- α), 128.1 (C-2',6'), 129.1 (C-3',5'), 130.4 (C-4'), 134.7 (C-1'), 139.8 (C- β), 144.1 (C-7), 154.5 (C-9), 161.4 (C-5), 163.2 (C-2), 183.4 (C-4); ms: (EI) m/z (relative intensity) 390 (M^{+} , 100), 389 (35), 372 (12), 263 (6), 262 (28), 234 (8), 135 (16), 128 (25), 127 (7), 102 (5), 79 (8).

Anal. Calcd. for $\text{C}_{17}\text{H}_{11}\text{O}_3\text{I}$: C, 52.33; H, 2.84. Found: C, 52.63; H, 2.96.

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