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Synthesis of Pyrazoles by Treatment of 3-Benzylchromones, 3-Benzylflavones and Their 4-Thio Analogues with Hydrazine

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Dedicated to Professor Dr. Miha Tisler on the occasion of his 80th birthday

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The synthesis of pyrazoles **13**–**24** has been accomplished by treatment of 3-benzylchromones **1**–**5**, 3-benzylflavones **6**–**12** and their 4-thio analogues **25**–**29** with hydrazine hydrate in hot pyridine. A plausible reaction mechanism for the formation of pyrazoles **13**–**24** is discussed. A ^{1}H NMR study in [D_6]DMSO allowed the presence of both pyrazole annular tautomers to be observed, due to the presence of intramolecular hydrogen bonds in each tautomer (**OH--N** and **NH--O**). GIAO/B3LYP/6-311++G** calculations were carried out on some model pyrazoles to provide a theoretical basis for the NMR experimental observations.

Introduction

Pyrazoles are well known five-membered nitrogen-containing heterocyclic compounds, and various procedures for their synthesis have been developed.[1,2] Thanks to their diverse bioactivities, these compounds are useful substances in the development of agricultural products[3] and in drug research.[4] Another example of their application is the utilisation of *N*-(2-hydroxyphenyl)pyrazoles as photoprotectors of polystyrene,[5,6] and *o*-hydroxyphenylpyrazoles have recently been used as ultraviolet stabilisers,[6] analytical reagents,[7] analgesic agents and platelet aggregation inhibitors.[8] As a consequence of this wide range of applicability, numerous pyrazoles have already been synthesised.

We had previously started a systematic study on the synthesis of *o*-hydroxyphenylpyrazoles by treatment of various chromone derivatives with hydrazines. For this purpose, 2-styrylchromones,[9] 2-methyl- and 2-phenylchromones[10] and 3-aroyl-5-hydroxyflavones[11] had already been used as starting materials, and simple and convenient procedures for the synthesis of new 3,4,5-trisubstituted pyrazoles in this way had been worked out as a result. The experience gained in the course of these studies prompted us to investigate the preparation of similar pyrazoles by treatment of 3-benzylchromones, 3-benzylflavones and their 4-thio analogues with hydrazines. In this paper, the reactions of these 3-substituted and 2,3-disubstituted chromone derivatives with hydrazine hydrate are reported.

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Results and Discussion

Chemistry

In the course of our investigation into the reactions between chroman-4-ones or 1-thiochroman-4-ones and aromatic aldehydes in the presence of piperidine as a catalyst, it had been found that 3-benzylchromones or 3-benzylflavones are formed if the aldehydes bear strongly electron-withdrawing substituent(s).[12] On the basis of this observation, we have developed a simple and convenient procedure for the synthesis of 3-benzylchromones, 3-benzylflavones and their 1-thio analogues.[12] The preparation of the 4-thio analogues of all these substances has been accomplished by treatment with Lawesson's reagent,[12–14] and these chromone derivatives have been utilised here as starting materials in their reaction with hydrazine hydrate.

We had previously carried out reactions between the related 3-(3-aryl-3-oxopropenyl)chromones and hydrazine in hot acetic acid; the chromone ring was opened under these

conditions to form the corresponding pyrazoles.[15] However, when 3-benzylchromones **1**–**5** or 3-benzylflavones **6**–**12** were allowed to react with hydrazine hydrate in hot acetic acid, the unchanged starting material was recovered in each case, whilst if methanol was used as solvent, the reactions between compounds **1**–**12** and hydrazine hydrate proved to be too slow. On the basis of our preliminary experiments, pyridine was found to be a convenient solvent for this purpose.

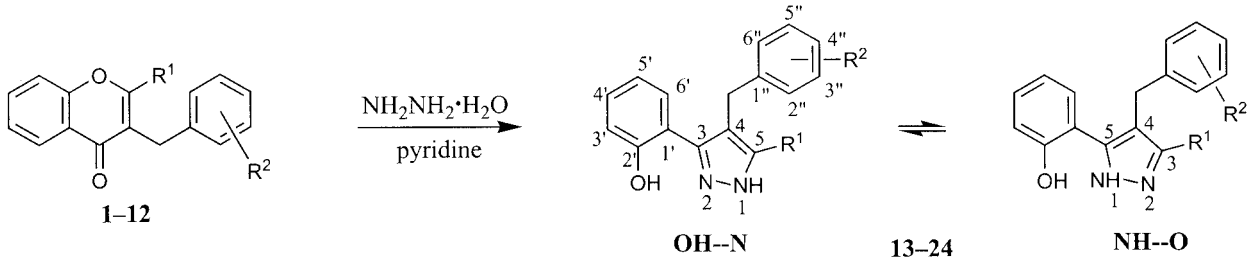
Compounds **1**–**12** and hydrazine hydrate were allowed to react in hot pyridine, and pyrazoles **13**–**24** were obtained in good yields (67–82%) (Scheme 1).

The same pyrazoles **13**, **14**, **19**, **22** and **23** were formed if 3-benzyl-4-thiochromones **25** and **26** and 3-benzyl-4-thioflavones **27**–**29** were treated with hydrazine hydrate under the same reaction conditions (Scheme 2).

It should also be mentioned that treatment of 3-(4-bromobenzyl)-1-thioflavone and 3-(3,4-dichlorobenzyl)-1-thioflavone with hydrazine hydrate in hot pyridine has been investigated, but no conversion occurred under these conditions, indicating that the C–S bond cannot be cleaved by the nucleophilic attack of the hydrazine.

The structures of the new compounds **13**–**24** were elucidated by elemental analyses and by combined utilisation of various spectroscopic methods. The elemental analyses and mass spectra unequivocally established the presence of two nitrogen atoms in each reaction product. In the IR spectra (see Experimental Section), NH and C=N bands characteristic of a pyrazole ring were assigned in each case. A lack of a distinct hydroxy band may be a consequence of a bridged hydroxy group, with reference to the dominance of the **OH--N** tautomers in the tautomeric mixtures of **OH--N** and **NH--O** forms. Structure elucidation of all new pyrazoles was completed by NMR spectroscopy (vide infra).

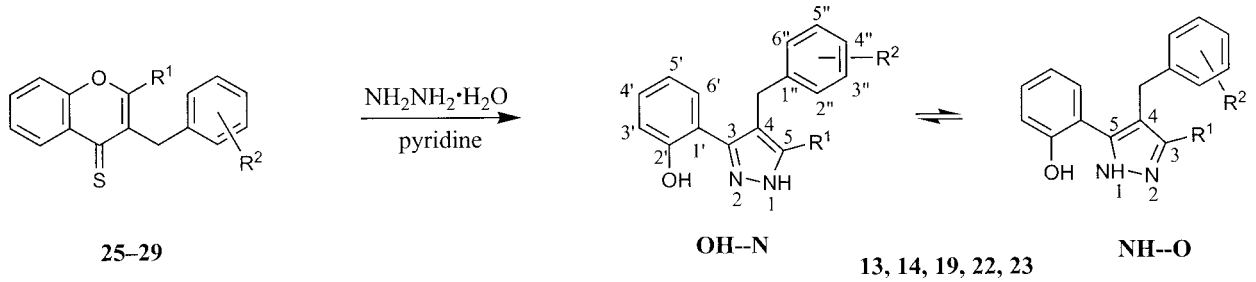
A proposed reaction mechanism is illustrated in Scheme 3. The first step corresponds to a nucleophilic attack at the C-2 carbon atom of the chromone nucleus, followed by a ring-opening. A hydrazine derivative is formed as an intermediate and can react with the carbonyl (X = O) or thiocarbonyl group (X = S) in the molecule to form the



1–12 **OH--N** **13–24** **NH--O**

1, **13:** R^1 = H, R^2 = 4-Cl
2, **14:** R^1 = H, R^2 = 4-Br
3, **15:** R^1 = H, R^2 = 4-NO_2
4, **16:** R^1 = H, R^2 = 2,4-Cl_2
5, **17:** R^1 = H, R^2 = 3,4-Cl_2
6, **18:** R^1 = Ph, R^2 = 2-Cl
7, **19:** R^1 = Ph, R^2 = 3-Cl
8, **20:** R^1 = Ph, R^2 = 4-Cl
9, **21:** R^1 = Ph, R^2 = 4-Br
10, **22:** R^1 = Ph, R^2 = 4-NO_2
11, **23:** R^1 = Ph, R^2 = 2,4-Cl_2
12, **24:** R^1 = Ph, R^2 = 3,4-Cl_2

Scheme 1.

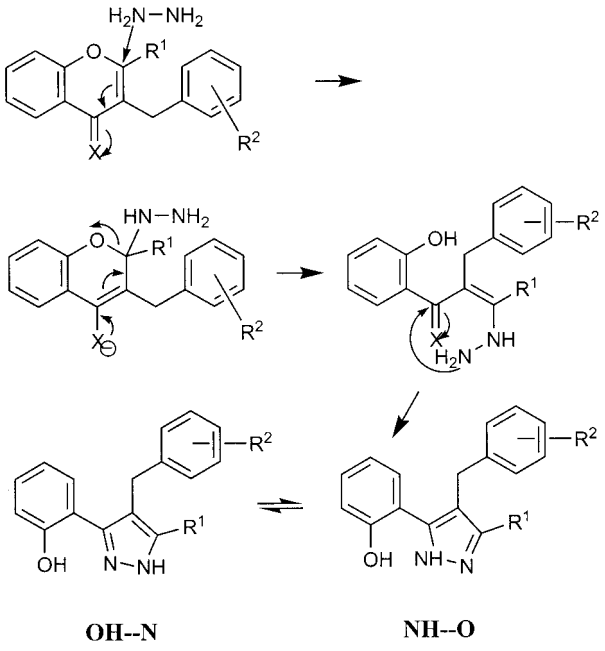


25–29 **OH--N** **13, 14, 19, 22, 23** **NH--O**

25, **13:** R^1 = H, R^2 = 4-Cl
26, **14:** R^1 = H, R^2 = 4-Br
27, **19:** R^1 = Ph, R^2 = 3-Cl
28, **22:** R^1 = Ph, R^2 = 4-NO_2
29, **23:** R^1 = Ph, R^2 = 2,4-Cl_2

Scheme 2.

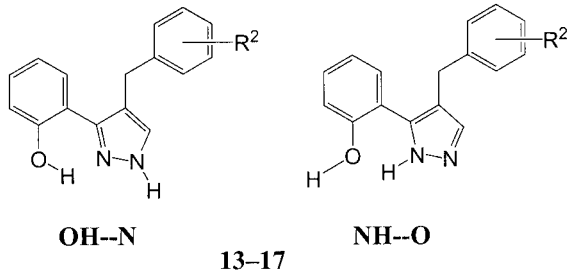
pyrazole ring. The obtained pyrazoles may exist as mixtures of **OH--N** and **NH--O** tautomers (Scheme 3).

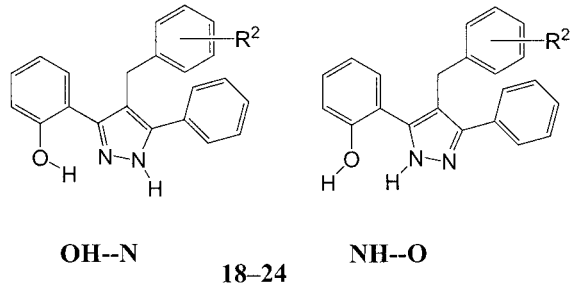


Scheme 3.

NMR and Theoretical Study of the Tautomerism of Pyrazoles 13–24

The ^{1}H NMR spectra of compounds **13**–**24** in $CDCl_3$ each showed the presence of two broad singlets at δ = 10.1–10.3 and 10.7–10.9 ppm, due to the resonances of the N*H* and 2′-O*H* protons. Since the solubilities of some of these compounds in $CDCl_3$ are very small, we also measured the ^{1}H NMR spectra of compounds **13**–**24** in [D_6]DMSO. In each of these cases, however, four broad singlets at higher frequency values were observed (Table 1), indicating that pyrazoles **13**–**24** exist in [D_6]DMSO as mixtures of tautomers (**OH--N** and **NH--O**; Scheme 4) while in $CDCl_3$ the proton exchange is too fast and only average signals were observed. The presence of the two tautomers in [D_6]DMSO solution is not related to dilution, since we performed the spectra at different concentrations and the four broad singlets were always observed. The assignment of the signals (since the ratios are not 50:50, those belonging to the same pyrazole are easily identifiable) is based on the calculated absolute shieldings (vide infra). In the cases of compounds **13**–**17** the **OH--N** tautomers are the more abundant (63%, $K \approx 1.7$), whilst in the cases of **18**–**24** the opposite applies, the **NH--O** tautomers being the major forms (59%, $K \approx 0.70$). This is the expected effect of the C-phenyl group,[16] but if it is assumed that this effect should be independent of R^2, the ratio of the K constants (K_H/K_{Ph}) should be constant. This is almost the case: on average they are 2.44 (between 2.35 and 2.57).





Scheme 4.

To fully characterise the structures of pyrazoles **13**–**24**, we added some drops of trifluoroacetic acid (TFA) to the [D_6]DMSO solution to increase the prototropy. The main features of the NMR spectroscopic data for the pyrazoles **13**–**17** are the resonances of the methylene groups (δ_H = 3.85–4.00 ppm, δ_C = 27.9–30.0 ppm) and those of atoms H-

Table 1. Proton chemical shifts (δ, ppm) of OH and NH of pyrazoles **13**–**24** in [D_6]DMSO.

Compound	OH···N	NH	NH···O	OH	Ratio (%)	*K*
13, R^2 = 4-Cl	13.11	10.96	12.68	9.88	66/34	1.941
14, R^2 = 4-Br	13.11	10.96	12.70	9.31	63:37	1.703
15, R^2 = 4-NO_2	13.13	10.80	12.75	9.89	61:39	1.564
16, R^2 = 2,4-Cl_2	13.12	10.81	12.76	9.88	63:37	1.703
17, R^2 = 3,4-Cl_2	13.10	10.78	12.72	9.89	62:38	1.632
18, R^2 = 2-Cl	13.58	10.62	13.01	9.91	43:57	0.754
19, R^2 = 3-Cl	13.48	10.53	12.94	9.90	41:59	0.695
20, R^2 = 4-Cl	13.51	10.66	12.94	8.89	43:57	0.754
21, R^2 = 4-Br	13.50	10.66	12.94	9.88	40:60	0.667
22, R^2 = 4-NO_2	13.46	10.40	13.00	9.83	41:59	0.695
23, R^2 = 2,4-Cl_2	13.55	10.45	13.04	9.93	41:59	0.695
24, R^2 = 3,4-Cl_2	13.49	10.46	12.99	9.91	41:59	0.695

5 (δ_H = 7.90–8.08 ppm), C-5 (δ_C = 133.6–134.4 ppm) and C-2′ (δ_C = 155.5–156.6 ppm). The resonances of the quaternary carbons, especially for C-3 (δ_C = 142.9–143.5 ppm) and C-4 (δ_C = 118.6–120.2 ppm), have been assigned on the basis of the connectivities found in HMBC spectra (Figure 1). In the cases of compounds **18**–**24** in relation to **13**–**17** there are some signals due to the presence of the 5-aryl groups. The assignments of the resonances of the pyrazole ring carbons ($\delta_{C\text{-}3}$ = 144.7–145.4 ppm, $\delta_{C\text{-}4}$ = 115.2–115.7 ppm and $\delta_{C\text{-}5}$ = 145.7–146.5 ppm) were also based on the connectivities found in the corresponding HMBC spectra (Figure 1).

We selected two pyrazoles, **14** and **15** (Scheme 5), in order to explore their structures in more detail, and in Table 2 we report the ^{13}C NMR signals of these two pyrazoles both in solution ([D$_6$]DMSO + drops of TFA to avoid broad unresolved signals) and in the solid state. It is known that, with very few exceptions (which should be apparent in their spectra), NH-pyrazoles exist in the solid state as only one tautomer.[16–18]

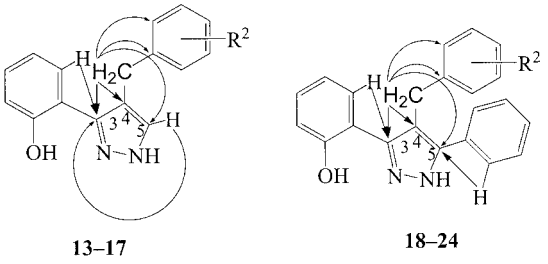
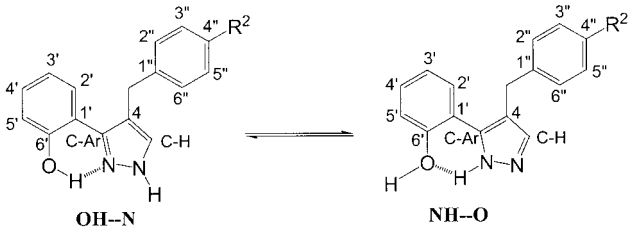


Figure 1. Main connectivities found in the HMBC spectra of pyrazoles **13**–**24**.



14: R^1 = Br, ratio 63:37
15: R^1 = NO$_2$, ratio 61:39

Scheme 5.

The splitting observed for some signals in the CPMAS spectra does not correspond to a mixture of tautomers but to some solid-state effects. We have compared the experimentally measured data with the calculated σ values for both tautomers, and the results are reported in Table 3. The point corresponding to C-4′′ of **14** (C–Br) was not used in the regressions because the carbon atoms bearing heavy atoms are not well calculated.[19,20] We treated **14** and **15** together because the individual equations were very similar.

Table 2. ^{13}C chemical shifts (δ, ppm) and absolute shieldings (σ, ppm) of pyrazoles **14** and **15**.

Carbon atom	Solution	Solid-state **14**	Shielding **OH--N**	Shielding **NH--O**
C-1′	114.9	116.0	61.3028	58.2479
C-2′	156.1	155.2	16.2644	23.7988
C-3′	116.8	117.0	59.3555	64.0356
C-4′	131.1	128.4	47.9487	51.5705
C-5′	119.7	117.0	60.7412	55.9917
C-6′	130.8	125.9	52.2124	51.0474
C–Ar	143.0	145.2[a]	26.2113	43.9166
C-4	119.6	117.0	57.2644	59.0052
C–H	133.9	132.8	49.0684	36.7606
CH_2	29.4	34.0	144.3961	143.7494
C-1′′	139.8	139.7[b]	37.0847	37.3344
C-2′′,6′′	131.1	132.0	46.8519	46.4592
C-3′′,5′′	131.8	132.0	45.1710	45.4290
C-4′′	119.9	118.1	36.5350	37.0812
Carbon atom	Solution	Solid-state **15**	Shielding **OH--N**	Shielding **NH--O**
C-1′	114.6	114.9	61.6602	58.6028
C-2′	156.4	155.9	16.2210	24.2397
C-3′	117.8	118.0	59.0704	63.7022
C-4′	132.4	128.8	47.5930	50.8207
C-5′	120.1	120.8	60.5880	55.8768
C-6′	131.3	130.3	52.4544	50.8641
C–Ar	148.5	147.0	26.1381	36.2125
C-4	119.4	119.4	58.5777	60.5592
C–H	134.4	131.2	49.3626	43.2217
CH_2	30.5	30.5	143.5382	142.8670
C-1′′	143.5	145.6	27.7899	27.3892
C-2′′,6′′	130.3	128.8	48.0791	47.7413
C-3′′,5′′	124.2	122.3[c]	52.6231	52.8009
C-4′′	147.1	146.7	28.8127	28.9622

[a] Average of two split signals at 144.5 and 146.0 ppm. [b] Average of two split signals at 138.8 and 140.6 ppm. [c] Average of two split signals at 121.4 and 123.2 ppm.

Table 3. Results of linear regressions (experimental δ vs. calculated σ, TMS, σ = 177 ppm).[21]

Compound	No. of points[a]	Tautomer	Intercept	Slope	r^2
14+**15** solid	32	**OH--N**	(175.7 ± 0.9)	–(0.983 ± 0.014)	**0.994**
	32	**NH--O**	(178.1 ± 1.0)	–(1.011 ± 0.019)	0.989
14+**15** solution	32	**OH--N**	(177.1 ± 1.2)	–(0.998 ± 0.018)	0.990
	32	**NH--O**	(179.6 ± 1.2)	–(1.029 ± 0.018)	0.991
	32	50:50	(178.7 ± 0.8)	–(1.019 ± 0.012)	**0.996**

[a] The point corresponding to 4′′ of **14** (C–Br) has been omitted.

The correlation coefficients of Table 3 indicate that the tautomer present in the solid state is the **OH--N** form, while in solution the best result is obtained with a 50:50 mixture of both tautomers. Although the experimentally determined ratios are 63:37 (**14**) and 61:39 (**15**) it is not possible to refine the 50:50 model further.

Having established the validity of our σ calculations for the ^{13}C NMR results, we will now turn to the ^{1}H NMR results. If we limit ourselves to the OH and NH signals of compounds **14** and **15** (Table 4), a plot of these data (Figure 2) shows that the assignment of these signals (used to determine the ratios of Table 1) is correct.

Table 4. ^{1}H NMR chemical shifts (δ, ppm) and absolute shieldings (σ, ppm) of the OH and NH signals of compounds **14** and **15**.

Pyrazole	Tautomer	Group	δ	σ
14	**OH--N**	OH	13.13	20.6479
		NH	10.80	23.1732
	NH--O	OH	9.89	27.5744
		NH	12.75	20.4029
15	**OH--N**	OH	13.11	20.7087
		NH	10.96	23.1616
	NH--O	OH	9.31	27.5346
		NH	12.70	20.3333

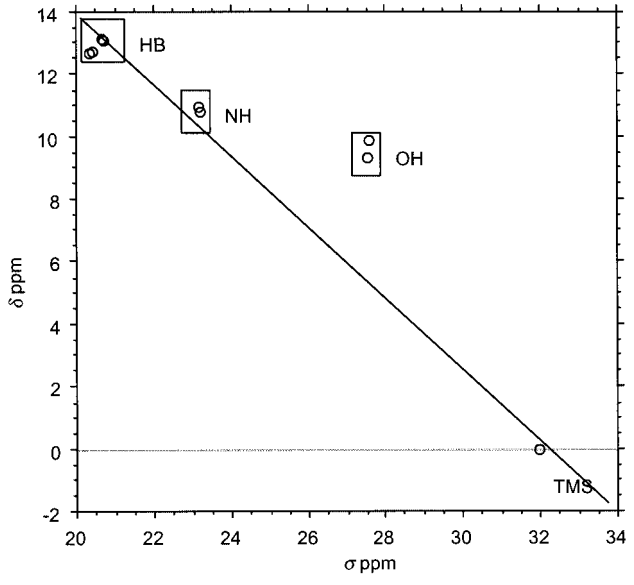


Figure 2. The line corresponds to the equation δ = (36.2 ± 1.4) – (1.12 ± 0.06) σ, n = 7, r^2 = 0.91, σ(TMS) = 31.97.[21]

The calculated regression line was calculated by removing the OH signals not involved in hydrogen bonds (**NH--O** tautomers). Even so, the correlation is not very good because some signals are very sensitive to medium effects, but it suffices for our purpose.

Since we had carried out B3LYP/6-311++G** calculations prior to the GIAO ones, here we report the corresponding energies (Table 5).

Table 5. Energies (absolute values in Hartrees, relative values in kJ·mol^{-1}).

Compound	**NH--O**	**OH--N**	E_{rel}	E_{rel} (DMSO)
14	–3376.6013	–3376.6100	22.7	12.1
15	–1007.6230	–1007.6308	20.7	11.5

Even with correction for the solvent effect (continuum model, see computational details) the stability of the **OH--N** tautomer is overestimated (at 300 K, the average experimental values correspond to 1.1–1.2 kJ·mol^{-1}). Probably the DMSO produces some specific effects, such as intermolecular hydrogen bonds. The most important conclusion from Table 5, however, is that there is no difference between the 4-Br and the 4-NO_2 derivatives in what tautomerism is involved, not a surprising result if the presence of a CH_2 group between the phenyl and the pyrazole rings is taken into account.

Experimental Section

General Remarks: Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. IR (KBr) spectra were recorded with Perkin–Elmer 16 PC and MATTSON 7000 FTIR spectrometers. Mass spectra were recorded with a VG Trio-2 instrument. Elemental analyses were obtained with a Carlo–Erba 1106 apparatus. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer (at 300.13 and 75.47 MHz, respectively) in [D_6]DMSO plus some drops of TFA; chemical shifts are reported in ppm (δ) with TMS as internal reference, and coupling constants (J) are given in Hz. The ^{1}H unequivocal assignments were made by 2D *g*COSY experiments, while ^{13}C assignments were made with the aid of 2D *g*HSQC and *g*HMBC (delays for one-bond and long-range J C/H couplings were optimised for 145 and 7 Hz, respectively) experiments. Starting materials **1**–**12** and **25**–**29** were synthesised by known procedures.[12,13]

Treatment of 3-Benzylchromones 1–5, 3-Benzylflavones 7–12 and Their 4-Thio Analogues 25–29 with Hydrazine Hydrate: A mixture of the appropriate starting material (**1**–**12** and **25**–**29**, 5.0 mmol), hydrazine hydrate (50.0 mmol) and pyridine (30 mL) was heated at reflux for 8 h, and then poured into water. The precipitate was filtered off, washed with water, dried and recrystallised from methanol to afford pyrazoles **13**–**24** (Scheme 1 and Scheme 2).

4-(4-Chlorobenzyl)-3(5)-(2-hydroxyphenyl)pyrazole (13): Yields 1.20 g (84.5%) (from **1**) and 1.17 g (82.4%) (from **25**). M.p. 140–141 °C (recrystallised from methanol). ^{1}H NMR: δ = 3.90 (s, 2 H, CH_2), 6.86 (dt, J = 7.5 and 1.0 Hz, 1 H, 5′-H), 7.00 (dd, J = 8.1 and 1.0 Hz, 1 H, 3′-H), 7.14 (d, J = 8.4 Hz, 2 H, 2′′,6′′-H), 7.27 (d, J = 8.4 Hz, 2 H, 3′′,5′′-H), 7.24–7.31 (m, 2 H, 4′-H and 6′-H), 7.90 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 29.2 (CH_2), 115.5 (C-1′), 116.5 (C-3′), 118.6 (C-4), 119.3 (C-5′), 128.5 (C-3′′,5′′), 130.2 (C-6′), 130.4 (C-2′′,6′′), 130.9 (C-4′), 131.1 (4′′), 133.6 (C-5), 139.4 (C-1′′), 142.9 (C-3), 155.7 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3259, 1594, 1492, 1457, 1405, 1292, 1263, 1245, 1089, 848, 827, 740, 713 cm^{-1}. MS: m/z = 284 [M]$^+$ (89), 256 (28), 173 (59), 125 (100). $C_{16}H_{13}ClN_2O$ (284.71): calcd. C 67.49, H 4.60, N. 9.83; found C 67.58, H 4.66, N 9.91.

4-(4-Bromobenzyl)-3(5)-(2-hydroxyphenyl)pyrazole (14): Yields 1.28 g (77.8%) (from **2**) and 1.25 g (76.0%) (from **26**). M.p. 153–154 °C. ^{1}H NMR: δ = 3.86 (s, 2 H, CH_2), 6.86 (dt, J = 7.5 and 1.0 Hz, 1 H, 5′-H), 7.01 (dd, J = 8.8 and 1.0 Hz, 1 H, 3′-H), 7.05 (d, J = 8.4 Hz, 2 H, 2′′,6′′-H), 7.25–7.30 (m, 2 H, 4′-H and 6′-H), 7.37 (d, J = 8.4 Hz, 2 H, 3′′,5′′-H), 7.99 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 29.4 (CH_2), 114.9 (C-1′), 116.8 (C-3′), 119.6 (C-4), 119.7 (C-5′), 119.9 (C-4′′), 130.8 (C-6′), 131.1 (C-4′ and C-2′′,6′′), 131.8 (C-3′′,5′′), 133.9 (C-5), 139.8 (C-1′′), 143.0 (C-3), 156.1 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3261, 1592, 1486, 1457, 1290, 1261, 1070, 1010, 846, 827, 740, 715 cm^{-1}. MS: m/z = 328/330 [M]$^+$ (84/84), 300/302 (16/16), 249 (13), 171 (100). $C_{16}H_{13}BrN_2O$ (329.17): calcd. C 58.38, H 3.98, N 8.51; found C 58.47, H 3.92, N 8.60.

3(5)-(2-Hydroxyphenyl)-4-(4-nitrobenzyl)pyrazole (15): Yield 1.01 g (68.5%). M.p. 173–174 °C (recrystallised from methanol). ^{1}H NMR: δ = 4.00 (s, 2 H, CH_2), 6.83 (t, J = 7.4 Hz, 1 H, 5′-H), 6.98 (d, J = 8.1 Hz, 1 H, 3′-H), 7.21–7.29 (m, 2 H, 4′-H and 6′-H), 7.31 (d, J = 8.6 Hz, 2 H, 2′′,6′′-H), 8.02 (d, J = 8.6 Hz, 2 H, 3′′,5′′-H), 8.06 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 30.0 (CH_2), 114.6 (C-1′), 117.8 (C-3′), 119.4 (C-4), 120.1 (C-5′), 124.2 (C-3′′,5′′), 130.3 (C-2′′,6′′), 131.3 (C-6′), 132.4 (C-4′), 134.4 (C-5), 143.5 (C-3), 147.1 (C-4′′), 148.5 (C-1′′), 156.4 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3374, 1583, 1504, 1450, 1346, 1253, 1083, 854, 842, 754, 730, 717 cm^{-1}. MS: m/z = 295 [M]$^+$ (100), 278 (45), 265 (30), 248 (38). $C_{16}H_{13}N_3O_3$ (295.26): calcd. C 65.08, H 4.43, N 14.22; found C 65.17, H 4.49, N 14.31.

4-(2,4-Dichlorobenzyl)-3(5)-(2-hydroxyphenyl)pyrazole (16): Yield 1.13 g (71.1%). M.p. 143–144 °C (recrystallised from methanol). ^{1}H NMR: δ = 3.92 (s, 2 H, CH_2), 6.85 (d, J = 7.5 Hz, 1 H, 5′-H), 7.00 (d, J = 8.1 Hz, 1 H, 3′-H), 7.08 (d, J = 8.3 Hz, 1 H, 6′′-H), 7.16 (dd, J = 8.3 and 2.1 Hz, 1 H, 5′′-H), 7.22–7.30 (m, 2 H, 4′-H and 6′-H), 7.39 (d, J = 2.1 Hz, 1 H, 3′′-H), 7.95 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 27.9 (CH_2), 114.7 (C-1′), 117.2 (C-3′), 118.9 (C-4), 120.1 (C-5′), 128.1 (C-5′′), 129.7 (C-3′′), 131.3 (C-6′), 132.6 (C-4′ and C-6′′), 133.2 (C-4′′), 134.3 (C-5), 134.9 (C-2′′), 136.9 (C-1′′), 143.5 (C-3), 156.6 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3347, 1587, 1473, 1457, 1442, 1286, 1257, 1089, 1049, 877, 854, 829, 728 cm^{-1}. MS: m/z = 318 [M]$^+$ (83), 283 (35), 173 (51), 159 (100). $C_{16}H_{12}Cl_2N_2O$ (319.17): calcd. C 60.21, H 3.79, N 8.77; found C 60.14, H 3.83, N 8.67.

4-(3,4-Dichlorobenzyl)-3(5)-(2-hydroxyphenyl)pyrazole (17): Yield 1.24 g (78.0%). M.p. 133–134 °C (recrystallised from methanol). ^{1}H NMR: δ = 3.85 (s, 2 H, CH_2), 6.85 (dt, J = 7.5 and 1.0 Hz, 1 H, 5′-H), 6.99 (d, J = 7.5 Hz, 1 H, 3′-H), 7.01 (dd, J = 8.2 and 2.2 Hz, 1 H, 6′′-H), 7.27 (d, J = 2.2 Hz, 1 H, 2′′-H), 7.22–7.30 (m, 2 H, 4′-H and 6′-H), 7.35 (d, J = 8.2 Hz, 1 H, 5′′-H), 8.08 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 29.3 (CH_2), 114.5 (C-1′), 117.5 (C-3′), 120.1 and 120.2 (C-4 and C-5′), 129.5 (C-6′′), 130.1 (C-4′′), 131.1 and 131.3 (C-2′′ and C-5′′), 131.5 (C-6′), 132.2 (C-3′′), 132.7 (C-4′), 134.4 (C-5), 141.5 (C-1′′), 143.3 (C-3), 155.5 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3265, 1592, 1514, 1471, 1454, 1259, 1238, 1129, 1088, 1011, 832, 745 cm^{-1}. MS: m/z = 318 [M]$^+$ (100), 290 (22), 173 (77), 159 (87). $C_{16}H_{12}Cl_2N_2O$ (319.17): calcd. C 60.21, H 3.79, N 8.77; found C 60.31, H 3.73, N. 8.85.

4-(2-Chlorobenzyl)-3(5)-(2-hydroxyphenyl)-5(3)-phenylpyrazole (18): Yield 1.39 g (77.2%). M.p. 189–190 °C (recrystallised from methanol). ^{1}H NMR: δ = 4.04 (s, 2 H, CH_2), 6.77 (dt, J = 7.5 and 0.8 Hz, 1 H, 5′-H), 6.90 (dt, J = 7.5 and 1.9 Hz, 1 H, 6′′-H), 6.97 (dd, J = 7.6 and 0.8 Hz, 1 H, 3′-H), 6.96–7.07 (m, 2 H, 4′′-H and 5′′-H), 7.18 (dd, J = 7.5 and 1.5 Hz, 1 H, 6′-H), 7.19–7.25 (m, 1 H, 4′-H), 7.24 (dd, J = 7.7 and 1.6 Hz, 1 H, 3′′-H), 7.38–7.42 (m, 3 H, 3′′′,4′′′,5′′′-H), 7.47–7.50 (m, 2 H, 2′′′,6′′′-H) ppm. ^{13}C NMR: δ = 27.7 (CH_2), 115.2 and 115.3 (C-1′ and C-4), 117.2 (C-3′), 120.0 (C-5′), 127.7 (C-5′′), 127.78, 128.86 and 129.0 (C-4′′, C-1′′′ and C-2′′′,6′′′), 129.8 (C-3′′′,5′′′), 130.0 (C-3′′), 130.4 (C-4′′′), 130.6 (C-6′′), 131.1 (C-6′), 132.3 (C-4′), 133.9 (C-2′′), 137.3 (C-1′′), 145.3 (C-3), 146.3 (C-5), 156.6 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3365, 1589, 1504, 1467, 1454, 1388, 1249, 1176, 1037, 981, 827, 767, 754, 692 cm^{-1}. MS: m/z = 360 [M]$^+$, (7), 345 (10), 311 (100), 233 (11). $C_{22}H_{17}ClN_2O$ (360.80): calcd. C 73.23, H 4.75, N 7.76; found C 73.29, H 4.61, N 7.85.

4-(3-Chlorobenzyl)-3(5)-(2-hydroxyphenyl)-5(3)-phenylpyrazole (19): Yields 1.39 g (77.2%) (from **7**) and 1.32 g (73.3%) (from **27**). M.p. 175–176 °C (recrystallised from methanol). ^{1}H NMR: δ = 4.01 (s, 2 H, CH_2), 6.83 (ddd, J = 7.7, 7.3 and 1.0 Hz, 1 H, 5′-H), 6.89 (dt, J = 7.7 and 1.0 Hz, 1 H, 4′′-H), 6.96 (t, J = 1.8 Hz, 1 H, 2′′-H), 6.99 (d, J = 7.8 Hz, 1 H, 3′-H), 7.05 (dt, J = 7.7 and 1.8 Hz, 1 H, 6′′-H), 7.10 (t, J = 7.7 Hz, 1 H, 5′′-H), 7.26 (d, J = 7.3 Hz, 1 H, 6′-H), 7.23–7.30 (m, 1 H, 4′-H), 7.42–7.45 (m, 3 H, 3′′′,4′′′,5′′′-H), 7.51–7.56 (m, 2 H, 2′′′,6′′′-H) ppm. ^{13}C NMR: δ = 28.9 (CH_2), 115.4 (C-1′), 115.7 (C-4), 116.9 (C-3′), 119.8 (C-5′), 126.7 (C-6′′), 127.1 (C-4′′), 128.4 (C-2′′), 128.8 (C-2′′′,6′′′), 128.9 (C-1′′′), 129.6 (C-3′′′,5′′′), 130.3 (C-4′′′), 130.5 (C-5′′), 131.1 (C-6′), 132.0 (C-4′), 133.8 (C-3′′), 142.7 (C-1′′), 144.8 (C-3), 145.9 (C-5), 156.3 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3365, 1585, 1504, 1451, 1382, 1247, 1166, 1133, 979, 925, 865, 829, 767, 690 cm^{-1}. MS: m/z = 360 [M]$^+$, (27), 345 (100), 311 (7), 233 (38). $C_{22}H_{17}ClN_2O$ (360.80): calcd. C 73.23, H 4.75, N 7.76; found C 73.16, H 4.69, N 7.70.

4-(4-Chlorobenzyl)-3(5)-(2-hydroxyphenyl)-5(3)-phenylpyrazole (20): Yield 1.37 g (76.1%). M.p. 208–209 °C (recrystallised from methanol). ^{1}H NMR: δ = 4.00 (s, 2 H, CH_2), 7.82 (dt, J = 7.5 and 0.9 Hz, 1 H, 5′-H), 6.95–7.00 (m, 3 H, 3′-H and 2′′,6′′-H), 7.14 (d, J = 8.4 Hz, 2 H, 3′′,5′′-H), 7.23 (d, J = 7.6 Hz, 1 H, 6′-H), 7.22–7.28 (m, 1 H, 4′-H), 7.41–7.45 (m, 3 H, 3′′′,4′′′,5′′′-H) 7.52–7.56 (m, 2 H, 2′′′,6′′′-H) ppm. ^{13}C NMR: δ = 29.6 (CH_2), 115.5 and 115.6 (C-1′ and C-4), 116.8 (C-3′), 119.7 (C-5′), 128.6 (C-2′′′,6′′′), 128.7 (C-3′′,5′′), 129.2 (C-1′′′), 129.5 (C-3′′′,,5′′′), 130.0 (C-4′′′), 130.1 (C-2′′,6′′), 130.9 (C-6′), 131.3 (C-4′′), 131.6 (C-4′), 139.2 (C-1′′), 144.7 (C-3), 145.7 (C-5), 156.2 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3374, 1585, 1504, 1488, 1452, 1247, 1130, 1110, 933, 908, 748, 694 cm^{-1}. MS: m/z = 360 [M]$^+$, (17), 345 (25), 124 (47), 109 (100). $C_{22}H_{17}ClN_2O$ (360.80): calcd. C 73.23, H 4.75, N 7.76; found C 73.32, H 4.79, N 7.68.

4-(4-Bromobenzyl)-3(5)-(2-hydroxyphenyl)-5(3)-phenylpyrazole (21): Yield 1.58 g (78.0%). M.p. 211–212 °C (recrystallised from methanol). ^{1}H NMR: δ = 3.99 (s, 2 H, CH_2), 6.83 (t, J = 7.8 Hz, 1 H, 5′-H), 6.91 (d, J = 8.4 Hz, 2 H, 2′′,6′′-H), 6.98 (d, J = 7.8 Hz, 1 H, 3′-H), 7.26 (d, J = 7.8 Hz, 1 H, 6′-H), 7.25–7.29 (m, 1 H, 4′-H), 7.28 (d, J = 8.4 Hz, 2 H, 3′′,5′′-H), 7.41–7.45 (m, 3 H, 3′′′,4′′′,5′′′-H), 7.53–7.56 (m, 2 H, 2′′′,6′′′-H) ppm. ^{13}C NMR: δ

= 28.7 (CH_2), 115.5 and 115.6 (C-1′ and C-4), 116.8 (C-3′), 119.72 and 119.76 (C-5′ and C-4′′), 128.6 (C-2′′′,6′′′), 129.1 (C-1′′′), 129.5 (C-3′′′,5′′′), 130.1 (C-4′′′), 130.6 (C-2′′,6′′), 130.9 (C-6′), 131.7 (C-4′ and C-3′′,5′′), 139.6 (C-1′′), 144.8 (C-3), 145.8 (C-5), 156.2 (C-2′) ppm. IR (KBr): ṽ = 3376, 1583, 1504, 1484, 1452, 1288, 1249, 1180, 1164, 1130, 1070, 1010, 981, 827, 792, 748, 694 cm^{-1}. MS: *m*/*z* = 404/406 [M]$^+$ (100/100), 389/391 (17/17), 325 (14), 249 (43). $C_{22}H_{17}BrN_2O$ (405.27): calcd. C 65.19, H 4.23, N 6.91; found C 65.26, H 4.27, N 6.83.

3(5)-(2-Hydroxyphenyl)-4-(4-nitrobenzyl)-5(3)-phenylpyrazole (22): Yields 1.24 g (66.8%) (from **10**) and 1.41 g (76.0%) (from **28**). M.p. 224–225 °C (recrystallised from methanol). ^{1}H NMR: δ = 4.13 (s, 2 H, CH_2), 6.79 (t, *J* = 7.5 Hz, 1 H, 5′-H), 6.95 (d, *J* = 8.5 Hz, 1 H, 3′-H), 7.18 (d, *J* = 8.5 Hz, 2 H, 2′′,6′′-H), 7.20 (d, *J* = 7.5 Hz, 1 H, 6′-H), 7.20–7.25 (m, 1 H, 4′-H), 7.37–7.41 (m, 3 H, 3′′′,4′′′,5′′′-H), 7.50–7.54 (m, 2 H, 2′′′,6′′′-H), 7.92 (d, *J* = 8.5 Hz, 2 H, 3′′,5′′-H) ppm. ^{13}C NMR: δ = 29.6 (CH_2), 115.4 and 115.5 (C-1′ and C-4), 117.1 (C-3′), 120.0 (C-5′), 124.1 (C-3′′,5′′), 129.0 (C-1′′′ and C-2′′′,6′′′), 129.8 and 129.9 (C-2′′,6′′ and C-3′′′,5′′′), 130.5 (C-4′′′), 131.3 (C-6′), 132.2 (C-4′), 145.1 (C-3), 146.2 (C-5), 146.9 (C-1′′), 148.5 (C-4′′), 156.5 (C-2′) ppm. IR (KBr): ṽ = 3361, 1594, 1511, 1452, 1346, 1249, 1164, 1133, 1109, 977, 846, 771, 750, 732, 700, 593 cm^{-1}. MS: *m*/*z* = 371 (100) [M]$^+$, 341 (30), 247 (27), 146 (48). $C_{22}H_{17}N_3O_3$ (371.36): calcd. C 71.15, H 4.62, N 7.54; found C 71.23, H 4.68, N 7.62.

4-(2,4-Dichlorobenzyl)-3(5)-(2-hydroxyphenyl)-5(3)-phenylpyrazole (23): Yields 1.52 g (77.2%) (from **11**) and 1.69 g (85.8%) (from **29**). M.p. 206–207 °C (recrystallised from methanol). ^{1}H NMR: δ = 3.99 (s, 2 H, CH_2), 6.78 (ddd, *J* = 7.6, 7.5 and 1.0 Hz, 1 H, 5′-H), 6.88 (d, *J* = 8.3 Hz, 1 H, 6′′-H), 6.94 (dd, *J* = 8.2 and 1.0 Hz, 1 H, 3′-H), 7.00 (dd, *J* = 8.3 and 2.1 Hz, 1 H, 5′′-H), 7.16 (dd, *J* = 7.6 and 1.6 Hz, 1 H, 6′-H), 7.22 (ddd, *J* = 8.2, 7.5 and 1.6 Hz, 1 H, 4′-H), 7.29 (d, *J* = 2.1 Hz, 1 H, 3′′-H), 7.39–7.42 (m, 3 H, 3′′′,4′′′,5′′′-H), 7.47–7.50 (m, 2 H, 2′′′,6′′′-H) ppm. ^{13}C NMR: δ = 27.5 (CH_2), 115.2 and 115.3 (C-4 and C-1′), 117.2 (C-3′), 120.1 (C-5′), 127.8 (C-5′′), 128.8 (C-1′′′), 129.1 (C-2′′′,6′′′), 129.5 (C-3′′), 129.9 (C-3′′′,5′′′), 130.8 (C-4′′′), 131.3 (C-6′), 131.9 (C-6′′), 132.5 (C-4′), 132.9 (C-4′′), 134.8 (C-2′′), 136.5 (C-1′′), 145.4 (C-3), 146.5 (C-5), 156.7 (C-2′) ppm. IR (KBr): ṽ = 3359, 1587, 1504, 1467, 1454, 1413, 1292, 1249, 1172, 1103, 1047, 979, 908, 867, 831, 771, 750, 698, 595 cm^{-1}. MS: *m*/*z* = 394 [M]$^+$ (100), 359 (85), 249 (27), 146 (77). $C_{22}H_{16}Cl_2N_2O$ (395.26): calcd. C 66.85, H 4.08, N 7.08; found C 66.94, H 4.13, N 6.98.

4-(3,4-Dichlorobenzyl)-3(5)-(2-hydroxyphenyl)-5(3)-phenylpyrazole (24): Yield 1.32 g (67.0%). M.p. 192–193 °C (recrystallised from methanol). ^{1}H NMR: δ = 3.99 (s, 2 H, CH_2), 6.94 (dd, *J* = 7.5 and 7.4 Hz, 1 H, 5′-H), 6.89 (dd, *J* = 8.3 and 2.0 Hz, 1 H, 6′′-H), 6.98 (d, *J* = 8.1 Hz, 1 H, 3′-H), 7.11 (d, *J* = 2.0 Hz, 1 H, 2′′-H), 7.22 (d, *J* = 7.5 Hz, 1 H, 6′-H), 7.24 (dd, *J* = 8.1 and 7.4 Hz, 1 H, 4′-H), 7.25 (d, *J* = 8.3 Hz, 1 H, 5′′-H), 7.37–7.45 (m, 3 H, 3′′′,4′′′,5′′′-H), 7.52–7.56 (m, 2 H, 2′′′,6′′′-H) ppm. ^{13}C NMR: δ = 28.7 (CH_2), 115.53 and 115.55 (C-4 and C-1′), 117.0 (C-3′), 119.9 (C-5′), 128.8 (C-6′′), 128.9 (C-2′′′,6′′′), 129.1 (C-1′′′), 129.6 (C-4′′), 129.7 (C-3′′′,5′′′), 130.3 (C-4′′′), 130.7 (C-2′′), 130.9 (C-5′′), 131.2 (C-6′), 131.8 (C-4′), 132.0 (C-3′′), 141.3 (C-1′′), 144.9 (C-3), 146.1 (C-5), 156.5 (C-2′) ppm. IR (KBr): ṽ = 3376, 1585, 1504, 1469, 1452, 1388, 1247, 1166, 1130, 1029, 979, 919, 827, 769, 750, 694. 580 cm^{-1}. MS: *m*/*z* = 394 [M]$^+$ (100), 359 (10), 249 (39), 146 (62). $C_{22}H_{16}Cl_2N_2O$ (395.26): calcd. C 66.85, H 4.08, N 7.08; found C 66.78, H 4.03, N 7.14.

Computational Details: Geometries of compounds **14** and **15** were fully optimised at the B3LYP theoretical level,[22] with the 6-311++G** basis set[23] as implemented in the Gaussian 03 program.[24] Harmonic frequency calculations verified the nature of the stationary points as minima (all real frequencies). Absolute shieldings of compounds **14** and **15** were calculated over the fully optimised geometries within the GIAO approximation.[25] The Miertus, Scrocco and Tomasi continuum model was used for the calculation of solvent effects.[26]

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