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Synthesis of 4-Aryl-3(5)-(2-hydroxyphenyl)pyrazoles by Reaction of Isoflavones and their 4-Thio Analogues with Hydrazine Derivatives*

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4-Aryl-3(5)-2-(hydroxyphenyl)pyrazoles have been prepared by the reaction of isoflavones and their 4-thio analogues with hydrazine hydrate and phenylhydrazine in hot pyridine. The reaction mechanism for the formation of these pyrazoles is discussed. All the new compounds have been fully characterized by NMR spectroscopy. In [D_6]DMSO, a ^{1}H NMR study allows observation of the presence of both pyrazole annular tautomers, due to the presence of intramolecular hydrogen bonds in each tautomer (OH···N and NH···O). Theoretical calculations have been carried out on tautomers and conformers of compounds **20** (3(5)-(2-hydroxy-4-methoxyphenyl)-5(3)-methyl-4-phenylpyrazole) and **21** (3(5)-(2-hydroxy-4-methoxyphenyl)-4-(2-methoxyphenyl)-5(3)-methylpyrazole), including the absolute shieldings (GIAO/B3 LYP/6–311++G**) of **21**.

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Introduction

Pyrazoles are well-known and widely investigated five-membered nitrogen-containing heterocyclic compounds and their syntheses have been summarized in principal textbooks.[1,2] Owing to the wide variety of their bioactivities, these compounds are useful materials in drug research[3] and in the development of agricultural chemicals.[4] Recently, it was demonstrated that *ortho*-hydroxyphenylpyrazoles possess analgesic activity, are platelet aggregation inhibitors[5] and potent inhibitors of Hsp90 ATPase activity (in particular, those derived from isoflavones)[6–10] and can act as analytical reagents.[11] Concerning their potential application, an interesting example is the application of *N*-(2-hydroxyphenyl)pyrazoles as photoprotectors of polystyrene.[12,13] All these features have stimulated the synthesis of numerous pyrazole-type compounds.

Formerly, we investigated the synthesis of *ortho*-hydroxyphenylpyrazoles by the reaction of several groups of chromones with hydrazines.[14–18] As a consequence, we developed simple and convenient procedures for the preparation of 3,4,5-trisubstituted pyrazoles. The experience gained in the course of the above-mentioned studies has prompted us to study the synthesis of new *ortho*-hydroxyphenylpyrazoles by the reaction of isoflavone analogues with several different hydrazines, which will be described in the present paper.

Recently, we demonstrated, using NMR spectroscopy, that 4-benzyl-3(5)-(*ortho*-hydroxyphenyl)-5(3)-phenylpyrazoles exists as a mixture of tautomers in [D_6]DMSO solution. The prototropic exchange is slow owing to the presence of intramolecular hydrogen bonds OH···N and NH···O, allowing observation of the signals of both tautomers. However, in $CDCl_3$, the proton exchange is too fast and only average signals were observed.[18] In the present study, we have also observed annular tautomers of the obtained pyrazoles in [D_6]DMSO solutions, and studied the steric effect of the 5-aryl group (using the numbering of the OH···N tautomer). These experimental results were complemented by a theoretical study that suggests that the in solid state, these compounds exist as the OH···N tautomer and in [D_6]DMSO solutions as a mixture of both tautomers, with the OH···N being predominant.

Results and Discussion

Chemistry

Although the synthesis of pyrazoles by the reaction of isoflavones and hydrazines has received some attention,[9,10,13,19–21] no systematic studies have been accomplished to assess the influence of some structural substituents of the isoflavones on their reactivity with hydrazines. It is well known that the reaction of chromones with hydrazines starts with a nucleophilic attack of the nitrogen atom of the hydrazine at C2 of the chromone skeleton. Therefore, the substituents at this position can be a decisive factor on this chemical transformation. For this reason, one of the aims of our present study was to investigate the influence of

*Dedicated to Professor Gábor Tóth on the occasion of his 65th birthday.

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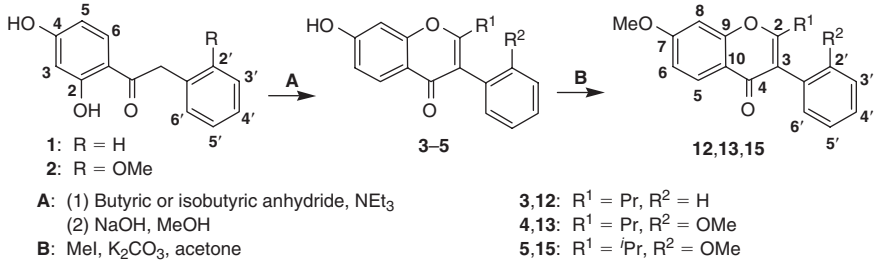
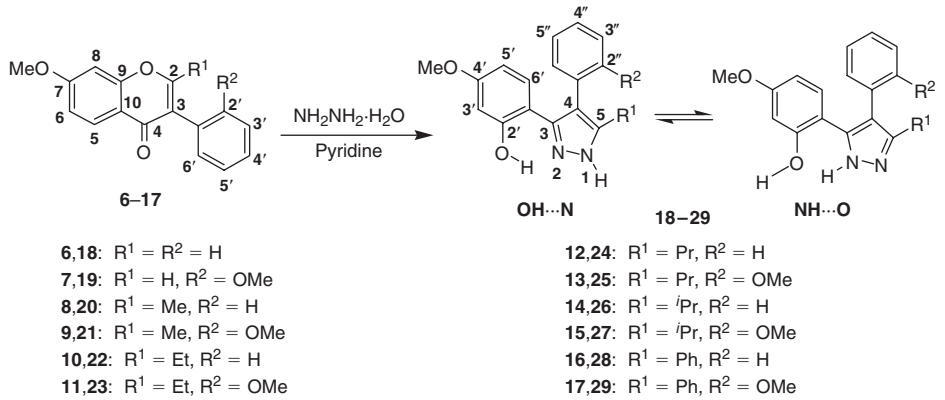
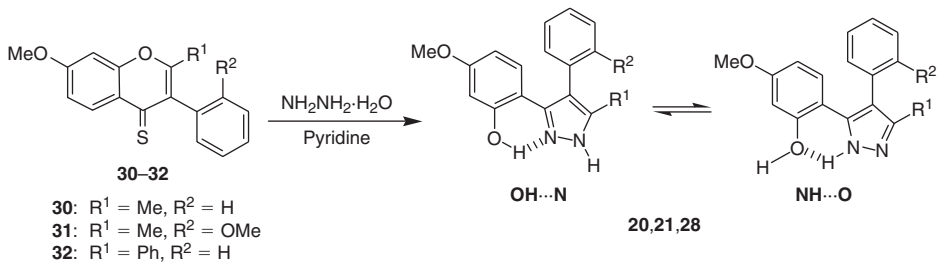


Scheme 1. Synthesis of isoflavones **12**, **13**, and **15**.



Scheme 2. Synthesis of 4-aryl-3(5)-(2-hydroxyphenyl)pyrazoles **18**–**29**.



Scheme 3. Synthesis of 4-aryl-3(5)-(2-hydroxyphenyl)pyrazoles **20**, **21**, and **28**.

the steric demand of the substituents attached to C2 of isoflavones on their reaction with hydrazines. Substituents chosen for the present study were hydrogen, methyl, ethyl, propyl, isopropyl, and phenyl groups. As the presence of a substituent in the *ortho*-position of the 3-phenyl group can also hinder the attack of a reagent at C2 of the isoflavone molecule, the influence of a C2′ methoxy group was also investigated.

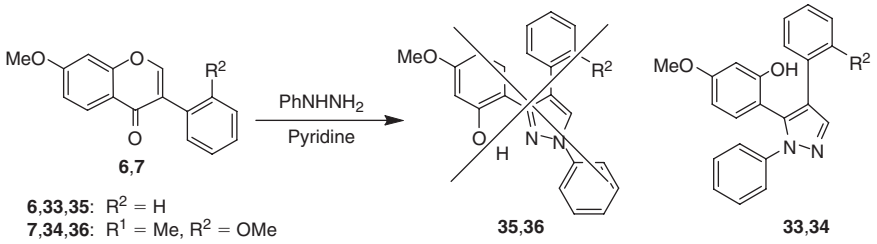
Starting materials **6**–**11**, **14**, **16**, and **17** are known compounds and were synthesized according to literature methods.[22–31] However, isoflavones **12**, **13**, and **15** are new compounds being synthesized by the first time in the current study. Ring closure of 2,4-dihydroxyphenyl benzyl ketones **1** and **2** by treatment with butyric or isobutyric anhydride in triethylamine followed by sodium hydroxide in methanol afforded 7-hydroxyisoflavones **3**–**5**. Methylation of compounds **3**–**5** with methyl iodide under basic conditions provided 7-methoxyisoflavones **12**, **13**, and **15** (Scheme 1).

Reactions of isoflavones **6**–**17** and hydrazine hydrate have been investigated in various solvents. If acetic acid, which proved to be a convenient solvent for the reaction of 3-(3-aryl-3-oxopropenyl)chromones,[17] was used, the starting material was recovered in each case. The reaction was too slow in hot methanol. Our preliminary experiments showed that pyridine can be used as a convenient solvent for this reaction. Compounds **6**–**17** and hydrazine hydrate were allowed to react in hot pyridine and pyrazoles **18**–**29** were obtained in good yields (69–87%; Scheme 2).

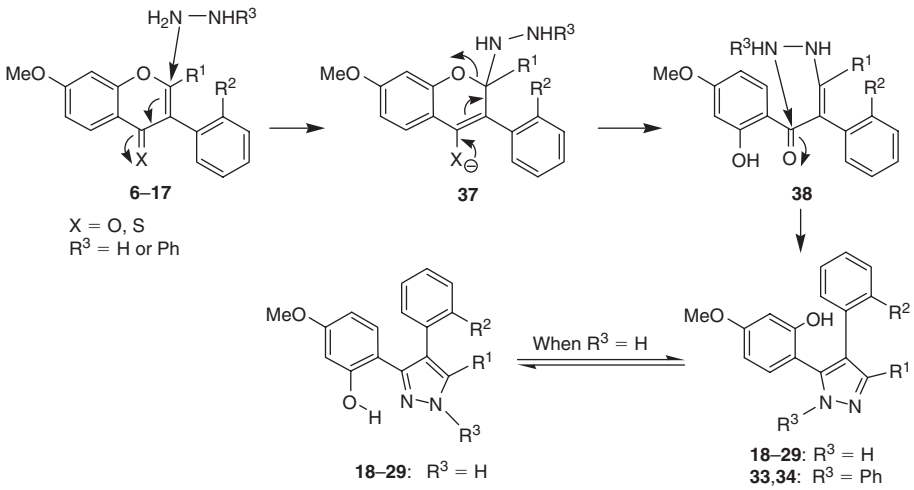
To investigate the influence of the replacement of the oxygen atom at C4 for a sulfur atom, 4-thioisoflavones **30**–**32** were treated with hydrazine hydrate in hot pyridine and the same pyrazoles (**20**, **21**, and **28**) were formed as in the case of their isoflavone congeners (**8**, **9**, and **16**) in similarly good yields (79–84%; Scheme 3). These results show that isoflavones and their 4-thio analogues react similarly with hydrazine, providing the same pyrazoles.

The effect of the steric demand of the C2 substituents of isoflavones was only an increase in the reaction time from 4 to 16 h (see Experimental). The presence of a 2′-methoxy group was almost without influence on this transformation. The reason for these findings may originate from the high nucleophilicity of the hydrazine, which makes possible an effective nucleophilic attack even at a crowded carbon atom.

We also studied the reaction of isoflavones **6**–**9**, **11**, **14**, and **16** with phenylhydrazine in hot pyridine. It was found that only the 7-methoxyisoflavone **6** and the 7,2′-dimethoxyisoflavone **7** reacted with phenylhydrazine to afford pyrazoles **33** and **34**,



Scheme 4. Synthesis of 4-aryl-3(5)-(2-hydroxyphenyl)-1-phenylpyrazoles **33** and **34**.



Scheme 5. Proposal of mechanism for the synthesis of pyrazoles **18**–**29** and **33**, **34**.

under longer reaction time (48 h) and in lower yields (29 and 25%; Scheme 4). The reaction was regioselective as the corresponding isomers **35** and **36** were not detected. Isoflavones substituted with a methyl (**8**, **9**), ethyl (**11**), isopropyl (**14**), or phenyl (**16**) group at their C2 carbon atom did not react with phenylhydrazine and were recovered unchanged even after such a long reaction time. These observations prove that a less nucleophilic hydrazine derivative cannot effectively attack the C2 carbon atom of an isoflavone substituted with an alkyl or a phenyl group at this position. Isoflavones **6** and **7** were allowed to react with 2-hydrazinopyridine under the same reaction conditions, but the starting materials were recovered in both cases. It appears that this less nucleophilic hydrazine derivative cannot cleave the isoflavone ring even with a hydrogen atom at position 2.

The structures of all newly synthesized pyrazoles (**18**–**29**, **33**, and **34**) were elucidated by elemental analyses and by spectroscopic methods. Both the elemental analyses and the mass spectra unambiguously proved the presence of two nitrogen atoms in each compound. In their infrared (IR) spectra (see Experimental) C=N and NH bands characteristic for a pyrazole ring were assigned in all cases. Structure elucidation of all new pyrazoles was completed by various NMR techniques (see below).

A plausible reaction mechanism is shown in Scheme 5. The first step is a nucleophilic attack of the most nucleophilic hydrazine nitrogen atom at the C2 carbon atom of the chromone nucleus, followed by ring opening affording structure **38**. The hydrazine moiety of the intermediate **38** can react with the carbonyl (X=O) or with the thiocarbonyl group (X=S) of this molecule to give rise to the pyrazole ring. Pyrazoles formed from the reaction of isoflavones with hydrazine hydrate may exist in a mixture of tautomers OH···N and NH···O. However, the reaction of isoflavones with phenylhydrazine gives only 4-aryl-1-phenyl-5-(2-hydroxyphenyl)pyrazoles **33**, **34**.

*NMR Study of the Tautomerism of Pyrazoles **18–29** and **33, 34***

The ^{1}H NMR spectra of compounds **18**–**29** in [D$_6$]DMSO show four broad singlets at higher frequency values (Table 1), indicating that under such conditions they exist as a mixture of tautomers (OH···N and NH···O; Schemes 2 and 3). The assignment of the signals (because the ratio is not 50:50, those belonging to the same tautomer are easily identified) is based on our previous work on related compounds.[18]

The OH signal is almost invariant (9.85 ± 0.10 ppm), OH···N and NH···O signals are quite regular for compounds **18**–**27** (13.08 ± 0.11 ppm and 12.38 ± 0.29 ppm, respectively), and they increase significantly when R^1 = Ph, compounds **28** and **29** (13.58 ppm and 12.83 ppm, respectively). The NH signal of the OH···N tautomer shows a clear dependence on the nature of R^2, from 11.0 ppm on average for R^2 = H to 11.6 ppm on average for R^2 = OMe. Table 1 also reports the percentages of both tautomers (ratio = [OH···N]/[NH···O]) as well as the corresponding equilibrium constant.

To fully characterize the structures of pyrazoles **18**–**29**, some drops of trifluoroacetic acid (TFA) were added to the [D$_6$]DMSO solution to increase the prototropy. In the discussion of the structural characterization of pyrazoles **18**–**29**, the numbering system of isomers OH···N will be used. The main features of the NMR data of these pyrazoles are the resonances of the pyrazole proton H5 for the 3,4-disubstituted pyrazoles **18** and **19** (δ_H 8.30, 8.44) and those of the alkyl groups of 5-alkyl-3,4-diarylpyrazoles **20**–**27**, whereas the spectra of triarylpyrazoles **28** and **29** are

Table 1. Chemical shifts (δ) of the OH and NH protons of pyrazoles 18–29 in [D_6]DMSO, percentages of tautomers, and ΔG^{293} values in kJ mol^{-1}

Compound	δ OH [OH···N] [ppm]	δ NH [OH···N] [ppm]	δ NH [NH···O] [ppm]	δ OH [NH···O] [ppm]	Ratio [%]	ΔG^{293} [kJ mol^{-1}]
18, $R^1 = R^2 = H$	13.15	10.33	12.77	9.81	39/61	1.1
19, $R^1 = H$, $R^2 = OMe$	13.22	11.27	12.63	9.81	68/32	−1.8
20, $R^1 = Me$, $R^2 = H$	13.04	11.09	12.39	9.76	76/24	−2.8
21, $R^1 = Me$, $R^2 = OMe$	13.01	11.62	12.20	9.84	89/11	−5.1
22, $R^1 = Et$, $R^2 = H$	13.07	11.21	12.38	9.78	80/20	−3.4
23, $R^1 = Et$, $R^2 = OMe$	13.05	11.69	12.22	9.89	91/09	−5.6
24, $R^1 = Pr$, $R^2 = H$	13.07	11.27	12.37	9.80	80/20	−3.4
25, $R^1 = Pr$, $R^2 = OMe$	13.03	11.70	12.22	9.90	92/08	−5.9
26, $R^1 = {}^i Pr$, $R^2 = H$	13.10	11.35	12.37	9.84	82/18	−3.7
27, $R^1 = {}^i Pr$, $R^2 = OMe$	13.04	11.73	12.20	9.92	92/08	−5.9
28, $R^1 = Ph$, $R^2 = H$	13.58	10.94	12.91	9.90	45/55	0.5
29, $R^1 = Ph$, $R^2 = OMe$	13.60	11.47	12.76	9.95	66/34	−1.6

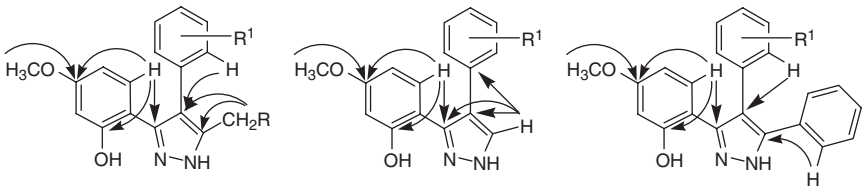


Fig. 1. Main connectivities found in the heteronuclear multiple bond coherence spectra of pyrazoles **18**–**29**.

characterized by the complex aromatic region. The resonances of the quaternary carbons, especially those of C3 (δ_C 141.6–143.5), C5 (δ_C 143.6–152.5, save for compounds **18** and **19** where they are methinic carbons and appear at δ_C 133.6, 134.8), C4 (δ_C 115.7–122.1), C2′ (δ_C 157.2–158.3) and C4′ (δ_C 162.3–163.5), have been assigned based on the connectivities found in heteronuclear multiple bond coherence (HMBC) spectra (Fig. 1). As expected, the resonances of C3 are similar in all pyrazoles **18**–**29**, but those of C4 and C5 are very sensitive to the substituents of those positions; those of C5 are shifted to high frequency values with the increase of steric hindrance of the substituents. The ^{1}H and ^{13}C NMR spectra of pyrazole **21** were also acquired in $CDCl_3$ and [D_6]DMSO (see Experimental) and the signals of the labile OH and NH protons appear as two broad singlets (δ_{NH} 10.03 and 11.64; δ_{OH} 11.36 and 13.00), those of the [D_6]DMSO solution appearing at higher frequency values. The carbon resonances of C3 and C5 have also been assigned by the connectivities found in the HMBC spectra and appear at δ_C 138.5 and 147.2 in the [D_6]DMSO solution and at δ_C 138.6 and 148.9 in the $CDCl_3$ solution. These ^{1}H and ^{13}C NMR data seem to indicate that in $CDCl_3$ and [D_6]DMSO solutions, the prototropy equilibrium is taking place, being almost oriented towards the OH···N isomers. The same conclusion could be found from the NMR data of pyrazole **22** in a $CDCl_3$ solution (see Experimental).

In the case of pyrazoles **33** and **34**, there is no prototropy and the main features of their NMR data are the resonances of the: (i) H5 and OH protons, which appear as narrow singlets at δ_H 7.90–8.08 and 9.71–9.83, respectively; (ii) C3 and C5 carbons appearing at δ_C 136.5–137.1 and 138.9–140.7, respectively; and (iii) C2′ and C4′, which appear at δ_C 157.0–157.2 and 160.8–161.1, respectively. The assignment of the quaternary carbon resonances of compounds **33** and **34** were based on the connectivities found in the HMBC spectra: C2′-OH → C1′, C2′ and C3′; H5 → C4 and C3; H6′ → C2′, C4′ and C3; H2″ → C4. The ^{1}H and ^{13}C NMR spectra of pyrazoles **33** and **34** acquired in [D_6]DMSO with some drops of TFA (see Experimental) led us to show that in these cases, the NMR spectra are not solvent-dependent, except for the resonances of the labile protons.

The ΔG^{293} values of Table 1 can be analyzed using a presence or absence matrix (1 when the substituent is present, 0 when the substituent is absent) with the following results (all values in kJ mol^{-1}): H 0.8, Me −2.8, Et −3.3, Pr −3.5, ^{i}Pr −3.6, Ph 0.6, and OMe −2.4. The six first coefficients correspond to R^1 and the last one to R^2. Excluding the phenyl group, the influence of the tautomerism, as measured by ΔG^{293}, is linearly related ($r^2 = 0.97$, slope = 2.8) to the Taft steric parameter E_s.[32] The steric effect (negative coefficients) increases the amount of tautomer OH···N. The effect of the phenyl group is not only steric like the others, but also electronic, and it slightly favours the NH···O tautomer, i.e. when R^1 = Ph, it prefers to be at position 3, a fact established for simple pyrazoles.[33] It has to be mentioned that the OMe group stabilizes the OH···N tautomer.

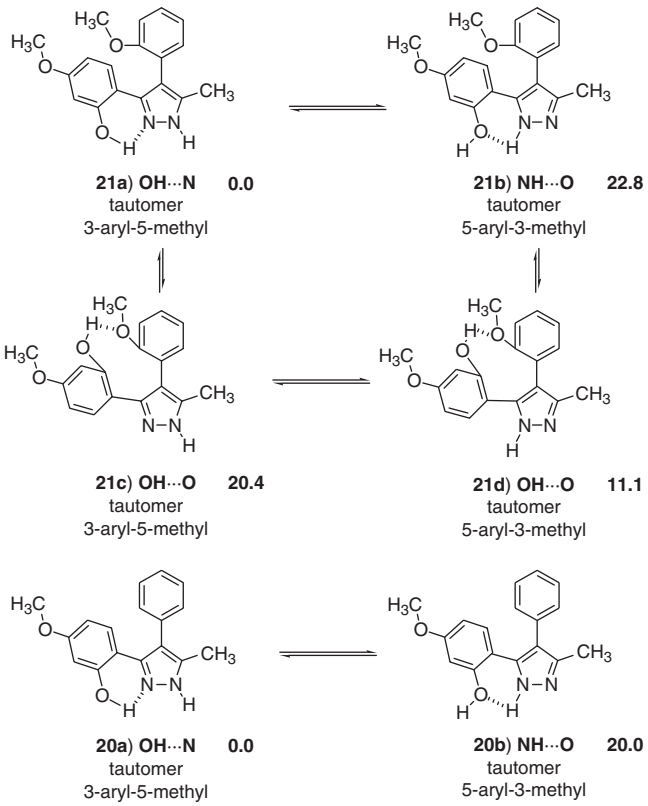
*Experimental and Theoretical NMR Study of the Tautomerism of Pyrazoles **20** and **21**: the Effect of the* ortho-*Methoxy Group at Position 2″ (R^2 = OMe)*

We have studied in detail compound **21** including the solid-state ^{13}C cross-polarization magic angle spinning (CPMAS) NMR spectrum (Table 2). A first observation is that the addition of a small amount of TFA, which was used to narrow the [D_6]DMSO ^{13}C signals by increasing the tautomerization rate, produces significant modifications of the chemical shifts, in particular, on C1′ ($\Delta\delta$ 3.6), C4′ ($\Delta\delta$ −3.3), C6′ ($\Delta\delta$ −4.5), C3 ($\Delta\delta$ 4.6), C4 ($\Delta\delta$ −4.1), and C5 ($\Delta\delta$ −5.5 ppm) as a result of a partial protonation at the pyrazole N2 position. This forbade the use of data in these conditions (see Experimental) for calculating tautomerism.

We have represented in Scheme 6 the different tautomeric forms of pyrazoles **21** and **20** with their associated differences in energy in kJ mol^{-1} (in **bold**, calculated at the B3 LYP/6–311++G** level). According to the DFT calculations, in the gas

Table 2. ^{13}C chemical shifts (δ) and absolute shieldings (σ, ppm) of pyrazole **21**

Carbon atom	δ [D$_6$]DMSO solution [ppm]	δ [D$_6$]DMSO + TFA solution [ppm]	δ Solid state [ppm]	δ OH···N **21a** [ppm]	δ NH···O **21b** [ppm]	δ 89% **21a** 11% **21b** [ppm]
C1′	110.9	107.3	110.2	110.7	112.9	111.0
C2′	157.4	157.6	157.2	160.0	153.2	159.3
C3′	101.4	102.2	98.9	97.3	102.3	97.8
C4′	159.5	162.8	160.6	160.6	158.7	160.4
C5′	104.7	106.1	108.4	107.0	100.0	106.2
C6′	127.2	131.7	129.7	126.9	129.5	127.2
C3	147.2	142.6	148.2	151.6	136.3	149.9
C4	112.5	116.6	112.0	116.5	114.3	116.3
C5	138.5	144.0	138.9	136.5	147.6	137.7
C1′	122.4	119.5	123.6	125.5	124.7	125.5
C2′	157.2	158.0	158.9	158.1	156.8	157.9
C3′	111.6	112.4	112.4	108.2	107.6	108.2
C4′	129.2	130.9	127.0	128.7	128.8	128.7
C5′	120.7	121.4	123.6	119.8	120.7	119.9
C6′	132.0	132.4	132.4	133.5	133.2	133.5
Me	9.6	10.5	7.5	10.3	15.3	10.9
OMe	55.0	55.6	54.7	53.5	53.6	53.5
OMe	55.3	55.8	56.1	53.8	53.1	53.8



Scheme 6. Tautomeric forms of pyrazoles **21** and **20** with their associated differences in energy in kJ mol^{-1}.

phase, for compound **21** there are two tautomers (**21c** and **21d**) that involve OH···O hydrogen bonds (HBs). One of them, **21d**, is the second most stable tautomer (11.1 kJ mol^{-1} above **21a**). Presumably in DMSO the OH···O HBs are not weaker than the NH···O HBs of **21b** (and all other pyrazoles). Therefore, from **20a**/**20b** (20.0 kJ mol^{-1}) to **21a**/**21b** (22.8 kJ mol^{-1}), there is a difference of -2.8 kJ mol^{-1}, comparable with -2.4 kJ mol^{-1} deduced from the analysis of Table 1 results (see above); that is, the methoxy group slightly destabilizes the NH···O tautomer (**20b**, **21b**).

We compared the experimental chemical shifts of compound **21** in [D$_6$]DMSO and in the solid state (CPMAS spectrum) with the calculated absolute shieldings of the four tautomers of Table 2. We used all the carbon atoms (including those of TMS) and also the four most sensitive to tautomerism (C2′, C6′, C3, and C5), the results being the same. In the solid state, the best fit is obtained with **21a** (OH···N) ($n = 19$, $r^2 = 0.997$, see below). In DMSO solution, the best fit is obtained with a mixture of 89% of **21a** and 11% of **21b** or **21d**, but for the reasons explained above, **21b** seems to be more appropriate ($n = 19$, $r^2 = 0.998$). The calculated δ values for tautomers **21a** and **21b** were obtained from the absolute shieldings σ through the following equation: $\delta(\text{CPMAS}) = 174.9 - 0.947\sigma$ (**21a**), $n = 19$, $r^2 = 0.977$. The 89/11 ratio was calculated from these values. Table 2 values correspond obviously in the case of CPMAS/**21a** to a slope of 1.000 and an r^2 value of 1.000 and in the case of DMSO/89% **21a**:11% **21b** mixture to a slope of 0.99 and $r^2 = 0.998$

Conclusions

The reaction of isoflavones and their thio analogues with hydrazine hydrate in hot pyridine gave new 4-aryl-3(5)-(2-hydroxyphenyl)-4-pyrazoles **18**–**29**. However, these compounds reacted in the same conditions with the less nucleophilic phenylhydrazine only when they did not have 2-substituents, giving rise to 4,5-diaryl-1-phenylpyrazoles (**33** and **34**). The present study showed that both annular tautomers of pyrazoles (**18**–**29**) exist in [D$_6$]DMSO solutions, owing to the presence of intramolecular hydrogen bonds (IMHBs) in each tautomer (OH···N and NH···O). The NMR data of pyrazoles (**18**–**29**) in [D$_6$]DMSO solutions also showed that the steric effect of a 5-substituent increased the amount of the tautomer OH···N. It is noticeable that the IMHBs are maintained in a solvent like DMSO, known to cleave HBs, thus proving how strong they are. A theoretical study with 3(5)-(2-hydroxy-4-methoxyphenyl)-4-(2-methoxyphenyl)-5(3)-methylpyrazole **21** suggests that, in solid state, this compound exist as the OH···N tautomer and in

[D_6]DMSO solutions as a mixture of both tautomers, with the OH···N being the predominant.

Experimental

Melting points were measured in a Kofler hot-stage apparatus and are uncorrected. IR (KBr) spectra were recorded on a Perkin–Elmer 16 PC spectrometer. Mass spectra were recorded on a VG Trio-2 instrument. Elemental analyses were obtained on a Carlo Erba 1106 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 spectrometer (at 300.13 and 75.47 MHz, respectively) unless stated otherwise; chemical shifts are reported in ppm (δ) using TMS as internal reference, and coupling constants (J) are given in Hz. The ^{1}H unequivocal assignments were made using two-dimensional gradient-selected COSY correlation spectroscopy (*g*COSY) experiments, while ^{13}C assignments were made with the aid of two-dimensional gradient-selected heteronuclear single quantum coherence (*g*HSQC) and *g*HMBC (delays for one-bond and long-range J C/H couplings were optimized for 145 and 7 Hz, respectively) experiments. ^{13}C CPMAS NMR spectra were recorded at 100.62 MHz on a Bruker Avance 400 spectrometer with the following conditions: 5 s of recycle delay, 1.5 ms of time contact, 90° pulse of 5 μs and acquisition time (AQ) of 33.8 ms. Column chromatography was performed with Merck silica gel 60, using 4:1 v/v toluene/ethyl acetate as eluent. Starting materials **6**–**11**, **14**, **16**, **17**, and **30**–**32** were synthesized according to known procedures.[22–31] Calculations were carried out with the *Gaussian 03* package[34] at the B3 LYP/6–311++G** levels; frequency calculations were carried out to confirm that the obtained structures corresponded to energy minima.[35,36] Absolute shieldings were calculated with the *GIAO* approximation[37] based on the B3 LYP/6–311++G** calculations.

*General Procedures for the Preparation of 7-Hydroxyisoflavones **3**–**5***

A mixture of 2,4-dihydroxydeoxybenzoin **1** (4.56 g, 20.0 mmol) or 2,4-dihydroxy-2′-methoxydeoxybenzoin **2** (5.16 g, 20.0 mmol), butyric anhydride (100 mL) or isobutyric anhydride (100 mL), and Et_3N (50 mL) was refluxed for 5 h, then poured onto crushed ice, and acidified with dilute HCl. The oily precipitate was extracted with $CHCl_3$, the solution was washed with brine, dried with $CaCl_2$, and the solvent was evaporated under reduced pressure. The residue was refluxed for 10 min in a mixture of MeOH (100 mL) and 2 M NaOH (50 mL), cooled to room temperature, and acidified with dilute HCl. The precipitate was separated by filtration, washed free of acid, and recrystallized from MeOH to afford 7-hydroxyisoflavones **3**–**5**.

*7-Hydroxy-2-propylisoflavone **3***

(3.31 g, 59%), mp 129–130°C. δ_H ($CDCl_3$) 0.91 (3H, t, J 7.4, CH_3), 1.71 (2H, sextet, J 7.4, $CH_2CH_2CH_3$), 2.53 (2H, t, J 7.4, $CH_2CH_2CH_3$), 6.77 (1, d, J 2.2, H8), 6.80 (1H, dd, J 2.2 and 8.7, H6), 7.27 (2H, dd, J 1.5 and 8.2, H2′,6′), 7.31–7.44 (3H, m, H3′,4′,5′), 8.00 (1H, d, J 8.7, H5). δ_C ($CDCl_3$) 13.7 (CH_3), 20.8 ($CH_2CH_2CH_3$), 34.4 ($CH_2CH_2CH_3$), 102.5 (C8), 115.6 (C6), 115.8 (C10), 122.9 (C3), 127.3 (C5), 127.8 (C4′), 128.5 (C3′,5′), 130.5 (C2′,6′), 133.0 (C1′), 158.0 (C9), 162.9 (C7), 167.1 (C2), 177.0 (C4). m/z 280 ($M^{+\bullet}$, 42), 265 (100), 251 (15), 237 (3). ν_{max}/cm^{-1} 3157, 1616, 1562, 1494, 1458, 1396, 1269, 1234, 1174, 1112, 1007, 852, 759, 704, 600 (Found: C 77.2, H 5.7. $C_{18}H_{16}O_3$ requires C 77.1, H 5.8%).

*7-Hydroxy-2′-methoxy-2-propylflavone **4***

(4.03 g, 65%), mp 153–154°C. δ_H ($CDCl_3$) 0.88 (3H, t, J 7.4, CH_3), 1.68 (2H, sextet, J 7.4, $CH_2CH_2CH_3$), 2.36–2.53 (2H, m, $CH_2CH_2CH_3$), 3.70 (3H, s, 2′-OCH_3), 6.76–6.80 (2H, m, H6 and H8), 6.91 (1H, d, J 8.0, H3′), 6.99 (1H, dt, J 0.9 and 7.4, H5′), 7.15 (1H, dd, J 1.8 and 7.4, H6′), 7.32 (1H, ddd, J 1.8, 7.4 and 8.0, H4′), 7.98 (1H, d, J 9.2, H5), 9.74 (1H, br s, 7-OH). δ_C ($CDCl_3$) 13.7 (CH_3), 20.4 ($CH_2CH_2CH_3$), 34.5 ($CH_2CH_2CH_3$), 55.3 (2′-OCH_3), 102.4 (C8), 110.9 (C3′), 115.4 (C6), 115.7 (C10), 119.4 (C3), 120.6 (C5′), 121.9 (C1′), 127.2 (C5), 129.7 (C4′), 131.9 (C6′), 157.4 (C2′), 158.1 (C9), 162.9 (C7), 167.4 (C2), 177.8 (C4). m/z 310 ($M^{+\bullet}$, 11), 279 (100), 267 (48), 250 (23). ν_{max}/cm^{-1} 3276, 1625, 1590, 1570, 1495, 1461, 1394, 1243, 1218, 1163, 1117, 1007, 853, 754, 704, 592 (Found: C 73.6, H 5.9. $C_{19}H_{18}O_4$ requires C 73.5, H 5.8%).

*7-Hydroxy-2-isopropyl-2′-methoxyisoflavone **5***

(4.16 g, 67%), mp 275–276°C. δ_H (500 MHz, [D_6]DMSO) 1.149 (3H, d, J 6.9, CH_3), 1.152 (3H, d, J 6.9, CH_3), 2.62 (1H, septet, J 6.9, $CH(CH_3)_2$), 3.70 (3H, s, 2′-OCH_3), 6.87 (1H, d, J 2.2, H8), 6.91 (1H, dd, J 2.2 and 8.7, H6), 7.00 (1H, t, J 7.5, H5′), 7.08 (1H, d, J 8.2, H3′), 7.10 (1H, dd, J 1.8 and 7.5, H6′), 7.37 (1H, ddd, J 1.8, 7.5 and 8.2, H4′), 7.85 (1H, d, J 8.7, H5). δ_C (125 MHz, [D_6]DMSO) 19.3 and 19.8 (2 × CH_3), 31.0 ($CH(CH_3)_2$), 55.3 (2′-OCH_3), 102.0 (C8), 111.2 (C3′), 114.6 (C6), 115.6 (C10), 117.3 (C3), 120.3 (C5′), 122.0 (C1′), 127.0 (C5), 129.4 (C4′), 131.7 (C6′), 157.1 (C2′), 157.3 (C9), 162.5 (C7), 168.6 (C2), 175.2 (C4). m/z 310 ($M^{+\bullet}$, 6), 295 (3), 279 (100), 267 (44). ν_{max}/cm^{-1} 3125, 1624, 1566, 1494, 1459, 1402, 1375, 1284, 1247, 1170, 1111, 989, 852, 761 (Found: C 73.5, H 5.8. $C_{19}H_{18}O_4$ requires C 73.5, H 5.8%).

*General Procedures for the Preparation of 7-Methoxyisoflavones **12**, **13**, and **15***

A mixture of the particular 7-hydroxyisoflavone (**3**–**5**, 2.8 or 3.1 g, 10.0 mmol), CH_3I (1.0 mL, 20.0 mmol), anhydrous acetone (150 mL), and K_2CO_3 (5.0 g) was refluxed for 6 h, and then the inorganic salts were filtered off. The solvent was evaporated under reduced pressure and the residue was crystallized from methanol to obtain 7-methoxyisoflavones **12**, **13**, and **15**.

*7-Methoxy-2-propylisoflavone **12***

(4.18 g, 71%), mp 97–98°C. δ_H ($CDCl_3$) 0.91 (3H, t, J 7.4, CH_3), 1.69–1.76 (2H, m, $CH_2CH_2CH_3$), 2.49–2.54 (2H, m, $CH_2CH_2CH_3$), 3.92 (3H, s, 7-OCH_3), 6.86 (1H, d, J 2.3, H8), 6.96 (1H, dd, J 2.3 and 8.9, H6), 7.23–7.27 (2H, m, H2′,6′), 7.33–7.46 (3H, m, H3′,4′,5′), 8.03 (1H, d, J 8.9, H5). δ_C ($CDCl_3$) 13.7 (CH_3), 20.8 ($CH_2CH_2CH_3$), 34.2 ($CH_2CH_2CH_3$), 57.7 (OCH_3), 99.8 (C8), 114.1 (C6), 117.3 (C10), 123.4 (C3), 127.6 (C5 and C4′), 128.3 (C3′,5′), 130.4 (C2′,6′), 133.2 (C1′), 157.6 (C9), 163.8 (C7), 165.8 (C2), 176.6 (C4). m/z 294 ($M^{+\bullet}$, 40), 279 (100), 265 (43), 251 (5). ν_{max}/cm^{-1} 1628, 1601, 1568, 1502, 1439, 1389, 1361, 1266, 1206, 1119, 1021, 1066, 947, 838, 756, 705, 601 (Found: C 77.6, H 6.1. $C_{19}H_{18}O_3$ requires C 77.5, H 6.2%).

*7,2′-Dimethoxy-2-propylisoflavone **13***

(4.80 g, 74%), mp 117–118°C. δ_H ($CDCl_3$) 0.89 (3H, t, J 7.4, CH_3), 1.70 (2H, septet, J 7.4, $CH_2CH_2CH_3$), 2.35–2.52 (2H, m, $CH_2CH_2CH_3$), 3.75 (3H, s, 2′-OCH_3), 3.91 (3H, s, 7-OCH_3), 6.85 (1H, d, J 2.4, H8), 6.94 (1H, dd, J 2.4 and 9.0, H6), 6.95–7.04 (2H, m, H3′ and H5′), 7.14 (1H, dd, J 1.8 and 7.4, H6′),

7.36 (1H, ddd, *J* 1.8, 7.5 and 8.2, H4′), 8.13 (1H, d, *J* 9.0, H5). δ_C ($CDCl_3$) 13.7 (CH_3), 20.4 ($CH_2CH_2CH_3$), 34.4 ($CH_2CH_2CH_3$), 55.5 (2′-OCH_3), 55.7 (7-OCH_3), 99.8 (C8), 111.0 (C3′), 113.9 (C6), 117.3 (C10), 119.8 (C3), 120.5 (C5′), 122.2 (C1′), 127.6 (C5), 129.4 (C4′), 131.9 (C6′), 157.4 (C2′), 157.7 (C9), 163.6 (C7), 166.0 (C2), 176.3 (C4). *m/z* 324 ($M^{+\bullet}$, 10), 293 (100), 281 (45), 264 (14). ν_{max}/cm^{-1} 1633, 1609, 1573, 1496, 1441, 1388, 1243, 1206, 1164, 1110, 1022, 846, 762 (Found: C 74.0, H 6.1. $C_{20}H_{20}O_4$ requires C 74.1, H 6.2%).

7,2′-Dimethoxy-2-isopropylisoflavone ***15***

(5.44 g, 84%), mp 173–174°C. δ_H (500 MHz, [D_6]DMSO) 1.179 (3H, d, *J* 6.8, CH_3), 1.182 (3H, d, *J* 6.8, CH_3), 2.66 (1H, septet, *J* 6.8, $CH(CH_3)_2$), 3.70 (3H, s, 2′-OCH_3), 3.92 (3H, s, 7-OCH_3), 7.01 (1H, dt, *J* 1.0 and 7.5, H5′), 7.04 (1H, dd, *J* 2.4 and 8.8, H6), 7.09 (1H, dd, *J* 1.0 and 7.9, H3′), 7.12 (1H, dd, *J* 1.8 and 7.5, H6′), 7.16 (1H, d, *J* 2.4, H8), 7.38 (1H, ddd, *J* 1.8, 7.5 and 7.9, H4′), 7.91 (1H, d, *J* 8.8, H5). δ_C (125 MHz, [D_6]DMSO) 19.3 and 19.7 (2 × CH_3), 31.0 ($CH(CH_3)_2$), 55.3 (2′-OCH_3), 56.1 (7-OCH_3), 100.2 (C8), 111.2 (C3′), 114.6 (C6), 116.5 (C10), 117.6 (C3), 120.3 (C5′), 122.0 (C1′), 126.6 (C5), 129.4 (C4′), 131.7 (C6′), 157.1 (C2′), 157.3 (C9), 163.7 (C7), 168.9 (C2), 175.1 (C4). *m/z* 324 ($M^{+\bullet}$, 4), 309 (3), 293 (100), 281 (53). ν_{max}/cm^{-1} 1633, 1609, 1494, 1440, 1278, 1201, 1167, 1122, 1028, 858, 790, 763 (Found: C 74.2, H 6.3. $C_{20}H_{20}O_4$ requires C 74.1, H 6.2%).

General Procedure for the Treatment of Isoflavones ***6–17*** *and 4-Thioisoflavones* ***30–32*** *with Hydrazine Hydrate*

A mixture of the appropriate isoflavone (**6–17** or **30–32**, 5.0 mmol), hydrazine hydrate (50.0 mmol), and pyridine (40 mL) was refluxed for 4–16 h, and poured into H_2O. The precipitate was separated by filtration, washed with water, dried, and recrystallized from methanol to afford pyrazoles **18–19**.

3(5)-(2-Hydroxy-4-methoxyphenyl)-4-phenylpyrazole ***18***

(985 mg, 74%; reaction time 4 h), mp 187–188°C. δ_H ([D_6]DMSO + drops TFA) 3.69 (3H, s, OCH_3), 6.40 (1H, dd, *J* 2.4 and 8.6, H5′), 6.54 (1H, d, *J* 2.4, H3′), 6.73 (1H, d, *J* 8.6, H6′), 7.18–7.30 (5H, m, H2″,3″,4″,5″,6″), 8.44 (1H, s, H5). δ_C ([D_6]DMSO drops TFA) 55.8 (4′-OCH_3), 102.6 (C3′), 106.4 (C5′), 107.4 (C1′), 122.1 (C4), 128.5 (C3″,4″,5″), 129.6 (C2″,6″), 131.8 (C1″), 132.8 (C6′), 133.6 (C5), 141.6 (C3), 158.1 (C2′), 163.3 (C4′). *m/z* 266 ($M^{+\bullet}$, 100), 235 (10), 223 (10), 161 (12). ν_{max}/cm^{-1} 3434, 1617, 1597, 1532, 1496, 1479, 1431, 1386, 1322, 1273, 1173, 1105, 1065, 1035, 952, 861, 823, 765, 702, 675, 564 (Found: C 72.3, H 5.3, N 10.6. $C_{16}H_{14}N_2O_2$ requires C 72.2, H 5.3, N 10.5%).

3(5)-(2-Hydroxy-4-methoxyphenyl)-4-(2-methoxyphenyl)pyrazole ***19***

(1.16 g, 78%; reaction time 4 h), mp 143–144°C. δ_H ([D_6]DMSO + drops TFA) 3.67 and 3.76 (2 × 3H, 2s, 2 × OCH_3), 6.42 (1H, dd, *J* 2.4 and 8.7, H5′), 6.63 (1H, d, *J* 2.4, H3′), 6.93 (1H, dt, *J* 0.8 and 7.5, H5″), 7.04 (1H, d, *J* 8.7, H6′), 7.06 (1H, d, *J* 7.9, H3″), 7.19 (1H, dd, *J* 1.7 and 7.6, H6″), 7.34 (1H, ddd, *J* 1.7, 7.5 and 7.9, H4″), 8.41 (1H, s, H5). δ_C ([D_6]DMSO + drops TFA) 55.8 and 56.0 (2 × OCH_3), 102.6 (C3′), 106.4 (C5′), 108.0 (C1′), 112.5 (C3″), 118.2 (C4), 120.3 (C1″), 121.5 (C5″), 130.6 (C4″), 131.5 (C6″), 132.1 (C6′), 134.8 (C5), 142.7 (C3), 157.7 and 157.8 (C2′ and C2″), 163.2 (C4′). *m/z* 296 ($M^{+\bullet}$, 100), 281 (4), 265 (10), 253 (7). ν_{max}/cm^{-1} 3247, 1627, 1581, 1500, 1459, 1427, 1346, 1251, 1199, 1162, 1112, 1022, 950, 836, 809, 755, 547 (Found: C 68.8, H 5.5, N 9.5. $C_{17}H_{16}N_2O_3$ requires C 68.9, H 5.4, N 9.5%).

3(5)-(2-Hydroxy-4-methoxyphenyl)-5(3)-methyl-4-phenylpyrazole ***20***

(1.14 g, 81% from **8**, and 1.18 g, 84% from **30**, reaction time 6 h), mp 182–183°C. δ_H ([D_6]DMSO + drops TFA) 2.28 (3H, s, CH_3), 3.63 (3H, s, 4′-OCH_3), 6.27 (1H, dd, *J* 2.4 and 8.6, H5′), 6.49 (1H, d, *J* 2.4, H3′), 6.87 (1H, d, *J* 8.6, H6′), 7.14 (2H, dd, *J* 1.7 and 7.9, H2″,6″), 7.21–7.31 (3H, m, H3″,4″,5″). δ_C ([D_6]DMSO + drops TFA) 10.8 (CH_3), 55.9 (4′-OCH_3), 102.7 (C3′), 106.6 (C5′), 107.2 (C1′), 120.7 (C4), 128.9 (C4″), 129.9 (C3″,5″), 130.6 (C2″,6″), 131.6 (C1″), 132.9 (C6′), 142.6 (C3), 143.6 (C5), 158.3 (C2′), 163.5 (C4′). *m/z* 280 ($M^{+\bullet}$, 100), 265 (3), 251 (5), 237 (15). ν_{max}/cm^{-1} 3264, 1627, 1573, 1515, 1432, 1332, 1251, 1164, 1043, 950, 856, 800, 777, 698, 630, 601 (Found: C 73.0, H 5.7, N 9.9. $C_{17}H_{16}N_2O_2$ requires C 72.8, H 5.8, N 10.0%).

3(5)-(2-Hydroxy-4-methoxyphenyl)-4-(2-methoxyphenyl)-5(3)-methylpyrazole ***21***

(1.33 g, 86% from **9**, and 1.27 g, 82% from **31**, reaction time 6 h), mp 177–178°C. δ_H ([D_6]DMSO + drops TFA) 2.17 (3H, s, CH_3), 3.58 and 3.64 (2 × 3H, 2s, 2 × OCH_3), 6.24 (1H, dd, *J* 2.5 and 8.7, H5′), 6.50 (1H, d, *J* 2.5, H3′), 6.82 (1H, d, *J* 8.7, H6′), 6.88 (1H, dt, *J* 0.9 and 7.4, H5″), 6.99–7.03 (2H, m, H3″ and H6″), 7.30 (1H, ddd, *J* 1.7, 7.4 and 8.4, H4″). δ_C ([D_6]DMSO + drops TFA) 10.5 (CH_3), 55.6 and 55.8 (2 × OCH_3), 102.2 (C3′), 106.1 (C5′), 107.3 (C1′), 112.4 (C3″), 116.6 (C4), 119.5 (C1″), 121.4 (C5″), 130.9 (C4″), 131.7 (C6′), 132.4 (C6″), 142.6 (C3), 144.0 (C5), 157.6 (C2′), 158.0 (C2″), 162.8 (C4′). *m/z* 310 ($M^{+\bullet}$, 100), 296 (16), 279 (23), 251 (8). ν_{max}/cm^{-1} 3334, 1625, 1589, 1523, 1438, 1374, 1270, 1205, 1168, 1122, 1093, 1014, 848, 759, 590 (Found: C 69.6, H 5.9, N 9.1. $C_{18}H_{18}N_2O_3$ requires C 69.7, H 5.8, N 9.0%).

δ_H ([D_6]DMSO) 2.05 (3H, s, CH_3), 3.63 and 3.66 (2 × 3H, 2s, 2 × OCH_3), 6.14 (1 H, dd, *J* 2.6 and 8.7, H5′), 6.41 (1H, d, *J* 2.6, H3′), 6.81 (1H, d, *J* 8.7, H6′), 6.99 (1H, t, *J* 7.4, H5″), 7.05 (2H, d, *J* 7.4, H3″ and H6″), 7.38 (1H, t, *J* 7.4, H4″), 11.64 (1H, br s, N*H*), 13.00 (1H, br s, 2′-O*H*). δ_C ([D_6]DMSO) 9.6 (CH_3), 55.0 and 55.3 (2 × OCH_3), 101.4 (C3′), 104.7 (C5′), 110.9 (C1′), 111.6 (C3″), 112.5 (C4), 120.7 (C5″), 122.4 (C1″), 127.2 (C6′), 129.2 (C4″), 132.0 (C6″), 138.5 (C5), 147.2 (C3), 157.2 (C2″), 157.4 (C2′), 159.5 (C4′).

δ_H ($CDCl_3$) 2.13 (3H, s, CH_3), 3.67 (3H, s, 2″-OCH_3), 3.74 (3H, s, 4′-OCH_3), 6.16 (1H, dd, *J* 2.6 and 8.8, H5′), 6.55 (1H, d, *J* 2.6, H3′), 6.91 (1H, d, *J* 8.8, H6′), 6.97–7.03 (2H, m, H3″ and H5″), 7.16 (1H, dd, *J* 1.7 and 7.5, H6″), 7.38 (1H, t, *J* 7.5, H4″), 10.03 (1H, br s, N*H*), 11.36 (1H, br s, 2′-O*H*). δ_C ($CDCl_3$) 9.8 (CH_3), 55.1 and 55.4 (2 × OCH_3), 101.4 (C3′), 105.3 (C5′), 110.8 (C1′), 111.2 (C3″), 113.1 (C4), 120.8 (C5″), 122.2 (C1″), 127.8 (C6′), 129.2 (C4″), 132.4 (C6″), 138.6 (C5), 148.9 (C3), 157.6 (C2′ and C2″), 159.9 (C4′).

5(3)-Ethyl-3(5)-(2-hydroxy-4-methoxyphenyl)-4-phenylpyrazole ***22***

(1.28 g, 87%, reaction time 6 h), mp 165–166°C. δ_H ([D_6]DMSO + drops TFA) 1.13 (3H, t, *J* 7.6, CH_3), 2.71 (2H, q, *J* 7.6, CH_2), 3.66 (3H, s, 4′-OCH_3), 6.30 (1H, dd, *J* 2.3 and 8.6, H5′), 6.50 (1H, d, *J* 2.3, H3′), 6.89 (1H, d, *J* 8.6, H6′), 7.17 (2H, dd, *J* 1.5 and 7.8, H2″,6″), 7.26–7.36 (3H, m, H3″,4″,5″).

δ_C ([D$_6$]DMSO + drops TFA) 13.2 (*C*H$_3$), 18.4 (*C*H$_2$), 55.6 (4′-O*C*H$_3$), 102.3 (C3′), 106.1 (C5′), 106.8 (C1′), 119.7 (C4), 128.6 (C4″), 129.5 (C3″,5″), 130.4 (C2″,6″), 131.2 (C1″), 132.5 (C6′), 142.4 (C3), 148.2 (C5), 157.8 (C2′), 162.9 (C4′). *m/z* 294 ($M^{+\bullet}$, 100), 279 (3), 265 (5), 237 (10). ν_{max}/cm^{-1} 3266, 1625, 1587, 1519, 1438, 1363, 1255, 1203, 1170, 1128, 1095, 1037, 952, 817, 773, 701, 588 (Found: C 73.5, H 6.2, N 9.6. $C_{18}H_{18}N_2O_2$ requires C 73. 5, H 6.2, N 9.5%).

δ_H ($CDCl_3$) 1.19 (3H, t, *J* 7.6, CH_3), 2.62 (2H, q, *J* 7.6, CH_2), 3.74 (3H, s, 4′-OCH_3), 6.16 (1H, dd, *J* 2.6 and 8.8, H5′), 6.56 (1H, d, *J* 2.6, H3′), 6.90 (1H, d, *J* 8.8, H6′), 7.27 (2H, dd, *J* 1.9 and 7.3, H2″,6″), 7.37–7.44 (3H, m, H3″,4″,5″). δ_C ($CDCl_3$) 13.4 (CH_3), 17.7 (CH_2), 55.1 (4′-O*C*H$_3$), 101.6 (C3′), 105.3 (C5′), 110.1 (C1′), 116.7 (C4), 127.3 (C4″), 128.6 (C6′), 128.7 (C3″,5″), 130.5 (C2″,6″), 133.6 (C1″), 143.6 (C5), 148.5 (C3), 157.7 (C2′), 160.1 (C4′).

5(3)-Ethyl-3(5)-(2-hydroxy-4-methoxyphenyl)-4-(2-methoxyphenyl)pyrazole ***23***

(1.18 g, 69%, reaction time 6 h), mp 98–99°C. δ_H ([D$_6$]DMSO4 + drops TFA) 1.06 (3H, t, *J* 7.6, CH_3), 2.52 (2H, q, *J* 7.6, CH_2), 3.52 and 3.55 (2 × 3H, 2s, 2 × OCH_3), 6.22 (1H, dd, *J* 2.4 and 8.7, H5′), 6.50 (1H, d, *J* 2.4, H3′), 6.81 (1H, d, *J* 8.7, H6′), 6.87 (1H, t, *J* 7.6, H5″), 6.99 (1H, d, *J* 8.4, H3″), 7.01 (1H, dd, *J* 1.7 and 7.6, H6″), 7.30 (1H, ddd, *J* 1.7, 7.6 and 8.4, H4″). δ_C ([D$_6$]DMSO + drops TFA) 13.0 (CH_3), 18.8 (CH_2), 55.7 and 55.9 (2 × OCH_3), 102.3 (C3′), 106.2 (C5′), 107.4 (C1′), 112.3 (C3″), 116.2 (C4), 119.7 (C1″), 121.5 (C5″), 131.0 (C4″), 131.8 (C6′), 132.6 (C6″), 142.8 (C3), 149.1 (C5), 157.7 (C2′), 158.2 (C2″), 162.9 (C4′). *m/z* 324 ($M^{+\bullet}$, 100), 309 (3), 295 (25), 267 (6). ν_{max}/cm^{-1} 3330, 1623, 1596, 1517, 1457, 1436, 1369, 1319, 1243, 1199, 1162, 1124, 1027, 950, 840, 755, 588 (Found: C 70.3, H 6.2, N 8.7. $C_{19}H_{20}N_2O_3$ requires C 70.4, H 6.2, N 8.6%).

3(5)-(2-Hydroxy-4-methoxyphenyl)-4-phenyl-5(3)-propylpyrazole ***24***

(1.26 g, 82%, reaction time 12 h), mp 153–154°C. δ_H ([D$_6$]DMSO + drops TFA) 0.66 (3H, t, *J* 7.5, C*H*$_3$), 1.41 (2H, sextet, *J* 7.5, $CH_2CH_2CH_3$), 2.53 (2H, t, *J* 7.5, $CH_2CH_2CH_3$), 3.64 (3H, s, 4′-OCH_3), 6.16 (1H, dd, *J* 2.5 and 8.6, H5′), 6.38 (1H, d, *J* 2.5, H3′), 6.76 (1H, d, *J* 8.6, H6′), 7.04 (2H, dd, *J* 1.8 and 7.6, H2″,6″), 6.95–7.29 (3H, m, H3″,4″,5″). δ_C ([D$_6$]DMSO + drops TFA) 14.0 (CH_3), 22.3 ($CH_2CH_2CH_3$), 26.9 ($CH_2CH_2CH_3$), 55.8 (4′-OCH_3), 102.5 (C3′), 106.3 (C5′), 107.0 (C1′), 120.4 (C4), 128.8 (C4″), 129.7 (C3″,5″), 130.6 (C2″,6″), 131.5 (C1″), 132.7 (C6′), 142.5 (C3), 147.1 (C5), 158.1 (C2′), 163.1 (C4′). *m/z* 308 ($M^{+\bullet}$, 100), 293 (11), 279 (21), 265 (6). ν_{max}/cm^{-1} 3300, 1627, 1586, 1519, 1375, 1317, 1253, 1203, 1162, 1132, 1027, 950, 833, 755, 702, 588 (Found: C 74.1, H 6.5, N 9.2. $C_{19}H_{20}N_2O_2$ requires C 74.0, H 6.5, N 9.1%).

3(5)-(2-Hydroxy-4-methoxyphenyl)-4-(2-methoxyphenyl)-5(3)-propylpyrazole ***25***

(1.25 g, 74%, reaction time 16 h), mp 135–136°C. δ_H ([D$_6$]DMSO + drops TFA) 0.76 (3H, t, *J* 7.4, CH_3), 1.48 (2H, sextet, *J* 7.4, $CH_2CH_2CH_3$), 2.51 (2H, t, *J* 7.4, $CH_2CH_2CH_3$), 3.60 (3H, s, 2″-OCH_3), 3.65 (3H, s, 4′-OCH_3), 6.25 (1H, dd, *J* 2.4 and 8.7, H5′), 6.51 (1H, d, *J* 2.4, H3′), 6.83 (1H, d, *J* 8.7, H6′), 6.91 (1H, dd, *J* 7.2 and 7.6, H5″), 7.01–7.05 (2H, m, H3″ and H6″), 7.33 (1H, ddd, *J* 1.6, 7.6 and 7.9, H4″). δ_C ([D$_6$]DMSO + drops TFA) 13.8 (CH_3), 21.6 ($CH_2CH_2CH_3$), 26.8 ($CH_2CH_2CH_3$), 55.5 and 55.7 (2 × OCH_3), 102.1 (C3′), 105.8 (C5′), 107.2 (C1′), 112.1 (C3″), 115.2 (C4), 119.6 (C1″), 121.3 (C5″), 130.8 (C4″), 131.6 (C6′), 132.6 (C6″), 142.7 (C3), 152.5 (C5), 157.5 (C2′), 158.1 (C2″), 162.5 (C4′). *m/z* 338 ($M^{+\bullet}$, 100), 323 (16), 307 (12), 295 (20). ν_{max}/cm^{-1} 3300, 1632, 1590, 1524, 1436, 1382, 1319, 1256, 1203, 1168, 1030, 954, 842, 810, 748, 591 (Found: C 70.9, H 6.6, N 8.4. $C_{20}H_{22}N_2O_3$ requires C 71.0, H 6.6, N 8.3%).

3(5)-(2-Hydroxy-4-methoxyphenyl)-5(3)-isopropyl-4-phenylpyrazole ***26***

(1.14 g, 74%, reaction time 12 h), mp 176–177°C. δ_H ([D$_6$]DMSO + drops TFA) 1.22 (6H, d, *J* 6.9, C*H*$_3$), 3.07 (1H, septet, *J* 6.9, CH), 3.66 (3H, s, 4′-OCH_3), 6.29 (1H, dd, *J* 1.8 and 8.6, H5′), 6.51 (1H, d, *J* 1.8, H3′), 6.88 (1H, d, *J* 8.6, H6′), 7.18 (2 H, d, *J* 6.5, H2″,6″), 7.30–7.36 (3H, m, H3″,4″,5″). δ_C ([D$_6$]DMSO + drops TFA) 21.9 (CH_3), 25.5 (CH), 55.5 (4′-OCH_3), 102.1 (C3′), 105.9 (C5′), 106.9 (C1′), 119.0 (C4), 128.5 (C4″), 129.3 (C3″,5″), 130.3 (C2″,6″), 131.3 (C1″), 132.2 (C6′), 142.5 (C3), 151.8 (C5), 157.7 (C2′), 162.5 (C4′). *m/z* 308 ($M^{+\bullet}$, 100), 293 (9), 279 (7), 265 (12). ν_{max}/cm^{-1} 3386, 1629, 1586, 1522, 1439, 1367, 1318, 1257, 1202, 1167, 1124, 1034, 952, 830, 774, 699, 589 (Found: C 73.9, H 6.6, N 9.0. $C_{19}H_{20}N_2O_2$ requires C 74.0, H 6.5, N 9.1%).

3(5)-(2-Hydroxy-4-methoxyphenyl)-5(3)-isopropyl-4-(2-methoxyphenyl)pyrazole ***27***

(1.30 mg, 77%, reaction time 16 h), mp 178–179°C. δ_H ([D$_6$]DMSO + drops TFA) 1.17 (6H, d, *J* 7.0, CH_3), 2.86 (1H, septet, *J* 7.0, CH), 3.62 (3H, s, 2″-OCH_3), 3.66 (3H, s, 4′-OCH_3), 6.25 (1H, dd, *J* 2.2 and 8.7, H5′), 6.51 (1H, d, *J* 2.3, H3′), 6.82 (1H, d, *J* 8.7, H6′), 6.90 (1H, dd, *J* 7.4 and 7.6, H5″), 7.02–7.04 (2H, m, H3″ and H6″), 7.33 (1 H, ddd, *J* 1.5, 7.6 and 7.8, H4″). δ_C ([D$_6$]DMSO + drops TFA) 21.6 (CH_3), 25.9 (CH), 55.5 and 55.7 (2 × OCH_3), 102.0 (C3′), 105.9 (C5′), 107.2 (C1′), 112.2 (C3″), 116.1 (C4), 119.5 (C1″), 121.3 (C5″), 131.8 (C4″), 131.4 (C6′), 132.3 (C6″), 142.5 (C3), 147.3 (C5), 157.4 (C2′), 157.9 (C2″), 162.5 (C4′). *m/z* 338 ($M^{+\bullet}$, 100), 323 (11), 307 (8), 295 (40). ν_{max}/cm^{-1} 3380, 1636, 1589, 1527, 1464, 1437, 1386, 1294, 1242, 1160, 1137, 1031, 973, 843, 769, 603 (Found: C 71.1, H 6.5, N 8.2. $C_{20}H_{22}N_2O_3$ requires C 71.0, H 6.6, N 8.3%).

4,5(3)-Diphenyl-3(5)-(2-hydroxy-4-methoxyphenyl)pyrazole ***28***

(1.47 g, 86% from **16**, and 1.35 g, 79% from **32**, reaction time 16 h), mp 213–214°C. δ_H ([D$_6$]DMSO + drops TFA) 3.56 (3H, s, 4′-OCH_3), 6.18 (1H, dd, *J* 2.4 and 8.6, H5′), 6.41 (1H, d, *J* 2.4, H3′), 6.81 (1H, d, *J* 8.6, H6′), 6.99–7.03 (2H, m, H2″,6″), 7.13–7.15 (3H, m, H3″,4″,5″), 7.22–7.28 (5H, m, Ph). δ_C ([D$_6$]DMSO + drops TFA) 55.6 (4′-OCH_3), 102.3 (C3′), 105.9 (C5′), 108.1 (C1′), 119.2 (C4), 128.4 (C1″), 129.1 (C4″), 129.2, 129.4 and 129.5 (C3″,5″, and 5-Ph), 130.2 (C4‴), 131.0 (C2″,6″), 132.1 and 132.2 (C6′ and C1‴), 143.5 (C3), 144.8 (C5), 158.0 (C2′), 162.3 (C4′). *m/z* 342 ($M^{+\bullet}$, 100), 313 (5), 237 (6), 165 (13). ν_{max}/cm^{-1} 3381, 1631, 1577, 1524, 1446, 1386, 1318, 1284, 1260, 1202, 1163, 1035, 953, 832, 771, 598 (Found: C 77.3, H 5.3, N 8.1. $C_{22}H_{18}N_2O_2$ requires C 77.2, H 5.3, N 8.2%).

3(5)-(2-Hydroxy-4-methoxyphenyl)-4-(2-methoxyphenyl)-5(3)-phenylpyrazole ***29***

(1.32 g, 71%, reaction time 16 h), mp 179–180°C. δ_H ([D$_6$]DMSO + drops TFA) 3.30 (3H, s, 2″-OCH_3), 3.54 (3H, s, 4′-OCH_3), 6.14 (1H, dd, *J* 1.7 and 8.6, H5′), 6.40 (1H, d, *J* 1.7, H3′), 6.81–6.88 (2H, m, H6′ and H5″), 6.84 (1H, d, *J* 8.4, H3″),

6.91 (1H, dd, *J* 1.3 and 7.3, H6″), 7.21–7.36 (6H, m, H4″ and 5-Ph). δ_C ([D$_6$]DMSO + drops TFA) 55.66 and 55.73 (2 × OCH$_3$), 102.3 (C3′), 106.0 (C5′), 108.1 (C1′), 112.5 (C3″), 115.7 (C4), 120.6 (C1″), 121.7 (C5″), 128.6, 129.0, 129.5, and 130.5 (Ph5), 131.0 (C4″), 131.5 (C6′), 132.8 (C6″), 144.3 (C3), 145.1 (C5), 157.9 (C2′), 158.5 (C2″), 162.5 (C4′). *m*/*z* 372 ($M^{+\bullet}$, 15), 358 (14), 340 (6), 327 (100). ν_{max}/cm^{-1} 3386, 1630, 1584, 1522, 1484, 1462, 1435, 1365, 1283, 1158, 1123, 1030, 971, 862, 754, 689, 624 (Found: C 74.1, H 5.5, N 7.6. $C_{23}H_{20}N_2O_3$ requires C 74.2, H 5.4, N 7.5%).

*General Procedure for the Reaction of Isoflavones **6**–**9**, **11**, **14**, and **16** with Phenylhydrazine*

A mixture of the appropriate starting material (**6**–**9**, **11**, **14**, and **16**, 5.0 mmol), phenylhydrazine (50.0 mmol) and pyridine (40 mL) was refluxed for 48 h and then poured into H_2O. The precipitate was separated by filtration, washed with H_2O, dried, and recrystallized from MeOH to obtain pyrazoles **33** and **34**. Isoflavones **8**, **9**, **11**, **14**, and **16** were recovered unchanged.

*1,4-Diphenyl-3(5)-(2-hydroxy-4-methoxyphenyl)pyrazole **33***

(1.32 g, 77%), mp 176–177°C. δ_H ([D$_6$]DMSO) 3.70 (3H, s, 4′-OCH$_3$), 6.38 (1H, br d, *J* 8.3, H5′), 6.43 (1H, br s, H3′), 6.92 (1H, d, *J* 8.3, H6′), 7.13–7.34 (10H, m, 1-Ph and 4-Ph), 8.08 (1H, s, H5), 9.83 (1H, s, 2′-OH). δ_C ([D$_6$]DMSO) 55.0 (4′-OCH$_3$), 101.3 (C3′), 105.2 (C5′), 109.9 (C1′), 122.1 (C4), 123.9 (C2‴,6‴), 126.1 (C4‴), 126.5 (C3‴,5‴), 127.0 (C4″), 128.5 and 128.7 (C2″,3″,5″,6″), 132.6 (C6′), 133.0 (C1″), 136.4 (C3), 138.9 (C5), 140.3 (C1‴), 157.2 (C2′), 161.1 (C4′). *m*/*z* 342 ($M^{+\bullet}$, 100), 327 (5), 251 (6), 77 (42). ν_{max}/cm^{-1} 3343, 1629, 1594, 1573, 1517, 1495, 1430, 1372, 1296, 1147, 1032, 954, 768, 697, 658 (Found: C 77.3, H 5.3, N 8.3. $C_{22}H_{18}N_2O_2$ requires C 77.2, H 5.3, N 8.2%).

δ_H ([D$_6$]DMSO + drops TFA) 3.68 (3H, s, 4′-OC*H*$_3$), 6.36 (1H, br d, *J* 8.4, H5′), 6.44 (1H, br s, H3′), 6.91 (1H, d, *J* 8.4, H6′), 7.09–7.32 (10H, m, 1-Ph and 4-Ph), 8.04 (1H, s, H5). δ_C ([D$_6$]DMSO + drops TFA) 55.2 (4′-OCH$_3$), 101.8 (C3′), 105.6 (C5′), 110.3 (C1′), 122.7 (C4), 124.4 (C2‴,6‴), 126.5 (C4″), 127.0 (C3‴,5‴), 127.4 (C4″), 128.8 and 129.1 (C2″,3″,5″,6″), 133.0 (C6′), 133.5 (C1′), 137.0 (C3), 139.2 (C5), 140.8 (C1‴), 157.7 (C2′), 161.6 (C4′).

*3(5)-(2-Hydroxy-4-methoxyphenyl)-4-(2-methoxyphenyl)-1-phenylpyrazole **34***

(465 mg, 25%), mp 214–215°C. δ_H ([D$_6$]DMSO) 3.66 (3H, s, 2″-OCH$_3$), 3.70 (3H, s, 4′-OCH$_3$), 6.31 (1H, br d, *J* 8.4, H5′), 6.35 (1H, s, H3′), 6.75 (1H, t, *J* 7.5, H5″), 6.83 (1H, d, *J* 8.4, H6′), 6.99 (2H, d, *J* 7.5, H3″ and H6″), 7.16 (1H, t, *J* 7.5, H4″), 7.21–7.36 (5H, m, 1-Ph), 7.90 (1H, s, H5), 9.71 (1H, s, 2′-OH). δ_C ([D$_6$]DMSO) 54.9 (2″-OCH$_3$), 55.2 (4′-O*C*H$_3$), 101.1 (C3′), 104.8 (C5′), 110.2 (C1′), 111.3 (C3″), 118.7 (C4), 120.1 (C5″), 121.6 (C1″), 123.7 (C2‴,6‴), 126.7 (C4‴), 127.8 (C4″), 128.6 (C3‴,5‴), 129.8 (C6″), 132.4 (C6′), 137.1 (C3), 140.6 (C1‴), 140.7 (C5), 156.5 (C2″), 157.0 (C2′), 160.8 (C4′). *m*/*z* 372 ($M^{+\bullet}$, 100), 357 (5), 250 (23), 77 (55). ν_{max}/cm^{-1} 3190, 1621, 1594, 1526, 1498, 1432, 1379, 1297, 1244, 1166, 1130, 1027, 960, 836, 752, 691, 666 (Found: C 74.1, H 5.5, N 7.5. $C_{23}H_{20}N_2O_3$ requires C 74.2, H 5.4, N 7.5%).

δ_H ([D$_6$]DMSO + drops TFA) 3.65 (3H, s, 2″-OCH$_3$), 3.70 (3H, s, 4′-OCH$_3$), 6.29 (1H, dd, *J* 2.3 and 8.44, H5′), 6.35 (1H, d, *J* 2.3, H3′), 6.74 (1H, t, *J* 7.5, H5″), 6.83 (1H, d, *J* 8.4, H6′), 6.95 (1H, d, *J* 7.9, H3″), 7.01 (2H, dd, *J* 1.4 and 7.5, H6″), 7.13 (1H, dt, *J* 1.4, 7.5 and 7.9, H4″), 7.19–7.33 (5H, m, 1-Ph), 7.91 (1H, s, H5). δ_C ([D$_6$]DMSO + drops TFA) 55.2 (2″-OCH$_3$), 55.5 (4′-OCH$_3$), 101.7 (C3′), 105.3 (C5′), 110.7 (C1′), 111.7 (C3″), 119.3 (C4), 120.6 (C5″), 122.2 (C1″), 124.3 (C2‴,6‴), 127.2 (C4‴), 128.2 (C4″), 129.0 (C3‴,5‴), 130.4 (C6′), 132.9 (C6′), 137.9 (C3), 141.06 (C1‴), 141.13 (C5), 157.1 (C2″), 157.5 (C2′), 161.4 (C4′).

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