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The 3-(2-benzyloxy-6-hydroxyphenyl)-5-(methyl, phenyl or styryl)pyrazoles were prepared from the reaction of 2-(methyl, phenyl or styryl)chromones with methylhydrazine. The structure of these compounds has been determined by several nmr techniques, and the reaction mechanism is discussed.

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Introduction.

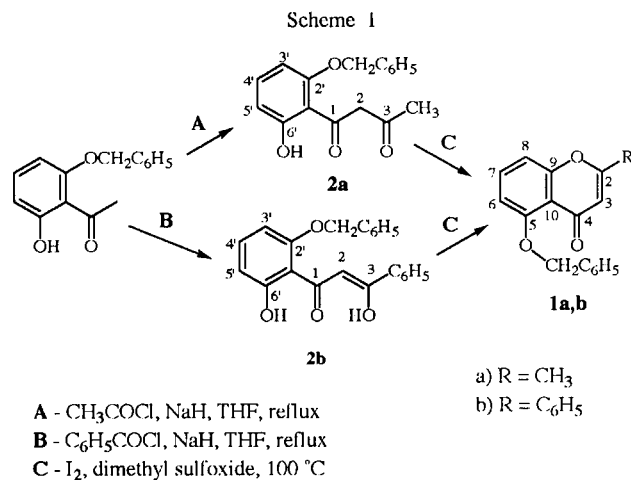
Pyrazoles are well known five-membered heterocyclic compounds and several procedures for their syntheses have been extensively studied [1,2]. Such studies have been stimulated by various promising applications, especially in the case of *N*-substituted pyrazole derivatives [1,2]. In fact, certain *N*-substituted pyrazoles are used as pharmaceuticals (e.g. the analgesic, anti-inflammatory and antipyretic difenamizole) [3], agrochemicals (e.g. the herbicide difenzoquat) [3] and photoprotectors of polystyrene [e.g. *N*-(2-hydroxyphenyl)pyrazoles] [4,5], whereas some others are being studied for their medical interest [6-8].

The knowledge of such applications has pointed out that *N*-substituted pyrazoles are important targets to be prepared. Following our interest on synthesis and molecular structure determination of some types of pyrazoles [9,10], we devote our attention to the synthesis of 3-(2-benzyloxy-6-hydroxyphenyl)-1-methylpyrazoles. These compounds were obtained by the reaction of 2-substituted chromones with methylhydrazine. The reaction of hydrazine hydrate with chromone, 2-methyl- and 2-phenylchromone was first studied in 1940s and 1950s. The research groups involved in these studies agreed that the reaction products were 5(3)-(o-hydroxyphenyl)pyrazoles and not the hydrazones derived from the chromones as previously believed [11-13]. In 1986, Takagi *et al.* [14] studied the reaction of 3-nitro-2-methylchromone with hydrazine hydrate and methylhydrazine and established that the products obtained were 3-(o-hydroxyphenyl)pyrazoles and 3-(o-hydroxyphenyl)-1-methylpyrazoles, respectively. We report here the synthesis and structural characterisation of 3-(2-benzyloxy-6-hydroxyphenyl)-1-methylpyrazoles **3a-g**; the reaction mechanism is also discussed.

Results and Discussion.

Chemistry.

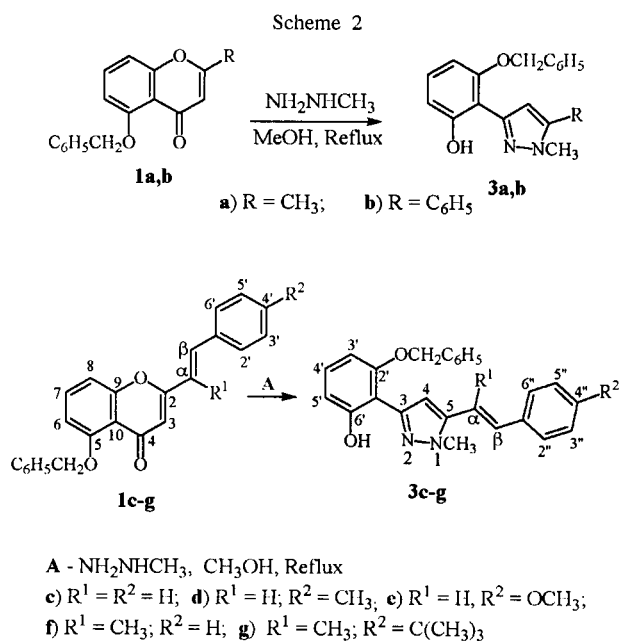
The 5-benzyloxy-2-(methyl or phenyl)chromones **1a,b** were prepared according to the two-step synthesis shown in Scheme 1. For this purpose, 1,3-diketones **2a,b** were prepared in one step from the reaction of 2'-benzyloxy-6'-



hydroxyacetophenone (*vide experimental*) with acetyl or benzoyl chloride in the presence of sodium hydride under nitrogen. The cyclization of these 1,3-diketones **2a,b** into the desired chromone **1a,b** was achieved by heating them with iodine in dimethyl sulfoxide.

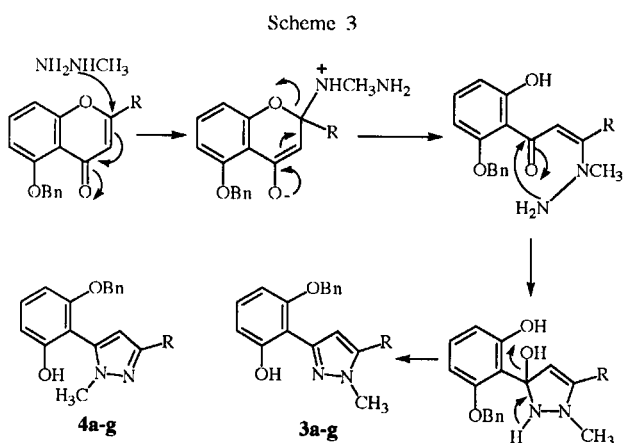
The 5-benzyloxy-2-styrylchromones **1c-g** were prepared in good overall yields according the modified Baker-Venkataraman method and the oxidative cyclization of 2'-hydroxycinnamylideneacetophenones [10].

The treatment of 5-benzyloxy-2-methylchromone **1a** with 2 equivalents of methylhydrazine in refluxing methanol for 24 hours lead to the formation of 3-(2-benzyloxy-6-hydroxyphenyl)-1,5-dimethylpyrazole **3a** in 13% yield (Scheme 2). A longer reaction time decreased the yield of pyrazole **3a**. In the new attempt of this transformation, 5-benzyloxy-2-methylchromone **1a** was treated with four batches (2 equivalents each) of methylhydrazine in refluxing methanol for 24 hours. These four batches were consecutively added with 5 hours interval. In this case pyrazole **3a** was obtained in better yield (49%) than the above, with chromone **1a** recovered (33%). The treatment of 5-benzyloxy-2-methylchromone **1a** with only one batch of 8 equivalents of methylhydrazine added at once, gave only 20% of pyrazole **3a**, with chromone **1a** (30%).



The results obtained in the case of chromone **1a** prompted us to treat the other chromones **1b-g** with four batches (2 equivalents each) of methylhydrazine (consecutively added with 5 hours interval) in refluxing methanol for 24 hours. The 3-(2-benzyloxy-6-hydroxyphenyl)-1-methylpyrazoles **3b-g** were obtained in moderate yields (38-53%) (Scheme 2), with chromones **1b-g** recovered (38-50%) (*vide experimental*).

The reaction mechanism of chromones with hydrazine has been reported to involve a nucleophilic attack at C-2 of the chromone and consequent ring opening, followed by the intramolecular dehydration between the hydrazino and carbonyl groups [10]. In our case, only the 3-(2-benzyloxy-6-hydroxyphenyl)-1-methylpyrazoles **3a-g** were obtained as shown in Scheme 3. Compounds **4a-g** are not produced theoretically.



Nuclear Magnetic Resonance Spectroscopy.

The ¹H nmr spectrum of compound **2a** shows the methyl, methylene and hydroxy proton signals at δ 1.70, 4.03 and 13.08 ppm. These data are only compatible with a β-diketone structure of the 1-(2-benzyloxy-6-hydroxyphenyl)-1,3-butanedione **2a**, as shown in Scheme 1. In the ¹H nmr spectrum of compound **2b** it is possible to observe the presence of two signals at δ 12.93 and 15.74 ppm, which are due to proton resonances of two hydroxyl groups involved in intramolecular hydrogen bonds. One can conclude that this compound **2b** exist in the enolic form, as shown in Scheme 1, and the former signal corresponds to the resonance of the phenolic proton whereas the latter one is due to the 3-OH proton. This conclusion was also supported by the connectivities of this 3-OH proton and those of the C-2 (δ 98.9 ppm), C-3 (δ 177.3 ppm) and C-1'' (δ 133.7 ppm), that were found in the HMBC spectrum of compound **2b**.

The existence of compound **2b** in the enolic form, while **2a** exists as a β-diketone structure, is probably due to the stabilisation of the conjugated system formed by the α,β-unsaturated keto and the 3-phenyl moieties in the case of **2b**.

The main feature of the ¹H nmr spectra of chromones **1a,b** is the resonance of H-3. This proton resonance appears as a singlet (δ 6.71 ppm) in the case of **1b** and as a quartet (δ 6.12 ppm) in the case of **1a**.

From the reactions of 5-benzyloxychromones **1a-g** with methylhydrazine one can expect the two possible isomers 3-(2-benzyloxy-6-hydroxyphenyl)-1-methylpyrazoles **3a-g** and 5-(2-benzyloxy-6-hydroxyphenyl)-1-methylpyrazoles **4a-g**, as shown in Scheme 3. However, the ¹H nmr spectra of the obtained pyrazoles exhibit the 6'-OH proton signals at δ 11.82-12.02 ppm, which is consistent with a hydrogen bond between the 6'-OH proton and the pyrazole (N-2) (Figure 1) and proves the structure of the 3-(2-benzyloxy-6-hydroxyphenyl)-1-methylpyrazoles **3a-g**. The ¹³C nmr resonance of the C-methyl group of pyrazole **3a** (δ 11.3 ppm) is similar to that observed for 3-phenyl-1,5-dimethylpyrazole (δ 11.9 ppm) and not with that of 5-phenyl-1,3-dimethylpyrazole (δ 13.2 ppm) [15].

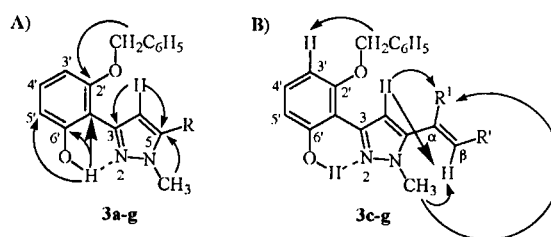


Figure 1

The connectivities that were found in the HMBC spectra of pyrazoles **3a-g** (A, Figure 1) allowed the assignment of the resonances of C-3 and C-5 of the pyrazole ring and those of the carbons of the 2-benzyloxy-6-hydroxyphenyl ring.

The *trans* configuration of the vinylic system of pyrazoles **3c-g** was established on the basis of the vicinal coupling constants $^3J_{\text{H}\alpha\text{-H}\beta} \sim 16$ Hz for **3c-e** and on the absence of NOE between the α -methyl group and H- β for **3f-g**. Some of the NOE cross peaks found in the NOESY spectra of pyrazoles **3c-g** (B, Figure 1) gave unequivocal support for the free rotation around C5-C α bond.

EXPERIMENTAL

Measurements.

Melting points were determined on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform solutions (ca. 0.3%) on a Bruker AMX 300 spectrometer, at 300.13 and 75.47 MHz, respectively; the chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane as internal reference. Unequivocal ^1H assignments were made by using 2D COSY and NOESY (mixing time of 800 ms) experiments, while ^{13}C assignments were made using HETCOR and HMBC (delay for long-range J C/H couplings were optimised for 7 Hz) experiments. Mass spectra were obtained at 70 eV electron impact ionisation using a VG Aupospec Q mass spectrometer. Elemental analyses were carried out in the Chemistry Department at the Coimbra University.

Preparative thin layer chromatography was carried out on silica gel plates (Riedel silica gel 60 DGF₂₅₄). Column chromatography was also performed on silica gel (Merck silica gel 60, 70-230 mesh). All other chemicals and solvents used herein were obtained from commercial sources and used as received or dried using standard procedures.

Synthesis.

Synthesis of 2'-Benzyloxy-6'-hydroxyacetophenone.

To a solution of 2',6'-dihydroxyacetophenone (5 g, 33 mmoles) in acetone (50 mL) were added potassium carbonate (15 g, 106 mmoles), potassium iodide (9 g, 53 mmoles) and benzyl bromide (4.6 mL, 39.6 mmoles). The mixture was refluxed (-80 °C) for 12 hours, then the inorganic salts were filtered off and washed with acetone (3 x 15 mL). The organic layer was evaporated to dryness; the residue was taken in chloroform washed with water and purified by column chromatography, using dichloromethane as eluent. The solvent was evaporated to dryness and the residue was recrystallized from ethanol; the expected 2'-benzyloxy-6'-hydroxyacetophenone crystallised as yellowish needles (5.75 g, 72%); mp 110-111 °C (lit 109-110 °C [16]); ^1H nmr: δ 2.62 (s, 3 H, 2-CH₃), 5.13 (s, 2 H, 2'-OCH₂C₆H₅), 6.47 (d, $J = 8.4$ Hz, 1 H, H-5'), 6.59 (d, $J = 8.2$ Hz, 1 H, H-3'), 7.34 (dd, $J = 8.4$ and 8.2 Hz, 1 H, H-4'), 7.39-7.45 (m, 5 H, 2'-OCH₂C₆H₅), 13.26 (s, 1 H, 6'-OH); ^{13}C nmr: δ 34.1 (2-CH₃), 71.1 (2'-OCH₂C₆H₅), 102.2 (C-3'), 111.0 (C-5'), 111.5 (C-1'), 128.0 (C-2,6 of 2'-OCH₂C₆H₅), 128.5 (C-4 of 2'-OCH₂C₆H₅), 128.8 (C-3,5 of 2'-OCH₂C₆H₅), 135.8 (C-1 of

2'-OCH₂C₆H₅), 136.1 (C-4'), 160.6 (C-6'), 164.7 (C-2'), 205.2 (C-1); ms (EI): m/z (relative intensity) 242 (M⁺, 17), 224 (12), 200 (34), 199 (7), 181 (7), 165 (8), 137 (10), 123 (11), 105 (10), 91 (100), 77 (9).

Anal. Calcd. for C₁₅H₁₄O₃·1/2H₂O: C, 71.69; H, 6.01. Found: C, 71.71; H, 6.08.

Synthesis of 1-(2-Benzyloxy-6-hydroxyphenyl)-1,3-butanedione **2a** and 1-(2-Benzyloxy-6-hydroxyphenyl)-3-hydroxy-3-phenyl-2-propen-1-one **2b**.

Sodium hydride (88 mg, 2.0 mmoles) was added to a solution of 2'-benzyloxy-6'-hydroxyacetophenone (727 mg, 2.0 mmoles) in dry THF (30 mL), followed by the addition of acetyl or benzoyl chloride (3 mmoles). The mixture was refluxed, under nitrogen, for 4 hours. After that period it was poured into a mixture of ice (50 g), water (100 mL) and hydrochloric acid (pH adjusted to 5-6). The obtained solid was removed by filtration, dissolved in chloroform (10 mL) and purified by silica gel column chromatography, using dichloromethane as eluent. The solvent was evaporated to dryness and the residue was recrystallized from ethanol giving the expected products **2a,b**.

1-(2-Benzyloxy-6-hydroxyphenyl)-1,3-butanedione (**2a**).

This compound was obtained as white needles in 66% yield, mp 95-96 °C; ^1H nmr: δ 1.70 (s, 3 H, 4-CH₃), 4.03 (s, 2 H, 2-CH₂), 5.06 (s, 2 H, 2'-OCH₂C₆H₅), 6.45 (d, $J = 8.3$ Hz, 1 H, H-5'), 6.62 (d, $J = 8.3$ Hz, 1 H, H-3'), 7.36 (t, $J = 8.3$ Hz, 1 H, H-4'), 7.40-7.43 (m, 5 H, 2'-OCH₂C₆H₅), 13.08 (s, 1 H, 6'-OH); ^{13}C nmr: δ 29.5 (4-CH₃), 59.6 (2-CH₂), 71.4 (2'-OCH₂C₆H₅), 102.1 (C-3'), 111.2 (C-1'), 111.3 (C-5'), 128.6 (C-2,6 of 2'-OCH₂C₆H₅), 128.9 (C-4 of 2'-OCH₂C₆H₅), 129.0 (C-3,5 of 2'-OCH₂C₆H₅), 135.2 (C-4'), 136.8 (C-1 of 2'-OCH₂C₆H₅), 160.0 (C-6'), 165.1 (C-2'), 200.6 (C-3), 202.4 (C-1); ms (EI): m/z (relative intensity) 284 (M⁺, 17), 269 (17), 241 (11), 200 (13), 177 (15), 137 (16), 91 (100), 65 (20).

Anal. Calcd. for C₁₇H₁₆O₄: C, 71.82; H, 5.67. Found: C, 71.87; H, 5.60.

1-(2-Benzyloxy-6-hydroxyphenyl)-3-hydroxy-3-phenyl-2-propen-1-one (**2b**).

This compound was obtained as yellow needles in 67% yield, mp 155-157 °C; ^1H nmr: δ 5.10 (s, 2 H, 2'-OCH₂C₆H₅), 6.56 (d, $J = 8.3$ Hz, 1 H, H-5'), 6.64 (d, $J = 8.3$ Hz, 1 H, H-3'), 7.12-7.56 (m, 12 H, H-4', H-2, 3-C₆H₅ and 2'-OCH₂C₆H₅), 12.93 (s, 1 H, 6'-OH), 15.74 (s, 1 H, 3-OH); ^{13}C nmr: δ 71.4 (2'-OCH₂C₆H₅), 98.9 (C-2), 102.4 (C-3'), 110.2 (C-1'), 111.5 (C-5'), 126.7 (C-2',6"), 128.5 (C-2,6 of 2'-OCH₂C₆H₅), 128.7 (C-4 of 2'-OCH₂C₆H₅), 129.0 (C-3',5" and C-3,5 of 2'-OCH₂C₆H₅), 131.8 (C-4"), 133.7 (C-1"), 135.2 (C-4'), 135.6 (C-1 of 2'-OCH₂C₆H₅), 159.6 (C-6'), 164.5 (C-2'), 177.3 (C-3), 194.5 (C-1); ms (EI): m/z (relative intensity) 346 (M⁺, 13), 328 (13), 255 (13), 241 (12), 209 (16), 137 (16), 105 (49), 91 (100), 77 (25), 65 (16).

Anal. Calcd. for C₂₂H₁₈O₄: C, 76.27; H, 5.24. Found: C, 75.90; H, 5.30.

Synthesis of 5-Benzyloxy-2-(methyl or phenyl)chromones **1a,b**.

Iodine (12 mg, 0.047 mmoles) was added to a solution of the appropriate ketone **2a,b** (1.0 mmoles) in dimethyl sulfoxide (20 mL). The mixture was heated at 100 °C for 24 hours; after that period the mixture was poured into a mixture of ice (50 g), water

(100 mL) and some crystals of sodium thiosulfate (~100 mg); the obtained solid was collected by filtration. The collected solid was dissolved in chloroform (10 mL) and purified by silica gel column chromatography, using dichloromethane as eluent. The solvent was evaporated to dryness and the residue was recrystallized from ethanol giving the expected chromones **1a,b**.

5-Benzyloxy-2-methylchromone (**1a**).

This compound was obtained as white needles in 54% yield, mp 107-108 °C; ¹H nmr: δ 2.54 (d, *J* = 1.2 Hz, 3 H, 2-CH₃), 5.15 (s, 2 H, 5-OCH₂C₆H₅), 6.12 (q, *J* = 1.2 Hz, 1 H, H-3), 6.81 (d, *J* = 8.4 Hz, 1 H, H-6), 6.96 (d, *J* = 8.4 Hz, 1 H, H-8), 7.38-7.43 (m, 6 H, H-7 and 5-OCH₂C₆H₅); ¹³C nmr: δ 24.9 (2-CH₃), 71.3 (5-OCH₂C₆H₅), 107.2 (C-6), 110.3 (C-8), 110.8 (C-10), 114.7 (C-3), 127.8 (C-2,6 of 5-OCH₂C₆H₅), 128.4 (C-4 of 5-OCH₂C₆H₅), 128.8 (C-3,5 of 5-OCH₂C₆H₅), 131.7 (C-7), 135.8 (C-1 of 5-OCH₂C₆H₅), 154.1 (C-9), 155.4 (C-2), 157.2 (C-5), 160.7 (C-4); ms (EI): *m/z* (relative intensity) 266 (M⁺, 35), 176 (5), 147 (6), 119 (3), 91 (100), 65 (20).

Anal. Calcd. for C₁₇H₁₄O₃: C, 76.68; H, 5.30. Found: C, 76.36; H, 5.37.

5-Benzyloxy-2-phenylchromone (**1b**).

This compound was obtained as white needles in 65% yield, mp 151-152 °C; ¹H nmr: δ 5.26 (s, 2 H, 5-OCH₂C₆H₅), 6.71 (s, 1 H, H-3), 6.82 (dd, *J* = 8.4 and 0.8 Hz, 1 H, H-6), 7.10 (dd, *J* = 8.3 and 0.8 Hz, 1 H, H-8), 7.29 (t, *J* = 7.5 Hz, 1 H, H-4 of 5-OCH₂C₆H₅), 7.39 (t, *J* = 7.5 Hz, 2 H, H-3,5 of 5-OCH₂C₆H₅), 7.48 (dd, *J* = 8.4 and 8.3 Hz, 1 H, H-7), 7.46-7.50 (m, 3 H, H-3,4,5 of 2-C₆H₅), 7.63 (d, *J* = 7.5 Hz, 2 H, H-2,6 of 5-OCH₂C₆H₅), 7.84-7.89 (m, 2 H, H-2,6 of 2-C₆H₅); ¹³C nmr: δ 70.7 (5-OCH₂C₆H₅), 108.3 (C-6), 108.9 (C-3), 110.3 (C-8), 114.9 (C-10), 125.9 (C-2,6 of 2-C₆H₅), 126.5 (C-2,6 of 5-OCH₂C₆H₅), 127.5 (C-4 of 5-OCH₂C₆H₅), 128.4 (C-3,5 of 5-OCH₂C₆H₅), 128.8 (C-3,5 of 2-C₆H₅), 131.2 (C-4 of 2-C₆H₅), 131.3 (C-1 of 2-C₆H₅), 133.5 (C-7), 136.5 (C-1 of 5-OCH₂C₆H₅), 158.1 (C-9), 158.4 (C-5), 160.9 (C-2), 177.9 (C-4); ms (EI): *m/z* (relative intensity) 328 (M⁺, 70), 327 (11), 222 (64), 194 (20), 120 (13), 91 (100), 65 (18).

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

General Procedure for the Synthesis of 3-(2-Benzyloxy-6-hydroxyphenyl)-5-(methyl, phenyl or styryl)-1-methylpyrazoles **3a-g**.

Four batches (2 mmoles each) of methylhydrazine were consecutively added by 5 hours interval to a methanolic solution (50 mL) of the appropriate 5-benzyloxychromone **1a-g** (1.0 mmoles). The mixture was heated (80-90 °C), under nitrogen, for 24 hours; after that period the solvent was evaporated to dryness. The residue was taken in chloroform (50 mL), washed with water and purified by silica gel column chromatography. Pyrazoles **3a-g** were eluted with dichloromethane and the starting 5-benzyloxychromones **1a-g** were recovered by using chloroform as eluent. The solvent was evaporated to dryness and the residue, in each case, was recrystallized from ethanol. The yields of the obtained 1-methylpyrazoles **3a-f** and of the recovered chromones **1a-f** were as follows: **3a**, 49% and **1a**, 33%; **3b**, 53% and **1b**, 38%; **3c**, 40% and **1c**, 48%; **3d**, 40% and **1d**, 44%; **3e**, 40% and **1e**, 47%; **3f**, 38% and **1f**, 42%; **3g**, 39% and **1g**, 50%.

3-(2-Benzyloxy-6-hydroxyphenyl)-1,5-dimethylpyrazole (**3a**).

This compound was obtained as white needles, mp 119-120 °C; ¹H nmr: δ 2.21 (s, 3 H, 5-CH₃), 3.76 (s, 3 H, N-CH₃), 5.14 (s, 2 H, 2'-OCH₂C₆H₅), 6.51 (d, *J* = 8.2 Hz, 1 H, H-3'), 6.68 (dd, *J* = 8.2 and 1.0 Hz, 1 H, H-5'), 6.70 (s, 1 H, H-4), 7.08 (t, *J* = 8.2 Hz, 1 H, H-4'), 7.30-7.41 (m, 3 H, H-3,4,5 of 2'-OCH₂C₆H₅), 7.45 (d, *J* = 8.0 Hz, 2 H, H-2,6 of 2'-OCH₂C₆H₅), 12.02 (s, 1 H, 6'-OH); ¹³C nmr: δ 11.3 (5-CH₃), 36.3 (N-CH₃), 71.0 (2'-OCH₂C₆H₅), 103.3 (C-3'), 107.2 (C-1'), 107.6 (C-4), 110.6 (C-5'), 128.0 (C-2,6 of 2'-OCH₂C₆H₅), 128.3 (C-4 of 2'-OCH₂C₆H₅), 128.6 (C-4'), 128.9 (C-3,5 of 2'-OCH₂C₆H₅), 137.4 (C-1 of 2'-OCH₂C₆H₅), 138.7 (C-5), 147.3 (C-3), 157.3 (C-2'), 158.3 (C-6'); ms (EI): *m/z* (relative intensity) 294 (M⁺, 100), 293 (17), 279 (14), 277 (22), 264 (13), 217 (28), 204 (13), 188 (20), 175 (38), 106 (10), 91 (61), 77 (10), 65 (16), 56 (20).

Anal. Calcd. for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.50; H, 6.48; N, 9.35.

3-(2-Benzyloxy-6-hydroxyphenyl)-1-methyl-5-phenylpyrazole (**3b**).

This compound was obtained as white needles, mp 105-106 °C; ¹H nmr: δ 3.91 (s, 3 H, N-CH₃), 5.17 (s, 2 H, 2'-OCH₂C₆H₅), 6.54 (dd, *J* = 8.2 and 1.0 Hz, 1 H, H-3'), 6.72 (dd, *J* = 8.2 and 1.0 Hz, 1 H, H-5'), 7.04 (s, 1 H, H-4), 7.12 (t, *J* = 8.2 Hz, 1 H, H-4'), 7.30-7.48 (m, 10 H, H-2',3',4',5',6" and H-2,3,4,5,6 of 2'-OCH₂C₆H₅), 11.88 (s, 1 H, 6'-OH); ¹³C nmr: δ 37.4 (N-CH₃), 70.7 (2'-OCH₂C₆H₅), 103.1 (C-3'), 106.6 (C-1'), 107.9 (C-4), 110.3 (C-5'), 127.6 (C-2,6 of 2'-OCH₂C₆H₅), 127.9 (C-4 of 2'-OCH₂C₆H₅), 128.5 (C-2',6"), 128.57, 128.64 and 128.65 (C-4', C-3',4',5" and C-3,5 of 2'-OCH₂C₆H₅), 130.1 (C-1"), 137.0 (C-1 of 2'-OCH₂C₆H₅), 143.5 (C-5), 147.4 (C-3), 157.0 (C-2'), 157.9 (C-6'); ms (EI): *m/z* (relative intensity) 356 (M⁺, 100), 355 (21), 339 (18), 326 (12), 279 (30), 266 (18), 250 (20), 237 (35), 165 (10), 118 (21), 91 (66), 77 (14), 65 (17).

Anal. Calcd. for C₂₃H₂₀N₂O₂: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.69; H, 5.76; N, 7.99.

3-(2-Benzyloxy-6-hydroxyphenyl)-1-methyl-5-styrylpyrazole (**3c**).

This compound was obtained as white needles, mp 99-100 °C; ¹H nmr: δ 3.94 (s, 3 H, N-CH₃), 5.18 (s, 2 H, 2'-OCH₂C₆H₅), 6.58 (dd, *J* = 8.2 and 1.0 Hz, 1 H, H-3') 6.71 (dd, *J* = 8.2 and 1.0 Hz, 1 H, H-5'), 6.82 (AB, *J* = 16.2 Hz, 1 H, H-α), 6.88 (AB, *J* = 16.2 Hz, 1 H, H-β), 7.14 (t, *J* = 8.2 Hz, 1 H, H-4'), 7.18 (s, 1 H, H-4), 7.28-7.49 (m, 8 H, H-2',3',4',5",6" and H-3,4,5 of 2'-OCH₂C₆H₅), 7.55 (d, *J* = 7.9 Hz, 2 H, H-2,6 of 2'-OCH₂C₆H₅), 11.82 (s, 1 H, 6'-OH); ¹³C nmr: δ 36.4 (N-CH₃), 70.8 (2'-OCH₂C₆H₅), 102.9 (C-3'), 104.5 (C-4), 106.5 (C-1'), 110.3 (C-5'), 113.7 (C-α), 126.5 (C-2',6"), 128.09 (C-4 of 2'-OCH₂C₆H₅), 128.11 (C-2,6 of 2'-OCH₂C₆H₅), 128.4 (C-4"), 128.6 (C-4' and C-3,5 of 2'-OCH₂C₆H₅), 128.8 (C-3',5"), 132.8 (C-β), 136.3 (C-1"), 137.0 (C-1 of 2'-OCH₂C₆H₅), 140.6 (C-5), 147.3 (C-3), 157.1 (C-2'), 157.9 (C-6'); ms (EI): *m/z* (relative intensity) 382 (M⁺, 100), 381 (24), 365 (15), 356 (22), 305 (26), 292 (16), 291 (16), 276 (17), 263 (24), 144 (11), 91 (37), 65 (12).

Anal. Calcd. for C₂₅H₂₂N₂O₂: C, 78.51; H, 5.80; N, 7.33. Found: C, 78.18; H, 5.79; N, 7.53.

3-(2-Benzyloxy-6-hydroxyphenyl)-5-(4-methylstyryl)-1-methylpyrazole (**3d**).

This compound was obtained as white needles, mp 165-168 °C; ^1H nmr: δ 2.38 (s, 3 H, 4''-CH₃), 3.95 (s, 3 H, N-CH₃), 5.19 (s, 2'-OCH₂C₆H₅), 6.58 (d, J = 8.2 Hz, 1 H, H-3'), 6.71 (d, J = 8.2 Hz, 1 H, H-5'), 6.81 (AB, J = 15.6 Hz, 1 H, H- α), 6.83 (AB, J = 15.6 Hz, 1 H, H- β), 7.14 (t, J = 8.2 Hz, 1 H, H-4'), 7.16 (s, 1 H, H-4), 7.19 (d, J = 8.1 Hz, 2 H, H-3'',5''), 7.34 (d, J = 8.1 Hz, 2 H, H-2'',6''), 7.41-7.49 (m, 3 H, H-3,4,5 of 2'-OCH₂C₆H₅), 7.56 (d, J = 7.8 Hz, 2 H, H-2,6 of 2'-OCH₂C₆H₅), 11.83 (s, 1 H, 6'-OH); ^{13}C nmr: δ 21.3 (4''-CH₃), 36.4 (N-CH₃), 70.9 (2'-OCH₂C₆H₅), 102.9 (C-3'), 104.4 (C-4), 106.6 (C-1'), 110.3 (C-5'), 112.7 (C- α), 126.5 (C-3'',5''), 128.08 (C-4 of 2'-OCH₂C₆H₅), 128.11 (C-2,6 of 2'-OCH₂C₆H₅), 128.5 (C-4'), 128.6 (C-3,5 of 2'-OCH₂C₆H₅), 129.5 (C-2'',6''), 132.9 (C- β), 133.5 (C-1''), 137.0 (C-1 of 2'-OCH₂C₆H₅), 138.5 (C-4''), 140.9 (C-5), 147.3 (C-3), 157.1 (C-2'), 158.0 (C-6'); ms (EI): m/z (relative intensity) 396 (M⁺, 94), 395 (48), 379 (20), 370 (12), 319 (37), 305 (48), 290 (45), 277 (37), 207 (10), 173 (16), 158 (25), 149 (45), 129 (11), 119 (45), 105 (33), 91 (100), 77 (18), 65 (30).

Anal. Calcd. for C₂₆H₂₄N₂O₂: C, 78.76; H, 6.10; N, 7.06. Found: C, 78.89; H, 6.06; N, 7.22.

3-(2-Benzyloxy-6-hydroxyphenyl)-5-(4-methoxystyryl)-1-methylpyrazole (**3e**).

This compound was obtained as white needles, mp 144-146 °C; ^1H nmr: δ 3.84 (s, 3 H, 4''-OCH₃), 3.93 (s, 3 H, N-CH₃), 5.18 (s, 2 H, 2'-OCH₂C₆H₅), 6.58 (d, J = 8.2 Hz, 1 H, H-3'), 6.71 (d, J = 8.2 Hz, 1 H, H-5'), 6.74 (AB, J = 16.4 Hz, 1 H, H- α), 6.78 (AB, J = 16.4 Hz, 1 H, H- β), 6.92 (d, J = 8.8 Hz, 2 H, H-3'',5''), 7.14 (s, 1 H, H-4), 7.14 (t, J = 8.2 Hz, 1 H, H-4'), 7.38 (d, J = 8.8 Hz, 2 H, H-2'',6''), 7.40-7.48 (m, 3 H, H-3,4,5 of 2'-OCH₂C₆H₅), 7.56 (d, J = 7.8 Hz, 2 H, H-2,6 of 2'-OCH₂C₆H₅), 11.85 (s, 1 H, 6'-OH); ^{13}C nmr: δ 36.4 (N-CH₃), 55.4 (4''-OCH₃), 70.9 (2'-OCH₂C₆H₅), 103.0 (C-3'), 104.2 (C-4), 106.7 (C-1'), 110.4 (C-5'), 111.6 (C- α), 114.3 (C-3'',5''), 127.9 (C-2'',6''), 128.08 (C-4 of 2'-OCH₂C₆H₅), 128.13 (C-2,6 of 2'-OCH₂C₆H₅), 128.55 (C-4'), 128.61 (C-3,5 of 2'-OCH₂C₆H₅), 132.5 (C- β), 129.1 (C-1''), 137.1 (C-1 of 2'-OCH₂C₆H₅), 141.1 (C-5), 147.3 (C-3), 157.2 (C-2'), 158.0 (C-6'), 159.9 (C-4''); ms (EI): m/z (relative intensity) 412 (M⁺, 100), 411 (32), 395 (17), 335 (30), 322 (21), 306 (31), 305 (29), 293 (35), 291 (28), 278 (10), 223 (10), 174 (20), 135 (13), 121 (17), 91 (50), 65 (17).

Anal. Calcd. for C₂₆H₂₄N₂O₃: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.55; H, 6.08; N, 7.00.

3-(2-Benzyloxy-6-hydroxyphenyl)-5-(α -methylstyryl)-1-methylpyrazole (**3f**).

This compound was obtained as white needles, mp 98-99 °C; ^1H nmr: δ 2.14 (d, J = 1.5 Hz, 3 H, α -CH₃), 3.96 (s, 3 H, N-CH₃), 5.16 (s, 2 H, 2'-OCH₂C₆H₅), 6.56 (dd, J = 8.2 and 1.0 Hz, 1 H, H-3'), 6.61 (s broad, 1 H, H- β), 6.71 (dd, J = 8.2 and 1.0 Hz, 1 H, H-5'), 6.95 (s, 1 H, H-4), 7.13 (t, J = 8.2 Hz, 1 H, H-4'), 7.26-7.42 (m, 8 H, H-2'',3'',4'',5'',6'' and H-3,4,5 of 2'-OCH₂C₆H₅), 7.50 (d, 2 H, J = 7.1 Hz, H-2,6 of 2'-OCH₂C₆H₅), 11.89 (s, 1 H, 6'-OH); ^{13}C nmr: δ 18.7 (α -CH₃), 37.9 (N-CH₃), 70.8 (2'-OCH₂C₆H₅), 102.9 (C-3'), 106.6 (C-1'), 107.1 (C-4), 110.3 (C-5'), 126.9 (C- α), 127.3 (C-4''), 127.8 (C-2,6 of 2'-OCH₂C₆H₅), 128.0 (C-4 of 2'-OCH₂C₆H₅), 128.3 (C-2'',6''),

128.5 (C- β and C-3,5 of 2'-OCH₂C₆H₅), 129.0 (C-3'',5''), 132.0 (C-4'), 136.6 (C-1''), 136.9 (C-1 of 2'-OCH₂C₆H₅), 146.0 (C-5), 147.1 (C-3), 157.1 (C-2'), 158.0 (C-6'); ms (EI): m/z (relative intensity) 396 (M⁺, 100), 395 (22), 381 (14), 379 (15), 356 (9), 319 (36), 306 (20), 305 (18), 290 (23), 277 (32), 158 (16), 115 (17), 91 (70), 77 (9), 65 (17).

Anal. Calcd. for C₂₆H₂₄N₂O₂: C, 78.76; H, 6.10; N, 7.06. Found: C, 78.94; H, 5.68; N, 6.92.

3-(2-Benzyloxy-6-hydroxyphenyl)-1-methyl-5-(4-*t*-butyl- α -methylstyryl)pyrazole (**3g**).

This compound was obtained as white needles, mp 119-121 °C; ^1H nmr: δ 1.35 [s, 9 H, 4''-C(CH₃)₃], 2.15 (d, J = 1.5 Hz, 3 H, α -CH₃), 3.95 (s, 3 H, N-CH₃), 5.16 (s, 2 H, 2'-OCH₂C₆H₅), 6.55 (dd, J = 8.3 and 0.9 Hz, 1 H, H-3'), 6.57 (s broad, 1 H, H- β), 6.71 (dd, J = 8.3 and 0.9 Hz, 1 H, H-5'), 6.93 (s, 1 H, H-4), 7.13 (t, J = 8.3 Hz, 1 H, H-4'), 7.29 (d, J = 8.4 Hz, 2 H, H-2'',6''), 7.32-7.38 (m, 3 H, H-3,4,5 of 2'-OCH₂C₆H₅), 7.42 (d, J = 8.4 Hz, 2 H, H-3'',5''), 7.49 (d, J = 8.0 Hz, 2 H, H-2,6 of 2'-OCH₂C₆H₅), 11.91 (s, 1 H, 6'-OH); ^{13}C nmr: δ 18.8 (α -CH₃), 31.2 [4''-C(CH₃)₃], 34.6 [4''-C(CH₃)₃], 37.8 (N-CH₃), 70.8 (2'-OCH₂C₆H₅), 102.9 (C-3'), 106.7 (C-1'), 107.0 (C-4), 110.3 (C-5'), 125.3 (C-3'',5''), 126.2 (C- α), 127.9 (C-2,6 of 2'-OCH₂C₆H₅), 128.0 (C-4 of 2'-OCH₂C₆H₅), 128.5 (C- β and C-3,5 of 2'-OCH₂C₆H₅), 128.8 (C-2'',6''), 131.9 (C-4'), 133.8 (C-1''), 136.9 (C-1 of 2'-OCH₂C₆H₅), 146.3 (C-5), 147.1 (C-3), 150.4 (C-4''), 157.1 (C-2'), 158.0 (C-6'); ms (EI): m/z (relative intensity) 452 (M⁺, 100), 451 (25), 437 (15), 375 (17), 362 (23), 346 (20), 333 (27), 319 (25), 305 (18), 161 (10), 115 (10), 91 (60), 65 (15), 57 (18).

Anal. Calcd. for C₃₀H₃₂N₂O₂: C, 79.61; H, 7.13; N, 6.19. Found: C, 79.78; H, 6.92; N, 6.31.

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