# New Bis(chalcones) and Their Transformation into Bis(pyrazoline) and Bis(pyrazole) Derivatives

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The reaction of bis(chalcones) **1a**–**d** and bis(chalcone) tetrabromo derivatives **3a**–**d** with hydrazine hydrate gave bis(pyrazolines) **4a**–**d** and bis(pyrazoles) **5a**–**d**, respectively. Bis(pyrazoles) **5e**,**f** bearing hydroxyphenyl substituents have been prepared from the reaction of bis(chromones) **6c**,**d** with hydrazine hydrate, because their synthesis from the corresponding benzyloxy-substituted **5c**,**d** gave very poor yields. The structures of all new compounds have been established by extensive NMR spectroscopic studies.



## Introduction

Chalconoids constitute an important class of naturally occurring flavonoid compounds exhibiting a wide spectrum of biological activities, which include potential applications as artificial sweeteners, new drugs, and agrochemicals.[1−10] The term chalconoid has been used to designate the whole family of compounds possessing a 1,3-diarylpropane skeleton, which can be functionalised in the propane chain by the presence of olefinic, keto and/or hydroxy groups. The most common and widespread compounds of the chalconoid group are the chalcones, which possess a 1,3-diaryl-2-propen-1-one carbon framework,[1,3,5] but there are also other important derivatives of this family, such as the dihydrochalcones.[2,4,9]

Chalcones, one class of the anthochlor pigments, usually give yellow to orange colours to the tissues in which they are located. Although these compounds are not responsible for pigmentation in the most-yellow-coloured flowers, they are still attractive to insects and in such a way they contribute to the flowers' pollination.[11] The importance of these compounds is due not only to their colours, but also to their biological activities and the fact that they are intermediates in the synthesis and biosynthesis of other flavonoids.[1−3,5−10] Following our interest in the chemistry of flavonoid-type compounds we have synthesised new chalcone derivatives **1** and studied their transformations into new bis(2-pyrazolines) **4** and bis(pyrazoles) **5**.

Pyrazoles and their reduced forms pyrazolines are well-known nitrogen-containing heterocyclic compounds and various procedures have been developed for their syntheses.[12] As a result, a wide variety of pyrazoles and pyrazolines have hitherto been described in the literature.[12,13] This interest of scientists in such compounds has been stimulated by their promising pharmacological, agrochemical, and analytical applications. For instance, in the last decade 2-(hydroxyphenyl)pyrazoles have been used as ultraviolet stabilisers,[14] as analytical reagents in the complexation of transition metal ions,[15] and also as analgesic agents and as platelet aggregation inhibitors.[16] These applications — especially their ability to form complexes with a variety of metal ions[15] and our interest in the preparation and molecular structure of 2-(hydroxyphenyl)-pyrazoles[17−19] — have prompted us to devote our attention to new types of these compounds, the 3-aryl-5-[3- and 4-(3-arylpyrazol-5-yl)phenyl]pyrazoles, and some other derivatives.

The most common method for the synthesis of 2-(hydroxyphenyl)pyrazoles involves the treatment of β-diketones with hydrazine hydrate.[12] Our recent studies indicate, however, that these pyrazoles can be obtained in good overall yields from the reaction of hydrazine hydrate with chromones.[18−19] There are, however, reports indicating that the treatment of 2-hydroxychalcones or 2-hydroxychalcone dibromides with phenylhydrazine in an alkaline medium affords pyrazoline derivatives.[20] Here we report the synthesis of 3-aryl-5-[3- and 4-(3-aryl-2-pyrazolin-5-yl)-phenyl]-2-pyrazolines **4a**−**d** and 3-aryl-5-[3- and 4-(3-aryl-pyrazol-5-yl)phenyl]pyrazoles **5a**−**f** from bis(chalcones) **1a**−**f** and bis(chalcone) tetrabromo derivatives **3a**−**f**.[21]

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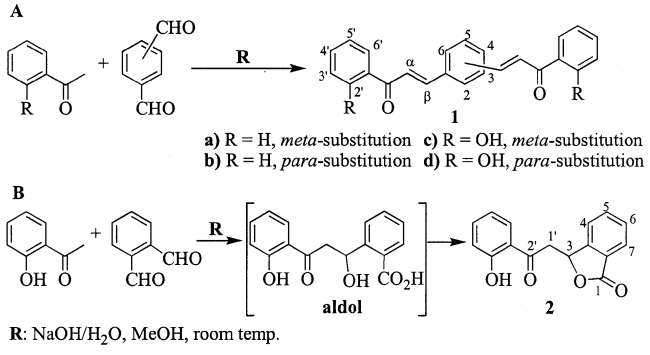
## Results and Discussion

### Chemistry

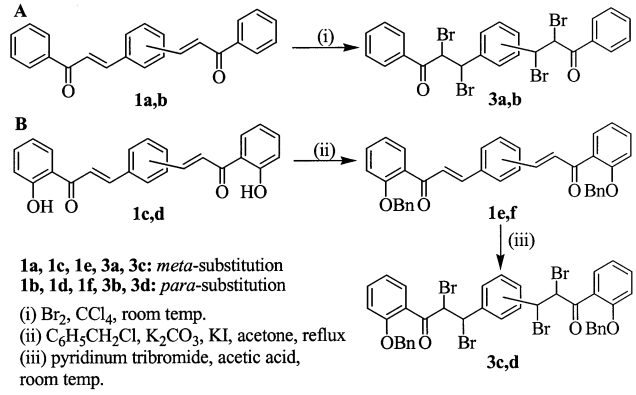
Bis(chalcones) **1a**−**d** were obtained in moderate yields (42−56%) from the base-catalysed aldol reaction of 2′-hy-

droxyacetophenone and appropriate phthaldicarboxaldehydes (Scheme 1, A). In this synthesis the desired chalcones resulted from the condensation of two molecules of 2′-hydroxyacetophenone with the appropriate dialdehyde. It seems, however, that the second condensation competes with a Cannizzaro reaction, since an amount of 2′-hydroxychalcones bearing carboxyl or hydroxymethyl groups in the B ring were obtained (see Exp. Sect.). The former of these derivatives could also have been obtained by the oxidation of the second carboxaldehyde. The formation of these by-products is responsible for the moderate yields of the bis(chalcones). The reaction of 2′-hydroxyacetophenone with *ortho*-phthaldicarboxaldehyde, under the same conditions, gave the products of the Cannizzaro reaction and a new compound **2** in a poor yield. Some changes in the experimental procedure, such as protection from daylight and adding the *ortho*-phthaldicarboxaldehyde after degassing the reaction mixture, allowed the synthesis of compound **2** to proceed in good yield, but still we could not obtain the desired chalcone. This result indicates that, under our experimental conditions, oxidation of the second carboxaldehyde group is easier in *ortho*-phthaldicarboxaldehyde than in the *meta*- or *para*-phthaldicarboxaldehydes. Thus, after the aldol intermediate has formed a cyclisation reaction occurs to give lactone **2** (Scheme 1, B). The presence of this compound is concluded from its NMR spectroscopic data, such as the carbonyl carbon atoms at δ = 169.9 ppm (lactone) and δ = 201.6 ppm (ketone), the hydroxy group involved in an intramolecular hydrogen bond (δ = 12.02 ppm) and an ABX spin system (2 × 1′-H and 3-H).



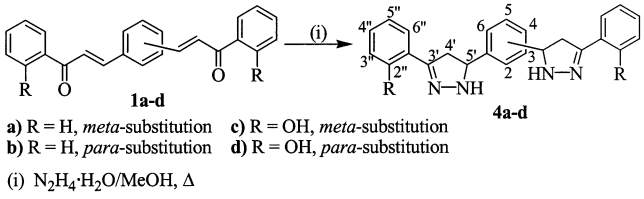

Scheme 1

The bis(chalcone) tetrabromo derivatives **3a**,**b** were obtained in good yields by treatment of a carbon tetrachloride solution of the appropriate bis(chalcones) **1a**,**b** with bromine (Scheme 2, A). We did not apply the same procedure to bis(chalcones) **1c**,**d** since their A ring is activated and there was the possibility that halogenation could occur in this ring. Generally the bromination of 2′-hydroxychalcones gives poor yields, but if the hydroxy group is protected the reaction gives the corresponding dibromo derivatives in good yields.[22] Taking this feature into account, the bis(chalcones) **1e**,**f** were obtained in very good yields by treating the appropriate bis(chalcones) **1c**,**d** with benzyl chloride (Scheme 2, B). Following our previous work on the bromination of 2-styrylchromones,[23] we used a similar procedure for the bromination of bis(chalcones) **1e**,**f**, which proved also to be a convenient method for these substrates because the corresponding tetrabromo derivatives **3c**,**d** were obtained in good yields (Scheme 2, B).




Scheme 2

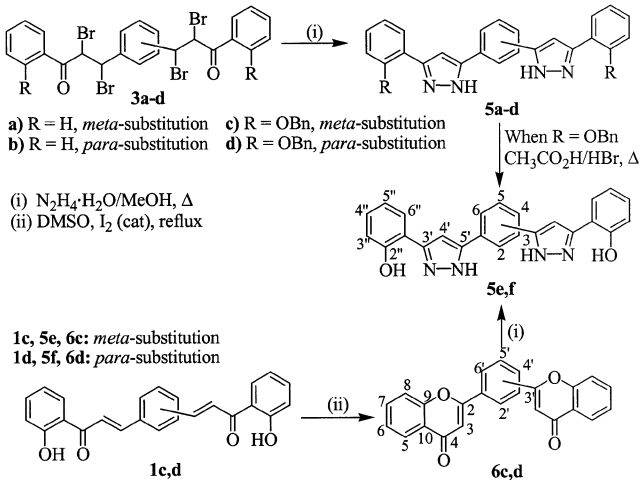
Our first approach to the synthesis of bis(pyrazoles) **5a**−**d** began with the reaction in methanol under reflux of the bis(chalcones) **1a**−**d** with an excess of hydrazine hydrate (Scheme 3). These reactions yielded the corresponding bis(2-pyrazolines) **4a**−**d**, which precipitated in the reaction medium and were removed by filtration and washed with ethanol. Next, we attempted to oxidise these bis(2-pyrazolines) **4a**−**d** into pyrazole derivatives by treatment with chloranil in toluene at reflux. This oxidant proved to be too strong, causing the pyrazoline ring to be destroyed and the isolation of the bis(chalcones) **1a**−**d**. Several other oxidation methods ($MnO_2$, $O_2$, $S_8$) were tested, but similar results were obtained.




Scheme 3

To circumvent the oxidation step for the conversion of bis(pyrazolines) **4a**−**d** into the corresponding bis(pyrazoles) **5a**−**d**, we decided to use the bis(chalcone) tetrabromo derivatives **3a**−**d**. Treatment of compounds **3a**−**d** with an excess of hydrazine hydrate, in methanol under reflux, afforded the desired pyrazoles **5a**−**d** in good overall yields (50−61%, Scheme 4). This synthetic approach constitutes a new method for the preparation of these types of pyrazoles. The debenzylation of pyrazoles **5c**,**d** was carried out with hydrogen bromide in glacial acetic acid (33%), but the corresponding bis[3-(2-hydroxyphenyl)pyrazoles] **5e**,**f** were obtained in poor yields and their purification was difficult.

Recalling our previous work on pyrazoles from 2-substituted chromones,[18,19] we tried to prepare these bis[3-(2-hydroxyphenyl)pyrazoles] **5e**,**f** from chromones **6c**,**d**. This method proved to be a suitable one since the desired pyrazoles **5e**−**f** were obtained in good overall yields (Scheme 4). Chromones **6c**,**d** were obtained by oxidative cyclisation of chalcone derivatives **1c**−**d** with a catalytic amount of iodine in refluxing DMSO.




Scheme 4

## NMR Spectroscopy

The most important features of the $^1$H and $^{13}$C NMR spectra of bis(chalcones) **1a**−**f** are: i) the coupling constants $J_{H\alpha\text{-}H\beta} \approx 16$ Hz indicating the presence of a trans configuration of the double bond; ii) the C-β carbon atom resonances (δ = 141.6−146.6 ppm) appeared downfield of those of the C-α atoms (δ = 121.4−128.0 ppm), because of the mesomeric deshielding effect of the carbonyl group; iii) the singlets at δ = 12.51−12.77 ppm and 5.15−5.18 ppm, assigned to the resonances of the hydroxy groups of **1c**,**d** and the benzylic $CH_2$ units of **1e**,**f**, respectively; iv) the carbonyl carbon atom resonances at δ = 190.2−196.3 ppm; v) the singlet in the range δ = 7.28−7.75 ppm in the cases of **1b**,**d**,**f**, corresponding to the 2,3,5,6-H protons resonance, arising because of the symmetry of the molecule; vi) the broad singlet in the range δ = 7.39−8.47 ppm for **1a**,**c**,**e**, which is assigned to the resonance of protons 2-H.

From the $^1$H and $^{13}$C NMR spectra of bis(chalcone) dibromides **3a**−**d**, it is important to note the doublets at δ = 5.51−5.68 and 5.82−6.34 ppm corresponding to the resonances of H-β and H-α, respectively, and also the resonances of C-β (δ ≈ 49 ppm) and C-α (δ ≈ 47 ppm). The coupling $J_{H\alpha\text{-}H\beta}$ = 11.2−11.5 Hz indicates a *trans* diaxial orientation of these protons, which confirms the expected anti addition of bromine to the two vinylic moieties of bis(chalcones) **1a**,**b**,**e**,**f**. These two additions must give rise to the formation of two diastereoisomers of bis(chalcone) dibromides **3a**−**d**, but the NMR spectroscopic data suggests the presence of only one compound. This apparent diastereoselectivity might arise from a chiral induction from the first bromine addition to the other, or by the superposition of the NMR spectra of the possible two diastereoisomers.

The main characteristics in the structural characterisation of bis(chromones) **6c,d** are the resonances of the 3-H (s, δ ≈ 6.9 ppm) and C-3 (δ ≈ 108 ppm) atoms, the resonance of 2,3,5,6-H appearing as a singlet at δ = 8.11 ppm in the case of **6d**, and the resonance of 2-H appearing as a triplet at δ = 8.49 ppm in the case of **6c**.

The reaction of bis(chalcones) **1a**−**d** with hydrazine hydrate afforded solid products. The TLC analysis of these solids revealed the presence, in each case, of a single spot and their $^1$H NMR spectra seem to indicate that they are constituted by pure bis(2-pyrazolines) **4a**−**d** (two inequivalent protons of a methylene group coupled with a methine proton, and an NH proton at δ = 7.86 ppm). These reactions may give rise to a mixture of two diastereoisomers (one being a pair of enantiomers and the other a *meso* structure), but the $^1$H NMR spectra of the products suggested, in each case, the presence of a single compound. In the $^{13}$C NMR spectra of these products, however, there are duplications of some carbon resonances, supporting the expected mixture of two isomers. Separating these mixtures by using a chiral HPLC column, or by using a lanthanide shift reagent {europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]}, proved unsuccessful as were all attempts to grow single crystals of pyrazolines **4a**−**d**.

The detailed analysis of the $^{13}$C NMR spectra of bis(2-pyrazolines) **4a**−**c** allowed us to identify two sets of resonances, one being less intense than the other (Table 1 shows these two sets for compounds **4a**, the resonances in brackets correspond to the less-intense ones). These data suggest that one of the diastereomers, either the *meso* or the *d,l* pair, was formed with slight selectively. AM1 calculations for the two isomers of bis(2-pyrazoline) **4d** indicate that the meso diastereomer is the most stable ($\Delta H_f$ = 2 kcal mol$^{-1}$) (Figure 1). Thus, we assume tentatively that the most-abundant isomer is the *meso* one. Taking these data into account, we can consider that the mechanism of formation of bis(2-pyrazolines) **4a**−**d** involves two steps: i) First there is the reaction of each bis(chalcone) with one molecule of hydrazine giving a racemic mixture of a compound bearing one pyrazoline ring and a chalcone moiety; ii) secondly, there is the reaction of these compounds with a second molecule of hydrazine. The $^{13}$C NMR and AM1 data suggest that in this second step there is a small chiral induction, leading to the mixture of diastereoisomers, of which the meso form is the more stable. One can rationalise that the chiral induction is minor because there is a great distance between the resulting stereogenic centres.

Table 1. $^{13}$C NMR chemical shifts of the two diastereoisomers of bis(2-pyrazoline) **4a**

| | | | | | |
|---|---|---|---|---|---|
| C-1,3 | 137.0 (136.8) | C-3′ | 170.6 (171.0) | C-1′′ | 129.8 (129.9) |
| C-2 | 127.7 | C-4′ | 41.7 (41.9) | C-2′′,6′′ | 128.44 (128.41) |
| C-4,6 | 128.7 (129.0) | C-5′ | 61.5 | C-3′′,5′′ | 129.4 |
| C-5 | 128.0 | | | C-4′′ | 132.5 (135.6) |

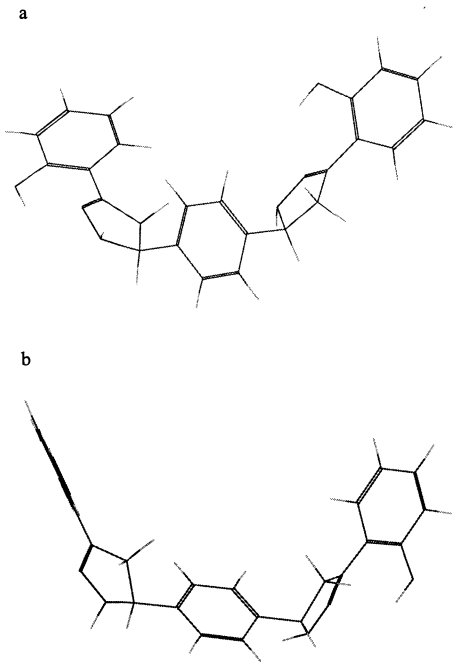



Figure 1. a. Compound **4d**, *meso* isomer; b. compound **4d**, *d,l* isomer

The $^1$H NMR spectra of **4a**−**d** revealed other characteristic signals such as: i) the 2′′-OH proton resonances appearing as sharp singlets at δ = 11.17 ppm in pyrazolines **4c**,**d**, indicating the presence of an intramolecular hydrogen bond; ii) the 2,3,5,6-H resonances at δ = 7.39−7.60 ppm in pyrazolines **4b**,**d** appearing as singlets because of the symmetry of the molecules; iii) the 2-H resonances at δ = 7.50 ppm in pyrazolines **4a**,**c** appearing as broad singlets because of small coupling with 4,6-H.

Because of the symmetry of bis(pyrazoles) **5a**−**f** their NMR spectra are simple. The most characteristic $^1$H NMR resonances of bis(pyrazoles) **5a**−**f** are those attributable to the NH and 4′-H protons, which appear, respectively, in the ranges δ = 13.12−13.75 and 7.21−7.52 ppm. It is worth noting the singlets at δ = 5.31 ppm attributable to the resonance of the $CH_2$ protons of the 2′′-$OCH_2C_6H_5$ groups in the cases of pyrazoles **5c**,**d**, as well as the broad singlets at δ = 10.70−10.90 ppm for the resonance of 2′′-OH protons in the cases of pyrazoles **5e**,**f**. The assignment of the resonances of the protonated carbon atoms in the $^{13}$C NMR spectra of pyrazoles **5a**−**f** was based on the analysis of HSQC spectra, whereas those of the quaternary carbon atoms were based on the connectivities found in HMBC spectra (Figure 2 shows the most important ones).

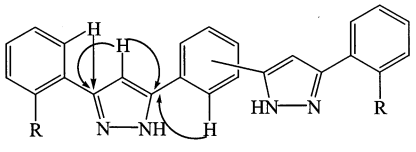



Figure 2. Main connectivities found in the HMBC spectra of pyrazoles **5a**−**f**

## Conclusion

We have synthesised the bis(pyrazoles) **5a**−**f** from the reactions of bis(chalcones) **1a**−**d** and bis(chalcone) tetrabromo derivatives **3a**−**d** with hydrazine hydrate. The former reaction gave the corresponding bis(2-pyrazolines) **4a**−**d**, but attempts at their oxidation were unsuccessful; the reaction, however, starting with bis(chalcone) tetrabromo derivatives **3a**−**d** gave the corresponding bis(pyrazoles) **5a**−**d** in good yields. Since the preparation of bis(pyrazoles) **5e**,**f** bearing hydroxyphenyl substituents from the corresponding benzyloxy-substituted compounds **5c**,**d** gave very poor yields, these compounds were instead synthesised in good yields by the reaction of bis(chromones) **6c**,**d** with hydrazine hydrate. All of these reactions allowed us to establish new synthetic methods for the preparation of novel bis(pyrazoles) **5a**−**f**.

## 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), with $CDCl_3$ as solvent if not stated otherwise. Chemical shifts (δ) are reported 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 optimised 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 analyser (University of Aveiro). Preparative thin-layer chromatography was performed with Merck silica gel 60 $DGF_{254}$. Column chromatography was performed with Merck silica gel 60, 70−230 mesh. All other chemicals and solvents used were obtained from commercial sources and used as received or dried using standard procedures.

**Synthesis of Bis(chalcones) (1a−d):** An aqueous solution of sodium hydroxide (60%, 150 mL) was added slowly to a methanolic solution (200 mL) of the appropriate acetophenone (33 mmol). After cooling the solution to room temperature, a methanolic suspension (50 mL) of isophthaldialdehyde or terephthaldialdehyde (2.2 g, 16.4 mmol) was added. The reaction mixture was stirred at room temperature for 20 h, and then it was poured into a mixture of ice and commercial hydrochloric acid (pH was adjusted to about 2). The resulting solid was filtered, dissolved in dichloromethane (150 mL), and washed with a saturated solution of sodium hydrogen carbonate (2 × 100 mL). The solvent was evaporated to dryness and the residue was purified by column chromatography using dichloromethane as eluent. The compounds eluted in this order: hydroxymethylchalcone derivatives, bis(chalcones) **1a**−**d**, then carboxychalcones. Finally, each of these compounds was crystallised from ethanol. We describe here as examples the characterisation of only one hydroxymethylchalcone and one carboxychalcone.

**3-(3-Oxo-3-phenylpropenyl)chalcone (1a):** Yield 50% (5.58 g). M.p. 141−143 °C (recrystallised from ethanol). $^1$H NMR: δ = 7.47−7.56 (m, 5 H, 2 × 3′,5′-H and 5-H), 7.59 (d, *J* = 15.7 Hz, H-α), 7.59−7.64 (m, 2 H, 2 × 4′-H), 7.70 (dd, *J* = 7.7, 1.5 Hz, 2 H, 4,6-H), 7.84 (d, *J* = 15.7 Hz, H-β), 7.89 (s br, 1 H, 2-H), 8.05

(d, $J$ = 8.1 Hz, 4 H, 2 × 2′,6′-H) ppm. $^{13}$C NMR: δ = 122.9 (2 × C-α), 128.2 (C-2), 128.5 (2 × C-2′,6′), 128.7 (2 × C-3′,5′), 129.6 (C-5), 130.1 (C-4,6), 133.0 (2 × C-4′), 137.9 (2 × C-1′), 135.7 (C-1,3), 143.8 (2 × C-β), 190.3 (2 × C=O) ppm. EI-MS: $m/z$ (rel. int.) = 338 (99) [M$^{+\cdot}$], 337 (41), 309 (10), 233 (100), 215 (6), 207 (23), 178 (7), 155 (8), 127 (11), 105 (72), 77 (68). $C_{24}H_{18}O_2$ (338.13): calcd. C 85.18, H 5.36; found C 85.15, H 5.60.

**4-(3-Oxo-3-phenylpropenyl)chalcone (1b):** Yield 56% (6.25 g). M.p. 196−197 °C (recrystallised from ethanol). $^1$H NMR: δ = 7.52 (dd, $J$ = 7.5, 6.5 Hz, 4 H, 2 × 3′,5′-H), 7.59 (d, $J$ = 15.7 Hz, 2 × H-α), 7.61 (t, $J$ = 7.5 Hz, 2 H, 2 × 4′-H), 7.70 (s, 4 H, 2,3,5,6-H), 7.82 (d, $J$ = 15.7 Hz, 2 × H-β), 8.04 (d, $J$ = 6.5 Hz, 4 H, 2 × 2′,6′-H) ppm. $^{13}$C NMR: δ = 123.0 (2 × C-α), 128.5 (2 × C-2′,6′), 128.7 (2 × C-3′,5′), 128.9 (C-2,3,5,6), 133.0 (2 × C-4′), 136.8 (2 × C-1′), 138.0 (C-1,4), 143.5 (2 × C-β), 190.2 (2 × C=O) ppm. EI-MS: $m/z$ (rel. int.) = 338 (100) [M$^{+\cdot}$], 337 (29), 309 (11), 261 (8), 233 (86), 207 (11), 178 (10), 127 (11), 105 (41), 77 (54). EI-HRMS ($C_{24}H_{18}O_2$ [M$^{+\cdot}$]): calcd. 338.1306, found 338.1305.

**2′-Hydroxy-3-[3-(2-hydroxyphenyl)-3-oxopropenyl]chalcone (1c):** Yield 42% (5.13 g). M.p. 180−181 °C (recrystallised from ethanol). $^1$H NMR ([D$_6$]DMSO): δ = 7.02 (d, $J$ = 8.4 Hz, 2 H, 2 × 3′-H), 7.03 (t, $J$ = 8.1 Hz, 2 H, 2 × 5′-H), 7.55−7.61 (m, 3 H, 2 × 4′-H and 5-H), 7.88 (d, $J$ = 15.6 Hz, 2 H, 2 × H-β), 8.00 (dd, $J$ = 7.8, 1.2 Hz, 2 H, 4,6-H), 8.14 (d, $J$ = 15.6 Hz, 2 H, 2 × H-α), 8.28 (dd, $J$ = 8.1, 1.2 Hz, 2 H, 2 × 6′-H), 8.47 (s br, 1 H, 2-H), 12.51 (s, 2 H, 2 × 2′-OH) ppm. $^{13}$C NMR ([D$_6$]DMSO): δ = 117.8 (2 × C-3′), 119.3 (2 × C-5′), 120.8 (2 × C-1′), 122.7 (2 × C-α), 129.5 (C-2), 129.7 (C-5), 131.0 (2 × C-6′), 131.4 (C-4,6), 135.2 (C-1,3), 136.5 (2 × C-4′), 144.1 (2 × C-β), 161.9 (2 × C-2′), 193.7 (2 × C=O) ppm. EI-MS: $m/z$ (rel. int.) = 370 (79) [M$^{+\cdot}$], 369 (25), 249 (50), 236 (13), 223 (10), 202 (7), 165 (8), 147 (85), 128 (13), 121 (100), 102 (12), 93 (29), 77 (15), 65 (57). $C_{24}H_{18}O_4$ (370.40): calcd. C 77.82, H 4.90; found C 78.08, H 4.66.

**2′-Hydroxy-4-[3-(2-hydroxyphenyl)-3-oxopropenyl]chalcone (1d):** Yield 51% (6.23 g). M.p. 259−261 °C (recrystallised from ethanol). $^1$H NMR: δ = 6.98 (t, $J$ = 7.7 Hz, 2 H, 2 × 5′-H), 7.06 (d, $J$ = 7.7 Hz, 2 H, 2 × 3′-H), 7.54 (t, $J$ = 7.7 Hz, 2 H, 2 × 4′-H), 7.73 (d, $J$ = 15.3 Hz, 2 H, H-α), 7.75 (s, 4 H, 2,3,5,6-H), 7.94 (d, $J$ = 15.3 Hz, 2 H, 2 × H-β), 7.95 (d, $J$ = 7.7 Hz, 2 H, 2 × 6′-H), 12.77 (s, 2 H, 2 × 2′-OH) ppm. $^{13}$C NMR: δ = 118.7 (2 × C-3′), 119.9 (2 × C-1′), 121.1 (2 × C-5′), 121.4 (2 × C-α), 129.9 (C-2,3,5,6), 130.8 (2 × C-6′), 137.2 (C-1,4), 138.6 (2 × C-4′), 146.6 (2 × C-β), 162.0 (2 × C-2′), 196.3 (2 × C=O) ppm. EI-MS: $m/z$ (rel. int.) = 370 (100) [M$^{+\cdot}$], 369 (47), 353 (9), 249 (63), 236 (16), 223 (12), 202 (9), 165 (8), 147 (64), 130 (19), 121 (76), 102 (8), 93 (24), 77 (13), 65 (42). EI-HRMS ($C_{24}H_{18}O_4$ [M$^{+\cdot}$]): calcd. 370.1205, found 370.1195.

**2′-Hydroxy-3-hydroxymethylchalcone:** Yield 20% (1.68 g). M.p. 192−194 °C (recrystallised from ethanol). $^1$H NMR ([D$_6$]acetone): δ = 5.15 (s, 2 H, 3-C$H_2$OH), 7.42−7.47 (m, 2 H, 3′-H and 5′-H), 7.86−7.95 (m, 2 H, 4-H and 5-H), 8.02 (dt, $J$ = 7.8, 1.7 Hz, 1 H, 4′-H), 8.20 (d, $J$ = 6.9 Hz, 1 H, 6-H), 8.31 (s broad, 1 H, 2-H), 8.39 (d, $J$ = 15.5 Hz, 1 H, H-β), 8.51 (d, $J$ = 15.5 Hz, 1 H, α), 8.72 (dd, $J$ = 8.4, 1.7 Hz, 1 H, 6′-H), 13.38 (s, 1 H, 2′-O$H$) ppm. $^{13}$C NMR ([D$_6$]acetone): δ = 64.2 (3-$C$H$_2$OH), 118.7 (C-3′), 119.8 (C-5′), 120.8 (C-1′), 121.2 (C-α), 127.7 (C-2), 128.5 (C-6), 129.7 (C-5), 131.3 (C-6′), 130.0 (C-4), 135.4 (C-1), 144.3 (C-3), 137.4 (C-4′), 146.3 (C-β), 164.4 (C-2′), 194.9 (C=O) ppm. EI-MS: $m/z$ (rel. int.) = 254 (100) [M$^{+\cdot}$], 253 (71), 236 (56), 223 (42), 207 (18), 178 (14), 165 (17), 147 (63), 131 (15), 121 (45), 115 (17), 92 (17), 77 (20), 65 (21).

**3-Carboxy-2′-hydroxychalcone:** Yield 25% (2.21 g). M.p. 212−214 °C (recrystallised from ethanol). $^1$H NMR ([D$_6$]DMSO): δ = 6.90−7.02 (m, 2 H, 3′-H and 5′-H), 7.54−7.65 (m, 2 H, 4-H and 5-H), 8.01−8.13 (m, 2 H, 4′-H and 6-H), 8.39 (s broad, 1 H, 2-H), 7.88 (d, $J$ = 15.6 Hz, 1 H, H-β), 8.10 (d, $J$ = 15.6 Hz, 1 H, H-α), 8.26 (d, $J$ = 7.8 Hz, 1 H, 6′-H), 12.45 (s broad, 1 H, 2′-O$H$) ppm. $^{13}$C NMR ([D$_6$]DMSO): δ = 117.8 (C-3′), 119.4 (C-1′ and C-5′), 121.0 (C-α), 123.1 (C-2), 129.4 (C-5), 129.8 (C-1), 131.1 (C-6′), 132.9 (C-4), 134.9 (C-6), 131.6 (C-3), 136.5 (C-4′), 143.9 (C-β), 161.8 (C-2′), 167.5 (3-$CO_2$H), 193.6 (C=O) ppm. EI-MS: $m/z$ (rel. int.) = 268 (90) [M$^{+\cdot}$], 267 (74), 251 (31), 222 (27), 194 (17), 165 (32), 147 (100), 131 (22), 121 (59), 92 (13), 77 (13), 65 (14).

**Synthesis of Lactone 2:** An aqueous solution of sodium hydroxide (60%, 150 mL) was added slowly to a degassed methanolic solution (200 mL) of 2′-hydroxyacetophenone (4.0 mL, 33 mmol) that was protected from daylight. After cooling the solution to room temperature, a methanolic suspension (50 mL) of *ortho*-phthaldicarboxaldehyde (2.2 g, 16.4 mmol) was added. The reaction mixture was stirred at room temperature for 20 h, and then it was poured into a mixture of ice and commercial hydrochloric acid (pH was adjusted to ≈2). The resulting solid was filtered, dissolved in dichloromethane (150 mL), and then washed with a saturated solution of sodium hydrogen carbonate (2 × 100 mL). The solvent was evaporated to dryness and the residue was purified by column chromatography using dichloromethane as eluent to yield 3-[2-(2-hydroxyphenyl)-2-oxoethyl]-2-benzofuran-1(3$H$)-one (**2**) (6.16 g, 70%), which was crystallised from ethanol. M.p. 134−136 °C (recrystallised from ethanol). $^1$H NMR: δ = 3.46 (dd, $J$ = 17.7, 6.5 Hz, 1 H, 1′$_{cis}$-H), 3.79 (dd, $J$ = 17.7, 6.5 Hz, 1 H, 1′$_{trans}$-H), 6.17 (t, $J$ = 6.5 Hz, 1 H, 3-H), 6.91 (dd, $J$ = 8.0, 7.4 Hz, 1 H, 5′′-H), 7.02 (d, $J$ = 8.8 Hz, 1 H, 3′′-H), 7.52 (dd, $J$ = 8.8, 7.4 Hz, 1 H, 4′′-H), 7.55−7.60 (m, 2 H, 4-H and 6-H), 7.65 (d, $J$ = 8.0 Hz, 1 H, 6′′-H), 7.70 (t, $J$ = 7.5 Hz, 1 H, 5-H), 7.93 (d, $J$ = 7.9 Hz, 1 H, 7-H), 12.02 (s, 1 H, 2′′-O$H$) ppm. $^{13}$C NMR: δ = 43.2 (C-1′), 76.6 (C-3), 118.7 (C-3′′), 119.0 (C-1′′), 119.3 (C-5′′), 122.6 (C-6), 125.9 (C-7 and C-8), 129.6 (C-4), 129.8 (C-6′′), 134.4 (C-5), 137.2 (C-4′′), 149.2 (C-9), 162.5 (C-2′′), 169.9 (C-1), 201.6 (C-2′) ppm. EIMS: $m/z$ (rel. int.) = 268 (48) [M$^{+\cdot}$], 267 (7), 250 (25), 223 (27), 222 (14), 194 (7), 147 (100), 133 (58), 121 (61), 120 (38), 105 (19), 77 (23), 65 (19). EI-HRMS ($C_{16}H_{12}O_4$ [M$^{+\cdot}$]): calcd. 268.0736, found 268.0730.

**Benzylation of Bis(chalcones) 1c,d. Synthesis of 2′-Benzyloxychalcones 1e,f:** Potassium carbonate (32.4 mmol, 4.47 g), potassium iodide (2.69 g, 16.2 mmol) and benzyl chloride (1.5 mL, 12.96 mmol) were added to a solution of chalcones **1c**,**d** (5.4 mmol) in acetone (100 mL). The mixture was heated under reflux for 12 h and then the inorganic solids were removed by filtration and washed with acetone (2 × 20 mL). The solvent was evaporated to dryness and the residue was purified by column chromatography using dichloromethane as eluent. Finally, the 2′-benzyloxychalcones **1e,f** were crystallised from ethanol.

**2′-Benzyloxy-3-[3-(2-benzyloxyphenyl)-3-oxopropenyl]chalcone (1e):** Yield 71% (2.11 g). M.p. 136−137 °C (recrystallised from ethanol). $^1$H NMR: δ = 5.15 (s, 4 H, 2′-OC$H_2$C$_6$H$_5$), 7.06−7.11 (m, 4 H, 2 × 3′-H and 2 × 5′-H), 7.20−7.26 (m, 7 H, 5-H and 3,4,5-H of 2′-OCH$_2$C$_6$$H_5$), 7.32−7.41 (m, 7 H, 2,4,6-H and 2 × 2,6-H of 2′-OCH$_2$C$_6$$H_5$), 7.50 (ddd, $J$ = 8.0, 7.7, 1.8 Hz, 2 H, 2 × 4′-H), 7.57 (AB, $J$ = 15.9 Hz, 2 H, 2 × H-α), 7.74 (AB, $J$ = 15.9 Hz, 2 H, 2 × H-β), 7.77 (dd, $J$ = 7.8, 1.8 Hz, 2 H, 2 × 6′-H) ppm. $^{13}$C NMR: δ = 70.6 (2 × 2′-OC$H_2$C$_6$H$_5$), 112.8 (2 × C-3′), 121.2 (2 × C-5′), 127.4 (2 × C-2,6 of 2′-OCH$_2$$C_6$H$_5$), 127.8 (2 × C-α), 128.2 (2 × C-4 of 2′-OCH$_2$$C_6$H$_5$), 128.3 (C-2), 128.6 (2 × C-1′ and 2 × C-3,5

of 2′-OCH$_2$*C*$_6$H$_5$), 129.1 (C-5), 129.5 (C-4,6), 130.9 (2 × C-6′), 133.4 (2 × C-4′), 135.6 (C-1,3), 136.0 (2 × C-1 of 2′-OCH$_2$*C*$_6$H$_5$), 141.7 (2 × C-β), 157.6 (2 × C-2′), 191.8 (2 × C=O) ppm. EIMS: *m*/*z* (rel. int.) = 550 (3) [M$^{+\cdot}$], 459 (10), 339 (12), 236 (13), 211 (11), 121 (24), 91 (100), 65 (7). $C_{38}H_{30}O_{40}$ (550.64): calcd. C 82.89, H 5.49; found C 82.65, H 5.36.

**2′-Benzyloxy-4-[3-(2-benzyloxyphenyl)-3-oxopropenyl]chalcone (1f):** Yield 77% (2.29 g). M.p. 179−180 °C (recrystallised from ethanol). $^1$H NMR: δ = 5.18 (s, 4 H, 2′-OC*H*$_2$C$_6$H$_5$), 7.09 (dd, *J* = 7.9, 7.2 Hz, 2 H, 2 × 5′-H), 7.10 (d, *J* = 7.8 Hz, 2 H, 2 × 3′-H), 7.25−7.29 (m, 6 H, 2 × 3,4,5-H of 2′-OCH$_2$C$_6$*H*$_5$), 7.28 (s, 4 H, 2,3,5,6-H), 7.41−7.49 (m, 4 H, 2 × 2,6-H of 2′-OCH$_2$C$_6$*H*$_5$), 7.50 (ddd, *J* = 7.8, 7.2, 1.8 Hz, 2 H, 2 × 4′-H), 7.53 (AB, *J* = 15.9 Hz, 2 H, 2 × H-α), 7.63 (AB, *J* = 15.9 Hz, 2 H, 2 × H-β), 7.76 (dd, *J* = 7.9, 1.8 Hz, 2 H, 2 × 6′-H) ppm. $^{13}$C NMR: δ = 70.7 (2 × 2′-O*C*H$_2$C$_6$H$_5$), 112.9 (2 × C-3′), 121.2 (2 × C-5′), 127.5 (2 × C-2,6 of 2′-OCH$_2$*C*$_6$H$_5$), 128.0 (2 × C-α), 128.1 (2 × C-4 of 2′-OCH$_2$*C*$_6$H$_5$), 128.7 (C-2,3,5,6 and 2 × C-3,5 of 2′-OCH$_2$*C*$_6$H$_5$), 129.1 (2 × C-1′), 131.0 (2 × C-6′), 133.4 (2 × C-4′), 136.1 (C-1 and C-4), 136.7 (2 × C-1 of 2′-OCH$_2$*C*$_6$H$_5$), 141.6 (2 × C-β), 157.6 (2 × C-2′), 191.8 (2 × C=O) ppm. EIMS: *m*/*z* (rel. int.) = 550 (5) [M$^{+\cdot}$], 459 (8), 369 (5), 339 (5), 235 (5), 223 (5), 211 (5), 121 (17), 91 (100), 65 (11). $C_{38}H_{30}O_4$ (550.64): calcd. C 82.89, H 5.49; found C 82.73, H 5.20.

**Synthesis of Bis(chalcone) Tetrabromides 3a,b:** Bromine was added slowly to a solution of bis(chalcones) **1a**,**b** (5.9 mmol) in carbon tetrachloride (80 mL) until the reaction mixture became red, and then the mixture was stirred at room temperature until the consumption of the starting material was complete. The resulting bis(chalcone) tetrabromo derivatives **3a**,**b** were removed by filtration, washed with carbon tetrachloride (2 × 10 mL), and then recrystallised from carbon tetrachloride.

**α,β-Dibromo-3-(1,2-dibromo-3-oxo-3-phenylpropenyl)-α,β-dihydrochalcone (3a):** Yield 80% (3.11 g). M.p. 205−206 °C (recrystallised from carbon tetrachloride). $^1$H NMR: δ = 5.69 (d, *J* = 11.2 Hz, 2 H, 2 × β), 5.82 (d, *J* = 11.2 Hz, 2 H, 2 × α), 7.49−7.53 (m, 1 H, 5-H), 7.57 (d, *J* = 6.7 Hz, 2 H, 4,6-H), 7.58 (dd, *J* = 7.7, 7.3 Hz, 4 H, 2 × 3′,5′-H), 7.65 (s br, 1 H, 2-H), 7.69 (t, *J* = 7.3 Hz, 2 H, 2 × 4′-H), 8.13 (d, *J* = 7.7 Hz, 4 H, 2 × 2′,6′-H) ppm. $^{13}$C NMR: δ = 46.8 (2 × C-α), 49.0 (2 × C-β), 128.7 (C-2), 128.9 (2 × C-2′,6′), 129.0 (2 × C-3′,5′), 129.2 (C-4,6), 129.5 (C-5), 134.3 (2 × C-4′ and C-1,3), 139.0 (2 × C-1′), 191.0 (2 × C=O) ppm. EIMS: *m*/*z* (rel. int.) = 662 (M$^{+\cdot}$, 0.01), 577 (0.4), 429 (2), 417 (3), 393 (2), 338 (43), 233 (44), 207 (12), 105 (100), 77 (45). $C_{24}H_{18}Br_4O_2$ (658.01): calcd. C 43.81, H 2.76; found C 43.90, H 2.46.

**α,β-Dibromo-4-(1,2-dibromo-3-oxo-3-phenylpropenyl)-α,β-dihydrochalcone (3b):** Yield 83% (3.22 g). M.p. 237−238 °C (recrystallised from carbon tetrachloride). $^1$H NMR (CDCl$_3$/TFA): δ = 5.68 (d, *J* = 11.4 Hz, 2 H, 2 × H-β), 5.93 (d, *J* = 11.4 Hz, 2 H, 2 × H-α), 7.64 (dd, *J* = 7.9, 7.4 Hz, 4 H, 2 × 3′,5′-H), 7.66 (s, 4 H, 2,3,5,6-H), 7.79 (t, *J* = 7.4 Hz, 2 H, 2 × 4′-H), 8.16 (d, *J* = 7.9 Hz, 4 H, 2 × 2′,6′-H) ppm. $^{13}$C NMR: δ = 47.0 (2 × C-α), 48.5 (2 × C-β), 129.3 (C-2,3,5,6), 129.7 (2 × C-2′,3′,5′,6′), 134.3 (2 × C-1′), 135.9 (2 × C-4′), 139.4 (C-1,3), 196.7 (2 × C=O) ppm. EIMS: *m*/*z* (rel. int.) = 662 (2) [M$^{+\cdot}$, $^{81}$Br], 338 (27) 233 (29), 181 (44), 131 (59), 105 (100), 69 (100). $C_{24}H_{18}Br_4O_2$ (658.01): calcd. C 43.81, H 2.76; found C 43.70, H 2.50.

**Synthesis of Bis(chalcone) Tetrabromo Derivatives 3c,d:** Pyridinium tribromide (3.84 mg, 12 mmol) was added to a solution of bis(chalcones) **1e**,**f** (6 mmol) in acetic acid (100 mL). The mixture then stood at room temperature until the consumption of the starting material was complete. After 4 h the mixture was poured into ice and the bis(chalcone) tetrabromo derivatives **3c**,**d** were removed by filtration, washed with water, and recrystallised from carbon tetrachloride.

**2′-Benzyloxy-3-[3-(2-benzyloxyphenyl)-1,2-dibromo-3-oxopropenyl]-α,β-dibromo-α,β-dihydrochalcone (3c):** Yield 72% (3.76 g). M.p. 179−180 °C (recrystallised from carbon tetrachloride). $^1$H NMR: δ = 5.21 (s, 4 H, 2 × 2′-OC*H*$_2$C$_6$H$_5$), 5.42 (d, *J* = 11.5 Hz, 2 H, 2 × H-β), 6.25 (d, *J* = 11.5 Hz, 2 H, 2 × H-α), 6.77−6.86 (m, 3 H, 2-H and 4,6-H), 7.05−7.16 (m, 5 H, 5-H and 2 × 3′,5′-H), 7.52−7.62 (m, 12 H, 2 × 4′-H and 2 × 2,3,4,5,6-H of 2′-OCH$_2$C$_6$*H*$_5$), 8.04−8.06 (m, 2 H, 2 × 6′-H) ppm. $^{13}$C NMR: δ = 49.3 (2 × C-β), 51.4 (2 × C-α), 71.3 (2 × 2′-O*C*H$_2$C$_6$H$_5$), 112.8 (2 × C-3′), 121.4 (2 × C-5′), 124.2 (2 × C-1′), 128.1 (C-2), 128.4 (C-4,6), 128.9 (2 × C-2,6 of 2′-OCH$_2$*C*$_6$H$_5$), 129.1 (2 × C-3,5 of 2′-OCH$_2$*C*$_6$H$_5$), 129.2 (2 × C-4 of 2′-OCH$_2$*C*$_6$H$_5$), 129.0 (C-5), 132.8 (2 × C-4′), 135.2 (2 × C-6′), 135.3 (2 × C-1 of 2′-OCH$_2$*C*$_6$H$_5$), 139.0 (C-1,3), 158.2 (2 × C-2′), 191.8 (2 × C=O) ppm. FAB-MS: *m*/*z* (rel. int.) = 875 (0.5) [[M + H]$^+$, $^{81}$Br], 713 (3), 663 (24), 647 (11), 555 (16), 316 (11), 288 (17), 211 (100), 165 (7), 154 (51) 91 (35). $C_{38}H_{30}O_4Br_4$ (870.26): C 52.44, H 3.47, found: C 52.15, H 3.17.

**2′-Benzyloxy-4-[3-(2-benzyloxyphenyl)-1,2-dibromo-3-oxopropenyl]-α,β-dibromo-α,β-dihydrochalcone (3d):** Yield 70% (3.65 g). M.p. 217−219 °C (recrystallised from carbon tetrachloride). $^1$H NMR (CDCl$_3$/TFA): δ = 5.27 (s, 4 H, 2 × 2′-OC*H*$_2$C$_6$H$_5$), 5.51 (d, *J* = 11.5 Hz, 2 H, 2 × H-β), 6.34 (d, *J* = 11.5 Hz, 2 H, 2 × H-α), 6.92 (s, 4 H, 2,3,5,6-H), 7.17 (t, *J* = 7.9 Hz, 2 H, 2 × 5′-H), 7.21 (d, *J* = 8.2 Hz, 2 H, 2 × 3′-H), 7.47−7.52 (m, 6 H, 2 × 3,4,5-H of 2′-OCH$_2$C$_6$*H*$_5$), 7.58−7.62 (m, 4 H, 2 × 2,6-H of 2′-OCH$_2$C$_6$*H*$_5$), 7.67 (dd, *J* = 8.2, 7.9 Hz, 2 H, 2 × 4′-H), 8.03 (d, J = 7.9 Hz, 2 H, 2 × 6′-H) ppm. $^{13}$C NMR (CDCl$_3$/TFA): δ = 48.8 (2 × C-β), 51.0 (2 × C-α), 71.7 (2 × 2′-O*C*H$_2$C$_6$H$_5$), 113.4 (2 × C-3′), 121.8 (2 × C-5′), 123.8 (2 × C-1′), 128.6 (2 × C-2,6 of 2′-OCH$_2$C$_6$*H*$_5$), 129.0 (C-5), 129.1 (C-2,3,5,6), 129.2 (2 × C-3,4,5 of 2′-OCH$_2$C$_6$H$_5$), 132.9 (2 × C-6′), 135.1 (2 × C-1 of 2′-OCH$_2$*C*$_6$H$_5$), 136.9 (2 × C-4′), 138.5 (C-1,3), 159.1 (2 × C-2′), 196.6 (2 × C=O) ppm. EIMS: *m*/*z* (rel. int.) = 660 (3) [M − 2OBn]$^{+\cdot}$, 441 (5) 331 (5), 281 (5), 181 (44), 131 (59), 91 (30). $C_{38}H_{30}O_4Br_4$ (870.26): C 52.44, H 3.47, found: C 52.40, H 3.27.

**Synthesis of Bis(2-pyrazolines) 4a−d:** Hydrazine hydrate (22 mmol) was added to a methanolic suspension (100 mL) of bis(chalcones) **1a−d** (1.35 mmol). The reaction mixture was then heated under reflux for 24 h under nitrogen. The bis(2-pyrazolines) **4a−d** were removed by filtration, washed with ethanol, and precipitated from methanolic solutions.

**3-Phenyl-5-[3-(3-phenyl-2-pyrazolin-5-yl)phenyl]-2-pyrazoline (4a):** Yield 59% (292 mg). M.p. 138−140 °C. $^1$H NMR ([D$_6$]DMSO/TFA): δ = 3.56 (dd, *J* = 17.8, 9.3 Hz, 2 H, 2 × 4′-H$_{trans}$), 3.90 (dd, *J* = 17.8, 9.9 Hz, 2 H, 2 × 4′$_{cis}$-H), 5.22 (dd, *J* = 9.9, 9.3 Hz, 2 H, 2 × 5′-H), 7.45−7.67 (m, 9 H, 4,5,6-H and 2 × 3′′,4′′,5′′-H), 7.66 (s br, 1 H, 2-H), 7.84 (d, *J* = 7.0 Hz, 4 H, 2 × 2′′,6′′-H) ppm. $^{13}$C NMR ([D$_6$]DMSO/TFA): δ = 41.7 and 41.9 (2 × C-4′), 61.5 (2 × C-5′), 127.7 (C-2), 128.0 (C-5), 128.41 and 128.44 (2 × C-2′′,6′′), 128.7 and 129.0 (C-4,6), 129.4 (2 × C-3′′,5′′), 129.8 and 129.9 (2 × C-1′′), 132.5 and 132.6 (2 × C-4′′), 136.8 and 137.0 (C-1,3), 170.6 and 171.0 (2 × C-3′) ppm. EIMS: *m*/*z* (rel. int.) = 366 (100) [M$^+$], 337 (10), 320 (8), 248 (8), 222 (18), 192 (15), 145 (50), 119 (20), 104 (15), 91 (20), 77 (28). FAB-HRMS ($C_{24}H_{23}N_4$ [M + H]$^+$): calcd. 367.1923, found 367.1924.

**3-Phenyl-5-[4-(3-phenyl-2-pyrazolin-5-yl)phenyl]-2-pyrazoline (4b):** Yield 68% (336 mg). M.p. 190−192 °C. $^1$H NMR ([D$_6$]DMSO/

TFA): δ = 3.65 (dd, *J* = 17.1, 8.4 Hz, 2 H, 2 × 4′-H$_{trans}$), 3.90 (dd, *J* = 17.1, 9.1 Hz, 2 H, 2 × 4′-H$_{cis}$), 5.21 (dd, *J* = 9.1, 8.4 Hz, 2 H, 2 × 5′-H), 7.40 (dd, *J* = 7.3, 7.0 Hz, 4 H, 2 × 3′′,5′′-H), 7.43−7.50 (m, 2 H, 2 × 4′′-H), 7.50 (s, 4 H, 2,3,5,6-H), 7.81 (d, *J* = 7.3 Hz, 4 H, 2 × 2′′,6′′-H) ppm. $^{13}$C NMR ([D$_6$]DMSO/TFA): δ = 41.7 (2 × C-4′), 61.3 (2 × C-5′), 128.6 (2 × C-2′′,6′′), 129.1 (2 × C-3′′,5′′), 129.5 (C-2,3,5,6), 129.6 (2 × C-1′′), 132.9 (2 × C-4′′), 136.6 (2C, C-1,4), 172.3 and 172.4 (2 × C-3′) ppm. EIMS: *m*/*z* (rel. int.) = 366 (100) [M$^{+\cdot}$], 247 (11), 222 (15), 191 (10), 145 (50), 118 (17), 104 (14), 91 (23), 77 (30). FAB-HRMS (C$_{24}$H$_{23}$N$_4$ [M + H]$^+$): calcd. 367.1923, found 367.1940.

**3-Hydroxyphenyl-5-{3-[3-(2-hydroxyphenyl)-2-pyrazolin-5-yl]-phenyl}-2-pyrazoline (4c):** Yield 65% (349 mg). M.p. 147−149 °C. $^1$H NMR ([D$_6$]DMSO): δ = 2.99 (ddd, *J* = 16.4, 11.4, 3.6 Hz, 2 H, 2 × 4′-H$_{trans}$), 3.64 (dd, *J* = 16.4, 10.8 Hz, 2 H, 2 × 4′-H$_{cis}$), 4.86 (ddd, *J* = 11.4, 10.8, 3.6 Hz, 2 H, 2 × 5′-H), 6.88 (dt, *J* = 7.7, 0.8 Hz, 2 H, 2 × 5′′-H), 6.91 (d, *J* = 8.0 Hz, 2 H, 2 × 3′′-H), 7.23 (ddd, *J* = 8.0, 7.7, 1.4 Hz, 2 H, 2 × 4′′-H), 7.29 (dd, *J* = 7.7, 1.4 Hz, 2 H, 2 × 6′′-H), 7.31−7.34 (m, 3 H, 4,5,6-H), 7.50 (s, 1 H, 2-H), 7.86 (d, *J* = 3.6 Hz, 2 H, 2 × N*H*), 11.17 (s, 2 H, 2 × 2′′-O*H*) ppm. $^{13}$C NMR: δ = 41.0 and 41.1 (2 × C-4′), 62.18 and 62.21 (2 × C-5′), 115.8 (2 × C-3′′), 116.8 (2 × C-1′′), 119.2 (2 × C-5′′), 125.3 and 125.5 (C-2), 125.9 (C-4,6), 127.9 (2 × C-6′′), 128.8 (C-5), 129.9 (2 × C-4′′), 142.57 and 142.61 (C-1,3), 152.7 (2 × C-3′), 156.8 (2 × C-2′′) ppm. EIMS: *m*/*z* (rel. int.) = 398 (47) [M$^{+\cdot}$], 384 (26), 292 (35), 264 (25), 246 (53), 238 (57), 218 (14), 189 (22), 161 (100), 135 (56), 121 (67), 105 (34), 91 (52),77 (67), 65 (48). FAB-HRMS (C$_{24}$H$_{23}$N$_4$O$_2$ [M + H]$^+$): calcd. 399.1821, found 399.1836.

**3-Hydroxyphenyl-5-{4-[3-(2-hydroxyphenyl)-2-pyrazolin-5-yl]-phenyl}-2-pyrazoline (4d):** Yield 72% (387 mg). M.p. 197−199 °C. $^1$H NMR: ([D$_6$]DMSO): δ = 2.98 (dd, *J* = 16.6, 10.8 Hz, 2 H, 2 × 4′-H$_{trans}$), 3.61 (dd, *J* = 16.6, 10.7 Hz, 2 H, 2 × 4′-H$_{cis}$), 4.85 (dd, *J* = 10.8, 10.7 Hz, 2 H, 2 × 5′-H), 6.88 (t, *J* = 7.5 Hz, 2 H, 2 × 5′′-H), 6.91 (d, *J* = 8.0 Hz, 2 H, 2 × 3′′-H), 7.23 (ddd, *J* = 8.0, 7.5, 1.4 Hz, 2 H, 2 × 4′′-H), 7.29 (dd, *J* = 7.5, 1.4 Hz, 2 H, 2 × 6′′-H), 7.39 (s, 4 H, 2,3,5,6-H), 7.86 (s, 2 H, 2 × N*H*), 11.17 (s, 2 H, 2 × 2′′-O*H*) ppm. $^{13}$C NMR: δ = 40.9 (2 × C-4′), 61.9 (2 × C-5′), 115.8 (2 × C-3′′), 116.8 (2 × C-1′′), 119.2 (2 × C-5′′), 126.9 (2 × C-2,3,56), 127.8 (2 × C-6′′), 129.8 (2 × C-4′′), 141.4 (2 × C-1,4), 152.5 (2 × C-3′), 156.8 (2 × C-2′′) ppm. EIMS: *m*/*z* (rel. int.) = 398 (100) [M$^{+\cdot}$], 369 (6), 263 (8), 238 (75), 207 (8), 178 (6), 161 (77), 134 (21), 120 (17), 105 (17), 91 (27), 77 (25), 65 (15). FAB-HRMS (C$_{24}$H$_{23}$N$_4$O$_2$ [M + H]$^+$): calcd. 399.1821, found 399.1834.

**Synthesis of Bis(chromones) 6c,d:** Iodine (0.3 g, 1.2 mmol) was added to a solution of chalcones **1c**,**d** (2.5 mmol) in DMSO (8 mL). The mixture was heated under reflux for 1 h, and then was poured into ice (100 g) and water (100 mL) to precipitate the product. The solid was removed by filtration, dissolved in chloroform (80 mL), and washed with a 20% aqueous solution of sodium thiosulfate (2 × 100 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent evaporated to dryness. Finally, each compound was recrystallised from ethanol.

**3′-(2-Chromonyl)flavone 6c:** Yield 76% (695 mg). M.p. 249−250 °C (recrystallised from ethanol). $^1$H NMR: δ = 6.94 (s, 2 H, 2 × 3′-H), 7.47 (dt, *J* = 7.8, 1.0 Hz, 2 H, 2 × 6′-H), 7.65 (dd, *J* = 8.3, 1.0 Hz, 2 H, 2 × 8′-H), 7.72 (t, *J* = 7.8 Hz, 1 H, 5-H), 7.76 (ddd, *J* = 8.3, 7.8, 1.5 Hz, 2 H, 2 × 7′-H), 8.09 (dd, *J* = 7.8, 1.8 Hz, 2 H, 4,6-H), 8.26 (dd, *J* = 7.8, 1.5 Hz, 2 H, 2 × 5′-H), 8.49 (t, *J* = 1.8 Hz, 1 H, 2-H). $^{13}$C NMR: δ = 108.3 (2 × C-3′), 118.1 (2 × C-8′), 123.9 (2 × C-10′), 125.5 (2 × C-6′), 125.8 (2 × C-5′), 129.0 (C-4,6), 129.9 (C-5), 132.9 (C-1,3), 134.1 (2 × C-7′), 156.2 (2 × C-9′), 162.1 (2 × C-2′), 178.2 (2 × C-4′). EIMS: *m*/*z* (rel. int.) = 366 (100) [M$^{+\cdot}$], 367 (11), 338 (24), 246 (6), 218 (13), 189 (6), 155 (5), 120 (56), 92 (40), 64 (10). EI-HRMS (C$_{24}$H$_{14}$O$_4$ [M$^{+\cdot}$]): calcd. 366.0892, found 366.0889.

**4′-(2-Chromonyl)flavone (6d):** Yield 84% (769 mg). M.p. 298−299 °C (recrystallised from ethanol). $^1$H NMR: δ = 6.91 (s, 2 H, 2 × 3′-H), 7.45 (dd, *J* = 7.9, 7.4 Hz, 2 H, 0.9 Hz, 2 × 6′-H), 7.61 (dd, *J* = 8.1, 0.9 Hz, 2 H, 2 × 8′-H), 7.73 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 2 H, 2 × 7′-H), 8.09 (s, 4 H, 2,3,5,6-H), 8.26 (dd, *J* = 7.9, 1.7 Hz, 2 H, 2 × 5′-H) ppm. $^{13}$C NMR: δ = 108.6 (2 × C-3′), 118.1 (2 × C-8′), 124.2 (2 × C-10′), 125.5 (2 × C-6′), 125.9 (2 × C-5′), 126.9 (C-2,3,5,6), 134.0 (2 × C-7′), 134.7 (C-1,4), 156.4 (2 × C-9′), 161.9 (2 × C-2′), 178.1 (2 × C-4′) ppm. EIMS: *m*/*z* (rel. int.) = 366 (100) [M$^{+\cdot}$], 367 (12), 338 (16), 246 (14), 218 (15), 189 (7), 155 (10), 126 (10), 120 (42), 92 (32), 64 (9). EI-HRMS (C$_{24}$H$_{14}$O$_4$ [M$^{+\cdot}$]): calcd. 366.0892, found 366.0890.

**Synthesis of Bis(pyrazoles) 5a−d:** Hydrazine hydrate (15 mmol) was added to a methanolic suspension (100 mL) of tetrabromochalcones **3a−d** (1.0 mmol). The reaction mixture was heated under reflux for 24 h under nitrogen. The solvent was evaporated and the residue was washed with water and extracted with chloroform (3 × 30 mL). The solvent was evaporated to dryness and the residue purified by thin-layer chromatography, using a mixture of chloroform and acetone (9:1) as eluent. The main spot in each case was identified as bis(pyrazoles) **5a−d**.

**3-Phenyl-5-[3-(3-phenylpyrazol-5-yl)phenyl]pyrazole (5a):** Yield 53% (192 mg). Yellow oil. $^1$H NMR ([D$_6$]DMSO/TFA): δ = 7.31 (s, 2 H, 2 × 4′-H), 7.36 (t, *J* = 7.3 Hz, 2 H, 2 × 4′′-H), 7.47 (dd, *J* = 7.8, 7.3 Hz, 4 H, 2 × 3′′,5′′-H), 7.54 (t, *J* = 7.5 Hz, 1 H, 5-H), 7.83 (dd, *J* = 7.5, 1.6 Hz, 2 H, 4,6-H), 7.87 (d, *J* = 7.8 Hz, 4 H, 2 × 2′′,6′′-H), 8.35 (t, *J* = 1.6 Hz, 1 H, 2-H), 13.46 (s, 2 H, 2 × N*H*) ppm. $^{13}$C NMR ([D$_6$]DMSO/TFA): δ = 100.4 (2 × C-4′), 122.6 (C-2), 125.0 (C-4,6), 125.6 (2 × C-2′′,6′′), 128.4 (2 × C-4′′), 129.2 (2 × C3′′,5′′), 129.7 (C-5), 131.2 (2 × C-1′′), 132.2 (C-1,3), 147.4 (2 × C-3′), 147.8 (2 × C-5′) ppm. EIMS: *m*/*z* (rel. int.) = 362 (100) [M$^{+\cdot}$], 333 (5), 247 (6), 189 (6), 181 (10), 105 (10), 84 (34), 77 (12), 66 (41). EI-HRMS (C$_{24}$H$_{18}$N$_4$ [M$^{+\cdot}$]): calcd. 362.1531, found 362.1540.

**3-Phenyl-5-[4-(3-phenylpyrazol-5-yl)phenyl]pyrazole (5b):** Yield 57% (206 mg). Yellow oil. $^1$H NMR ([D$_6$]DMSO/TFA): δ = 7.30 (s, 2 H, 2 × 4′-H), 7.34 (t, *J* = 7.4 Hz, 2 H, 2 × 4′′-H), 7.44 (dd, *J* = 7.8, 7.4 Hz, 4 H, 2 × 3′′,5′′-H), 7.85 (d, *J* = 7.8 Hz, 4 H, 2 × 2′′,6′′-H), 7.96 (s, 4 H, 2,3,5,6-H), 13.42 (s, 2 H, 2 × NH) ppm. $^{13}$C NMR ([D$_6$]DMSO/TFA): δ = 101.2 (2 × C-4′), 126.4 (2 × C-2′′,6′′), 126.9 (C-2,3,5,6), 129.4 (2 × C-4′′), 129.7 (2 × C-3′′,5′′), 130.8 (2 × C-1′′), 131.2 (C-1,4), 148.0 and 148.1 (2 × C-3′ and 2 × C-5′) ppm. EIMS: *m*/*z* (rel. int.) = 362 (46) [M$^{+\cdot}$], 247 (5), 181 (5), 105 (15), 91 (8), 84 (82), 77 (16), 66 (100). EI-HRMS (C$_{24}$H$_{18}$N$_4$ [M$^{+\cdot}$]): calcd. 362.1531, found 362.1516.

**3-(2-Benzyloxyphenyl)-5-{3-[3-(2-benzyloxyphenyl)pyrazol-5-yl]-phenyl}pyrazole (5c):** Yield 52% (299 mg). M.p. 240−241 °C (recrystallised from methanol). $^1$H NMR ([D$_6$]DMSO/TFA): δ = 5.26 (s, 4 H, 2 × 2′′-OC*H*$_2$C$_6$H$_5$), 7.04 (dd, *J* = 7.8, 7.1 Hz, 2 H, 2 × 5′′-H), 7.19 (d, *J* = 7.8 Hz, 2 H, 2 × 3′′-H), 7.18−7.22 (m, 2 H, 2 × 4-H of 2′′-OCH$_2$C$_6$H$_5$), 7.25 (s, 2 H, 2 × 4′-H), 7.29−7.34 (m, 4 H, 2 × 3,5-H of 2′′-OCH$_2$C$_6$*H*$_5$), 7.31−7.36 (m, 2 H, 2 × 4′′-H), 7.46 (d, *J* = 7.2 Hz, 4 H, 2 × 2,6-H of 2′′-OCH$_2$C$_6$*H*$_5$), 7.47−7.53 (m, 1 H, 5-H), 7.75 (dd, *J* = 7.3, 1.5 Hz, 2 H, 4,6-H), 7.79 (dd, *J* = 7.1, 1.5 Hz, 2 H, 2 × 6′′-H), 8.22 (s br, 1 H, 2-H) ppm $^{13}$C NMR ([D$_6$]DMSO/TFA): δ = 70.1 (2 × 2′′-O*C*H$_2$C$_6$H$_5$),

103.7 (2 × C-4′), 113.7 (2 × C-3′′), 118.3 (2 × C-1′′), 121.3 (2 × C-5′′), 123.1 (C-2), 125.9 (C-4,6), 127.8 (2 × C-2,6 of 2′′-$OCH_2C_6H_5$), 128.1 (2 × C-4 of 2′′-$OCH_2C_6H_5$), 128.7 (2 × C-6′′ and 2 × C-3,5 of 2′′-$OCH_2C_6H_5$), 129.8 (C-5), 130.5 (2 × C-4′′), 131.8 (C-1,3), 137.2 (2 × C-1 of 2′′-$OCH_2C_6H_5$), 143.2 (2 × C-3′), 147.9 (2 × C-5′), 155.5 (2 × C-2′′). ) ppm. FABMS: *m*/*z* (rel. int.) = 575 (27), 369 (15), 221 (13), 219 (10), 203 (11), 191 (13), 187 (11), 177 (12), 165 (17), 161 (24), 159 (27), 154 (90), 91 (100). FAB-HRMS ($C_{38}H_{31}N_4O_2$ [M + H]$^+$): calcd. 575.2447, found 575.2468.

**3-(2-Benzyloxyphenyl)-5-{4-[3-(2-benzyloxyphenyl)pyrazol-5-yl]-phenyl}pyrazole (5d):** Yield 61% (350 mg). M.p. 265−266 °C (recrystallised from methanol). $^1$H NMR ([D$_6$]DMSO/TFA): δ = 5.31 (s, 4 H, 2 × 2′′-OC*H*$_2$C$_6$H$_5$), 7.06 (t, *J* = 7.5 Hz, 2 H, 2 × 5′′-H), 7.21 (s, 2 H, 2 × 4′-H), 7.22 (d, *J* = 7.3 Hz, 2 H, 2 × 3′′-H), 7.31−7.37 (m, 4 H, 2 × 4′′-H and 2 × 4-H of 2′′-OCH$_2$C$_6$*H*$_5$), 7.42 (dd, *J* = 7.7, 6.9 Hz, 4 H, 2 × 3,5-H of 2′′-OCH$_2$C$_6$*H*$_5$), 7.55 (d, *J* = 6.9 Hz, 4 H, 2 × 2,6-H of 2′′-OCH$_2$C$_6$*H*$_5$), 7.82 (s, 4 H, 2,3,5,6-H), 7.83 (dd, *J* = 7.5, 1.5 Hz, 2 H, 2 × 6′′-H), 13.12 (s br, 2 H, 2 × NH) ppm. $^{13}$C NMR ([D$_6$]DMSO/TFA): δ = 69.9 (2 × 2′′-O*C*H$_2$C$_6$H$_5$), 103.1 (2 × C-4′), 113.6 (2 × C-3′′), 119.3 (2 × C-1′′), 121.1 (2 × C-5′′), 125.7 (C-2,3,5,6), 127.9 (2 × C-2,6 of 2′′-O*C*H$_2$C$_6$H$_5$), 128.1 (2 × C-6′′ and 2 × C-4 of 2′′-$OCH_2C_6H_5$), 128.7 (2 × C-3,5 of 2′′-$OCH_2C_6H_5$), 129.6 (2 × C-4′′), 131.4 (C-1,4), 137.3 (2 × C-1 of 2′′-$OCH_2C_6H_5$), 142.9 (2 × C-3′), 147.6 (2 × C-5′), 155.1 (2 × C-2′′) ppm. EIMS: *m*/*z* (rel. int.) = 574 (16) [M$^{+\cdot}$], 484 (16), 394 (10), 314 (10), 132 (9), 105 (9), 91 (100). FAB-HRMS ($C_{38}H_{31}N_4O_2$ [M + H]$^+$): calcd. 575.2447, found 575.2425.

**Synthesis of Bis(pyrazoles) 5e,f**

**Method A. Debenzylation of Bis(pyrazoles) 5c,d:** A suspension of bis(pyrazoles) **5c**,**d** (0.5 mmol) in a solution of hydrobromic acid in acetic acid (33%, 10 mL) was refluxed for 1.5 h, and then the mixture was poured into ice (100 g) and water (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 100 mL) and the combined organic layers washed with water (2 × 100 mL). The solvent was evaporated to dryness and the residue purified by thin-layer chromatography using a mixture of chloroform and acetone (8:2) as eluent. The main eluted spot from the base line was identified as the expected bis(pyrazoles) **5e**,**f** (≈ 5% yield), which were recrystallised from methanol.

**Method B. From Bis(chromones) 6c,d:** Hydrazine hydrate (0.74 mL, 15.3 mmol) was added to a methanolic suspension (100 mL) of bis(chromones) **6c**,**d** (1.91 mmol). The reaction mixture was heated under reflux for 24 h under nitrogen. The solvent was evaporated and the residue was washed with water and extracted with chloroform (3 × 30 mL). The 3,5-diphenylpyrazoles **5e**,**f** were purified by thin-layer chromatography using a mixture of chloroform and acetone (8:2) as eluent. The main spot was identified as the expected bis(pyrazoles) [**5e**, 74% (557 mg); **5f**, 76% (572 mg)], which were recrystallised from methanol.

**3-(2-Hydroxyphenyl)-5-{3-[3-(2-hydroxyphenyl)pyrazol-5-yl]phenyl}-pyrazole (5e):** M.p. > 300 °C (recrystallised from methanol). $^1$H NMR ([D$_6$]DMSO/TFA): δ = 6.90 (dd, *J* = 7.8, 7.2 Hz, 2 H, 2 × 5′′-H), 6.99 (d, *J* = 7.6 Hz, 2 H, 2 × 3′′-H), 7.21 (ddd, *J* = 7.6, 7.2, 1.6 Hz, 2 H, 2 × 4′′-H), 7.45 (dt, *J* = 7.4, 2.2 Hz, 1 H, 5-H), 7.52 (s, 2 H, 4′-H), 7.75 (dd, *J* = 7.8, 1.6 Hz, 2 H, 6′′-H), 8.08 (t, *J* = 7.4 Hz, 2 H, 1.6 Hz, 4,6-H), 8.57 (s br, 1 H, 2-H), 10.70 (s br, 2 H, 2 × 2′′-O*H*) ppm. $^{13}$C NMR ([D$_6$]DMSO/TFA): δ = 102.0 (2 × C-4′), 116.8 (2 × C-3′′), 118.8 (2 × C-1′′), 119.7 (2 × C-5′′), 123.8 (C-2), 125.2 (C-4,6), 125.8 (C-5), 128.0 (2 × C-6′′), 129.1 (C-1,3), 130.1 (2 × C-4′′), 145.6 (2 × C-5′), 147.1 (2 × C-3′), 155.4 (2 × C-2′′) ppm. EIMS: *m*/*z* (rel. int.) = 394 (5) [M$^{+\cdot}$], 380 (100), 366 (47), 338 (11), 218 (5), 176 (5), 128 (5), 120 (25), 92 (15). EI-HRSM ($C_{24}H_{18}N_4O_2$ [M$^{+\cdot}$]): calcd.394.1430, found 394.1425.

**3-(2-Hydroxyphenyl)-5-{4-[3-(2-hydroxyphenyl)pyrazol-5-yl]phenyl}-pyrazole (5f):** M.p. > 300 °C (recrystallised from methanol). $^1$H NMR ([D$_6$]DMSO/TFA): δ = 6.91 (dd, *J* = 7.9, 7.6 Hz, 2 H, 2 × 5′′-H), 6.99 (d, *J* = 8.0 Hz, 2 H, 2 × 3′′-H), 7.22 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 2 H, 2 × 4′′-H), 7.41 (s, 2 H, 2 × 4′-H), 7.75 (dd, *J* = 7.9, 1.6 Hz, 2 H, 2 × 6′′-H), 8.00 (s, 4 H, 2,3,5,6-H), 10.90 (s br, 2 H, 2 × 2′′-O*H*), 13.75 (s br, 2 H, 2 × NH) ppm. $^{13}$C NMR ([D$_6$]DMSO/TFA): δ = 102.0 (2 × C-4′), 116.2 (2 × C-1′′), 117.1 (2 × C-3′′), 119.9 (2 × C-5′′), 126.9 (C-2,3,5,6), 128.2 (2 × C-6′′), 130.4 (2 × C-4′′ and C-1,4), 146.2 (2 × C-5′), 147.3 (2 × C-3′), 155.6 (2 × C-2′′) ppm. EIMS: *m*/*z* (rel. int.) = 394 (100) [M$^{+\cdot}$], 267 (7), 197 (10), 131 (7), 120 (5), 91 (5), 78 (15), 63 (16). EI-HRMS ($C_{24}H_{18}N_4O_2$ [M$^{+\cdot}$]): calcd. 394.1430, found 394.1421.

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