

Synthesis of spiro-1-pyrazolines by the reaction of exocyclic $\alpha,\beta,\gamma,\delta$ -unsaturated ketones with diazomethane

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Dedicated to Professor Dr. Károly Lempert on the occasion of his 85th birthday

Abstract

New exocyclic $\alpha,\beta,\gamma,\delta$ -unsaturated ketones have been synthesized by the base-catalyzed reaction of chromanone, flavanone, their 1-thio analogues and *trans*-cinnamaldehydes. These unsaturated ketones were reacted with diazomethane at ca. 4 °C to afford spiro-1-pyrazolines in regioselective and stereospecific reaction. Structure and stereochemistry of all these new compounds have been elucidated by combined utilization of various spectroscopic, mainly NMR techniques.

Keywords: 3-Cinnamylidenechromanones, 3-cinnamylidene-1-thiochromanones, spiro-1-pyrazolines, one- and two-dimensional NMR

Introduction

Reaction of α,β -enones with diazomethane is a simple versatile procedure for the preparation of a wide variety of 1-pyrazolines as primary products which spontaneously isomerise or can be converted into the appropriate 2-pyrazoline isomers.¹ Chalcones and related α,β -unsaturated ketones are especially useful starting materials for the synthesis of 2-pyrazolines by this method.² Synthesis of spiro-1-pyrazolines by the 1,3-dipolar cycloaddition reaction of exocyclic α,β -unsaturated ketones and diazomethane has been achieved in several research laboratories.³ These

studies proved that this 1,3-dipolar cycloaddition is stereospecific providing stereohomogeneous spiro-1-pyrazolines as stable pyrazoline isomers.

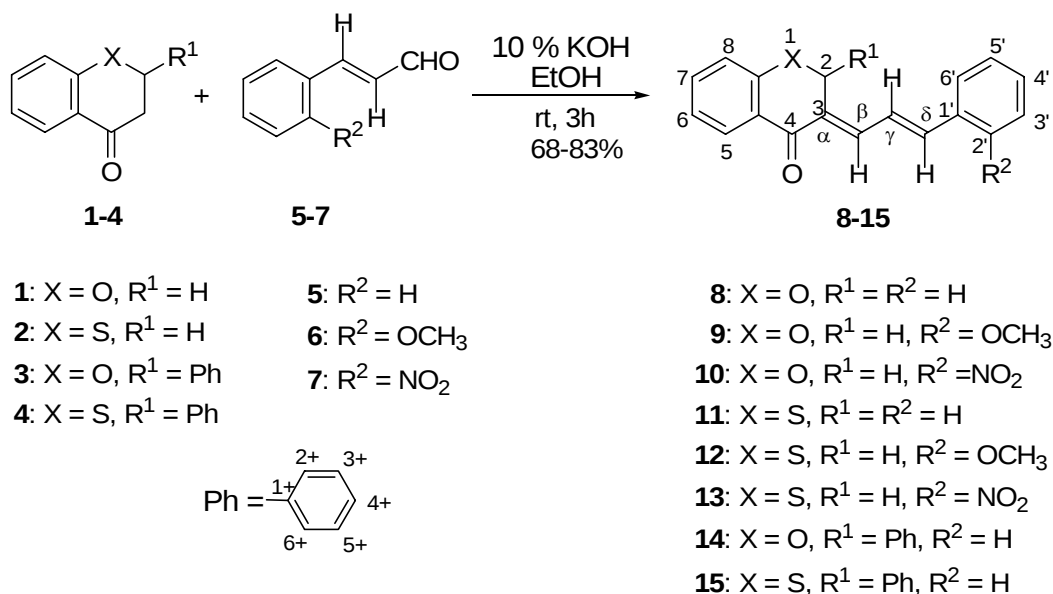
$\alpha,\beta,\gamma,\delta$ -Unsaturated ketones have been used as starting materials for the synthesis of styryl-2-pyrazolines.⁴ Previously we have investigated the reaction of $\alpha,\beta,\gamma,\delta$ -unsaturated ketones and diazomethane.⁵ This 1,3-dipolar cycloaddition reaction of (*E,E*)-cinnamylideneacetophenones was found to be regioselective affording 3-benzoyl-4-styryl-2-pyrazolines. As a continuation of our previous studies on the reaction of exocyclic α,β -unsaturated ketones^{3e,f,i,j} and (*E,E*)-cinnamylideneacetophenones⁵ with diazomethane, in our present paper this 1,3-dipolar cycloaddition reaction of exocyclic $\alpha,\beta,\gamma,\delta$ -unsaturated ketones derived from chromanone, flavanone and their 1-thio analogues and diazomethane is reported.

Results and Discussion

Exocyclic α,β -unsaturated ketones are well known compounds.⁶ However, the related exocyclic $\alpha,\beta,\gamma,\delta$ -unsaturated ketones have hitherto been scarcely mentioned in the chemical literature. Synthesis of a few representatives of 2-cinnamylidene-1-indanones, -1-tetralones and -1-benzosuberones was described in several papers.⁷ Since our aim was to study the 1,3-dipolar cycloaddition reaction of 3-cinnamylidenechromanones, -flavanones and their 1-thio analogues with diazomethane, first we needed to synthesize these previously unknown starting materials. We were going to investigate the influence of various structural elements of the starting exocyclic $\alpha,\beta,\gamma,\delta$ -unsaturated ketones, viz. the heteroatom in the cyclic ketone moiety of the molecule, a substituent present in the vicinity of the γ,δ -double bond.

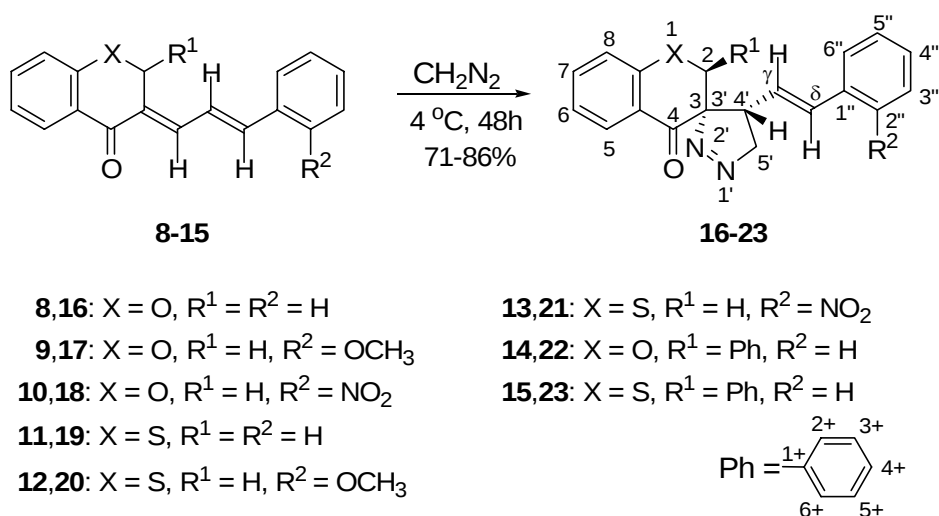
Chromanone (**1**), 1-thiochromanone (**2**), flavanone (**3**) and 1-thioflavanone (**4**) were allowed to react with *trans*-cinnamaldehydes (**5-7**) to afford the appropriate exocyclic $\alpha,\beta,\gamma,\delta$ -unsaturated ketones **8-15** (Scheme 1) in good yields (68-83%). Structure and stereochemistry of these new compounds have been elucidated by IR, mass and NMR spectroscopic measurements (*cf.* Experimental).

The value of the $^3J(\text{H-}\gamma,\text{H-}\delta)$ coupling (~ 15 Hz) reveals the (*E*) relative configuration of the double bond between C- γ and C- δ atoms. Considering the value of the $^3J(\text{H-}\beta,\text{H-}\gamma)$ coupling (~ 12 Hz) we can conclude the antiperiplanar arrangement of these hydrogen atoms in the preferred conformation. Due to the strong deshielding effect of the C=O group the chemical shift of H- β in *peri* position is ca. 0.5 ppm higher comparing to H- γ and H- δ . This observation and the detected H- β /H- δ and H-2/H- γ NOESY sterical proximities elucidate the (*Z*) arrangement of H- β and C-4 which corresponds to the (*E*) relative configuration of the exo-double bond (C-3=C- β) in compound where X = O but in the case of X = S compounds the same arrangement corresponds to the (*Z*) relative configuration.



Scheme 1

The 1,3-dipolar cycloaddition of diazomethane to (*E*)- and (*Z*)-isomers of exocyclic α,β -unsaturated ketones was found to be regioselective and stereospecific providing spiro-1-pyrazolines². The methylene moiety of the diazomethane was connected to the β -carbon atom of the α,β -enone and the stereochemistry of the starting α,β -unsaturated ketone was retained in each case. Reaction of (*E,E*)-cinnamylideneacetophenones and diazomethane have been found to be regioselective as well affording 3-benzoyl-4-styryl-2-pyrazolines as sole isolable products⁵. All these results prompted us to investigate this chemical transformation of our above-mentioned new exocyclic $\alpha,\beta,\gamma,\delta$ -unsaturated ketones **8-15**.



Scheme 2

Compounds **8-15** and diazomethane were allowed to react in a mixture of anhydrous diethyl ether and methylene chloride at *ca.* 4 °C to obtain *trans*-spiro-1-pyrazolines **16-23** in good yields (71-86%) (Scheme 2). The structure and stereochemistry of pyrazolines prepared have been elucidated by a combined utilization of various spectroscopic methods.

The cycloaddition of diazomethane on the C-3=C- β exo double bond results in the formation of two new stereogenic centres (C-3, C-4') in compounds **16-23**. The reactions gave racemates but for the sake of clarity, only one enantiomer with N-2' in „ α ” position is discussed. In the case of compounds X = O the configuration of C-3 is *S* whereas *R* when X = S. In this respect the configuration at C-4' and C-2 (in the case of 2-phenyl substitution) for the products **16-23** should be elucidated.

In accordance with the results of PM3 semiempirical calculations (Hyperchem 7)⁸ due to the ring strain caused by the N=N bond the pyrazoline ring is nearly planar. The condensed six-membered heterocyclic ring exists in an equilibrium of two half-chair conformers. In conformer “A” N-2' atom takes the quasi-equatorial, whereas in conformer “B” the quasi-axial position (Figure 1).

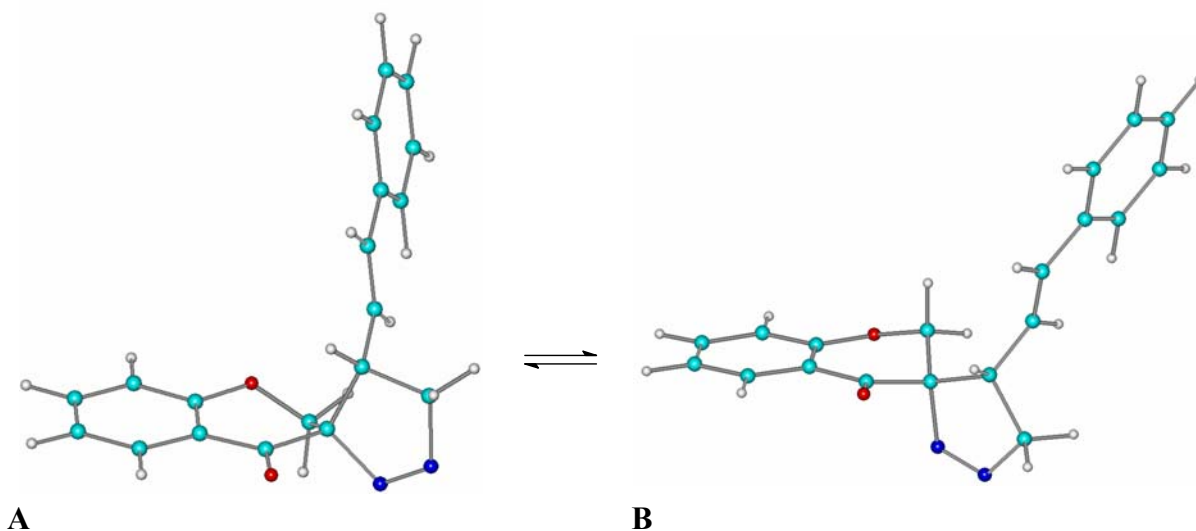
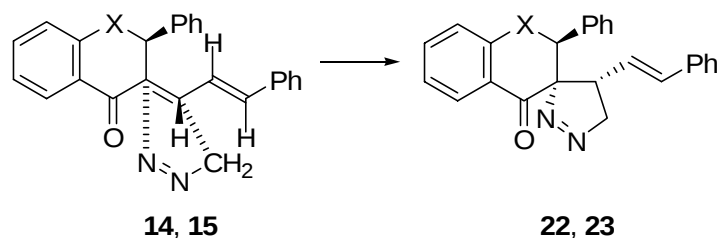


Figure 1. Stereostructure (Hyperchem 7, semiempirical, PM3)⁸ of compound **16**. The reactions yielded racemates but for the sake of clarity only one enantiomer with N-2' in „ α ” position is shown.

In the NOESY spectra we observed strong H- γ /H₂-2 correlations. Such type of steric proximities is possible only in the isomer shown in Figure 1. This observation correlates well with our previous results^{2a} concerning the synchronous type formation of the pyrazoline ring. Considering the ³*J*(H-4',H- γ) ~ 9.5 Hz coupling constant in addition to the H-4'/H- δ NOESY proximity we can conclude that H-4' and H- γ are antiperiplanar in the preferred conformation. As both H-2 geminal atoms strongly correlate with H- γ in the NOESY spectrum the A $\rightleftharpoons$ B

conformational equilibrium should be preferably shifted to the direction of B. A further evidence for this conformational preference can be concluded from the value of $J(\text{H-2a/C-8a}) = 3.4$ Hz and $J(\text{H-2b/C-8a}) = 5.7$ Hz couplings in compound **16** detected by J -HMBC measurements. Similar coupling constants (5.4 and 3.9 Hz) were measured for the thio analogue **19**.

Formation of one product was observed also for compounds **22** and **23** with $\text{R}^1 = \text{Ph}$. This can be explained well with the one-step character of diazomethane cycloaddition: in the transition state leading to **22** and **23** the diazomethane can link to the sterically non-hindered side (opposite to 2-phenyl)^{2a} affording the structures shown by Scheme 3 and Figure 2. The configuration of C-4' was determined by H-2/H- γ NOESY proximity.



Scheme 3

For the determination of the configuration at C-2 and investigation of the $\text{A} \rightleftharpoons \text{B}$ conformational equilibrium, the detected H-4'/H-2⁺,6⁺ NOESY correlation was decisive. These hydrogen atoms can occur in steric proximity (ca. 3.4 Å) only in the "B" conformer shown in Figure 2.

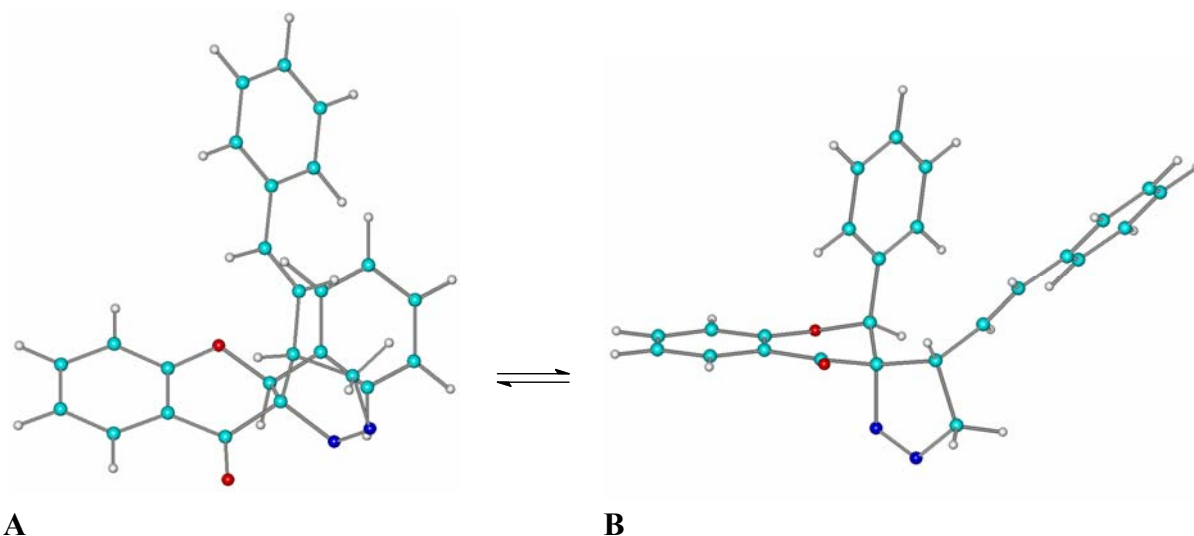


Figure 2. Stereostructure (Hyperchem 7, semiempirical, PM3)⁸ of compound **22**.

The $^3J(\text{H-4}', \text{H-}\gamma) \sim 9.7$ Hz coupling and the H-4'/H- δ NOESY cross-peak corroborate the antiperiplanar arrangement of H-4' and H- γ atoms in the preferred conformation. In conformer "B" H- γ and H- δ atoms are located above the plane of 2-phenyl group and due to its shielding the chemical shifts of these hydrogen atoms are ca. 0.3-0.5 ppm lower than those in compound **16**.

Conclusions

First synthesis of hitherto unknown group of 4'-styryl-spiro-1-pyrazolines has been achieved by the reaction of exocyclic $\alpha, \beta, \gamma, \delta$ -unsaturated ketones with diazomethane. This reaction proved to be regioselective and stereospecific as in the case of the related exocyclic α, β -unsaturated ketones. Stereospecific formation of these 1-pyrazolines is based on a one-step 1,3-dipolar cycloaddition of the diazomethane on the less hindered side of the α, β -double bond of the unsaturated ketones.

Experimental Section

General. Melting points were determined on a *Kofler* hot-stage apparatus and are uncorrected. ^1H - and ^{13}C -NMR spectra were recorded in CDCl_3 at room temperature with a Bruker Avance DRX-500. Chemical shifts are given on the δ -scale and were referenced to the solvents ($\delta_{\text{C}} = 77.05$ and $\delta_{\text{H}} = 7.27$). For the ^1H and ^{13}C signal assignments ^1H , ^{13}C , DEPT-135, APT and two-dimensional gradient selected $^1\text{H}/^1\text{H}$ -COSY, $^1\text{H}/^1\text{H}$ -NOESY, $^1\text{H}/^{13}\text{C}$ -HSQC, $^1\text{H}/^{13}\text{C}$ -HMQC, $^1\text{H}/^{13}\text{C}$ -HMBC and $^1\text{H}/^{13}\text{C}$ -J-HMBC spectra were measured. In the case of overlapping ^1H signals, the appropriate chemical shifts were determined utilizing the $^1\text{H}/^{13}\text{C}$ -HSQC or $^1\text{H}/^1\text{H}$ -COSY spectra. Regarding the monosubstituted phenyl groups (AA'MM'X spin system) simple first-order approximation was applied. The pulse programs of all experiments were taken from the Bruker software library. The IR spectra were obtained with a Perkin-Elmer 16 PC instrument. Mass spectra (CI) were recorded on a VG trio-2 apparatus. Elemental analyses (C,H,N) were measured in-house with a Carlo Erba 1106 instrument. TLC was performed on Kieselgel 60 F₂₅₄ (Merck) layer using toluene:ethyl acetate (4:1, v/v) as eluent.

General procedure for the synthesis of exocyclic $\alpha, \beta, \gamma, \delta$ -unsaturated ketones **8-15**

A mixture of chromanone (**1**), 1-thiochromanone (**2**), flavanone (**3**) or 1-thioflavanone (**4**) (10.0 mmol), *trans*-cinnamaldehyde (**5-7**, 12.0 mmol), 10% potassium hydroxide (20 mL) and ethanol (60 mL) was stirred at room temperature for 3 h, then poured onto crushed ice. The precipitate was separated by filtration, washed free of base, and recrystallized from methanol to obtain compounds **8-15** (Scheme 1).

(3E)-3-[(2E)-3-Phenylprop-2-en-1-ylidene]-3,4-dihydro-2H-1-benzopyran-4-one (8). Prepared as yellow needles in 73% yield, mp 136-137 °C; ¹H-NMR (δ, CDCl₃): 8.02 (dd, *J* = 7.9, 1.7 Hz, H-5), 7.52 (d, *J* = 7.2 Hz, H-2',6'), 7.50 (H-β), 7.45 (H-7), 7.41 (t, *J* = 7.2 Hz, H-3',5'), 7.36 (t, *J* = 7.2 Hz, H-4'), 7.09 (d, *J* = 15.3 Hz, H-δ), 7.08 (t, *J* = 7.5 Hz, H-6), 7.02 (dd, *J* = 15.3, 11.4 Hz, H-γ), 7.00 (d, *J* = 8.7 Hz, H-8), 5.27 (d, *J* = 1.5 Hz, H₂-2); ¹³C-NMR (δ, CDCl₃): 182.0 (C-4), 161.4 (C-8a), 143.3 (C-δ), 136.1 (C-1'), 136.0 (C-β), 135.6 (C-7), 129.5 (C-4'), 129.2 (C-3), 128.9 (C-3',5'), 127.9 (C-5), 127.5 (C-2',6'), 122.5 (C-4a), 121.9 (C-6), 121.6 (C-γ), 117.9 (C-8), 67.0 (C-2); IR (cm⁻¹): 1664, 1608, 1465, 1328, 1264, 1217, 1167, 1137, 1016, 975, 829, 748, 691, 520; MS (EI 70 eV): *m/z*(%) = 262 (M⁺, 61), 171 (58), 141 (58), 121 (100); Anal. Calcd. for C₁₈H₁₄O₂: C, 82.42; H, 5.38. Found: C, 82.51; H, 5.43.

(3E)-3-[(2E)-3-(2-Methoxyphenyl)prop-2-en-1-ylidene]-3,4-dihydro-2H-1-benzopyran-4-one (9). Obtained as yellow needles in 83% yield, mp 161-162 °C; ¹H-NMR (δ, CDCl₃): 8.02 (dd, *J* = 7.9, 1.7 Hz, H-5), 7.55 (H-6'), 7.54 (H-β), 7.47 (ddd, *J* = 8.4, 7.1, 1.7 Hz, H-7), 7.44 (d, *J* = 15.4 Hz H-δ), 7.32 (ddd, *J* = 8.6, 7.1, 1.6 Hz, H-4'), 7.10 (dd, *J* = 15.4, 12.0 Hz, H-γ), 7.07 (t, *J* = 7.5 Hz, H-6), 7.00 (d, *J* = 9.0 Hz, H-8), 6.98 (t, *J* = 8.2 Hz, H-5'), 6.92 (d, *J* = 8.3 Hz, H-3'), 5.26 (d, *J* = 1.5 Hz, H₂-2), 3.90 (s, 2'-OCH₃); ¹³C-NMR (δ, CDCl₃): 181.9 (C-4), 161.4 (C-8a), 157.8 (C-2'), 138.8 (C-δ), 137.2 (C-β), 135.4 (C-7), 130.7 (C-4'), 128.3 (C-3), 127.9 (C-6'), 127.8 (C-5), 125.0 (C-1'), 122.5 (C-4a), 122.4 (C-γ), 121.8 (C-6), 120.8 (C-5'), 117.8 (C-8), 111.2 (C-3'), 67.1 (C-2), 55.6 (2'-OCH₃); IR (cm⁻¹): 1654, 1604, 1576, 1464, 1249, 1184, 1159, 1139, 1018, 1001, 831, 758; MS (EI 70 eV): *m/z*(%) = 292 (M⁺, 44), 261 (5), 171 (93), 121 (100); Anal. Calcd. for C₁₉H₁₆O₃: C, 78.06; H, 5.52. Found: C, 78.17; H, 5.48.

(3E)-3-[(2E)-3-(2-Nitrophenyl)prop-2-en-1-ylidene]-3,4-dihydro-2H-1-benzopyran-4-one (10). Isolated as yellow plates in 79% yield, mp 198-199 °C; ¹H-NMR (δ, CDCl₃): 8.02 (H-5, H-3'), 7.73 (d, *J* = 7.7 Hz H-6'), 7.65 (t, *J* = 8.0 Hz, H-5'), 7.57 (d, *J* = 15.1 Hz H-δ), 7.52 (H-β), 7.51 (H-4'), 7.49 (H-7), 7.08 (td, *J* = 7.5, 0.7 Hz, H-6), 7.01 (d, *J* = 7.8 Hz, H-8), 6.97 (dd, *J* = 15.2, 11.9 Hz, H-γ), 5.27 (s, H₂-2); ¹³C-NMR (δ, CDCl₃): 181.0 (C-4), 161.4 (C-8a), 148.1 (C-2'), 137.3 (C-δ), 135.9 (C-7), 134.7 (C-β), 133.3 (C-5'), 131.8 (C-1'), 131.4 (C-3), 129.5 (C-4'), 128.6 (C-6'), 128.0 (C-5), 126.3 (C-γ), 125.1 (C-3'), 122.3 (C-4a), 122.1 (C-6), 117.9 (C-8), 66.9 (C-2); IR (cm⁻¹): 1670, 1608, 1511, 1465, 1342, 1255, 1218, 1165, 1140, 1034, 973, 864, 828, 792; MS (EI 70 eV): *m/z*(%) = 307 (M⁺, 2), 290 (54), 260 (21), 171 (100); Anal. Calcd. for C₁₈H₁₃NO₄: C, 70.35; H, 4.26. Found: C, 70.26; H, 4.31.

(3Z)-3-[(2E)-3-Phenylprop-2-en-1-ylidene]-3,4-dihydro-2H-1-benzothiopyran-4-one (11). Prepared as yellow needles in 82% yield, mp 144-145 °C; ¹H-NMR (δ, CDCl₃): 8.18 (dd, *J* = 7.9 1.1 Hz, H-5), 7.53 (d, *J* = 7.5 Hz, H-2',6'), 7.50 (d, *J* = 9.1 Hz, H-β), 7.39 (H-3',5'), 7.38 (H-7), 7.34 (H-4'), 7.33 (H-8), 7.25 (t, *J* = 8.1 Hz, H-6), 7.11 (H-γ), 7.10 (H-δ), 4.06 (s, H₂-2); ¹³C-NMR (δ, CDCl₃): 185.3 (C-4), 142.4 (C-δ), 140.9 (C-8a), 136.7 (C-β), 136.2 (C-1'), 132.7 (C-4a, C-7), 130.9 (C-3, C-5), 129.3 (C-4'), 128.8 (C-3',5'), 127.9 (C-8), 127.4 (C-2',6'), 125.8 (C-6), 122.5 (C-γ), 28.7 (C-2); IR (cm⁻¹): 1658, 1603, 1582, 1435, 1290, 1220, 1158, 1124, 1066, 1032, 975, 945, 897, 758, 735, 693; MS (EI 70 eV): *m/z*(%) = 278 (M⁺, 71), 263 (6), 187 (100), 141 (53); Anal. Calcd. for C₁₈H₁₄OS: C, 77.68; H, 5.07. Found: C, 77.76; H, 5.13.

(3Z)-3-[(2E)-3-(2-Methoxyphenyl)prop-2-en-1-ylidene]-3,4-dihydro-2H-1-benzothiopyran-4-one (12). Obtained as yellow plates in 78% yield, mp 135-136 °C; $^1\text{H-NMR}$ (δ , CDCl_3): 8.18 (dd, $J = 7.9, 1.3$ Hz, H-5), 7.56 (dd, $J = 7.7, 1.4$ Hz, H-6'), 7.54 (d, $J = 11.8$ Hz, H- β), 7.45 (d, $J = 15.4$ Hz, H- δ), 7.38 (td, $J = 7.5, 1.4$ Hz, H-7), 7.32 (d, $J = 7.4$ Hz, H-8), 7.31 (H-4'), 7.25 (td, $J = 7.5, 1.0$ Hz, H-6), 7.18 (dd, $J = 15.3, 11.8$ Hz, H- γ), 6.98 (t, $J = 7.5$ Hz, H-5'), 6.92 (d, $J = 8.3$ Hz, H-3'), 4.05 (s, H₂-2), 3.91 (s, 2'-OCH₃); $^{13}\text{C-NMR}$ (δ , CDCl_3): 185.3 (C-4), 157.7 (C-2'), 140.9 (C-8a), 138.0 (C- δ , C- β), 132.9 (C-4a), 132.6 (C-7), 130.5 (C-4'), 130.3 (C-5), 130.1 (C-3), 127.8 (C-8, C-6'), 125.7 (C-6), 125.2 (C-1'), 123.2 (C- γ), 120.8 (C-5'), 111.2 (C-3'), 55.6 (2'-OCH₃), 28.7 (C-2); IR (cm^{-1}): 1655, 1582, 1484, 1462, 1248, 1163, 1126, 1024, 976, 948, 750, 692; MS (EI 70 eV): $m/z(\%) = 308$ (M^+ , 43), 293 (6), 201 (9), 197 (100); Anal. Calcd. for $\text{C}_{19}\text{H}_{16}\text{O}_2\text{S}$: C, 74.01; H, 5.23; Found: C, 74.11; H, 5.18.

(3Z)-3-[(2E)-3-(2-Nitrophenyl)prop-2-en-1-ylidene]-3,4-dihydro-2H-1-benzothiopyran-4-one (13). Obtained as yellow needles in 76% yield, mp 179-180 °C; $^1\text{H-NMR}$ (δ , CDCl_3): 8.20 (dd, $J = 7.9, 1.4$ Hz, H-5), 8.02 (dd, $J = 8.2, 0.9$ Hz, H-3'), 7.75 (d, $J = 7.7$ Hz, H-6'), 7.65 (t, $J = 7.4$ Hz, H-5'), 7.59 (d, $J = 15.1$ Hz, H- δ), 7.50 (d, $J = 11.8$ Hz, H- β), 7.49 (t, $J = 8.2$ Hz, H-4'), 7.41 (td, $J = 7.6, 1.5$ Hz, H-7), 7.33 (d, $J = 7.4$ Hz, H-8), 7.27 (td, $J = 7.6, 1.0$ Hz, H-6), 7.07 (dd, $J = 15.1, 11.7$ Hz, H- γ), 4.06 (s, H₂-2); $^{13}\text{C-NMR}$ (δ , CDCl_3): 185.1 (C-4), 148.2 (C-2'), 140.9 (C-8a), 136.5 (C- δ), 135.4 (C- β), 133.3 (C-3), 133.2 (C-5'), 133.0 (C-7), 132.5 (C-4a), 132.0 (C-1'), 130.5 (C-5), 129.4 (C-4'), 128.6 (C-6'), 127.9 (C-8), 127.1 (C- γ), 126.0 (C-6), 125.1 (C-3'), 28.8 (C-2); IR (cm^{-1}): 1656, 1606, 1592, 1514, 1438, 1343, 1311, 1267, 1222, 1164, 1127, 967, 864, 757, 731, 699; MS (EI 70 eV): $m/z(\%) = 323$ (M^+ , 2), 306 (21), 276 (10), 187 (100); Anal. Calcd. for $\text{C}_{18}\text{H}_{13}\text{NO}_3\text{S}$: C, 66.87; H, 4.05; Found: C, 66.96; H, 4.01.

(3E)-2-Phenyl-3-[(2E)-3-phenylprop-2-en-1-ylidene]-3,4-dihydro-2H-1-benzopyran-4-one (14). Prepared as yellow needles in 68% yield, mp 142-143 °C; $^1\text{H-NMR}$ (δ , CDCl_3): 7.94 (dd, $J = 7.8, 1.7$ Hz, H-5), 7.79 (dd, $J = 11.9, 1.0$ Hz, H- β), 7.48 (H-2',6'), 7.45 (H-7), 7.41 (H-2',6'), 7.37 (H-3',5'), 7.35 (H-4'), 7.31 (H-3',5'), 7.26 (H-4'), 7.17 (d, $J = 15.2$ Hz, H- δ), 7.04 (dd, $J = 8.3, 1.0$ Hz, H-8), 6.99 (t, $J = 7.8$ Hz, H-6), 6.97 (dd, $J = 15.2, 12.0$ Hz, H- γ), 6.71 (H-2); $^{13}\text{C-NMR}$ (δ , CDCl_3): 181.6 (C-4), 159.4 (C-8a), 144.2 (C- δ), 138.6 (C-1'), 138.1 (C- β), 135.9 (C-7, C-1'), 129.6 (C-4'), 130.8 (C-3), 128.9 (C-3',5'), 128.7 (C-3',5'), 128.3 (C-4'), 127.6 (C-5), 127.5 (C-2',6'), 127.0 (C-2',6'), 122.3 (C-4a), 121.8 (C-6), 121.7 (C- γ), 118.5 (C-8), 77.2 (C-2); IR (cm^{-1}): 1655, 1606, 1580, 1461, 1325, 1214, 1154, 1029, 992, 942, 748, 693, 640; MS (EI 70 eV): $m/z(\%) = 338$ (M^+ , 40), 261 (38), 247 (100), 202 (39); Anal. Calcd. for $\text{C}_{24}\text{H}_{18}\text{O}_2$: C, 85.18; H, 5.36. Found: C, 85.09; H, 5.31.

(3Z)-2-Phenyl-3-[(2E)-3-phenylprop-2-en-1-ylidene]-3,4-dihydro-2H-1-benzothiopyran-4-one (15). Isolated as yellow plates in 72% yield, mp 134-135 °C; $^1\text{H-NMR}$ (δ , CDCl_3): 8.12 (dd, $J = 8.0, 1.5$ Hz, H-5), 7.71 (d, $J = 10.7$ Hz, H- β), 7.51 (H-2',6'), 7.45 (H-2',6'), 7.38 (H-3',5'), 7.36 (H-4'), 7.32 (H-7), 7.26 (H-8), 7.24 (H-3',5'), 7.20 (H-4'), 7.18 (H-6, H-8), 7.12 (dd, $J = 15.2, 10.7$ Hz, H- γ), 5.62 (H-2); $^{13}\text{C-NMR}$ (δ , CDCl_3): 185.2 (C-4), 143.3 (C- δ), 139.4 (C-1'), 137.7 (C- β), 137.5 (C-8a), 136.1 (C-1'), 132.6 (C-4a), 133.2 (C-3, C-7), 129.6 (C-5), 129.4 (C-4'), 128.8 (C-3',5'), 128.4 (C-3',5'), 128.2 (C-8), 127.5 (C-2',6', C-4'), 127.4 (C-2',6'),

125.9 (C-6), 122.2 (C- γ), 44.3 (C-2); IR (cm⁻¹): 1651, 1588, 1491, 1436, 1293, 1224, 1165, 1124, 1075, 955, 743, 692; MS (EI 70 eV): m/z (%) = 354 (M⁺, 27), 339 (5), 277 (10), 263 (100); Anal. Calcd. for C₂₄H₁₈OS: C, 81.34; H, 5.12. Found: C, 81.26; H, 5.18.

General method for the preparation of spiro-1-pyrazolines 16-23

A mixture of the appropriate $\alpha,\beta,\gamma,\delta$ -unsaturated ketone (**8-15**, 10.0 mmol), diazomethane (40.0 mmol, generated *in situ* by the reaction of N-nitroso-N-methylurea with potassium hydroxide), anhydrous diethyl ether (100 mL) and anhydrous methylenechloride (50 mL) was left to stand in a refrigerator (approx. 4 °C) for 48 h, then the solvent was evaporated under reduced pressure and the residue was crystallized from methanol to obtain spiro-1-pyrazolines **16-23** (Scheme 2).

4'[(E)-2-Phenylethenyl]-4',5',2,4-tetrahydrospiro[1-benzopyran-3,3'-pyrazole]-4-one (**16**).

Prepared as white needles in 86% yield, mp 155-156 °C; ¹H-NMR (δ , CDCl₃): 7.955 (dd, J = 7.9, 1.6 Hz, H-5), 7.57 (ddd, J = 8.4, 7.2, 1.6 Hz, H-7), 7.32 (H-3'',5''), 7.31 (H-2'',6''), 7.27 (H-4''), 7.10 (dd, J = 7.9, 7.2 Hz, H-6), 7.085 (d, J = 8.4 Hz, H-8), 6.48 (d, J = 15.8 Hz H- δ), 5.83 (dd, J = 15.8, 9.8 Hz, H- γ), 4.89 (dd, J = 18.0, 8.1 Hz, H_b-5'), 4.80 (d, J = 12.2 Hz, H_b-2), 4.795 (dd, J = 18.0, 4.3 Hz, H_a-5'), 4.58 (d, J = 12.2 Hz, H_a-2), 3.46 (ddd, J = 9.8, 8.1, 4.0 Hz, H-4'); ¹³C-NMR (δ , CDCl₃): 186.1 (C-4), 161.8 (C-8a), 137.0 (C-7), 135.9 (C-1''), 134.6 (C- δ), 128.7 (C-3'',5''), 128.2 (C-4''), 128.0 (C-5), 126.3 (C-2'',6''), 123.7 (C- γ), 122.0 (C-6), 119.7 (C-4a), 118.2 (C-8), 97.4 (C-3), 83.5 (C-5'), 69.2 (C-2), 39.9 (C-4'); IR (cm⁻¹): 1681, 1605, 1579, 1476, 1422, 1310, 1277, 1217, 1134, 980, 906, 835, 760, 692, 638; MS: m/z = 305 (M+H)⁺; Anal. Calcd. for C₁₉H₁₆N₂O₂: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.87; H, 5.36; N, 9.28.

4'[(E)-2-(2-Methoxyphenyl)ethenyl]-4',5',2,4-tetrahydrospiro[1-benzopyran-3,3'-pyrazole]-4-one (**17**).

Obtained as white needles in 79% yield, mp 148-149 °C; ¹H-NMR (δ , CDCl₃): 7.95 (dd, J = 8.5, 1.5 Hz, H-5), 7.57 (td, J = 7.8, 1.8 Hz, H-7), 7.32 (dd, J = 7.7, 1.5 Hz, H-6''), 7.25 (td, J = 7.8, 1.6 Hz, H-4''), 7.09 (H-6), 7.08 (H-8), 6.92 (t, J = 7.5 Hz, H-5''), 6.87 (d, J = 8.3 Hz, H-3''), 6.76 (d, J = 15.8 Hz H- δ), 5.86 (dd, J = 15.8, 9.7 Hz, H- γ), 4.88 (dd, J = 18.1, 8.0 Hz, H_b-5'), 4.81 (dd, J = 18.1, 4.1 Hz, H_a-5'), 4.79 (d, J = 12.4 Hz, H_b-2), 4.60 (d, J = 12.4 Hz, H_a-2), 3.83 (s, 2''-OCH₃), 3.48 (td, J = 8.9, 4.0 Hz, H-4') ; ¹³C-NMR (δ , CDCl₃): 186.2 (C-4), 161.8 (C-8a), 156.8 (C-2''), 136.9 (C-7), 129.6 (C- δ), 129.2 (C-4''), 128.0 (C-5), 127.1 (C-6''), 125.0 (C-1''), 124.5 (C- γ), 121.9 (C-6), 120.7 (C-5''), 119.8 (C-4a), 118.2 (C-8), 110.9 (C-3''), 97.5 (C-3), 83.8 (C-5'), 69.4 (C-2), 55.4 (2''-OCH₃), 40.3 (C-4'); IR (cm⁻¹): 1677, 1605, 1464, 1308, 1219, 989, 833, 755, 639; MS: m/z = 335 (M+H)⁺; Anal. Calcd. for C₂₀H₁₈N₂O₃: C, 71.84; H, 5.42; N, 8.37. Found: C, 71.93; H, 5.36; N, 8.44.

4'-[(E)-2-(2-Nitrophenyl)ethenyl]-4',5',2,4-tetrahydrospiro[1-benzopyran-3,3'-pyrazole]-4-one (**18**).

Isolated as white plates in 72% yield, mp 152-153 °C; ¹H-NMR (δ , CDCl₃): 7.97 (dd, J = 7.0, 1.0 Hz, H-3''), 7.95 (dd, J = 7.5, 1.5 Hz, H-5), 7.59 (H-7, H-5''), 7.48 (d, J = 7.8 Hz, H-6''), 7.44 (td, J = 7.7, 1.1 Hz, H-4''), 7.11 (t, J = 7.5 Hz, H-6), 7.09 (d, J = 8.3 Hz, H-8), 6.96 (d, J = 15.5 Hz H- δ), 5.78 (dd, J = 15.5, 9.7 Hz, H- γ), 4.92 (dd, J = 18.1, 8.1 Hz, H_b-5'), 4.83 (dd, J = 17.7 4.2 Hz, H_a-5'), 4.83 (d, J = 12.4 Hz, H_b-2), 4.61 (d, J = 12.4 Hz, H_a-2), 3.48 (ddd, J = 9.4, 8.3, 4.0 Hz, H-4'); ¹³C-NMR (δ , CDCl₃): 185.9 (C-4), 161.7 (C-8a), 147.6 (C-2''), 137.1 (C-7),

133.2 (C-5''), 132.0 (C-1''), 130.4 (C-8), 129.3 (C-γ), 128.9 (C-6''), 128.7 (C-4''), 128.0 (C-5), 124.7 (C-3''), 122.1 (C-6), 119.6 (C-4a), 118.2 (C-8), 97.4 (C-3), 83.8 (C-5'), 68.9 (C-2), 40.1 (C-4'); IR (cm⁻¹): 1685, 1606, 1579, 1523, 1477, 1345, 1308, 1218, 1149, 1040, 979, 907, 793, 765, 639; MS: *m/z* = 350 (M+H)⁺; Anal. Calcd. for C₁₉H₁₅N₃O₄: C, 65.32; H, 4.33; N, 12.02. Found: C, 65.41; H, 4.29; N, 12.11.

4'-[(E)-2-Phenylethenyl]-4',5',2,4-tetrahydrospiro[1-benzothiopyran-3,3'-pyrazole]-4-one (19). Obtained as white needles in 73% yield, mp 140-141 °C; ¹H-NMR (δ, CDCl₃): 8.12 (dd, *J* = 8.1, 1.0 Hz, H-5), 7.45 (td, *J* = 7.6, 0.9 Hz, H-7), 7.34 (H-3'',5''), 7.33 (H-2'',6''), 7.32 (H-8), 7.27 (H-4''), 7.23 (t, *J* = 7.6 Hz, H-6), 6.51 (d, *J* = 15.8 Hz H-δ), 5.94 (dd, *J* = 15.8, 9.3 Hz, H-γ), 4.81 (dd, *J* = 17.7, 3.3 Hz, H_b-5'), 4.70 (dd, *J* = 17.7, 7.5 Hz, H_a-5'), 3.97 (d, *J* = 13.9 Hz, H_b-2), 3.40 (ddd, *J* = 9.3, 7.7, 3.2 Hz, H-4'), 3.37 (d, *J* = 14.0 Hz, H_a-2); ¹³C-NMR (δ, CDCl₃): 187.7 (C-4), 142.2 (C-8a), 136.1 (C-1''), 134.5 (C-8), 134.0 (C-7), 130.7 (C-5), 129.4 (C-4a), 128.7 (C-3'',5''), 128.1 (C-4''), 127.5 (C-8), 126.3 (C-2'',6''), 124.9 (C-6, C-γ), 97.1 (C-3), 82.4 (C-5'), 41.7 (C-4'), 30.8 (C-2); IR (cm⁻¹): 1665, 1585, 1462, 1437, 1298, 1167, 1083, 983, 907, 751, 693; MS: *m/z* = 321 (M+H)⁺; Anal. Calcd. for C₁₉H₁₆N₂OS: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.32; H, 5.08; N, 8.83.

4'-[(E)-2-(2-Methoxyphenyl)ethenyl]-4',5',2,4-tetrahydrospiro[1-benzothiopyran]-4-one (20). Prepared as white plates in 71% yield, mp 118-119 °C; ¹H-NMR (δ, CDCl₃): 8.12 (dd, *J* = 8.0, 1.3 Hz, H-5), 7.45 (td, *J* = 7.6, 1.5 Hz, H-7), 7.33 (H-8, H-6''), 7.25 (td, *J* = 7.8, 1.6 Hz, H-4''), 7.22 (t, *J* = 7.5 Hz, H-6), 6.93 (t, *J* = 7.5 Hz, H-5''), 6.87 (d, *J* = 8.3 Hz, H-3''), 6.79 (d, *J* = 15.9 Hz H-δ), 5.98 (dd, *J* = 15.9, 9.3 Hz, H-γ), 4.85 (dd, *J* = 17.7, 3.2 Hz, H_b-5'), 4.70 (dd, *J* = 17.7, 7.5 Hz, H_a-5'), 3.96 (d, *J* = 13.9 Hz, H_b-2), 3.84 (s, 2''-OCH₃), 3.41 (d, *J* = 13.8 Hz, H_a-2), 3.39 (ddd, *J* = 9.1, 7.0, 3.2 Hz, H-4'); ¹³C-NMR (δ, CDCl₃): 187.9 (C-4), 156.8 (C-2''), 142.3 (C-8a), 133.9 (C-7), 130.7 (C-5), 129.6 (C-4a), 129.5 (C-8), 129.1 (C-4''), 127.5 (C-8), 127.1 (C-6''), 125.8 (C-γ), 125.3 (C-6), 125.2 (C-1''), 120.7 (C-5''), 111.0 (C-3''), 97.2 (C-3), 82.7 (C-5'), 55.4 (2''-OCH₃), 42.2 (C-4'), 30.9 (C-2); IR (cm⁻¹): 1667, 1583, 1488, 1436, 1291, 1242, 1211, 1022, 971, 911, 654; MS: *m/z* = 351 (M+H)⁺; Anal. Calcd. for C₂₀H₁₈N₂O₂S: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.47; H, 5.24; N, 8.06.

4'-[(E)-2-(2-Nitrophenyl)ethenyl]-4',5',2,4-tetrahydrospiro[1-benzothiopyran-3,3'-pyrazole]-4-one (21). Isolated as pale yellow plates in 74% yield, mp 151-152 °C; ¹H-NMR (δ, CDCl₃): 8.12 (dd, *J* = 8.0, 1.5 Hz, H-5), 7.96 (dd, *J* = 8.3, 1.1 Hz, H-3''), 7.58 (H-5''), 7.49 (H-6''), 7.46 (H-4''), 7.45 (H-7), 7.33 (H-8), 7.23 (H-6), 6.99 (d, *J* = 15.8 Hz H-δ), 5.89 (dd, *J* = 15.7, 9.4 Hz, H-γ), 4.83 (dd, *J* = 17.7, 3.6 Hz, H_b-5'), 4.75 (dd, *J* = 17.7, 7.5 Hz, H_a-5'), 3.99 (d, *J* = 13.9 Hz, H_b-2), 3.39 (d, *J* = 13.9 Hz, H_a-2), 3.45 (ddd, *J* = 9.4, 7.6, 3.4 Hz, H-4'); ¹³C-NMR (δ, CDCl₃): 187.6 (C-4), 147.6 (C-2''), 141.9 (C-8a), 133.8 (C-7), 131.9 (C-1''), 130.7 (C-5), 130.4 (C-γ), 130.1 (C-8), 129.3 (C-4a), 133.3 (C-5''), 128.8 (C-6''), 128.6 (C-4''), 127.8 (C-8), 125.4 (C-6), 124.7 (C-3''), 97.1 (C-3), 82.3 (C-5'), 41.7 (C-4'), 31.9 (C-2); IR (cm⁻¹): 1674, 1588, 1518, 1435, 1340, 1302, 1222, 974, 908, 788, 745; MS: *m/z* = 366 (M+H)⁺; Anal. Calcd. for C₁₉H₁₅N₃O₃S: C, 62.46; H, 4.14; N, 11.49. Found: C, 62.56; H, 4.19; N, 11.57.

2-Phenyl-4'-[(E)-2-phenylethenyl]-4',5',2,4-tetrahydrospiro[1-benzopyran-3,3'-pyrazole]-4-one (22). Obtained as white plates in 80% yield, mp 130-131 °C; ¹H-NMR (δ, CDCl₃): 7.97 (dd, *J* = 8.0, 1.7 Hz, H-5), 7.55 (ddd, *J* = 8.4, 7.2, 1.7 Hz, H-7), 7.42 (d, *J* = 7.5 Hz, H-2⁺, 6⁺), 7.29 (H-4⁺), 7.26 (H-3'', 5'', H-3⁺, 5⁺), 7.22 (H-4''), 7.09 (t, *J* = 7.5 Hz, H-6), 7.07 (d, *J* = 8.6 Hz, H-8), 7.00 (d, *J* = 6.9 Hz, H-2'', 6''), 6.07 (s, H-2), 5.97 (d, *J* = 15.8 Hz H-δ), 5.51 (dd, *J* = 15.8, 9.6 Hz, H-γ), 4.79 (dd, *J* = 17.9, 7.8 Hz, H_b-5'), 4.51 (dd, *J* = 17.0, 3.3 Hz, H_a-5'), 3.32 (td, *J* = 8.6, 3.3 Hz, H-4'); ¹³C-NMR (δ, CDCl₃): 187.1 (C-4), 160.4 (C-8a), 137.2 (C-7), 136.1 (C-1''), 135.4 (C-1⁺), 128.7 (C-4⁺), 133.3 (C-δ), 128.3-5 (C-3'', 5'', C-3⁺, 5⁺), 127.9 (C-2⁺, 6⁺), 127.8 (C-4''), 127.6 (C-5), 126.2 (C-2'', 6''), 124.7 (C-γ), 121.9 (C-6), 119.7 (C-4a), 118.6 (C-8), 101.0 (C-3), 84.1 (C-5'), 81.0 (C-2), 41.6 (C-4'); IR (cm⁻¹): 1681, 1604, 1463, 1299, 1215, 1148, 1110, 905, 759, 694; MS: *m/z* = 381 (M+H)⁺; Anal. Calcd. for C₂₅H₂₀N₂O₂: C, 78.93; H, 5.30; N, 7.36. Found: C, 78.84; H, 5.35; N, 7.44.

2-Phenyl-4'-[(E)-2-phenylethenyl]-4',5',2,4-tetrahydrospiro[1-benzothiopyran-3,3'-pyrazole]-4-one (23). Prepared as yellow plates in 82% yield, mp 144-145 °C; ¹H-NMR (δ, CDCl₃): 8.13 (d, *J* = 8.0 Hz, H-5), 7.44 (t, *J* = 7.6 Hz, H-7), 7.25 (H-3'', 5''), 7.24 (H-8), 7.22 (H-4''), 7.21 (H-4⁺), 7.20 (H-6), 7.17 (H-2⁺, 6⁺, H-3⁺, 5⁺), 7.03 (d, *J* = 7.4 Hz, H-2'', 6''), 5.89 (d, *J* = 15.8 Hz H-δ), 5.57 (dd, *J* = 15.5, 9.7 Hz, H-γ), 4.95 (H_b-5'), 4.79 (H_a-5'), 4.78 (s, H-2), 3.64 (t, *J* = 8.2 Hz, H-4'); ¹³C-NMR (δ, CDCl₃): 187.7 (C-4), 141.1 (C-8a), 139.2 (C-1⁺), 136.1 (C-1''), 134.5 (C-7), 134.0 (C-δ), 129.9 (C-5), 129.4 (C-4a), 128.6 (C-3⁺, 5⁺), 128.5 (C-3'', 5''), 128.1 (C-4⁺), 127.8 (C-4''), 127.6 (C-2⁺, 6⁺), 127.5 (C-8), 126.2 (C-2'', 6''), 125.1 (C-γ), 125.0 (C-6), 101.9 (C-3), 85.7 (C-5'), 49.0 (C-2), 41.1 (C-4'); IR (cm⁻¹): 1677, 1587, 1494, 1436, 1288, 1226, 1077, 1032, 905, 747, 693; MS: *m/z* = 397 (M+H)⁺; Anal. Calcd. for C₂₅H₂₀N₂OS: C, 75.74; H, 5.08; N, 7.06. Found: C, 75.84; H, 5.13; N, 7.01.

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