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ORIGINAL PAPER

Synthesis of (*E*)- and (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles

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Abstract An efficient synthesis method for the preparation of a series of new (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles was developed. The reaction of (*Z*)- and (*E*)-3-styrylchromones with hydrazine hydrate afforded the corresponding (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles, except for nitro derivatives, where both (*Z*)- and (*E*)-4′-nitro-3-styrylchromones afforded (*E*)-3(5)-(2-hydroxyphenyl)-4-(4-nitrostyryl)pyrazoles. The reaction mechanism for these transformations is discussed and the stereochemistries of all products were established by NMR experiments.

Keywords 3-Styrylchromones · 3(5)-(2-Hydroxyphenyl)-4-styrylpyrazoles · Nitrogen heterocycles · NMR spectroscopy · Reaction mechanism

Introduction

Pyrazoles are well known five-membered heterocyclic compounds possessing important pharmaceutical and agrochemical applications [1–7]. Certain derivatives have demonstrated potent antitumoral and cytotoxicity against several human cancer cell lines [8, 9], as well as significant monoamine oxidase and HMG-CoA reductase inhibitory activity, making them good candidates for the treatment of neurodegenerative diseases (such as Parkinson's and Alzheimer's) [10, 11] and hypercholesterolemia [12]. In the last decade, this type of compounds has received considerable attention, since some well-known drugs such as sildenafil (Viagra), rimonabant (Acomplia) and celecoxib (Celebrex) are pyrazole derivatives [1]. The numerous applications of pyrazoles have led to the development of numerous methods for the synthesis of this family of compounds [5–7].

The important properties of 3(5)-(2-hydroxyphenyl) pyrazoles as ultraviolet stabilizers [13, 14], analytical reagents in the complexation of transition metal ions [15], analgesic agents, platelet aggregation inhibitors [16], and also potent inhibitors of Hsp90 ATP-ase activity [17–21] highlight these particular compounds as targets for the preparation of new derivatives or/and to develop new strategies for their synthesis.

Previously we have started a systematic study on the synthesis of 3(5)-(2-hydroxyphenyl)pyrazoles by the reaction of various chromone derivatives with hydrazines. 2-Styrylchromones [22], 2-methyl- and 2-phenylchromones [23], 3-aroyl-5-hydroxyflavones [24], 3-(3-aryl-3-oxopropenyl)chromones [25], 3-benzylchromones and their thio analogs [26], and isoflavones [27] have hitherto been used as starting materials for this purpose. As a result, simple and convenient procedures have been worked out for the synthesis of new 3,4- and 3,5-disubstituted and 3,4,5-trisubstituted pyrazoles. The results obtained prompted us to investigate the preparation of similar pyrazoles by the reaction of 3-styrylchromones with hydrazine hydrate; preliminary results from this study have been already reported [28]. Herein we describe the complete study of the reaction of (*Z*)- and (*E*)-3-styrylchromones with hydrazine hydrate, leading to new (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles.

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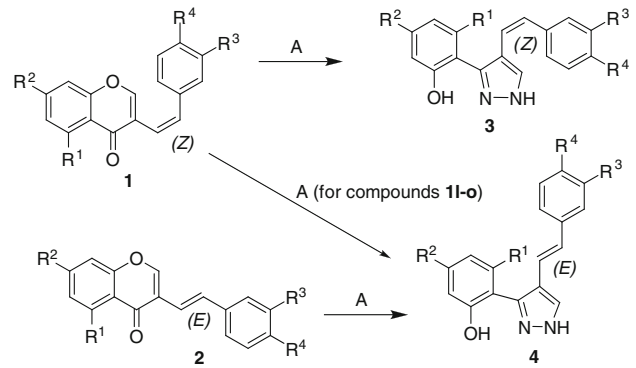
Results and discussion

Synthesis

The study started with the reaction of (*Z*)-3-styrylchromone (**1a**) with two molar equivalents of hydrazine hydrate at room temperature. The thin layer chromatography analysis (TLC) revealed that after reacting for 2 h the starting material had disappeared and (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazole (**3a**) was obtained in 88% yield (Scheme 1). The reaction of (*E*)-3-styrylchromone (**2a**) with hydrazine hydrate under identical conditions gave (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazole (**4a**) in 75% yield. The extension of the study to the reaction of (*E*)-3-styrylchromones **2b–2o** and (*Z*)-3-styrylchromones **1b–1j** led to the formation of (*E*)- and (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **4b–4o** and **3b–3j** (Scheme 1, Table 1).

The same procedure was applied in the reaction of (*Z*)-4′-nitro-3-styrylchromone (**1l**) with hydrazine hydrate, being (*E*)-3(5)-(2-hydroxyphenyl)-4-(4-nitrostyryl) pyrazole (**4l**) obtained in excellent yield (98%). Due to this unexpected result we decided to explore this transformation further, and other (*Z*)-4′-nitro-3-styrylchromones **1m–1o** were left to react with an excess of hydrazine hydrate. In all cases, these reactions gave (*E*)-3(5)-(2-hydroxyphenyl)-4-(4-nitrostyryl)pyrazoles **4m–4o** in very good yield (>73%). These results indicate that the 4′-nitro group has an important role in the (*Z*) → (*E*)-isomerization during the transformation of (*Z*)-4′-nitro-3-styrylchromones **1l–1o** into the corresponding (*E*)-4-(4-nitrostyryl)pyrazoles **4l–4o** [28].



a: $R^1 = R^2 = R^3 = R^4 = H$
b: $R^1 = OCH_3$; $R^2 = R^3 = R^4 = H$
c: $R^1 = R^3 = R^4 = H$; $R^2 = OCH_3$
d: $R^1 = R^2 = OCH_3$; $R^3 = R^4 = H$
e: $R^1 = R^2 = R^3 = H$; $R^4 = Cl$
f: $R^1 = OCH_3$; $R^2 = R^3 = H$; $R^4 = Cl$
g: $R^1 = R^3 = H$; $R^2 = OCH_3$; $R^4 = Cl$
h: $R^1 = R^2 = OCH_3$; $R^3 = H$; $R^4 = Cl$
i: $R^1 = R^2 = R^3 = H$; $R^4 = OC_2H_5$
j: $R^1 = R^3 = H$; $R^2 = OCH_3$; $R^4 = OC_2H_5$
k: $R^1 = R^2 = R^3 = H$; $R^4 = CF_3$
l: $R^1 = R^2 = R^3 = H$; $R^4 = NO_2$
m: $R^1 = OCH_3$; $R^2 = R^3 = H$; $R^4 = NO_2$
n: $R^1 = R^3 = H$; $R^2 = OCH_3$; $R^4 = NO_2$
o: $R^1 = R^2 = OCH_3$; $R^3 = H$; $R^4 = NO_2$
p: $R^1 = R^2 = R^4 = H$; $R^3 = NO_2$
q: $R^1 = OCH_3$; $R^2 = R^4 = H$; $R^3 = NO_2$
r: $R^1 = R^4 = H$; $R^2 = OCH_3$; $R^3 = NO_2$

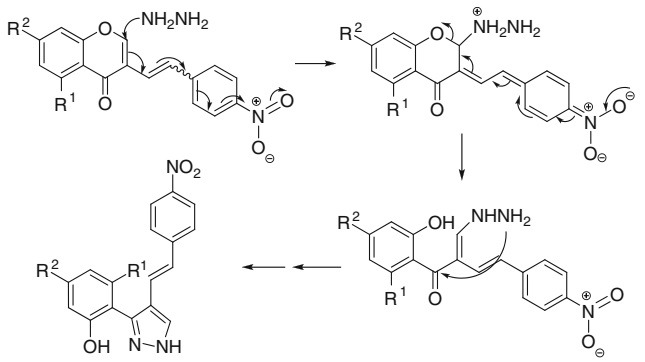
A: $NH_2NH_2.H_2O$, *Me*OH, room temperature, under N_2

Scheme 1

Table 1 Synthesis of (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a–3j**, **3p–3r**, and **4a–4o** (*yields obtained when using (*Z*)-3-styrylchromones **1l–1o** as starting materials)

Compounds **1** and **2**	Substituents				Yield/% of **3** and **4**	
	R^1	R^2	R^3	R^4	(*Z*)-**3**	(*E*)-**4**
a	H	H	H	H	88	75
b	OCH_3	H	H	H	89	40
c	H	OCH_3	H	H	89	70
d	OCH_3	OCH_3	H	H	81	92
e	H	H	H	Cl	94	95
f	OCH_3	H	H	Cl	89	58
g	H	OCH_3	H	Cl	74	97
h	OCH_3	OCH_3	H	Cl	70	65
i	H	H	H	OC_2H_5	93	70
j	H	OCH_3	H	OC_2H_5	92	68
k	–	–	H	CF_3	–	98
l	H	H	H	NO_2	–	87; 98*
m	OCH_3	H	H	NO_2	–	92; 95*
n	H	OCH_3	H	NO_2	–	52; 95*
o	OCH_3	OCH_3	H	NO_2	–	32; 73*
p	H	H	NO_2	H	Quantitative	–
q	OCH_3	H	NO_2	H	80	–
r	H	OCH_3	NO_2	H	87	–

The reaction mechanism of the unsubstituted or 2-substituted chromones with hydrazine has been reported to involve a nucleophilic attack at C-2 of the chromone nucleus and consequent ring opening, followed by the intramolecular reaction between hydrazine and carbonyl groups [22, 23, 28]. This seems to be the mechanism of the reaction of 3-styrylchromones **1a–1j** and **2a–2k** with hydrazine hydrate, which doesn't involve the 3-styryl group and consequently the configuration of the vinyl system is unchanged during their transformation into the corresponding (*Z*)- and (*E*)-4-styrylpyrazoles **3a–3j** and **4a–4k**. The results obtained with the (*Z*)-4′-nitro-3-styrylchromones **1l–1o** suggested that the mechanism should be different in these cases. While the nitro and carbonyl groups are considered strong electron-withdrawing groups, the nitro group is the more powerful one, suggesting that after the nucleophilic attack at C-2 of the chromone nucleus, the electronic conjugation should move towards the 4′-nitro-3-styryl moiety instead of the 4-carbonyl group. This conjugate addition allowed the (*Z*)- → (*E*)-isomerization of the vinylic double bond of the styryl group



Scheme 2

[28], the most stable configuration, and consequent ring opening. The last step of this reaction mechanism is the pyrazole ring closure through an intramolecular reaction of the hydrazine and carbonyl groups (Scheme 2). In order to reinforce the proposed mechanism, we studied the reaction of (*Z*)-3′-nitro-3-styrylchromones **1p–1r**, in which there is no electronic conjugation between the 3′-nitro group and the 3-styrylchromone moiety, with hydrazine hydrate. As expected, (*Z*)-3(5)-(2-hydroxyphenyl)-4-(3-nitrostyryl)pyrazoles **3p–3r** were obtained in very good yields (>80%), which supports the proposed mechanism [28].

NMR spectroscopy

The NMR spectra of 3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a–3j** and **4a–4k** were run in $CDCl_3$, while those of **3p–3r** and **4l–4o** were acquired in DMSO-d_6 due to their insolubility in the former solvent. The main features in the ^{1}H NMR spectra of these (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles are the resonances of: (i) H-5 appearing as a singlet at δ_H = 7.16–7.74 ppm for **3a–3j** and **3p–3r** and δ_H = 7.35–8.49 ppm for **4a–4o**; (ii) the vinylic protons H-α (δ_H = 6.15–6.80 ppm for **3a-3j** and **3p-3r**, and δ_H = 6.38–7.25 ppm for **4a–4o**) and H-β (δ_H = 6.37–6.80 ppm for **3a–3j** and **3p–3r**, and δ_H = 6.60–7.14 ppm for **4a–4o**). The values of the olefinic coupling constants ($^3J_{H\alpha-H\beta}$ = 11.6–12.1 Hz) in the case of compounds **3a–3j** and **3p–3r** indicate a *cis* configuration for this vinylic moiety, whereas those of compounds **4a–4o** ($^3J_{H\alpha-H\beta}$ = 16.0–17.4 Hz) indicate a *trans* configuration. This is the main criterion for distinguishing between compounds **3a–3j**, **3p–3r** and **4a–4o**. Usually H-α and H-β appears in the spectrum as doublets, but for some derivatives the H-α resonance appears as a double doublet due to the coupling with H-β and H-5, the latter appearing as a doublet in these cases instead of being a singlet. In some cases the H-α and H-β resonances appear as a singlet (**4d**) or as an AB spin system (**4b**, **4h**, **4n**).

The ^{1}H NMR spectra of (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a–3j** and **4a–4k** in $CDCl_3$ present two high-frequency broad singlets due to the proton resonances of the N*H* (δ_H = 9.88–10.64 ppm) and the 2′-O*H* (δ_H = 10.01–10.75 ppm) groups. The spectra of the pyrazoles **3p–3r** and **4l–4o** in DMSO-d_6 also present two broad singlets at high frequency values due to the N*H* (δ_H = 9.76–10.27 ppm) and 2′-O*H* (δ_H = 12.71–13.01 ppm) proton resonances. In DMSO-d_6 solution, both 1*H*- and 2*H*-tautomers of pyrazoles **3p–3r** and **4l–4o** are probably present, since the 2′-O*H*–N-2 hydrogen bond is broken and another is formed, 2′-O*H*–DMSO, which is responsible for the 2′-O*H* deshielding. The broadening of several signals in the ^{1}H and ^{13}C NMR spectra of these 4-styrylpyrazoles **3p–3r** and **4l–4o** confirms the existence of prototropy. The prototropy is relatively fast and average signals are observed. In order to fully characterize these compounds, we performed these spectra in DMSO-d_6 with some drops of TFA, which increases the prototropy.

The most characteristic signals in the ^{13}C NMR spectra of the (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a–3j**, **3p–3r** and **4a–4o** are the carbon resonances of the pyrazole moiety C-3 (δ_C = 137.8–149.0 ppm) and C-5 (δ_C = 127.3–134.1 ppm), which were confirmed by the connectivities found in their HMBC spectra (H-α → C-3 and C-5; H-5 → C-3, C-4). The characteristic C-4 resonances (δ_C = 114.4–117.4 ppm) of the (*Z*)-i somers **3a–3j** and **3p–3r** appear at lower frequencies as a consequence of the lack of coplanarity between the pyrazole moiety and the phenyl ring of the styryl group. In contrast, the conjugation between the pyrazole moiety and the styryl group in the (*E*)-i somers **4a–4o** explains the deshielding effect on C-4 (δ_C = 117.6–119.5 ppm). Other important connectivities found in the HMBC spectra of pyrazoles **3a–3j, 3p–3r** and **4a–4o** allowed the assignments of the remaining quaternary carbon resonances (H-3′ → C-1′; H-6′ → C-3, C-4; H-α → C-1″; H-β → C-2″, 6″; H-2″,6″ → C-4″).

Conclusion

We successfully applied 3-styrylchromones to prepare (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles in excellent yields. The influences of the 4′- and 3′-substituents of 3-styrylchromones in this transformation were studied, and it was demonstrated the reaction was stereospecific except when a 4′-nitro group is present. In this case, the reaction of both (*E*)- and (*Z*)-4′-nitro-3-styryl chromones gave only (*E*)-3-(2-hydroxyphenyl)-4-(4-nitrostyryl)pyrazoles.

Experimental

Melting points were determined on a Reichert (Vienna, Austria) Thermovar apparatus fitted with a microscope.

NMR spectra were recorded on Bruker (Wissembourg, France) Avance 300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C), with $CDCl_3$ used as solvent if not stated otherwise. Chemical shifts (δ) are reported in ppm values and coupling constants (J) in Hz. The internal standard was TMS. ^{1}H assignments were made using 2D *g*COSY spectra, while ^{13}C assignments were made using 2D *g*HSQC and *g*HMBC experiments (delays for one bond and long-range J C/H couplings were optimized for 145 and 7 Hz, respectively). Mass spectra (EI, 70 eV) were measured on a VG Autospec (Fisons Instruments, Manchester, UK) Q and M mass spectrometers, while mass spectra (ESI+) were measured on a Micromass (Manchester, UK) Q-TOF-2^{TH} spectrometer [diluting 1 mm^3 of the sample chloroform solution ($\sim 10^{-5}$ M) in 200 mm^3 of 0.1% trifluoroacetic acid/methanol solution; nitrogen was used as nebulizer gas and argon as collision gas; the needle voltage was set at 3,000 V, with the ion source set at 80 °C and desolvation temperature at 150 °C; cone voltage was 35 V]. HRMS were in good agreement (±0.5 ppm) with the calculated values. Elemental analyses were obtained with a LECO 932 CHN analyzer (University of Aveiro, Portugal), and were in good agreement (±0.4%) with the calculated values. Preparative thin-layer chromatography was carried out with Riedel (Seelze, Germany) silica gel 60, DGF254, and column chromatography using Merck (Darmstadt, Germany) 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. (*Z*)- and (*E*)-3-styrylchromones **1a–1j**, **1l–1r**, and **2a–2o** were prepared according to [29].

*General method used for the synthesis of (Z)- and (E)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a–3j, 3p–3r** and **4a–4o***

Hydrazine hydrate (0.08 cm^3, 1.61 mmol) was added to a solution of the appropriate 3-styrylchromone **1a–1j, 1l–1r** or **2a–2o** (8.06×10^{-1} mmol) in 50 cm^3 methanol. The reaction mixture was stirred at room temperature, under nitrogen atmosphere, until the disappearance of the starting material. The mixture was then poured into 100 cm^3 $CHCl_3$ and washed with 2×100 cm^3 acidified water (pH 5). The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated to dryness, and the solid residue was purified by column chromatography using $CHCl_3$ as eluent. The residue obtained after solvent evaporation was recrystallized from a mixture of CH_2Cl_2/cyclohexane. The (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a–3j, 3p–3r** and **4a–4o** were obtained in very good yields: **3a**, 186.0 mg, 88%; **4a**, 158.6 mg, 75%; **3b**, 209.7 mg, 89%; **4b**, 94.2 mg, 40%; **3c**, 209.7 mg, 89%; **4c**, 164.9 mg, 70%; **3d**, 210.4 mg, 81%; **4d**, 239.0 mg, 92%; **3e**, 224.8 mg, 94%; **4e**, 227.2 mg, 95%; **3f**, 234.4 mg, 89%; **4f**, 152.8 mg, 58%; **3g**, 194.9 mg, 74 %; **4g**, 255.5 mg, 97 %; **3 h**, 201.3 mg, 70%; **4h**, 186.9 mg, 65%; **3i**, 229.6 mg, 93%; **4i**, 172.8 mg, 70%; **3j**, 249.4 mg, 92%; **4j**, 184.4 mg, 68%; **4k**, 260.9 mg, 98%; **4l**, 243.4 mg, 98%, [from (*Z*)-4′-nitro-3-styrylchromone **1l**] and 216.0 mg, 87% [from (*E*)-4′-nitro-3-styrylchromone **2l**]; **4m**, 258.3 mg, 95% [from (*Z*)-5-methoxy-4′-nitro-3-styrylchromone **1m**] and 250.1 mg, 92% [from (*E*)-5-methoxy-4′-nitro-3-styrylchromone **2m**]; **4n**, 258.3 mg, 95% [from (*Z*)-7-methoxy-4′-nitro-3-styrylchromone **1n**] and 141.4 mg, 52% from [(*E*)-7-methoxy-4′-nitro-3-styrylchromone **2n**]; **4o**, 216.2 mg, 73% [from (*Z*)-5,7-dimethoxy-4′-nitro-3-styrylchromone **1o**] and 94.8 mg, 32% [from (*E*)-5,7-dimethoxy-4′-nitro-3-styrylchromone **2o**]; **3p**, 247.7 mg, quantitative yield; **3q**, 217.5 mg, 80%; **3r**, 236.5 mg, 87%.

(Z)-3(5)-(2-Hydroxy-6-methoxyphenyl)-4-styrylpyrazole (**3b**, $C_{18}H_{16}N_2O_2$)

Mp 109–111 °C; ^{1}H NMR: $\delta = 3.70$ (s, 6′-OCH_3), 6.52 (dd, $J = 12.1$, 1.1 Hz, H-α), 6.76 (d, $J = 12.1$ Hz, H-β), 6.81 (d, $J = 8.3$ Hz, H-5′), 6.93 (dd, $J = 8.4$, 0.7 Hz, H-3′), 7.20–7.29 (m, H-2″,3″,4″,5″,6″), 7.53 (dd, $J = 8.3$, 8.4 Hz, H-4′), 7.56 (d, $J = 1.1$ Hz, H-5) ppm; ^{13}C NMR: $\delta = 55.4$ (6′-O*C*H_3), 102.8 (C-3′), 106.8 (C-1′), 109.0 (C-5′), 117.4 (C-4), 121.1 (C-α), 126.9 (C-4″), 128.0 (C-β), 128.3 (C-2″,6″), 128.5 (C-3″,5″), 130.3 (C-4′), 131.4 (C-5), 138.1 (C-1″), 142.6 (C-3), 155.5 (C-2′), 157.9 (C-6′) ppm; MS (EI, 70 eV): *m/z* (%) = 292 ($M^{+\cdot}$, 34), 291 [$(M–H)^+$, 4], 279 (13), 275 [$(M–OH)^+$, 2], 261 [$(M–OCH_3)^+$, 5], 247 (2), 217 (22), 201 (100), 186 (28), 173 (10), 158 (6), 146 (3), 131 (3), 116 (3), 105 (9), 91 (13), 83 (22), 77 (16), 63 (10).

(E)-3(5)-(2-Hydroxy-6-methoxyphenyl)-4-styrylpyrazole (**4b**, $C_{18}H_{16}N_2O_2$)

Mp 181–183 °C; ^{1}H NMR ($T = 45$ °C): $\delta = 3.75$ (s, 6′-OCH_3), 6.56 (dd, $J = 8.3$, 0.8 Hz, H-5′), 6.69 (dd, $J = 8.3$, 0.8 Hz, H-3′), 6.79 (AB, $J = 16.5$ Hz, H-α), 6.82 (AB, $J = 16.5$ Hz, H-β), 7.18 (tt, $J = 7.2$, 1.4 Hz, H-4″), 7.23–7.30 (m, H-3″,5″, H-4′), 7.34–7.37 (m, H-2″,6″), 7.89 (br s, H-5) ppm; ^{13}C NMR ($T = 45$ °C): $\delta = 55.7$ (6′-O*C*H_3), 103.1 (C-5′), 106.7 (C-1′), 109.4 (C-3′), 119.4 (C-α, C-4), 126.1 (C-2″,6″), 127.2 (C-4′), 127.7 (C-β), 128.6 (C-3″,5″), 130.7 (C-5), 131.1 (C-4″), 137.8 (C-1″), 138.6 (C-3), 155.7 (C-2′), 158.0 (C-6′) ppm; MS (EI, 70 eV): *m/z* (%) = 292 ($M^{+\cdot}$, 100), 276 (6), 261 [$(M–OCH_3)^+$, 10], 247 (2), 231 (2), 215 [$(M–C_6H_5)^+$, 2], 201 (87), 189 [$(M–C_8H_7)^+$, 3], 186 (20), 171 (2), 165 (4), 149 (3), 146 (5), 128 (3), 115 (12), 105 (2), 102 (4), 91 (6), 83 (4), 77 (6), 69 (2), 65 (4), 57 (4).

(Z)-3(5)-(2-Hydroxy-4-methoxyphenyl)-4-styrylpyrazole (**3c**, $C_{18}H_{16}N_2O_2$)
Mp 102–104 °C; ^{1}H NMR: $\delta = 3.80$ (s, 4′-OCH_3), 6.51 (dd, J = 8.6, 2.4 Hz, H-5′), 6.51 (d, $J = 11.6$ Hz, H-α), 6.60 (d, $J = 2.4$ Hz, H-3′), 6.65 (d, $J = 11.6$ Hz, H-β), 7.16–7.32 (m, H-2″,3″,5″,6″, H-5), 7.20 (t, $J = 7.1$ Hz, H-4″), 7.73 (d, $J = 8.6$ Hz, H-6′), 10.64 (br s, N*H* and 2′-O*H*) ppm; ^{13}C NMR: $\delta = 55.2$ (4′-O*C*H$_3$), 101.7 (C-3′), 106.0 (C-5′), 110.5 (C-1′), 114.6 (C-4), 120.8 (C-α), 127.2 (C-4″), 128.3 (C-2″,6″), 128.6 (C-3″,5″), 128.8 (C-5), 129.0 (C-6′), 131.0 (C-β), 137.0 (C-1″), 148.4 (C-3), 157.2 (C-2′), 160.5 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 292 ($M^{+\cdot}$, 100), 291 [(M–H)$^+$, 28], 277 [(M–CH$_3$)$^+$, 12], 261 [(M–OCH$_3$)$^+$, 5], 249 (4), 231 (3), 221 (3), 215 [(M–C$_6$H$_5$)$^+$, 28], 202 (22), 201 (95), 191 (3), 186 (6), 178 (4), 167 (3), 158 (8), 152 (5), 146 (7), 128 (6), 119 (1), 115 (19), 102 (5), 91 (9), 77 (12), 69 (5), 63 (10).

(E)-3(5)-(2-Hydroxy-4-methoxyphenyl)-4-styrylpyrazole (**4c**, $C_{18}H_{16}N_2O_2$)
Mp 115–116 °C; ^{1}H NMR: $\delta = 3.82$ (s, 4′-OCH_3), 6.54 (dd, $J = 8.6$, 2.4 Hz, H-5′), 6.63 (d, $J = 2.4$ Hz, H-3′), 6.87 (d, J = 16.2 Hz, H-β), 7.13 (d, $J = 16.2$ Hz, H-α), 7.26 (t, $J = 7.3$ Hz, H-4″), 7.36 (dd, $J = 7.3$, 7.8 Hz, H-3″,5″), 7.46 (d, $J = 7.8$ Hz, H-2″,6″), 7.53 (d, $J = 8.6$ Hz, H-6′), 7.79 (s, H-5), 10.18 (br s, N*H* and 2′-O*H*) ppm; ^{13}C NMR: $\delta = 55.3$ (4′-O*C*H$_3$), 101.8 (C-3′), 106.2 (C-5′), 110.4 (C-1′), 117.8 (C-4), 119.0 (C-α), 126.2 (C-2″,6″), 127.5 (C-4″), 127.6 (C-5), 128.7 (C-3″,5″), 129.3 (C-6′), 129.7 (C-β), 137.3 (C-1″), 147.7 (C-3), 157.1 (C-2′), 160.7 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 292 ($M^{+\cdot}$, 100), 291 [(M–H)$^+$, 26], 277 [(M–CH$_3$)$^+$, 5], 261 [(M–OCH$_3$)$^+$, 4], 249 (3), 231 (3), 221 (2), 215 [(M–C$_6$H$_5$)$^+$, 25], 202 (22), 201 [(M–C$_7$H$_7$)$^+$, 96], 186 (5), 178 (3), 158 (5), 146 (11), 128 (2), 115 (14), 102 (4), 91 (5), 77 (6), 69 (2), 63 (4).

(Z)-3(5)-(2-hydroxy-4,6-dimethoxyphenyl)-4-styrylpyrazole (**3d**, $C_{19}H_{18}N_2O_3$)
Mp 78–79 °C; ^{1}H NMR: $\delta = 3.75$ (s, 6′-OCH_3), 3.81 (s, 4′-OCH_3), 6.11 (d, $J = 2.1$ Hz, H-5′), 6.15 (d, $J = 12.0$ Hz, H-α), 6.21 (d, $J = 2.1$ Hz, H-3′), 6.45 (d, $J = 12.0$ Hz, H-β), 7.18–7.30 (m, H-3″,4″,5″), 7.29 (s, H-5), 7.34 (d, $J = 7.1$ Hz, H-2″,6″) ppm; ^{13}C NMR: $\delta = 55.3$ (6′-O*C*H$_3$), 55.4 (4′-O*C*H$_3$), 91.3 (C-5′), 93.3 (C-3′), 99.7 (C-1′), 117.1 (C-4), 121.3 (C-α), 126.9 (C-4″), 127.6 (C-β), 128.4 (C-3″,5″), 128.5 (C-2″,6″), 131.4 (C-5), 138.2 (C-1″), 143.2 (C-3), 156.5 (C-2′), 158.7 (C-6′), 161.8 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 322 ($M^{+\cdot}$, 94), 321 [(M–H)$^+$, 13], 309 (14), 291 [(M–OCH$_3$)$^+$, 15], 279 (3), 259 (4), 247 (21), 231 (100), 216 (14), 203 (7), 187 (6), 179 (2), 173 (4), 161 (7), 152 (4), 131 (3), 115 (10), 105 (12), 91 (12), 77 (17), 69 (9), 63 (7).

(E)-3(5)-(2-Hydroxy-4,6-dimethoxyphenyl)-4-styrylpyrazole (**4d**, $C_{19}H_{18}N_2O_3$)
^{1}H NMR: $\delta = 3.71$ (s, 6′-OCH_3), 3.81 (s, 4′-OCH_3), 6.12 (s, H-3′), 6.28 (s, H-5′), 6.78 (s, H-α, H-β), 7.12–7.22 (m, H-4″), 7.29 (dd, $J = 8.0$, 7.3 Hz, H-3″,5″), 7.36 (d, $J = 7.3$ Hz, H-2″,6″), 7.89 (br s, H-5) ppm; ^{13}C NMR: $\delta = 55.4$ (6′-O*C*H$_3$), 55.5 (4′-O*C*H$_3$), 91.5 (C-3′), 93.7 (C-5′), 98.7 (C-1′), 119.0 (C-4, C-α), 126.0 (C-2″,6″), 127.2 (C-4″), 127.5 (C-β), 128.6 (C-3″,5″), 130.9 (C-5), 137.5 (C-1″), 145.1 (C-3), 156.5 (C-2′), 158.6 (C-6′), 162.2 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 322 ($M^{+\cdot}$, 100), 321 [(M–H)$^+$, 7], 307 [(M–CH$_3$)$^+$, 2], 305 [(M–OH)$^+$, 6], 291 [(M–OCH$_3$)$^+$, 11], 277 (3), 245 [(M–C$_6$H$_5$)$^+$, 5], 231 (88), 216 (11), 201 (4), 181 (3), 165 (5), 152 (4), 139 (3), 127 (3), 115 (11), 103 (3), 91 (6), 69 (6), 63 (3).

(Z)-4-(4-Chlorostyryl)-3(5)-(2-hydroxyphenyl)pyrazole (**3e**, $C_{17}H_{13}ClN_2O$)
Mp 154–156 °C; ^{1}H NMR: $\delta = 6.58$ (d, $J = 11.8$ Hz, H-α), 6.64 (d, $J = 11.8$ Hz, H-β), 6.93 (ddd, $J = 7.5$, 7.6, 1.0 Hz, H-5′), 7.06 (dd, J = 8.2, 1.0 Hz, H-3′), 7.19–7.29 (m, H-2″,3″,5″,6″, H-4′), 7.32 (s, H-5), 7.80 (dd, J = 7.6, 1.6 Hz, H-6′), 10.10 (br s, N*H*), 10.55 (br s, 2′-O*H*) ppm; ^{13}C NMR: $\delta = 115.1$ (C-4), 116.9 (C-3′), 117.1 (C-1′), 119.3 (C-5′), 121.5 (C-α), 128.1 (C-6′), 128.5 (C-3″,5″), 128.6 (C-5), 129.5 (C-4′), 129.96 (C-2″,6″), 130.0 (C-β), 132.9 (C-4″), 135.4 (C-1″), 148.9 (C-3), 155.8 (C-2′) ppm; MS (EI, 70 eV): *m/z* (%) = 298 [($M^{+\cdot}$, ^{37}Cl), 30], 296 [($M^{+\cdot}$, ^{35}Cl), 75], 295 (22), 260 (5), 202 (5), 185 [(M–C$_6$H$_4$Cl)$^+$, 25], 172 (17), 171 (100), 151 (5), 140 (5), 115 (21), 102 (8), 89 (7), 77 (6), 63 (7).

(E)-4-(4-Chlorostyryl)-3(5)-(2-hydroxyphenyl)pyrazole (**4e**, $C_{17}H_{13}ClN_2O$)
Mp 163–164 °C; ^{1}H NMR: $\delta = 6.84$ (d, $J = 16.3$ Hz, H-α), 6.97 (ddd, $J = 7.8$, 7.2, 1.1 Hz, H-5′), 7.07 (dd, $J = 7.7$, 1.1 Hz, H-3′), 7.13 (d, $J = 16.3$ Hz, H-β), 7.28–7.31 (m, H-4′), 7.32 (d, $J = 8.6$ Hz, H-2″,6″), 7.40 (d, $J = 8.6$ Hz, H-3″,5″), 7.58 (dd, $J = 7.8$, 1.5 Hz, H-6′), 7.85 (s, H-5), 10.06 (br s, N*H* and 2′-O*H*) ppm; ^{13}C NMR: $\delta = 117.0$ (C-3′), 117.1 (C-1′), 118.2 (C-4), 119.4 (C-α), 119.6 (C-5′), 127.4 (C-3″,5″), 127.7 (C-5), 128.5 (C-6′), 128.6 (C-β), 128.9 (C-2″,6″), 129.6 (C-4′), 133.2 (C-4″), 135.7 (C-1″), 147.7 (C-3), 155.5 (C-2′) ppm; MS (EI, 70 eV): *m/z* (%) = 298 [($M^{+\cdot}$, ^{37}Cl), 29], 296 [($M^{+\cdot}$, ^{35}Cl), 78], 295 [(M–H)$^+$,15], 281 (3), 260 (3), 242 (1), 231 (2), 215 (2), 202 (3), 185 [(M–C$_6$H$_4$Cl)$^+$, 16], 177 (2), 172 (12), 171 (100), 165 (1), 155 (1), 149 (4), 130 (3), 120 (2), 115 (12), 102 (5), 89 (4), 77 (3), 63 (4).

(Z)-4-(4-Chlorostyryl)-3(5)-(2-hydroxy-6-methoxyphenyl)pyrazole (**3f**, $C_{18}H_{15}ClN_2O_2$)
Mp 97–98 °C; ^{1}H NMR: $\delta = 3.73$ (s, 6′-OCH_3), 6.58 (d, 1H, $J = 8.2$ Hz, H-3′), 6.71 (d, $J = 8.6$ Hz, H-5′), 6.76–

6.80 (m, H-α, H-β), 7.16–7.32 (m, H-2″,3″,5″,6″), 7.24–7.37 (m, H-4′), 7.41 (s, H-5) ppm; ^{13}C NMR: δ = 55.6 (6′-O*C*H$_3$), 102.8 (C-3′), 106.9 (C-1′), 109.3 (C-5′), 115.4 (C-4), 119.9 (C-α), 126.0 (C-β), 127.9 (C-3″,5″), 128.5 (C-2″,6″), 130.7 (C-5, C-4′), 132.5 (C-4″), 136.0 (C-1″), 147.7 (C-3), 155.5 (C-2′), 157.7 (C-6′) ppm; MS (EI, 70 eV): *m/z* (%) = 328 [(M$^{+\cdot}$, ^{37}Cl), 19], 326 [(M$^{+\cdot}$, ^{35}Cl), 50], 325 (4), 313 (13), 311 [(M–CH$_3$)$^+$, 11], 295 [(M–OCH$_3$)$^+$, 6], 246 (2), 216 (20), 215 [(M–C$_6$H$_4$Cl)$^+$, 3], 201 (100), 186 (30), 173 (11), 158 (6), 149 (4), 139 (8), 127 (4), 115 (7), 102 (5), 89 (8), 83 (6), 77 (11), 63 (8).

(E)-4-(4-Chlorostyryl)-3(5)-(2-hydroxy-6-methoxyphenyl)pyrazole (**4f**, C$_{18}$H$_{15}$ClN$_2$O$_2$)
Mp 204–205 °C; ^{1}H NMR: δ = 3.78 (s, 6′-OC*H*$_3$), 6.58 (dd, *J* = 7.9, 0.8 Hz, H-5′), 6.72 (dd, *J* = 8.2, 0.8 Hz, H-3′), 6.76 (d, *J* = 16.0 Hz, H-α), 6.82 (d, *J* = 16.0 Hz, H-β), 7.26 (d, *J* = 8.8 Hz, H-3″,5″), 7.27–7.32 (m, H-4′), 7.31 (d, *J* = 8.8 Hz, H-2″,6″), 7.95 (s, H-5) ppm; ^{13}C NMR: δ = 55.6 (6′-O*C*H$_3$), 102.8 (C-1′,3′), 109.3 (C-5′), 117.8 (C-4), 119.9 (C-α), 126.1 (C-β), 127.2 (C-2″,6″), 128.8 (C-3″,5″), 128.9 (C-4′), 130.7 (C-5), 132.7 (C-4″), 136.1 (C-1″), 140.9 (C-3), 155.5 (C-2′), 157.6 (C-6′) ppm; MS (EI, 70 eV): *m/z* (%) = 328 [(M$^{+\cdot}$, ^{37}Cl), 38], 326 [(M$^{+\cdot}$, ^{35}Cl), 89], 325 (5), 310 (6), 311 [(M–CH$_3$)$^+$, 4], 295 [(M–OCH$_3$)$^+$, 11], 215 [(M–C$_6$H$_4$Cl)$^+$, 3], 201 (100), 186 (28), 177 (3), 176 (3), 138 (5), 125 (5), 115 (10), 102 (4), 89 (4), 77 (4), 63 (4).

(Z)-4-(4-Chlorostyryl)-3(5)-(2-hydroxy-4-methoxyphenyl)pyrazole (**3g**, C$_{18}$H$_{15}$ClN$_2$O$_2$)
Mp 158–160 °C; ^{1}H NMR: δ = 3.82 (s, 4′-OC*H*$_3$), 6.51 (dd, *J* = 8.7, 2.5 Hz, H-5′), 6.55 (d, *J* = 12.0 Hz, H-α), 6.61 (d, *J* = 2.5 Hz, H-3′), 6.62 (d, *J* = 12.0 Hz, H-β), 7.18–7.23 (m, H-2″,3″,5″,6″), 7.29 (s, H-5), 7.70 (d, *J* = 8.7 Hz, H-6′), 10.63 (br s, N*H* and 2′-O*H*) ppm; ^{13}C NMR: δ = 55.3 (4′-O*C*H$_3$), 101.7 (C-3′), 106.1 (C-5′), 110.3 (C-1′), 114.4 (C-4), 121.6 (C-α), 128.4 (C-5), 128.5 (C-3″,5″), 128.9 (C-6′), 129.9 (C-β), 130.0 (C-2″,6″), 132.9 (C-4″), 135.4 (C-1″), 149.0 (C-3), 157.4 (C-2′), 160.7 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 328 [(M$^{+\cdot}$, ^{37}Cl), 42], 326 [(M$^{+\cdot}$, ^{35}Cl), 93], 325 (26), 311 [(M–CH$_3$)$^+$, 4], 295 [(M–OCH$_3$)$^+$, 4], 215 [(M–C$_6$H$_4$Cl)$^+$, 29], 202 (23), 201 (100), 186 (6), 177 (4), 165 (5), 158 (9), 151 (4), 137 (6), 125 (4), 115 (13), 102 (5), 85 (16), 75 (6), 63 (8).

(E)-4-(4-Chlorostyryl)-3(5)-(2-hydroxy-4-methoxyphenyl)pyrazole (**4g**, C$_{18}$H$_{15}$ClN$_2$O$_2$)
Mp 170–172 °C; ^{1}H NMR: δ = 3.84 (s, 4′-OC*H*$_3$), 6.54 (dd, *J* = 8.6, 2.5 Hz, H-5′), 6.63 (d, *J* = 2.5 Hz, H-3′), 6.82 (d, *J* = 16.2 Hz, H-β), 7.10 (d, *J* = 16.2 Hz, H-α), 7.32 (d, *J* = 8.6 Hz, H-3″,5″), 7.39 (d, *J* = 8.6 Hz, H-2″,6″), 7.49 (d, *J* = 8.6 Hz, H-6′), 7.80 (br s, H-5), 10.12 (br s, N*H*) ppm; ^{13}C NMR: δ = 55.3 (4′-O*C*H$_3$), 101.9 (C-3′), 106.2 (C-5′), 110.3 (C-1′), 117.6 (C-4), 119.6 (C-α), 127.4 (C-2″,6″), 127.7 (C-5), 128.3 (C-β), 128.9 (C-3″,5″), 129.2 (C-6′), 133.1 (C-4″), 135.8 (C-1″), 147.7 (C-3), 157.1 (C-2′), 160.8 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 328 [(M$^{+\cdot}$, ^{37}Cl), 42], 326 [(M$^{+\cdot}$, ^{35}Cl), 93], 325 (26), 311 [(M–CH$_3$)$^+$, 4], 295 [(M–OCH$_3$)$^+$, 4], 215 [(M–C$_6$H$_4$Cl)$^+$, 29], 202 (23), 201 (100), 186 (6), 177 (4), 165 (5), 158 (9), 151 (4), 137 (6), 125 (4), 115 (13), 102 (5), 85 (16), 75 (6), 63 (8).

(Z)-4-(4-Chlorostyryl)-3(5)-(2-hydroxy-4,6-dimethoxyphenyl)pyrazole (**3h**, C$_{19}$H$_{17}$ClN$_2$O$_3$)
Mp 68–69 °C; ^{1}H NMR: δ = 3.72 (s, 6′-OC*H*$_3$), 3.80 (s, 4′-OC*H*$_3$), 6.08 (d, *J* = 1.9 Hz, H-5′), 6.19 (d, *J* = 1.9 Hz, H-3′), 6.19 (d, *J* = 11.9 Hz, H-α), 6.37 (d, *J* = 11.9 Hz, H-β), 7.20 (d, *J* = 8.7 Hz, H-3″,5″), 7.25 (d, *J* = 8.7 Hz, H-2″,6″), 7.31 (br s, H-5) ppm; ^{13}C NMR: δ = 55.2 (6′-O*C*H$_3$), 55.4 (4′-O*C*H$_3$), 91.2 (C-5′), 93.4 (C-3′), 99.7 (C-1′), 116.8 (C-4), 122.0 (C-α), 126.3 (C-β), 128.4 (C-3″,5″), 129.8 (C-2″,6″), 131.0 (C-5), 132.4 (C-4″), 136.5 (C-1″), 144.1 (C-3), 156.5 (C-2′), 158.6 (C-6′), 161.8 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 358 [(M$^{+\cdot}$, ^{37}Cl), 35], 356 [(M$^{+\cdot}$, ^{35}Cl), 100], 355 (5), 339 [(M–OH)$^+$, 4], 325 [(M–OCH$_3$)$^+$, 8], 299 (2), 245 [(M–C$_6$H$_4$Cl)$^+$, 4], 231 (85), 219 [(M–C$_8$H$_6$Cl)$^+$, 1], 215 (12), 201 (2), 187 (2), 178 (7), 149 (4), 115 (5), 101 (2), 77 (2), 69 (6).

(E)-4-(4-Chlorostyryl)-3(5)-(2-hydroxy-4,6-dimethoxyphenyl)pyrazole (**4h**, C$_{19}$H$_{17}$ClN$_2$O$_3$)
Mp 100–102 °C; ^{1}H NMR: δ = 3.71 (s, 6′-OC*H*$_3$), 3.81 (s, 4′-OC*H*$_3$), 6.15 (s, H-3′), 6.22 (s, H-5′), 6.74 (AB, *J* = 17.2 Hz, H-α,β), 7.13–7.31 (m, H-2″,3″,5″,6″), 7.80 (br s, H-5) ppm; ^{13}C NMR: δ = 55.4 (6′-O*C*H$_3$), 55.6 (4′-O*C*H$_3$), 91.6 (C-3′), 93.6 (C-5′), 98.6 (C-1′), 119.5 (C-α, C-4), 126.2 (C-β), 128.7 (C-2″,6″), 130.7 (C-3″,5″), 130.9 (C-5), 133.1 (C-4″), 136.1 (C-1″), 148.8 (C-3), 156.1 (C-2′), 158.7 (C-6′), 162.2 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 358 [(M$^{+\cdot}$, ^{37}Cl), 11], 356 [(M$^{+\cdot}$, ^{35}Cl), 29], 355 (2), 339 [(M–OH)$^+$, 2], 325 [(M–OCH$_3$)$^+$, 4], 284 (1), 256 (1), 245 [(M–C$_6$H$_4$Cl)$^+$, 5], 231 (29), 215 (4), 201 (2), 178 (4), 170 (30), 149 (3), 134 (1), 125 (100), 115 (2), 94 (5), 89 (19), 83 (2), 69 (4), 63 (11).

(Z)-4-(4-Ethoxystyryl)-3(5)-(2-hydroxyphenyl)pyrazole (**3i**, C$_{19}$H$_{18}$N$_2$O$_2$)
Mp 107–109 °C; ^{1}H NMR: δ = 1.39 (t, *J* = 7.0 Hz, 4″-OCH$_2$C*H*$_3$), 4.00 (q, *J* = 7.0 Hz, 4″-OC*H*$_2$CH$_3$), 6.45 (dd, *J* = 11.8, 0.8 Hz, H-α), 6.63 (d, *J* = 11.8 Hz, H-β), 6.75 (d, *J* = 8.7 Hz, H-3″,5″), 6.92 (ddd, *J* = 7.2, 7.8, 1.3 Hz, H-5′), 7.05 (dd, *J* = 8.2, 1.3 Hz, H-3′), 7.23 (d, *J* = 8.7 Hz, H-2″,6″), 7.24–7.27 (m, H-4′), 7.37 (d, *J* = 0.8 Hz, H-5), 7.86 (dd, *J* = 7.8, 1.6 Hz, H-6′), 10.21 (br s, N*H*), 10.70 (br s, 2′-O*H*) ppm; ^{13}C NMR: δ = 14.8 (4″-OCH$_2$*C*H$_3$), 63.4 (4″-O*C*H$_2$CH$_3$), 114.2 (C-3″,5″), 115.7 (C-4), 116.8 (C-3′), 117.3 (C-1′), 119.0 (C-α), 119.3 (C-5′), 128.1

(C-6′), 128.6 (C-5), 129.27 (C-4′), 129.34 (C-1″), 129.9 (C-2″,6″), 131.0 (C-*β*), 148.7 (C-3), 155.8 (C-2′), 158.1 (C-4″) ppm; MS (EI, 70 eV): *m/z* (%) = 306 ($M^{+\cdot}$, 100), 305 $[(M–H)^+$, 15], 291 $[(M–CH_3)^+$, 3], 278 (9), 277 $[(M–C_2H_5)^+$, 34], 261 $[(M–C_2H_5O)^+$, 2], 247 (4), 232 (3), 222 (3), 205 (3), 191 (1), 185 $[(M–C_8H_9O)^+$, 11], 176 (2), 171 (78), 160 (1), 155 (4), 140 (2), 131 (8), 115 (8), 107 (3), 102 (7), 91 (4), 77 (9), 65 (6).

(E)-4-(4-Ethoxystyryl)-3(5)-(2-hydroxyphenyl)pyrazole (**4i**, $C_{19}H_{18}N_2O_2$)

Mp 149–151 °C; ^{1}H NMR: δ = 1.40 (t, J = 7.0 Hz, 4″-OCH_2CH_3), 4.06 (q, J = 7.0 Hz, 4″-OCH_2CH_3), 6.84 (d, J = 16.2 Hz, H-*β*), 6.90 (d, J = 8.7 Hz, H-3″,5″), 6.95 (ddd, J = 7.8, 8.6, 0.9 Hz, H-5′), 7.01 (d, J = 16.2 Hz, H-*α*), 7.07 (dd, J = 7.0, 0.9 Hz, H-3′), 7.26 (ddd, J = 8.6, 7.0, 1.5 Hz, H-4′), 7.40 (d, J = 8.7 Hz, H-2″,6″), 7.64 (dd, J = 7.8, 1.5 Hz, H-6′), 7.81 (br s, H-5), 10.14 (br s, N*H* and 2′-O*H*) ppm; ^{13}C NMR: δ = 14.8 (4″-OCH_2CH_3), 63.5 (4″-OCH_2CH_3), 114.7 (C-3″,5″), 116.6 (C-*α*), 116.9 (C-3′), 117.4 (C-1′), 118.8 (C-4), 119.5 (C-5′), 127.5 (C-2″,6″, C-5), 128.5 (C-6′), 129.4 (C-4′), 129.6 (C-*β*), 129.9 (C-1″), 147.5 (C-3), 155.6 (C-2′), 158.6 (C-4″) ppm; MS (EI, 70 eV): *m/z* (%) = 306 ($M^{+\cdot}$, 100), 305 $[(M–H)^+$, 13], 291 $[(M–CH_3)^+$, 2], 277 $[(M–C_2H_5)^+$, 35], 260 (2), 247 (4), 232 (3), 222 (2), 205 (2), 191 (1), 185 $[(M–C_8H_9O)^+$, 10], 176 (1), 171 (71), 165 (3), 155 (4), 140 (2), 139 (6), 131 (8), 120 (3), 115 (7), 107 (3), 102 (6), 91 (5), 83 (3), 77 (8), 65 (6).

(Z)-4-(4-Ethoxystyryl)-3(5)-(2-hydroxy-4-methoxyphenyl)pyrazole (**3j**, $C_{20}H_{20}N_2O_3$)

Mp 167–169 °C; ^{1}H NMR: δ = 1.40 (t, J = 7.0 Hz, 4″-OCH_2CH_3), 3.82 (s, 4′-OCH_3), 4.00 (q, J = 7.0 Hz, 4″-OCH_2CH_3), 6.42 (d, J = 11.8 Hz, H-*α*), 6.50 (dd, J = 8.6, 2.6 Hz, H-5′), 6.61 (d, J = 2.6 Hz, H-3′), 6.62 (d, J = 11.8 Hz, H-*β*), 6.75 (d, J = 8.7 Hz, H-3″,5″), 7.23 (d, J = 8.7 Hz, H-2″,6″), 7.35 (d, J = 0.6 Hz, H-5), 7.76 (d, J = 8.6 Hz, H-6′), 10.50 (br s, N*H* and 2′-O*H*) ppm; ^{13}C NMR: δ = 14.8 (4″-OCH_2CH_3), 55.3 (4′-OCH_3), 63.4 (4″-OCH_2CH_3), 101.7 (C-3′), 105.9 (C-5′), 110.5 (C-1′), 114.2 (C-3″,5″), 115.1 (C-4), 119.1 (C-*α*), 128.3 (C-5), 128.9 (C-6′), 129.4 (C-1″), 129.9 (C-2″,6″), 131.0 (C-*β*), 143.8 (C-3), 157.4 (C-2′), 158.1 (C-4″), 160.6 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 336 ($M^{+\cdot}$, 100), 321 $[(M–CH_3)^+$, 1], 307 (18), 291 (2), 277 (2), 263 (2), 247 (2), 235 (2), 221 (2), 215 (9), 201 (67), 186 (3), 165 (2), 154 (6), 138 (2), 131 (4), 115 (2), 103 (2), 77 (3), 65 (1).

(E)-4-(4-Ethoxystyryl)-3(5)-(2-hydroxy-4-methoxyphenyl)pyrazole (**4j**, $C_{20}H_{20}N_2O_3$)

Mp 165–167 °C; ^{1}H NMR: δ = 1.42 (t, J = 7.0 Hz, 4″-OCH_2CH_3), 3.82 (s, 4′-OCH_3), 4.02 (q, J = 7.0 Hz, 4″-OCH_2CH_3), 6.38 (d, J = 16.4 Hz, H-*α*), 6.50 (dd, J = 8.7, 1.7 Hz, H-5′), 6.60 (d, J = 16.4 Hz, H-*β*), 6.61 (d, J = 1.7 Hz, H-3′), 6.75 (d, J = 8.5 Hz, H-3″,5″), 7.23 (d, J = 8.5 Hz, H-2″,6″), 7.35 (br s, H-5), 7.76 (d, J = 8.7 Hz, H-6′), 9.88 (br s, N*H*), 10.75 (br s, 2′-O*H*) ppm; ^{13}C NMR: δ = 14.8 (4″-OCH_2CH_3), 55.3 (4′-OCH_3), 63.5 (4″-OCH_2CH_3), 101.8 (C-3′), 106.1 (C-5′), 110.5 (C-1′), 114.7 (C-3″,5″), 116.7 (C-*α*), 117.8 (C-4), 127.4 (C-2″,6″, C-5), 129.2 (C-6′), 129.4 (C-*β*), 129.9 (C-1″), 147.6 (C-3), 157.1 (C-2′), 158.6 (C-4″), 160.6 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 336 ($M^{+\cdot}$, 100), 321 $[(M–CH_3)^+$, 2], 307 (24), 291 (2), 277 (3), 263 (3), 247 (3), 235 (3), 221 (2), 215 (12), 201 (67), 186 (4), 168 (2), 154 (10), 137 (3), 131 (5), 115 (3), 103 (3), 77 (5), 65 (2).

(E)-3(5)-(2-Hydroxyphenyl)-4-(4-trifluoromethylstyryl) pyrazole (**4k**, $C_{18}H_{13}F_3N_2O$)

Mp 186–188 °C; ^{1}H NMR: δ = 6.92 (d, J = 16.2 Hz, H-*β*), 6.98 (ddd, J = 7.5, 7.0, 0.8 Hz, H-5′), 7.09 (dd, J = 8.2, 0.8 Hz, H-3′), 7.25 (d, J = 16.2 Hz, H-*α*), 7.30 (ddd, J = 8.2, 7.5, 1.6 Hz, H-4′), 7.56 (d, J = 8.1 Hz, H-2″,6″), 7.57 (dd, J = 7.0, 1.6 Hz, H-6′), 7.61 (d, J = 8.1 Hz, H-3″,5″), 7.89 (s, H-5), 10.01 (br s, N*H* and 2′-O*H*) ppm; ^{13}C NMR: δ = 117.0 (C-1′), 117.1 (C-3′), 118.0 (C-4), 119.6 (C-5′), 121.4 (C-*α*), 125.7 (q, J = 3.9 Hz, C-3″,5″), 126.0 (q, J = 284.6 Hz, *C*F_3), 126.3 (C-2″,6″), 127.9 (C-5), 128.3 (C-*β*), 128.5 (C-6′), 128.7 (q, J = 31.8 Hz, C-4″), 129.7 (C-4′), 140.6 (C-1″), 143.2 (C-3), 155.6 (C-2′) ppm; MS (EI, 70 eV): *m/z* (%) = 330 ($M^{+\cdot}$, 92), 329 $[(M–H)^+$, 32], 311 (12), 301 (6), 275 (4), 260 (3), 243 (2), 233 (4), 214 (2), 202 (4), 185 (29), 171 (100), 164 (4), 155 (14), 140 (5), 115 (15), 102 (8), 89 (4), 65 (5).

(E)-3(5)-(2-Hydroxy-6-methoxyphenyl)-4-(4-nitrostyryl)pyrazole (**4m**, $C_{18}H_{15}N_3O_4$)

Mp 231–233 °C; ^{1}H NMR (DMSO-d6 with TFA)**:** δ = 3.70 (s, 6′-OCH_3), 6.62 (d, J = 8.3 Hz, H-5′), 6.66 (d, J = 8.3 Hz, H-3′), 6.93 (d, J = 16.5 Hz, H-*α*), 7.10 (d, J = 16.5 Hz, H-*β*), 7.30 (t, J = 8.3 Hz, H-4′), 7.60 (d, J = 8.8 Hz, H-2″,6″), 8.13 (d, J = 8.8 Hz, H-3″,5″), 8.49 (s, H-5), 9.76 (without TFA; s, N*H*), 12.80 (without *TFA*; s, 2′-O*H*) ppm; ^{13}C NMR (DMSO-d6 with TFA): δ = 56.1 (6′-OCH_3), 102.8 (C-5′), 103.5 (C-1′), 109.4 (C-3′), 119.5 (C-4), 123.5 (C-*α*), 124.6 (C-3″,5″), 126.4 (C-*β*), 127.2 (C-2″,6″), 132.5 (C-4′), 133.5 (C-5), 138.3 (C-3), 144.5 (C-1″), 146.7 (C-4″), 157.5 (C-2′), 159.2 (C-6′) ppm; MS (EI, 70 eV): *m/z* (%) = 337 ($M^{+\cdot}$, 88), 336 $[(M–H)^+$, 5], 320 $[(M–OH)^+$, 8], 307 $[(M–NO)^+$, 26], 306 $[(M–OCH_3)^+$, 10], 290 (17), 276 (8), 262 (11), 244 (7), 229 (2), 215 (5), 201 (100), 186 (24), 171 (20), 128 (7), 115 (12), 91 (12), 69 (22), 57 (30).

(E)-3(5)-(2-Hydroxy-4-methoxyphenyl)-4-(4-nitrostyryl)pyrazole (**4n**, $C_{18}H_{15}N_3O_4$)
Mp 197–198 °C; ^{1}H NMR (DMSO-d6 with TFA): δ = 3.76 (s, 4′-OC*H*$_3$), 6.54–6.57 (m, H-5′), 6.53 (d, J = 2.4 Hz, H-3′), 7.13 (AB, J = 17.4 Hz, H-α, H-β), 7.25 (d, J = 8.9 Hz, H-6′), 7.64 (d, J = 8.8 Hz, H-2″,6″), 8.05 (br s, H-5), 8.16 (d, J = 8.8 Hz, H-3″,5″), 10.14 (without *TFA*; br s, N*H*), 12.77 (without *TFA*; br s, 2′-O*H*) ppm; ^{13}C NMR (DMSO-d6 with TFA): δ = 55.7 (4′-O*C*H$_3$), 102.6 (C-3′), 106.4 (C-5′), 108.0 (C-1′), 118.5 (C-4), 123.6 (C-α), 124.8 (C-3″,5″), 127.1 (C-β), 127.5 (C-2″,6″), 132.6 (C-6′), 133.4 (C-5), 142.5 (C-3), 144.8 (C-1″), 147.0 (C-4″), 157.5 (C-2′), 162.8 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 337 ($M^{+\cdot}$, 100), 336 [$(M–H)^+$, 28], 320 [$(M–OH)^+$, 3], 307 [$(M–NO)^+$, 9], 290 (17), 247 (2), 231 (2), 215 [$(M–C_6H_4NO_2)^+$, 15], 201 (74), 186 (3), 169 (3), 163 (3), 145 (2), 115 (5), 102 (2), 89 (3), 78 (4), 63 (10).

(E)-3(5)-(2-Hydroxy-4,6-dimethoxyphenyl)-4-(4-nitrostyryl)pyrazole (**4o**, $C_{19}H_{17}N_3O_5$)
Mp 220–222 °C; ^{1}H NMR (DMSO-d6 with TFA): δ = 3.70 (s, 6′-OC*H*$_3$), 3.78 (s, 4′-OC*H*$_3$), 6.24 (s, H-3′, H-5′), 6.93 (d, J = 16.5 Hz, H-α), 7.09 (d, J = 16.5 Hz, H-β), 7.63 (d, J = 8.8 Hz, H-2″,6″), 8.16 (d, J = 8.8 Hz, H-3″,5″), 8.40 (s, H-5), 9.79 (without *TFA*; br s, N*H*), 12.71 (without TFA; br s, 2′-O*H*) ppm; ^{13}C NMR (DMSO-d6 with TFA): δ = 55.4 (4′-O*C*H$_3$), 55.9 (6′-O*C*H$_3$), 90.5 (C-3′), 94.1 (C-5′), 96.3 (C-1′), 118.9 (C-4), 123.9 (C-α), 124.4 (C-3″,5″), 125.2 (C-β), 126.8 (C-2″,6″), 133.6 (C-5), 137.8 (C-3), 144.5 (C-1″), 146.2 (C-4″), 157.9 (C-2′), 159.7 (C-6′), 162.7 (C-4′) ppm; MS (EI, 70 eV): *m/z* (%) = 368 [$(M + H)^+$, 22], 367 ($M^{+\cdot}$, 100), 350 [$(M–OH)^+$, 7], 337 (15), 320 (11), 306 (3), 290 (4), 277 (1), 261 (2), 245 (3), 231 (82), 215 (12), 205 (3), 189 (3), 174 (8), 159 (3), 139 (2), 131 (5), 115 (5), 91 (3), 77 (5), 69 (4), 57 (2).

(Z)-3(5)-(2-Hydroxy-6-methoxyphenyl)-4-(3-nitrostyryl)pyrazole (**3q**, $C_{18}H_{15}N_3O_4$)
Mp 127–129 °C; ^{1}H NMR (DMSO-d6 with TFA): δ = 3.59 (s, 6′-OC*H*$_3$), 6.26 (d, J = 11.9 Hz, H-α), 6.38 (d, J = 8.3 Hz, H-5′), 6.48 (d, J = 8.3 Hz, H-3′), 6.57 (d, J = 11.9 Hz, H-β), 7.11 (t, J = 8.3 Hz, H-4′), 7.34 (t, J = 8.2 Hz, H-5″), 7.39–7.43 (m, H-6″), 7.74 (s, H-5), 7.84 (t, J = 1.9 Hz, H-2″), 7.91 (ddd, J = 8.2, 1.9, 1.7 Hz, H-4″), 9.85 (without TFA; br s, N*H*), 12.76 (without TFA; br s, 2′-O*H*) ppm; ^{13}C NMR (DMSO-d6 with TFA): δ = 56.6 (6′-O*C*H$_3$), 103.4 (C-5′), 103.5 (C-1′), 110.1 (C-3′), 119.3 (C-4), 122.1 (C-α), 123.3 (C-4″), 124.0 (C-2″), 131.0 (C-β), 131.1 (C-5″), 133.6 (C-5), 133.8 (C-4′), 135.9 (C-6″), 139.8 (C-1″), 140.9 (C-3), 149.5 (C-3″), 158.2 (C-2′), 159.9 (C-6′) ppm. MS (ESI^+): *m/z* (%) = 338 [$(M + H)^+$, 100].

(Z)-3(5)-(2-Hydroxy-4-methoxyphenyl)-4-(3-nitrostyryl)pyrazole (**3r**, $C_{18}H_{15}N_3O_4$)
Mp 115–117 °C; ^{1}H NMR (DMSO-d6 with TFA): δ = 3.63 (s, 4′-OC*H*$_3$), 6.34 (dd, J = 8.6, 2.3 Hz, H-5′), 6.40 (d, J = 2.3 Hz, H-3′), 6.43 (d, J = 12.0 Hz, H-α), 6.62 (d, J = 12.0 Hz, H-β), 7.18 (d, J = 8.6 Hz, H-6′), 7.32 (t, J = 8.0 Hz, H-5″), 7.40–7.44 (m, H-6″), 7.73 (s, H-5), 7.83 (t, J = 2.0 Hz, H-2″), 7.89 (ddd, J = 8.0, 2.0, 0.9 Hz, H-4″), 10.20 and 10.63 (without TFA; br s, N*H*), 12.80 and 13.15 (without TFA; br s, 2′-O*H*) ppm; ^{13}C NMR (DMSO-d6 with TFA): δ = 56.2 (4′-O*C*H$_3$), 103.0 (C-3′), 107.0 (C-5′), 107.6 (C-1′), 117.0 (C-4), 122.1 (C-α), 123.4 (C-4″), 124.0 (C-2″), 131.0 (C-5″), 131.5 (C-β), 132.8 (C-6′), 134.0 (C-5), 135.9 (C-6″), 139.8 (C-1″), 143.7 (C-3), 149.4 (C-3″), 158.1 (C-2′), 163.9 (C-4′) ppm. MS (ESI^+): *m/z* (%) = 338 [$(M + H)^+$, 25].

The following products have been reported in the literature and in this work were identified on the basis of their melting points: (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazole (**3a**, $C_{17}H_{14}N_2O$), Mp 119–121 °C (Lit.: 119–121 °C) [28]; (*Z*)-3(5)-(2-hydroxyphenyl)-4-(3-nitrostyryl)pyrazole (**3p**, $C_{17}H_{13}N_3O_3$), Mp 108–110 °C (Lit.: 108–110 °C) [28]; (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazole (**4a**, $C_{17}H_{14}N_2O$), Mp 138–140 °C (Lit.: 138–140 °C) [28]; (*E*)-3(5)-(2-hydroxyphenyl)-4-(4-nitrostyryl)pyrazole (**4l**, $C_{17}H_{14}N_3O_3$), Mp 212–214 °C (Lit.: 212–214 °C) [28].

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