Synthesis of spiro-1-pyrazolines by the reaction of exocyclic α,β,γ,δ-unsaturated ketones with diazomethane

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

Abstract
New exocyclic α,β,γ,δ-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.

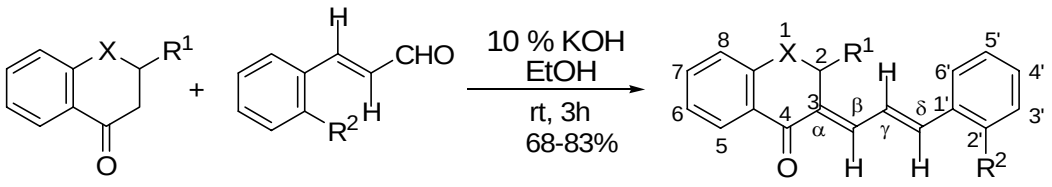
α,β,γ,δ-Unsaturated ketones have been used as starting materials for the synthesis of styryl-2-pyrazolines.[4] Previously we have investigated the reaction of α,β,γ,δ-unsaturated ketones and diazomethane.[5]. This 1,3-dipolar cycloaddition reaction of (*E,E*)-cinnamylideneacetophenones was found to be 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*)-cinnamylideneacetophenones[5] with diazomethane, in our present paper this 1,3-dipolar cycloaddition reaction of exocyclic α,β,γ,δ-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 α,β,γ,δ-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 α,β,γ,δ-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 α,β,γ,δ-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).

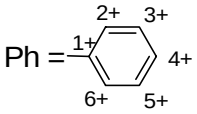
The value of the ^{3}J(H-γ,H-δ) coupling (~15 Hz) reveals the (*E*) relative configuration of the double bond between C-γ and C-δ atoms. Considering the value of the ^{3}J(H-β,H-γ) coupling (~12 Hz) we can conclude the antiperiplanar arrangement of these hydrogen atoms in the preferred conformation. 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.



1-4 **5-7** **8-15**

1: X = O, R^1 = H
2: X = S, R^1 = H
3: X = O, R^1 = Ph
4: X = S, R^1 = Ph

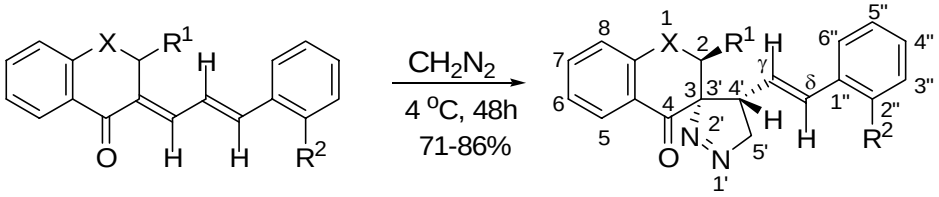
5: R^2 = H
6: R^2 = OCH_3
7: R^2 = NO_2



8: X = O, R^1 = R^2 = H
9: X = O, R^1 = H, R^2 = OCH_3
10: X = O, R^1 = H, R^2 = NO_2
11: X = S, R^1 = R^2 = H
12: X = S, R^1 = H, R^2 = OCH_3
13: X = S, R^1 = H, R^2 = NO_2
14: X = O, R^1 = Ph, R^2 = H
15: X = S, R^1 = Ph, R^2 = H

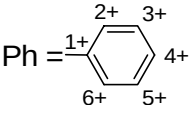
Scheme 1

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-pyrazolines[2]. 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 products[5]. All these results prompted us to investigate this chemical transformation of our above-mentioned new exocyclic α,β,γ,δ-unsaturated ketones **8-15**.



8-15 **16-23**

8,**16**: X = O, R^1 = R^2 = H
9,**17**: X = O, R^1 = H, R^2 = OCH_3
10,**18**: X = O, R^1 = H, R^2 = NO_2
11,**19**: X = S, R^1 = R^2 = H
12,**20**: X = S, R^1 = H, R^2 = OCH_3
13,**21**: X = S, R^1 = H, R^2 = NO_2
14,**22**: X = O, R^1 = Ph, R^2 = H
15,**23**: X = S, R^1 = Ph, R^2 = H



Scheme 2

Compounds **8-15** and diazomethane were allowed to react in a mixture of anhydrous diethyl ether and methylene chloride at *ca*. 4 ^{o}C to obtain *trans*-spiro-1-pyrazolines **16-23** in good yields (71-86%) (Scheme 2). The structure and sterochemistry 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).

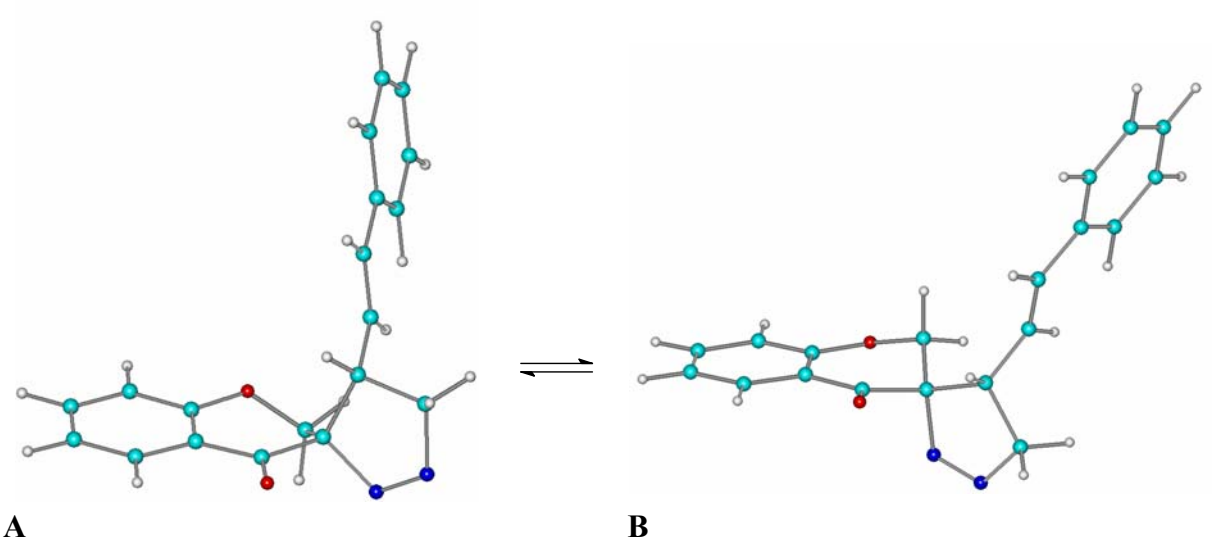
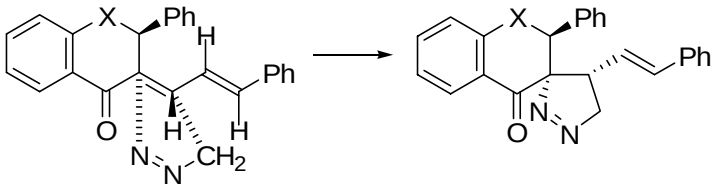


Figure 1. Stereostructure (Hyperchem 7, semiempirical, PM3)[8] of compound **16**. The reactions yielded racemates but for the sake of clarity only one enantiomer with N-2' in „α" position is shown.

In the NOESY spectra we observed strong H-γ/H_2-2 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 ⇌ 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*(H-2a/C-8a) = 3.4 Hz and *J*(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**.

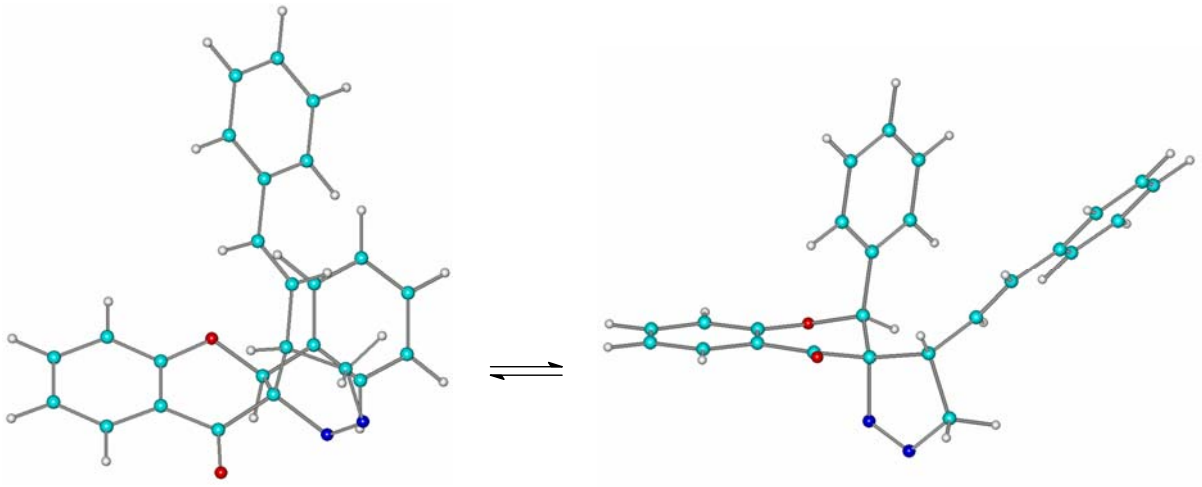
Formation of one product was observed also for compounds **22** and **23** with R^1 = Ph. This can be explained well with the one-step character of diazomethane cycloaddition: in the transition state leading to **22** and **23** the diazomethane can link to the sterically non-hindered side (opposite 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.



14, **15** **22**, **23**

Scheme 3

For the determination of the configuration at C-2 and investigation of the A ⇌ 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.



A **B**

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

The ^{3}J(H-4',H-γ) ~ 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 α,β,γ,δ-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. ^{1}H- 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 (δ_C = 77.05 and δ_H = 7.27). For the ^{1}H and ^{13}C signal assignments ^{1}H, ^{13}C, DEPT-135, APT and two-dimensional gradient selected ^{1}H/^{1}H–COSY, ^{1}H/^{1}H–NOESY, ^{1}H/^{13}C–HSQC, ^{1}H/^{13}C–HMQC, ^{1}H/^{13}C–HMBC and ^{1}H/^{13}C–J-HMBC spectra were measured. In the case of overlapping ^{1}H signals, the appropriate chemical shifts were determined utilisig the ^{1}H/^{13}C–HSQC or ^{1}H/^{1}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 F_{254} (Merck) layer using toluene:ethyl acetate (4:1, v/v) as eluent.

General procedure for the synthesis of exocyclic α,β,γ,δ-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).

(3*E*)-3-[(2*E*)-3-Phenylprop-2-en-1-ylidene]-3,4-dihydro-2*H*-1-benzopyran-4-one (8). Prepared as yellow needles in 73% yield, mp 136-137 °C; ^{1}H-NMR (δ, $CDCl_3$): 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, H_2-2); ^{13}C-NMR (δ, $CDCl_3$): 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 $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.51; H, 5.43.

(3*E*)-3-[(2*E*)-3-(2-Methoxyphenyl)prop-2-en-1-ylidene]-3,4-dihydro-2*H*-1-benzopyran-4-one (9). Obtained as yellow needles in 83% yield, mp 161-162 °C; ^{1}H-NMR (δ, $CDCl_3$): 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, H_2-2), 3.90 (s, 2'-OCH_3); ^{13}C-NMR (δ, $CDCl_3$): 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'-OCH_3); 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 $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.17; H, 5.48.

(3*E*)-3-[(2*E*)-3-(2-Nitrophenyl)prop-2-en-1-ylidene]-3,4-dihydro-2*H*-1-benzopyran-4-one (10). Isolated as yellow plates in 79% yield, mp 198-199 °C; ^{1}H-NMR (δ, $CDCl_3$): 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, H_2-2); ^{13}C-NMR (δ, $CDCl_3$): 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 $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26. Found: C, 70.26; H, 4.31.

(3*Z*)-3-[(2*E*)-3-Phenylprop-2-en-1-ylidene]-3,4-dihydro-2*H*-1-benzothiopyran-4-one (11). Prepared as yellow needles in 82% yield, mp 144-145 °C; ^{1}H-NMR (δ, $CDCl_3$): 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, H_2-2); ^{13}C-NMR (δ, $CDCl_3$): 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 $C_{18}H_{14}OS$: C, 77.68; H, 5.07. Found: C, 77.76; H, 5.13.

(3*Z*)-3-[(2*E*)-3-(2-Methoxyphenyl)prop-2-en-1-ylidene]-3,4-dihydro-2*H*-1-benzothiopyran-4-one (12). Obtained as yellow plates in 78% yield, mp 135-136 °C; ^{1}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, H_2-2), 3.91 (s, 2'-OCH_3); ^{13}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'-OCH_3), 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 $C_{19}H_{16}O_2S$: C, 74.01; H, 5.23; Found: C, 74.11; H, 5.18.

(3*Z*)-3-[(2*E*)-3-(2-Nitrophenyl)prop-2-en-1-ylidene]-3,4-dihydro-2*H*-1-benzothiopyran-4-one (13). Obtained as yellow needles in 76% yield, mp 179-180 °C; ^{1}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, H_2-2); ^{13}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 $C_{18}H_{13}NO_3S$: C, 66.87; H, 4.05). Found: C, 66.96; H, 4.01.

(3*E*)-2-Phenyl-3-[(2*E*)-3-phenylprop-2-en-1-ylidene]-3,4-dihydro-2*H*-1-benzopyran-4-one (14). Prepared as yellow needles in 68% yield, mp 142-143 °C; ^{1}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}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 $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.09; H, 5.31.

(3*Z*)-2-Phenyl-3-[(2*E*)-3-phenylprop-2-en-1-ylidene]-3,4-dihydro-2*H*-1-benzothiopyran-4-one (15). Isolated as yellow plates in 72% yield, mp 134-135 °C; ^{1}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-δ), 7.12 (dd, *J* = 15.2, 10.7 Hz, H-γ), 5.62 (H-2); ^{13}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 $C_{24}H_{18}OS$: 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 α,β,γ,δ-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; ^{1}H-NMR (δ, $CDCl_3$): 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'); ^{13}C-NMR (δ, $CDCl_3$): 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 $C_{19}H_{16}N_2O_2$: 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; ^{1}H-NMR (δ, $CDCl_3$): 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"-OCH_3), 3.48 (td, *J* = 8.9, 4.0 Hz, H-4') ; ^{13}C-NMR (δ, $CDCl_3$): 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"-OCH_3), 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 $C_{20}H_{18}N_2O_3$: 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; ^{1}H-NMR (δ, $CDCl_3$): 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'); ^{13}C-NMR (δ, $CDCl_3$): 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-δ), 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 $C_{19}H_{15}N_3O_4$: 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; ^{1}H-NMR (δ, $CDCl_3$): 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); ^{13}C-NMR (δ, $CDCl_3$): 187.7 (C-4), 142.2 (C-8a), 136.1 (C-1”), 134.5 (C-δ), 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 $C_{19}H_{16}N_2OS$: 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; ^{1}H-NMR (δ, $CDCl_3$): 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”-OCH_3), 3.41 (d, *J* = 13.8 Hz, H_a-2), 3.39 (ddd, *J* = 9.1, 7.0, 3.2 Hz, H-4’); ^{13}C-NMR (δ, $CDCl_3$): 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-δ), 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”-OCH_3), 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 $C_{20}H_{18}N_2O_2S$: 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; ^{1}H-NMR (δ, $CDCl_3$): 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’); ^{13}C-NMR (δ, $CDCl_3$): 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-δ), 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 $C_{19}H_{15}N_3O_3S$: 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 ^{o}C; ^{1}H-NMR (δ, $CDCl_3$): 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'); ^{13}C-NMR (δ, $CDCl_3$): 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 $C_{25}H_{20}N_2O_2$: 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 ^{o}C; ^{1}H-NMR (δ, $CDCl_3$): 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'); ^{13}C-NMR (δ, $CDCl_3$): 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 $C_{25}H_{20}N_2OS$: C, 75.74; H, 5.08; N, 7.06. Found: C, 75.84; H, 5.13; N, 7.01.

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