Scientific paper

A New Pyrrole Derivative From the Extracts of the Fungus *Monascus Pilosus*-Fermented Rice

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Received: 08-07-2009

Abstract

A chemical study on the *n*-BuOH-soluble fraction of the 95% EtOH extract of red yeast rice fermented with the fungus *Monascus pilosus* BCRC 38093 (Eurotiaceae) has resulted in the isolation of one new natural pyrrole derivative, designated as monascuspyrrole (**1**) together with nine known compounds, 3β-hydroxystigmast-5-en-7-one (**2**), β-sitostenone (**3**), monascin (**4**), ankaflavin (**5**), *N-trans*-feruloyltyramine (**6**), *N-cis*-feruloyltyramine (**7**), vanillic acid (**8**), methyl paraben (**9**), and syringaldehyde (**10**). The structure of the new compound **1** was identified by 1D and 2D NMR spectroscopy, as well as by high-resolution mass spectrometry. Other known compounds were identified by comparison of their spectral data with the literature data of authentic samples. Compounds **1** and **4** displayed mild inhibitory effect of nitric oxide production. Among the nine known isolates, compounds **2**, **3**, **6**, and **7** were found for the first time in this species.

Keywords: *Monascus pilosus*; fungus; red yeast rice; pyrrole; monascuspyrrole; nitric oxide production

1. Introduction

Red fermented rice (also called red mold rice), which is also known as red yeast rice, koji, red koji, anka, angkak, and ben-koji, has been used as a traditional food additive for improving the color of meat, fish, and soybean products, and is also described to have conserving properties in oriental countries for centuries. The fungus of *Monascus pilosus* produced useful secondary metabolites such as pigments,[1] monacolin K,[2] γ-aminobutyric acid (GABA),[3] dimerumic acid,[4] and citrinin.[5] Several secondary metabolites from *Monascus pilosus* have recently been found to have some beneficial pharmacological effects in decreasing blood pressure,[6] lowering plasma cholesterol levels[2,7,8] and antibacterial activity.[9] In the present day, they are mainly used as a natural colorant. *Monascus purpureus*, *Monascus pilosus*, and *Monascus anka* (Eurotiaceae) are representatives of the *Monascus* fungi traditionally used in East Asia as a source of pigments. The red yeast rice produces some red pigments and some physiologically and biologically active metabolites when grown on cooked rice.[10] Many secondary metabolites useful as food additives and pharmaceuticals have been reported to be produced by *Monascus pilosus*.[10] These metabolites were identified from the *Monascus* species, including azaphilones, furanoisophthalides, amino acids, polyketides, pyranoindole alkaloids, benzenoids, furans, and fatty acids in previous studies.[1,5,10–19] In a series of studies on the nitric oxide production and inhibitory activity from natural sources, we were especially interested to study the chemical composition of red yeast rice, and *Monascus pilosus* BCRC 38093 has been found to be one of the active species. Careful examination of the *n*-BuOH-soluble fraction of a 95% EtOH extract of the red yeast rice produced by *Monascus pilosus* BCRC 38093 led to the isolation of new pyrrole derivative, monascuspyrrole (**1**), along with nine known compounds (Figure 1). The structural elucidation of the new pyrrole derivative **1,** and the inhibitory effect on nitric oxide production by macrophages of the two isolates (**1** and **4**) are presented.

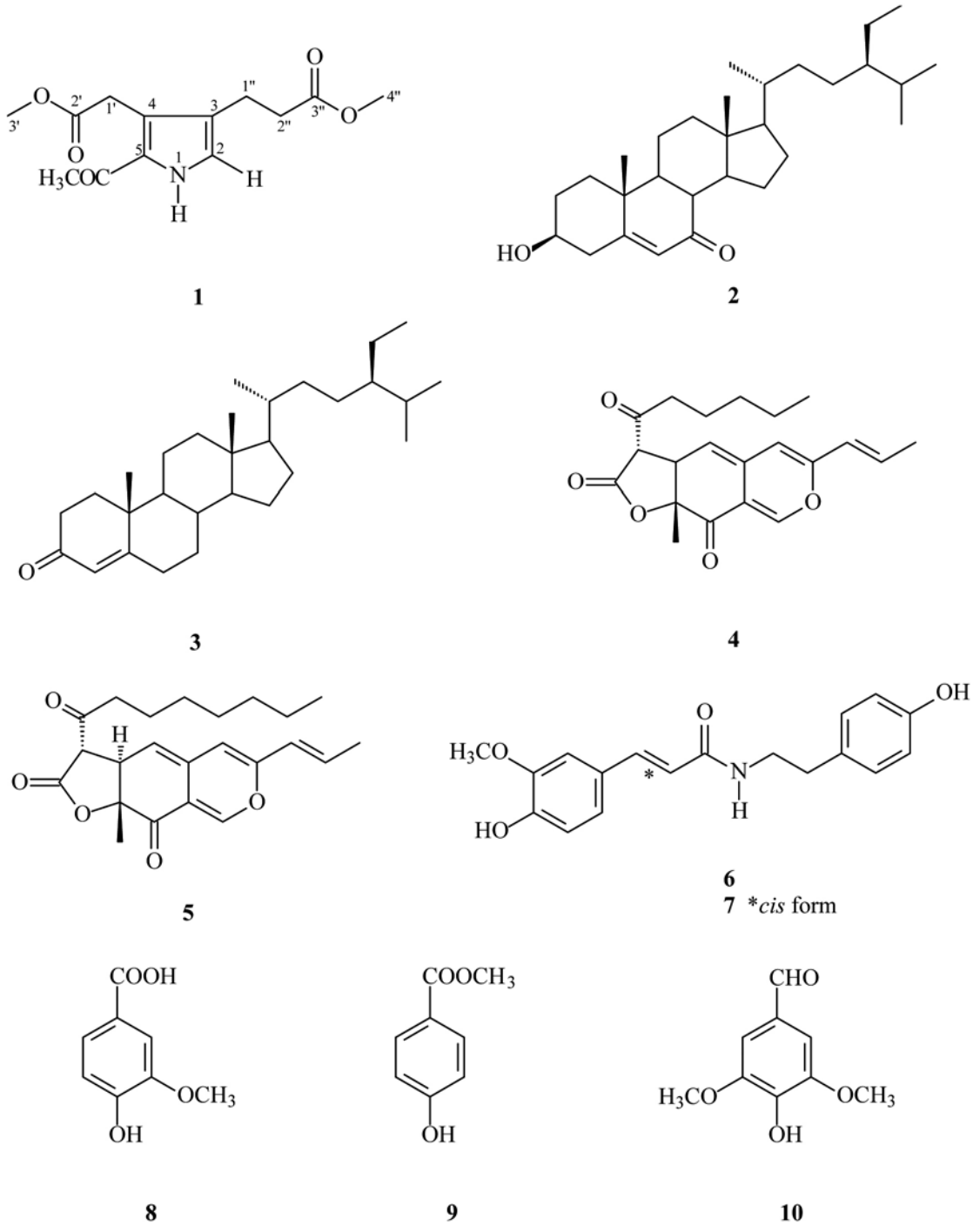

Figure 1: Structures of compounds **1–10** isolated from *Monascus pilosus* BCRC 38093.

2. Experimental

2. 1. General

All melting points were determined on a Yanaco micro-melting point apparatus and were uncorrected. Optical rotations were measured on a Jasco P-1020 digital polarimeter, UV spectra were obtained on a Jasco UV-240 spectrophotometer in MeOH, and IR spectra (KBr or neat) were taken on a Perkin-Elmer System 2000 FT-IR spectrometer. 1D (^{1}H, ^{13}C, DEPT) and 2D (COSY, NOESY, HSQC, HMBC) NMR spectra using $CDCl_3$ as solvent were recorded on a Varian Unity Plus 400 (400 MHz, ^{1}H NMR; 100 MHz, ^{13}C NMR) spectrometer. Chemical shifts were internally referenced to the solvent signals in $CDCl_3$ (^{1}H, δ 7.26; ^{13}C, δ 77.0) with TMS as the internal standard. Low-resolution ESI-MS spectra were ob-

tained on an API 3000 (Applied Biosystems) and high-resolution ESI-MS spectra on a Bruker Daltonics APEX II 30e spectrometer. Low-resolution EI-MS spectra were recorded on a Quattro GC/MS spectrometer having a direct inlet system. Silica gel (70–230 and 230–400 mesh, Merck) was used for column chromatography, and silica gel 60 F-254 plates (Merck) were used for TLC and preparative TLC.

Monascus pilosus BCRC 38093 was used throughout this study, and specimens deposited at the Bioresource Collection and Research Center (BCRC) of the Food Industry Research and Development Institute.

2. 2. Cultivation and Preparation of Red Yeast Rice

Monascus pilosus BCRC 38093 was maintained on potato dextrose agar (PDA) and the strain was cultured on potato dextrose agar slants at 25 °C for 7 days. After that the spores were harvested by sterile water. The spores (5×10^5) were seeded into 300 ml shake flasks containing 50 ml RGY medium (3% rice starch, 7% glycerol, 1.1% polypeptone, 3% soybean powder, 0.1 % $MgSO_4$, and 0.2% $NaNO_3$), and cultivated with shaking (150 rpm) at 25 °C for 3 days. After the mycelium enrichment step, an inoculum mixing of 100 ml mycelium broth and 100 ml of RGY medium was inoculated into plastic boxes (25 cm × 30 cm) containing 1 kg of sterile rice, and cultivated at 25 °C for producing red yeast rice. Above mentioned RGY medium was added for maintaining the growth. After 28 days of cultivation, the red yeast rice was harvested, and used as a sample for further extraction.

For extraction, isolation, and characterization data (UV, IR, 1D and 2D NMR, and HR ESI-MS spectra) see Supporting material.

2. 3. Determination of NO Production and Cell Viability Assay

Macrophage cell line culture

The murine macrophage cell line RAW264.7 (BCRC 60001 = ATCC TIB-71) was cultured in Dulbecco´s modified Eagle´s medium (DMEM, Gibco BRL Life Technologies Inc.) supplemented with 10% heat inactivated fetal bovin serum (FBS) and incubated at 37 °C in a humidified 5% CO_2 atmosphere with 96-well flat-bottomed culture plate. After 24 hours the medium was replaced with fresh DMEM and FBS. Then the test compounds (0, 1, 5, 10 or 20 μg/ml) were added in the presence of lipopolysaccharide (LPS, 1 μg/ml, Sigma) and incubated at the same conditions for 24 hours. The cultured cells were then centrifuged and the supernatants used for NO production measurement, with a MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay used to determine cell viability.

Measurement of nitrite concentration

The supernatant was mixed with an equal volume of the Griess reagent (1% sulfanilamide and 0.1% N-(1-naphthyl)ethylenediamine dihydrochloride in 2.5% phosphoric acid solution) and incubated for 10 min at room temperature. Nitrite concentration was determined by measuring the absorbance at 540 nm using an ELISA plate reader (μ Quant).[20]

Cell viability

The MTT colorimetric assay was modified from that reported by Mosmann.[21] Test is based upon the selective ability of living cells to reduce the yellow soluble salt, MTT, to a purple-blue insoluble formazan MTT solution (Merck, dissolved in phosphate-buffered saline at 5 mg/ml). MTT solution was added into the attached cells mentioned above (10 μl per 100 μl culture) and incubated at 37 °C for 4 hours. After that DMSO was added and amount of colored formazan metabolite formed was determined by measuring of the absorbance at 550 nm. The optical density of formazan formed in control (untreated) cells was taken as 100% viability.

3. Results and Discussion

Compound **1**, obtained as yellowish oil, have the molecular formula $C_{13}H_{17}NO_5$, as determined from HR ESI-MS data (*m/z* = 290.1004 $(M + Na)^+$; calculated, 290.1006) in combination with its ^{1}H NMR, ^{13}C NMR and DEPT spectroscopy data (Figures S1-S4 in Supporting material). The IR spectrum revealed the presence of a pyrrole N–H stretching band (3300 cm^{-1}) and multiple carbonyl C=O groups (1740, 1650 cm^{-1}). One carbonyl group is conjugated with a pyrrole ring (by UV analysis; λ_{max}, 255 and 290 nm).[22,23] Five of six degrees of unsaturation inherent in the formula were accounted by ^{13}C NMR as one conjugated carbonyl, two ester carbonyls, and four olefinic carbons. Therefore, the compound **1** contained a single pyrrole ring.[22,23,24] The ^{1}H and ^{13}C NMR spectra indicated six quaternary C-atoms, one CH, three CH_2, and three CH_3 groups (Figures S1 and S2 in Supporting material). In the ^{1}H NMR spectrum, there were typical signals for two OCH_3 groups at δ 3.65 (3H, s) and 3.70 (3H, s), one acetyl moiety at δ 2.40 (3H, s), signals of α-methylene protons of a ketone at δ_H 3.81 (2H, s) and 2.55 (2H, t, J = 7.6 Hz), one β-methylene resonance of a ketone group at δ 2.75 (2H, t, J = 7.6 Hz), one signal for a pyrrol olefinic proton at δ 6.74 (1H, s), as well as one N–H proton at δ 9.52 (1H, br s), indicating that **1** contains a pyrrole ring moiety[22,23,24] possessing a conjugated carbonyl group. The carbons of the pyrrole derivative were assigned from ^{13}C NMR and DEPT experiments (Figures S2 and S3 in Supporting material). There were resonances for three C=O functions (δ 187.7, α, β-unsaturated C=O group;

171.7 and 173.4, ester C=O group), two C=C bonds (δ 120.9, 121.2, 124.7, and 129.9), one olefinic carbon (δ 121.2), two methoxy groups (δ 51.6 and 52.1), one acetoxy methyl moiety (δ 27.3), and three aliphatic methylene C atoms (δ 20.0, 31.0, and 34.6). The above data for **1** are also in line with similar compounds with pyrrole ring moiety.[22,23]

The above observation accompanied by the ^{1}H, ^{1}H–COSY (Figure 2), and HMBC (Figure 3) spectrum of **1** established the presence of three partial fragments: methoxycarbonylmethylene group (CH_2COOCH_3), methyl propanoyl group ($CH_2CH_2COOCH_3$), and acetyl group ($COCH_3$). The entire skeleton of **1** was constructed by the aid of HMBC spectrum (Figure 3).

In the HMBC and NOESY (Figure 4) spectra, the significant correlations between δ_H 2.75 (CH_2–1″) and δ_C 121.1 (C-2)/124.7 (C-3)/120.9 (C-4), δ_H 3.81 (CH_2-1′) and δ_C 124.7 (C-3)/120.9 (C-4)/129.9 (C-5), δ_H 2.40 (5-MeOC) and δ_C 129.9 (C-5), δ_H 2.75 (CH_2-1″) and δ_H 2.55 (CH_2-2″), δ_H 2.40 (5-MeOC) and δ_H 3.81 (CH_2-1′), as well as δ_H 2.75 (CH_2-1″) and δ_H 3.81 (CH_2-1′), suggested that the methoxycarbonylmethylene, methyl propanoyl, and acetyl groups were connected to C-4, C-3 and C-5 of the pyrrole ring, respectively. The other key HMBC correlations of **1** revealed selected cross-peaks as shown in Figure 3. The assignments were further verified by significant correlations of NH-1 (δ_H = 9.52)/H-2 (δ_H = 6.74), and H-2 (δ_H = 6.74)/CH_2-1″ and CH_2-1′ (δ_H = 2.75 and 3.81) in the NOESY experiments (Figure 4 and S7 in Supporting material) to support the positions of each substituent on the pyrrole ring.

From the above data, compound **1** was characterized as 3-(5-acetyl-4-methoxycarbonylmethyl-1*H*-pyrrol-3-yl)-propionic acid methyl ester, named monascuspyrrole and its structure was further confirmed by COSY (Figure 2), NOESY (Figure 4), HSQC, and HMBC

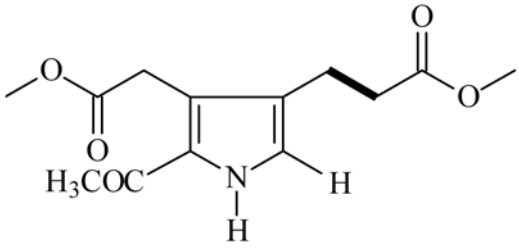

Figure 2: Important COSY (–) contacts of **1**.

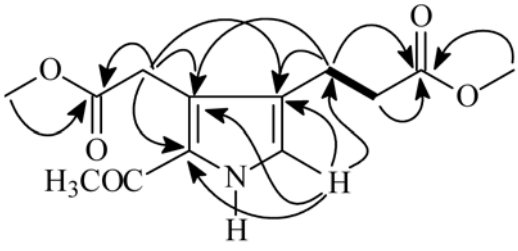

Figure 3: Key HMBC (H↔C) correlations of **1**.

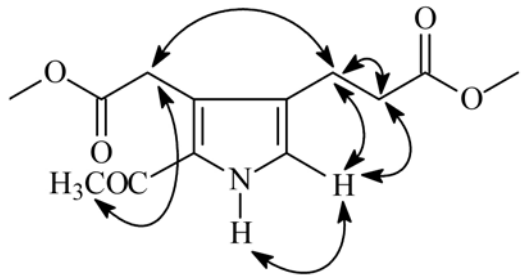

Figure 4: Major NOESY (H↔H) correlations of **1**.

(Figure 3) experiments (see also Figures S5 – S8 in Supporting material).

The other known isolates, 3 β-hydroxystigmast-5-en-7-one (**2**),[25] β-sitostenone (**3**),[26] monascin (**4**),[27] ankaflavin (**5**),[27] *N-trans*-feruloyltyramine (**6**),[26] *N-cis*-feruloyltyramine (**7**),[28] vanillic acid (**8**),[29] methyl paraben (**9**),[29] and syringaldehyde (**10**)[29] were readily identified by comparison of their spectral data (UV, IR, ^{1}H NMR, MS) with the literature data. Among them, all known compounds except **4**, **5** and **8**–**10**, were isolated from *Monascus pilosus* for the first time.

Due to the small quantity of most isolated compounds, we evaluated the inhibitory effects of monascuspyrrole (**1**) and monascin (**4**) on the production of NO induced by LPS. Compounds **1** and **4** showed mild inhibition on NO production (IC_{50}, 33.7 μM and 25.2 μM). Among the tested compounds, compound **4** showed strong inhibition of NO production of macrophages consistent with anti-inflammatory activity. The high cell viability (> 80%) indicated that the inhibitory activity of LPS-induced nitrite production by compound **4** (at 20 μg/mL) did not result from its cytotoxicity. Compound **1** also showed mild inhibition of NO production of macrophages, but the low cell viability (62.0%) suggested the possibility of cytotoxicity.

4. Conclusions

In this study, we focused on the minor secondary metabolites appearing in the *n*-BuOH-soluble fraction of a 95% EtOH extract of the red yeast rice produced by *Monascus pilosus* BCRC 38093. The new metabolite **1**, found in this study is novel, naturally occurring compounds. It is worthy to mention that this is the first report of a pyrrole derivative isolated from *Monascus pilosus.* Two isolates (**1** and **4**) were evaluated for their inhibitory effects on nitric oxide production by macrophages. Compound **4** showed strong inhibition of NO production, whereas **1** showed mild inhibition of NO production of macrophages. However, the chemical characteristics, as well as the biological activities of many *Monascus* metabolites still remain unclear. Therefore, the different biological activities of *Monascus pilosus* and related diverse secondary metabolites seems to be worth of further studies.

5. Acknowledgments

The first two authors (M.-D. Wu and M.-J. Cheng) contributed equally to this work and should both be regarded as first author of this publication. This investigation was supported by a grant from the Ministry of Economic Affairs of Republic of China (Grant No. 94-EC-17-A-17-R7-0563). The authors also thank senior technician Ms. Chyi-Jia Wang from Center for Resources, Research and Development (CRRD) of Kaohsiung Medical University for acquiring the 2D NMR data.

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Povzetek

Prispevek predstavlja kemijsko študijo frakcije kvasovk rdečega riža, fermentiranih z gobo *Monascus pilosus* BCRC 38093 (Eurotiaceae) iz 95 % etanolnega ekstrakta, topnega v *n*-butanolu. Avtorji so izolirali nov naravni derivat pirola, poimenovan kot monaskuspirol (**1**), poleg še devetih znanih spojin: 3β-hidroksistigmast-5-en-7-on (**2**), β-sitostenon (**3**), monaskin (**4**), ankaflavin (**5**), *N-trans*-feruloiltiramin (**6**), *N-cis*-feruloiltiramin (**7**), vanilijevo kislino (**8**), metil paraben (**9**) in siringaldehid (**10**). Struktura novega derivata pirola **1** je bila identificirana s pomočjo 1D in 2D NMR spektroskopije, in masne spektrometrije z visoko ločljivostjo. Ostale znane spojine so bile identificirane s pomočjo primerjave spektroskopskih podatkov z literaturnimi podatki avtentičnih spojin. Spojini **1** in **4** kažeta zmeren inhibicijski efekt pri tvorbi dušikovega oksida. Med devetimi znanimi izoliranimi spojinami so bile spojine **2**, **3**, **6** in **7** prvič najdene v ekstraktu fermentiranih kvasovk rdečega riža.

Supporting material

2. 4. Extraction and Isolation

The red yeast rice of the *Monascus pilosus* BCRC 38093 (2.5 kg) were extracted three times with 95% EtOH at room temperature. The ethanol syrup extract was partitioned between *n*-BuOH and H_2O (1:1) to afford *n*-BuOH (fraction A, 1.3 g) and H_2O (fraction B, 970 mg) soluble fractions, and an insoluble precipitate (fraction C, 150 mg). The *n*-BuOH-soluble fraction (1.3 g) was chromatographed over silica gel (70–230 mesh), eluting with CH_2Cl_2 and enriched with acetone/MeOH to produce 8 fractions (A1–A8). Fr. A-1 (120 mg) was chromatographed over silica gel, eluting with CH_2Cl_2-EtOAc (15:1 → 5:1) to obtain 4 fractions (A-1-1–A-1-4). Fr. A-1-3 (45 mg) was purified by preparative TLC to afford 3β-hydroxystigmast-5-en-7-one (**2**) (1.2 mg) and β-sitostenone (**3**) (1.5 mg). Fraction A-2 (230 mg) was chromatographed over silica gel, eluting with CH_2Cl_2-MeOH (7:1 → 0:1) to obtain 8 fractions (A-2-1–A-2-8). Fraction A-2-3 (26.3 mg) was repeatedly purified by preparative TLC to afford monascuspyrrole (**1**) (7.5 mg). Fraction A-2-7 (40.1 mg) was purified by preparative TLC (*n*-hexane–EtOAc, 3:1) to give monascin (**4**) (5.7 mg) and ankaflavin (**5**) (1.3 mg). Fraction A-6 (263 mg) was resubjected to silica gel column chromatography (CH_2Cl_2-MeOH, 12:1 → 1:1) to afford 4 fractions (A-6-1–A-6-4). Fraction A-6-1 (25.8 mg) was repeatedly purified by preparative TLC (CH_2Cl_2–EtOAc, 15:1) to afford *N-trans*-feruloyltyramine (**6**) (1.6 mg), methyl paraben (**9**) (1.8 mg), and syringaldehyde (**10**) (2.4 mg). Fraction A-6-2 (34.2 mg) was repeatedly purified by preparative TLC (CH_2Cl_2–MeOH, 25:1) to afford *N-cis*-feruloyltyramine (**7**) (1.1 mg) and vanillic acid (**8**) (2.4 mg).

2. 5. Characterization Data

Compound **1**: Yellowish oil; UV λMeOH max (nm): 255 (3.78), 290 (4.15); IRν_{max}^{Neat} Neat max (cm^{-1}): 3300 (NH), 1740, 1650 (C=O); ESI-MS: *m/z* 267 $[M+Na]^+$; HR-ESI-MS *m/z* 290.1004 $[M+Na]^+$ (calcd for $C_{13}H_{17}NO_5Na$, 290.1006); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s, COMe), 2.55 (2H, t, *J* = 7.6 Hz, CH_2-2″), 2.75 (2H, t, *J* = 7.6 Hz, CH_2-1″), 3.65 (3H, s, Me-4″), 3.70 (3H, s, Me-3´), 3.81 (1H, s, CH_2-1´), 6.74 (1H, s, H-2), 9.52 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3 (COMe), 20.0 (CH_2-1″), 31.0 (CH_2-1´), 34.6 (CH_2-2″), 51.6 (Me-4″), 52.1 (Me-3´), 120.9 (C-4), 121.2 (C-2), 124.7 (C-3), 129.9 (C-5), 171.7 (C-2´), 173.4 (C-3″), 187.7 (COMe).

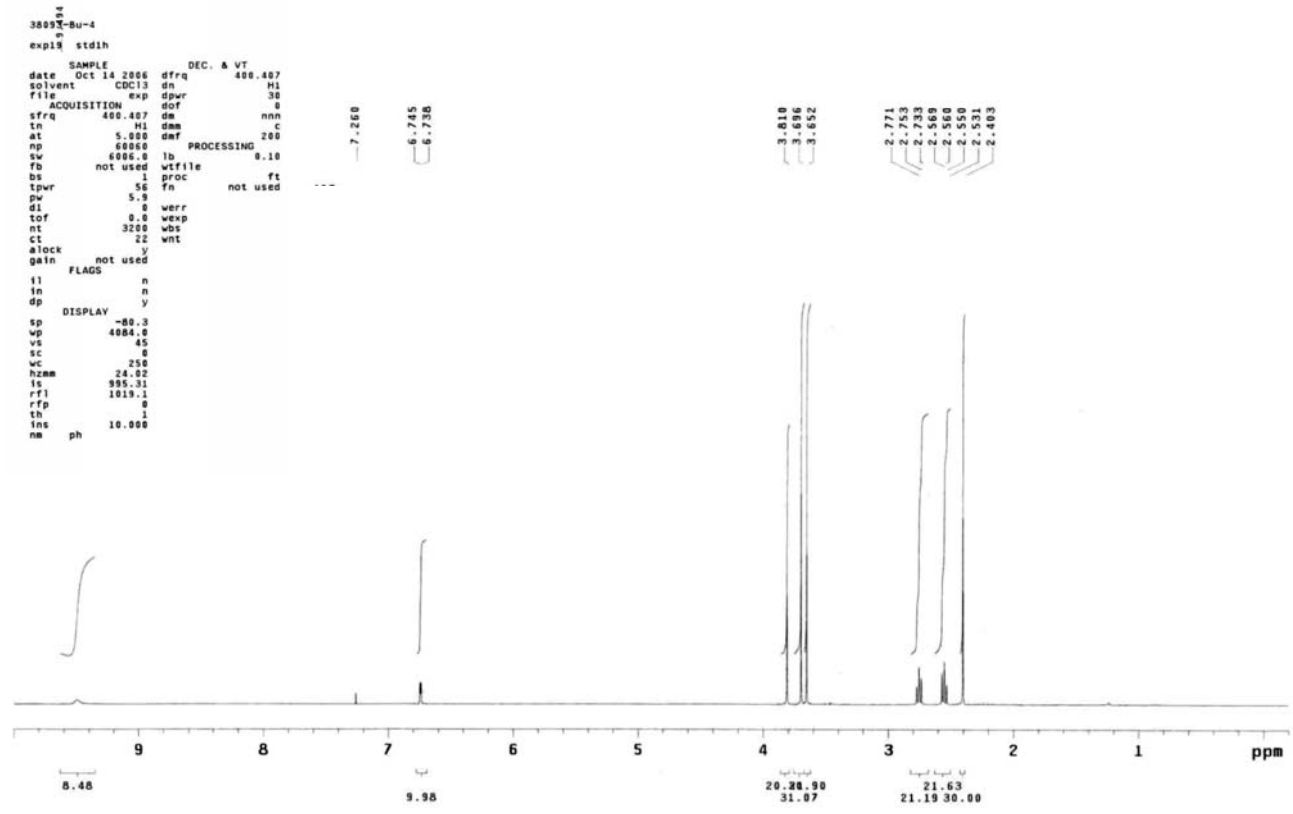

Figure S1. ^{1}H NMR spectrum of monascuspyrrole (**1**).

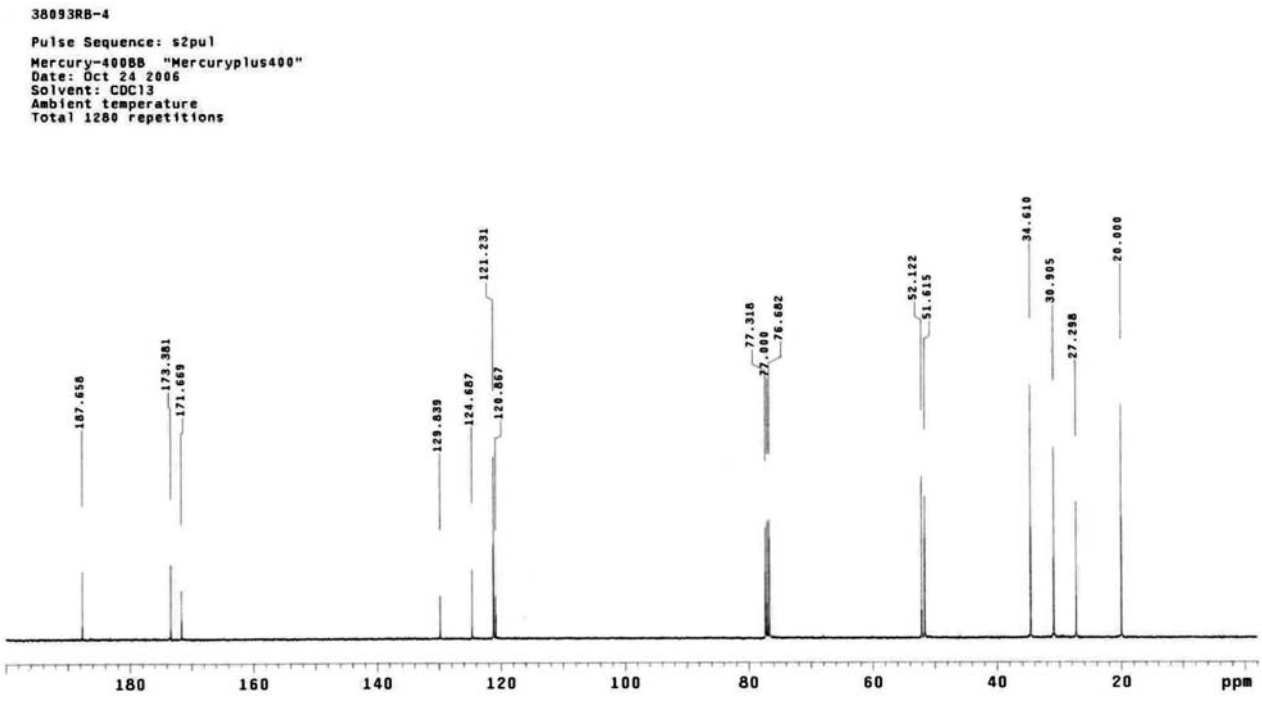

Figure S2. ^{13}C NMR spectrum of monascuspyrrole (**1**).

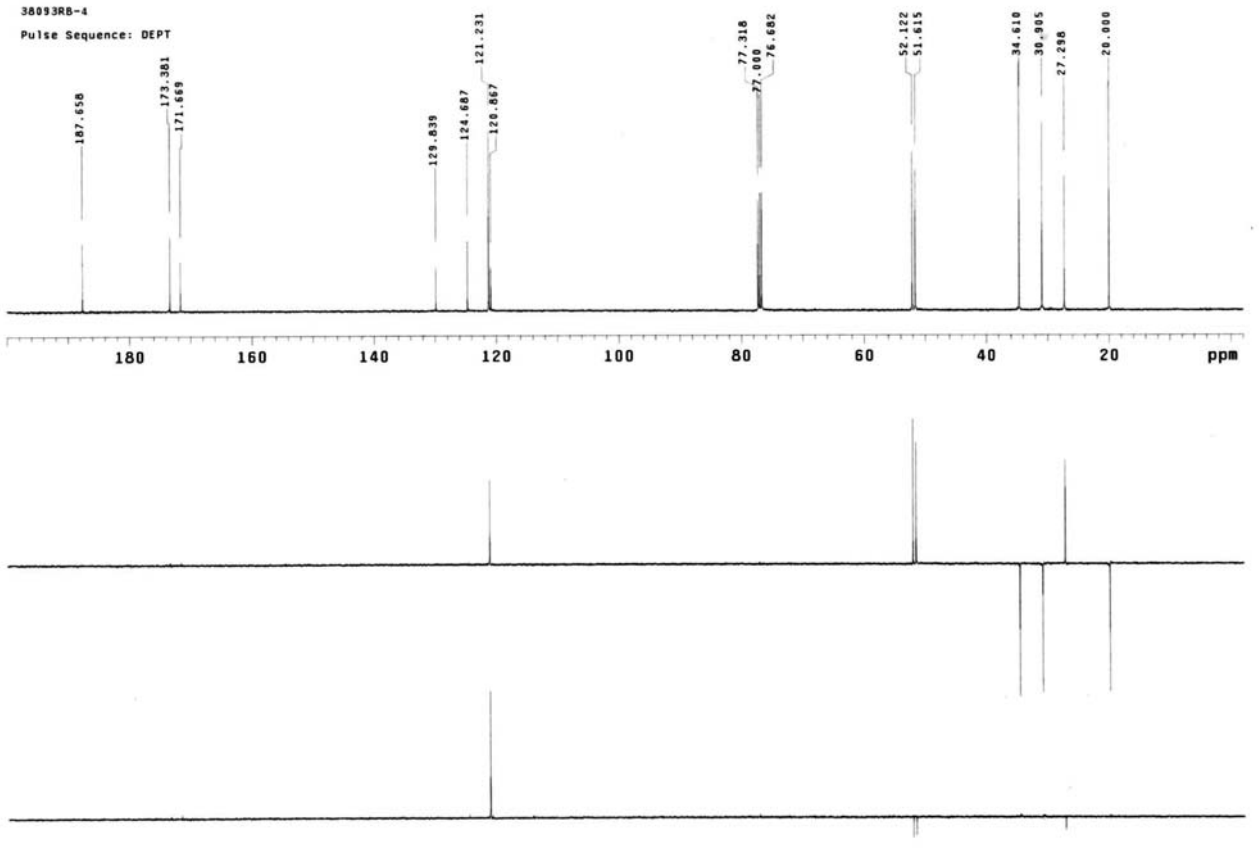

Figure S3. DEPT spectrum of monascuspyrrole (**1**).

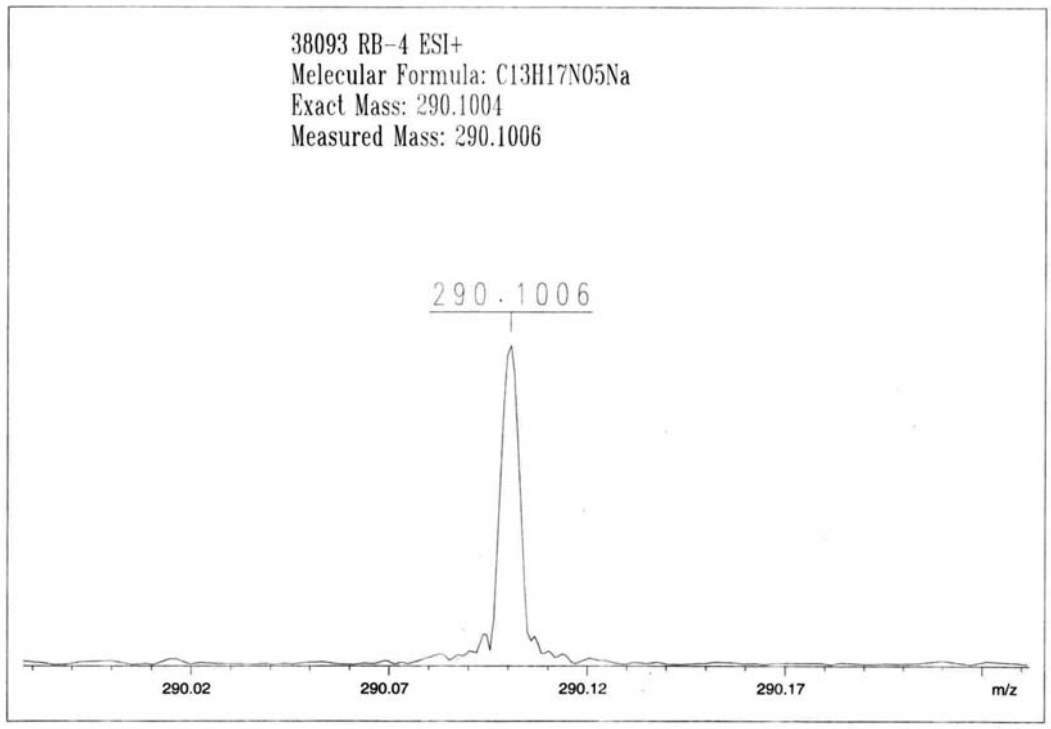

Figure S4. HR-ESIMS spectrum of monascuspyrrole (**1**).

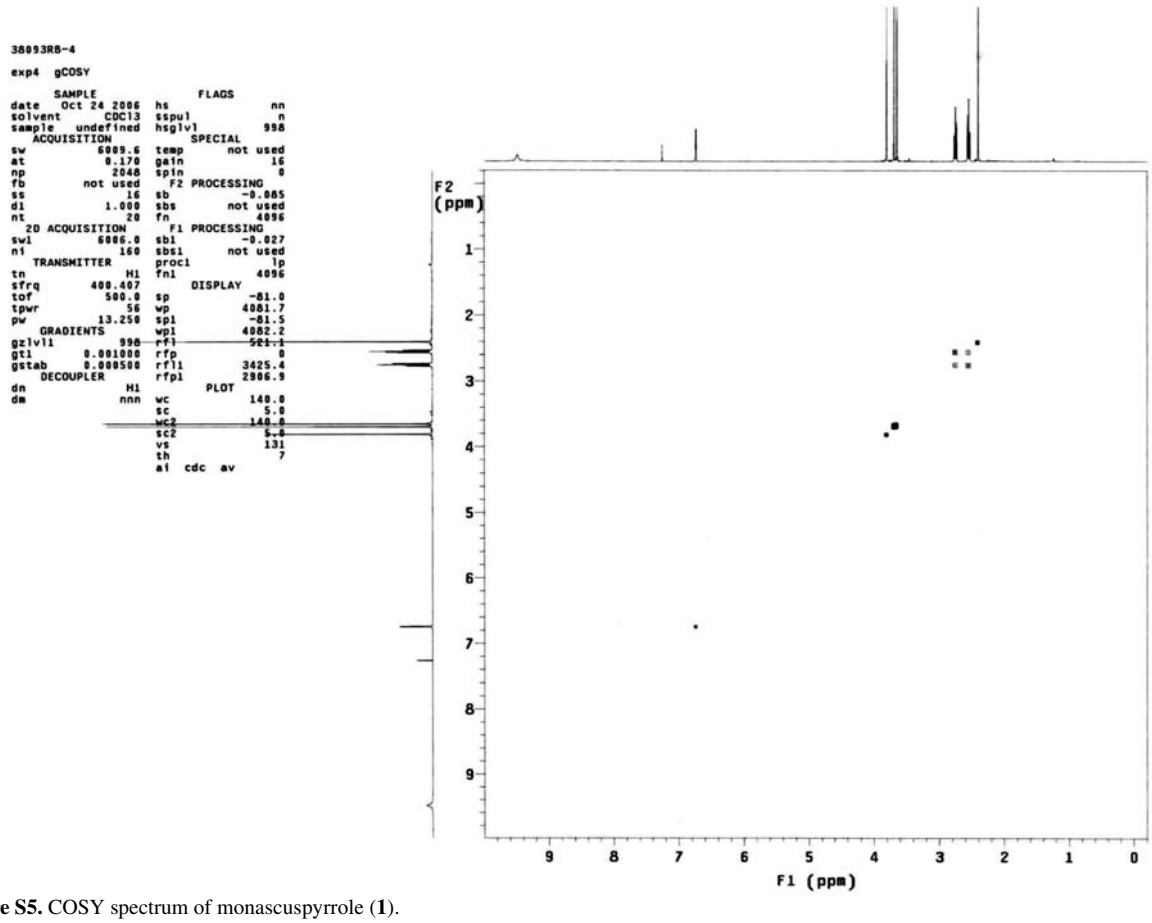

Figure S5. COSY spectrum of monascuspyrrole (**1**).

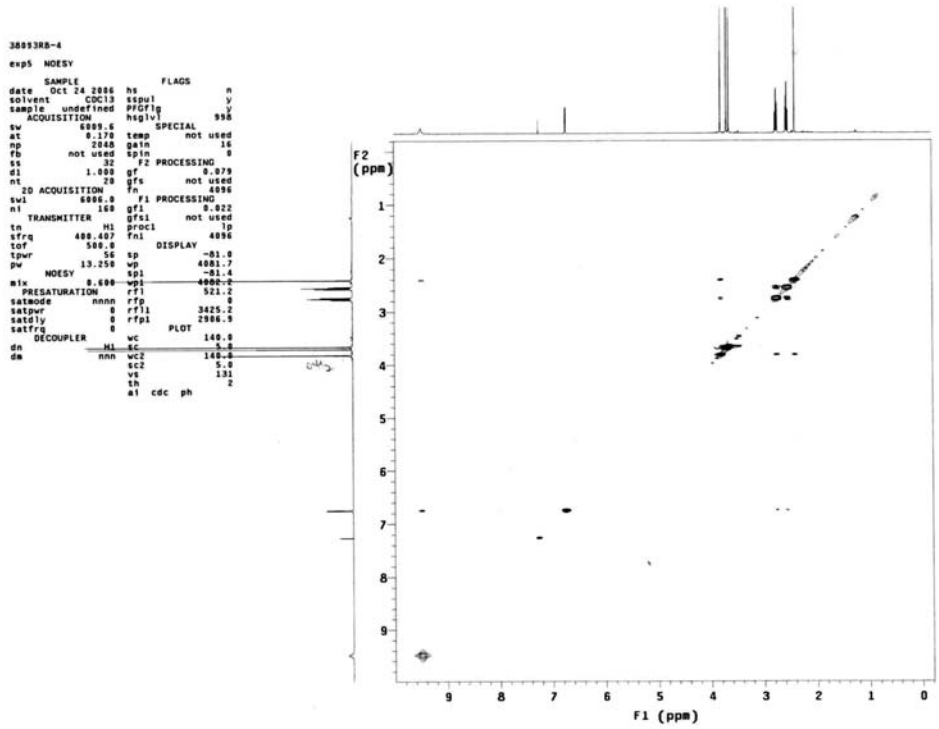

Figure S6. HMBC spectrum of monascuspyrrole (**1**).

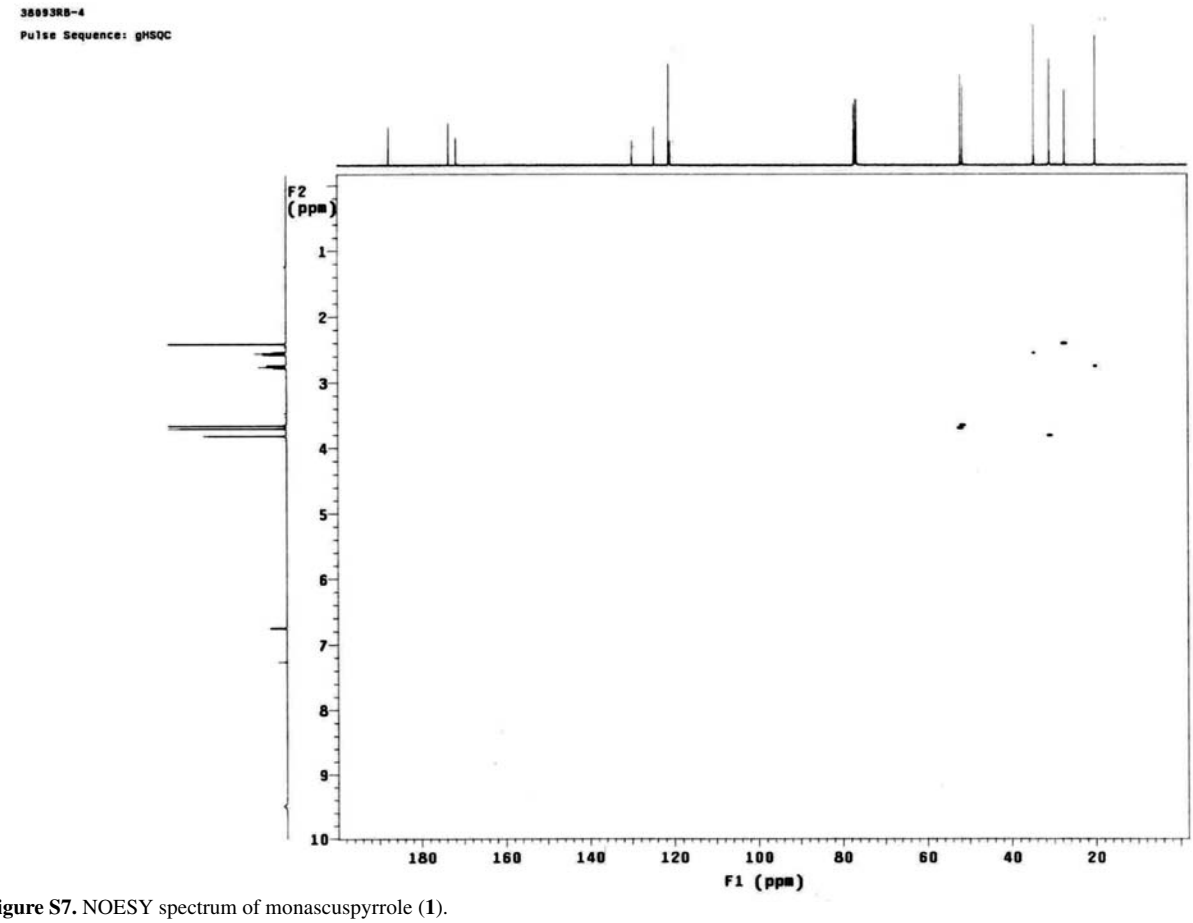

Figure S7. NOESY spectrum of monascuspyrrole (**1**).

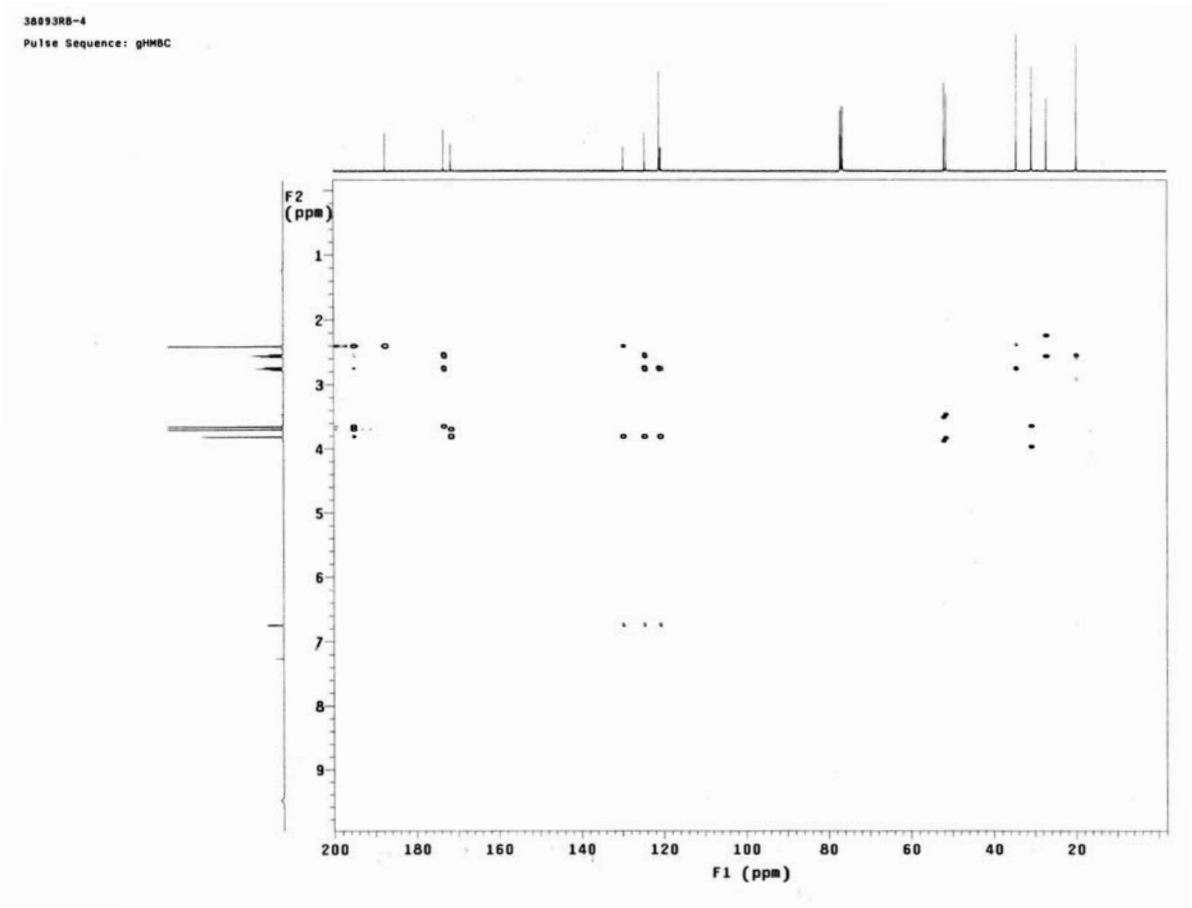

Figure S8. HSQC spectrum of monascuspyrrole (**1**).