http://dx.doi.org/10.5935/0103-5053.20130184

J. Braz. Chem. Soc., Vol. 24, No. 9, 1544-1548, 2013.
Printed in Brazil - ©2013 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Short Report

Phenolic Compounds from the Roots of *Valeriana officinalis* var. *latifolia*

Peng-Cheng Wang,[a] Xin-Hui Ran,[a] Huai-Rong Luo,[a] Qing-Yun Ma,[b] Yu-Qing Liu,[a] Jun Zhou*,[a] and You-Xing Zhao*,[b]

[a]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, People's Republic of China

[b]Key Laboratory of Biology and Genetic Resources of Tropical Crops, Ministry of Agriculture, Institute of Tropical Bioscience and Biotechnology, Chinese Academy of Tropical Agriculture Sciences, Haikou 571101, People's Republic of China

Uma nova neolignana benzofurânica, isovalerato de 9-di-hidrodesidrodiconiferila, além de 10 compostos fenólicos conhecidos, olivil, pinoresinol, 8-hidroxipinoresinol, pinorespiol, 8-hidroxi-7-epipinoresinol, ácido *trans-p*-hidroxifenil-propenoico, ácido *cis-p*-hidroxifenil-propenoico, ácido isoferúlico e isovanilina foram isolados a partir das raízes da *Valeriana officinalis* var. *latifolia*. Suas estruturas e configurações foram elucidadas com base em métodos espectroscópicos. A atividade inibitória da acetilcolinesterase (AChE) e a atividade intensificada do fator de crescimento neural (NGF) mediada pelo crescimento de neurites em células PC12 pelos compostos isovalerato de 9-di-hidrodesidrodiconiferila e olivil foram avaliadas.

A new benzofuran neolignan, dihydrodehydrodiconiferyl alcohol 9-isovalerate, along with ten known phenolic compounds, olivil, pinoresinol, 8-hydroxypinoresinol, pinorespiol, 8-hydroxy-7-epipinoresinol, *trans-p*-hydroxyphenyl- propenoic acid, *cis-p*-hydroxyphenyl-propenoic acid, ferulic acid, isoferulic acid and isovanillin were isolated from the roots of *Valeriana officinalis* var. *latifolia*. Their structures and configurations were elucidated on the basis of spectroscopic methods. The inhibitory activity for acetylcholinesterase (AChE) and enhancing activity on nerve growth factor (NGF)-mediated neurite outgrowth in PC12 cells of dihydrodehydrodiconiferyl alcohol 9-isovaterate and olivil were evaluated.

Keywords: Valerianaceae, *Valeriana officinalis* var. *latifolia*, lignan, chemical constituents, acetylcholinesterase inhibitory

Introduction

The genus *Valeriana* (Valerianaceae) consists of about 200 species, and there are about 30 species distributed in China.[1,2] The roots of the plants of the genus *Valeriana*, especially *Valeriana officinalis*, have been widely used as a mild sedative and sleep aid for centuries in Europe, Asia and North America.[1] Phytochemistry studies revealed the sesquiterpenoids and iridoids were the characteristic constituents in the plants of this genus,[3-6] including our works,[7-12] which showed various pharmacological properties, such as anxiolytic, antidepressant, antispasmodic, sedative and anti-HIV activities.[13-16] Lignans were another important group of components of plants from this genus, which showed antioxidative, vasorelaxant[17] and partial agonistic activity at A1 adenosine receptors.[18]

V. officinalis is mainly distributed in Europe but does not grow in P. R. China, and is the official species used in Europe and America. *V. officinalis* var. *latifolia* is similar to *V. officinalis* in botanical morphology characteristics, which was mainly distributed in P. R. China and Japan, and it was always used as the alternative species of *V. officinalis* in folk medicine in P. R. China.[2] Our further studies on the roots of *V. officinalis* var. *latifolia* lead to the isolation of a new benzofuran neolignan, dihydrodehydrodiconiferyl alcohol 9-isovalerate (**1**) (Figure 1), along with ten

*e-mail: zhoujun3264@yahoo.com.cn, zhaoyouxing@itbb.org.cn

known phenolic compounds. The known compounds were identified as olivil (**2**),[19] pinoresinol (**3**),[20] 8-hydroxypinoresinol (**4**),[21] pinorespiol (**5**),[22] 8-hydroxy-7-epipinoresinol (**6**),[23] *trans-p*-hydroxyphenyl-propenoic acid (**7**),[24] *cis-p*-hydroxyphenyl-propenoic acid (**8**),[24] ferulic acid (**9**),[25] isoferulic acid (**10**)[26] and isovanillin (**11**)[27] by comparison their spectroscopic data with the literature values. In this paper, we reported the isolation and structure elucidation of the new compound (**1**), as well as the AChE inhibitory and NGF-mediated neurite outgrowth enhancing activities of compounds **1** and **2**.

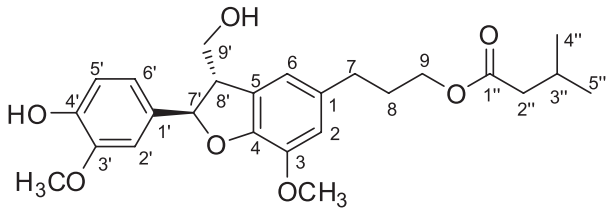

Figure 1. Chemical structure of compound **1**.

Experimental

General procedures

Optical rotations were taken on a Horiba SEAP-300 polarimeter. IR spectra were measured with a Bio-Rad FTS-135 spectrometer with KBr pellets. UV spectra were obtained on a Hitachi UV 210A spectrophotometer. Electron impact mass spectrometry (EIMS) (70 eV) was recorded on a VG Auto Spec-3000 spectrometer, ESIMS was recorded with an API QSTAR Pulsar i spectrometer. 1D and 2D nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-400 or DRX-500 or Avance-600 NMR spectrometer with the residual solvent as the internal standard. Column chromatography was performed either on silica gel (200-300 mesh, Qindao Marine Chemical Inc., Qingdao, P. R. China) or RP-18 gel (LiChroprep, 40-63 μm, Merck, Darmstadt, Germany). Sephadex LH-20 for chromatography was purchased from Amersham Biosciences. Fractions were monitored by thin layer chromatography (TLC), and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH.

Plant material

The plants of *V. officinalis* var. *latifolia* were collected at the Badong country, Hubei province, P. R. China in October 2008. The sample was identified by Professor You-Wei Wang, School of Pharmaceutical Sciences, Wuhan University, P. R. China. A voucher specimen (KIB-XC0810) was preserved at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, the Chinese Academy of Sciences, P. R. China.

Extract and isolation

The dried root powder of *V. officinalis* var. *latifolia* (14 kg) was extracted with 95% EtOH (3 × 25 mL) at room temperature for three times, three days for one time, and the residue (3 kg) was obtained after removal of solvent under reduced pressure. The EtOH extract was suspended in H_2O (6 L) and then partitioned successively with $CHCl_3$ (3 × 4 L) and *n*-BuOH (3 × 4 L), respectively. The $CHCl_3$ extract (800 g) was subjected to silica gel column chromatography (CC, 10 × 100 cm, 2400 g) eluted with petroleum ether/acetone (100:1-1:1) to afford fractions A-D. Fraction D (120 g) was separated by CC over RP-18 (5.0 × 50 cm, 300 g) eluted with a MeOH/H_2O gradient system (30-90%) to yield five fractions D1-D5. Fraction D1 (15 g) was chromatographed over silica gel (3.0 × 50 cm, 200 g) eluted with petroleum ether/acetone (80:1-1:1) to afford four fractions D1a-D1d. Fraction D1a (4 g) was subjected to CC (2.5 × 30 cm, 120 g) over silica gel eluted with petroleum ether/EtOAc (50:1-2:1) and followed by Sephadex LH-20 CC (2.0 × 100 cm, 200 g) eluted with $CHCl_3$/MeOH (1:1) and preparative TLC eluted with petroleum ether/acetone (10:1) to obtain compounds **1** (7 mg), **2** (8 mg), **6** (12 mg) and **11** (8 mg). Compounds **7** and **8** (12 mg) were obtained as a mixture from fraction D1b by CC (1.0 × 30 cm, 30 g) over silica gel eluted with petroleum ether/acetone (50:1-2:1). Compounds **3** (7 mg), **4** (10 mg) and **5** (8 mg) were isolated from fraction D1d by CC (1.0 × 50 cm, 250 g) over silica gel eluted with petroleum ether/acetone (50:1-1:1) and purified by a Sephadex LH-20 CC eluted with $CHCl_3$/MeOH (1:1). Fraction D2 (25 g) was chromatographed over silica gel (5 × 50 cm, 500 g) eluted with petroleum ether/EtOAc (50:1-1:1) to give six fractions D2a-D2f. Compounds **9** and **10** (15 mg) were separated as a mixture from fraction D2b by CC (1.0 × 50 cm, 10 g) over silica gel eluted with $CHCl_3$/CH_3OH (30:1-1:1).

Dihydrodehydrodiconiferyl alcohol 9-isovalerate (**1**)

White amorphous solid; $[\alpha]_D^{22.6}$ –1.28 (*c* 0.31, CH_3OH); UV (CH_3OH) λ_{max}/nm (log ε) 206 (4.70), 282 (3.76); IR (KBr) ν_{max}/cm^{-1} 3439, 2934, 2872, 1730, 1611, 1517, 1465, 1368, 1270, 1188, 1143; ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) data see Table 1; (+)-ESI-MS *m/z* 467 $[M + Na]^+$; HR-EIMS *m/z* 444.2151 $[M]^+$ (calcd. for $C_{25}H_{32}O_7$ 444.2148).

Table 1. ^{1}H NMR (500 MHz) and ^{13}C NMR (100 MHz) data of compound **1** in $CDCl_3$

Position	δ_C, mult	δ_H (*J* / Hz)	Position	δ_C, mult	δ_H (*J* / Hz)
1	134.6, qC		1'	133.0, qC	
2	112.3, CH	6.64, d, 3.4	2'	108.8, CH	6.94, s
3	144.2, qC		3'	146.6, qC	
4	146.6, qC		4'	145.6, qC	
5	127.8, qC		5'	114.2, CH	6.86, overlapped
6	116.0, CH	6.64, d, 3.4	6'	119.4, CH	6.90, overlapped
7	32.0, CH_2	2.64, t, 2H, 7.5	7'	87.8, CH	5.54, d, 7.5
8	30.6, CH_2	1.95, m, 2H	8'	53.8, CH	3.60, dd, 12.2, 5.7
9	63.4, CH_2	4.09, m	9'	63.8, CH_2	3.96, m
					3.90, m
1"	173.3, qC		3-OCH_3	56.0, CH_3	3.88, s
2"	43.5, CH_2	2.20, m, 2H	3'-OCH_3	56.0, CH_3	3.86, s
3"	25.7, CH	2.10, m			
4"	22.1, CH_3	0.97, d, 6.5			
5"	22.1, CH_3	0.97, d, 6.5			

The bioassay of acetylcholinesterase (AChE) inhibitory activity

Acetylcholinesterase inhibitory activity of these compounds was assayed by the spectrophotometric method developed by Ellman *et al.*[28] *S*-Acetylthiocholine iodide, *S*-butyrylthiocholine iodide, 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB, Ellman's reagent), tacrine, acetylcholinesterase and butyrylcholinesterase derived from human erythrocytes were purchased from Sigma Chemical Company. Acetylthiocholine iodide (Sigma, ≥ 98%) was used as substrate in the assay. The testing compounds were dissolved in dimethylsulfoxide (DMSO). The reaction mixture contained 1100 μL of phosphate buffer (pH 8.0), 10 μL of tested compound solutions (50 μmol L^{-1}) and 40 μL of acetylcholinesterase (Sigma) solution (0.04 U 100 μL^{-1}), which were mixed and incubated for 20 min (30 °C). The reaction was initiated by the addition of 20 μL of 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB 6.25 mmol L^{-1}, Sigma, ≥ 98%) and 20 μL of acetylthiocholine (Sigma, ≥ 98%). The hydrolysis of acetylthiocholine was monitored at 405 nm after 30 min. Tacrine (Sigma, ≥ 98%, 0.33 μmol L^{-1}) was used as positive control; the same volume of DMSO was used as negative control. All the reactions were performed in triplicate. The percentage inhibition was calculated as follows: inhibition (%) = (E – S)/E × 100 (E is the activity of the enzyme without test compound and S is the activity of enzyme with test compound).

Cell culture and bioassay of neurite outgrowth-promoting activity

The neurotrophic activity of the studied compounds was examined following the assay using PC12 cells reported previously.[29] Nerve growth factor (NGF) was purchased from R&D Systems, F12 medium, poly-L-lysine, fetal bovine serum (FBS) and horse serum (HS) were purchased from Sigma Chemical Company, and PC12 cells were purchased from the cell bank of Kunming Institute of Zoology, Chinese Academy of Science. Briefly, PC12 cells were maintained in F12 supplemented with 12.5% HS and 2.5% FBS, saturated atmosphere of 5% CO_2 and incubated at 37 °C. Compounds were dissolved in DMSO. For the bioassay of neurite outgrowth-promoting activity, PC12 cells were seeded at a density of 2×10^4 cells mL^{-1} in 48 well plate coated with poly-L-lysine. After 24 h, the medium was changed to test medium containing various concentrations of NGF (50 ng mL^{-1} for positive control, 5 ng mL^{-1} for the negative control and compound group), 10% HS and 5% FBS, then 50 μmol L^{-1} test compounds were added (the final concentration of DMSO was 0.05%), the same concentration of DMSO was added into negative control. After 72 h incubation, the neurite outgrowth was assessed under a phase-contrast microscope (Olympus X51). Neurites processes with a length equal to or greater than the diameter of the neuron cell body were scored as neurite bearing cells. The ratio of the neurite-bearing cells to total cells (with at least 100 cells examined

per view area; 5 viewing area *per* well) was determined and expressed as percentage.

Results and Discussion

Compound **1** was isolated as white amorphous solid. Its molecular formula was determined as $C_{25}H_{32}O_7$ by HREIMS (*m/z* 444.2151, calcd. for $C_{25}H_{32}O_7$ $[M]^+$, 444.2148), with ten degrees of unsaturation. The IR absorption bands indicated the presence of hydroxyl (3439 cm^{-1}), carbonyl (1730 cm^{-1}) and benzene ring (1611 and 1517 cm^{-1}) groups. The ^1H NMR spectrum of compound **1** (Table 1) exhibited five aromatic proton signals [δ_H 6.94, s (1H, s, H-2'), 6.86 (1H, overlapped, H-5'), 6.90 (d, 1H, *J* 9.5 Hz, H-6'), 6.64 (d, 2H, *J* 3.4 Hz, H-2, H-6)] and two methoxyl groups [δ_H 3.88 (3-OCH_3), δ_H 3.87 (3'-OCH_3)]. The ^{13}C NMR and DEPT (distortionless enhancement by polarization transfer) spectroscopic data of compound **1** (Table 1) revealed 25 carbon resonances, including four methyl (counting two methoxyl), five methylene (two were oxygenated), eight methine (including five sp^2 methine), seven sp^2 quaternary carbons (four were oxygenated), and a carbonyl group, which were similar to those of dihydrodehydrodiconiferyl alcohol,[30] indicating a benzofuran neolignan. The dramatic difference of the ^{13}C NMR spectroscopic data between compound **1** and dihydrodehydrodiconiferyl alcohol was the appearance of an additional isovalerate moiety[8] [H-2" (δ_H 2H, 2.20), H-3" (δ_H 2.10), H-4", 5" (δ_H 0.97, d, 6H, *J* 6.5 Hz); C-1" (δ_C 173.3), C-2" (δ_C 43.5), C-3" (δ_C 25.7), C-4", 5" (δ_C 22.1)] in compound **1**, in accordance with the molecular weight of **1** higher than dihydrodehydrodiconiferyl alcohol by 84 Da ($-C_5H_8O$). The presence of the isovalerate group was further confirmed by the ^1H-^1H COSY correlations (Figure 2) of H-2"/H-3", H-3"/H-4" (H-5") and the long-range (HMBC) ^1H-^{13}C correlations (Figure 2) from H-4" and H-5" to C-2" and C-3". Furthermore, the isovalerate group was established to connect to C-9 based on the HMBC correlation from H-9 (δ_H 4.09) to C-1". In the HMBC spectrum, the correlations from H-7 (δ_H 2.64) to C-1 (δ_C 134.6), C-2 (δ_C 112.3), C-6 (δ_C 116.0), C-8 (δ_C 30.6), and C-9 (δ_C 63.4), correlations from H-7' (δ_H 5.54) to C-1' (δ_C 133.0), C-2' (δ_C 108.8), C-6' (δ_C 119.4), C-8' (δ_C 53.8), C-9' (δ_C 63.8), and C-4 (δ_C 146.6), and correlations from H-8' (δ_H 3.60) to C-7' (δ_C 87.8), C-9', C-1', C-4, and C-5 (δ_C 127.8) further confirmed the connections and assignments of compound **1**, in accordance with the ^1H-^1H COSY correlations of H-7/H-8, H-8/H-9, H-7'/H-8', and H-8'/H-9'. The two methoxyl groups were deduced to locate at C-3 (δ_C 144.2) and C-3' (δ_C 146.6) on the bases of the HMBC correlations from 3-OCH_3 to C-3 and from 3'-OCH_3 to C-3', respectively.

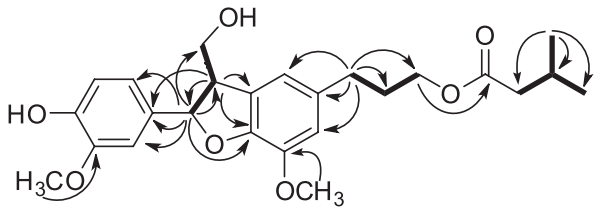

Figure 2. The key ^1H-^1H COSY (—) and HMBC (⌒) correlations of **1**.

The coupling constant of H-7' and H-8' was 7.5 Hz, along with the ROESY (rotating-frame Overhauser effect spectroscopy) correlation of H-7'/H-9' that indicated the *trans*-configuration of H-7' and H-8'.[31,32] The absolute configuration at C-7' and C-8' was deduced to 7'*R*, 8'*S* from its rotation value ($[\alpha]_D^{22.6}$ –1.28, *c* 0.31, CH_3OH).[30] Thus, the structure of compound **1** was identified as dihydrodehydrodiconiferyl alcohol-9-isovalerate.

The acetylcholinesterase (AChE) inhibitory activity of **1** and **2** was assayed by the spectrophotometric method developed by Ellman *et al.*[28] with slightly modification, and they do not show inhibitory activity at the concentration of 50 μmol L^{-1}. Tacrine (0.33 μmol L^{-1}) was used as the positive control, and showed 50.1% inhibition. Compound **4** showed weak AChE inhibitory activity in our previous studies.[11]

Compounds **1** and **2** were also evaluated for the enhancing activity on NGF-mediated neurite outgrowth in PC12 cells.[29] The result indicated that the proportion of the NGF (5 ng mL^{-1})-induced neurite-bearing cells was not enhanced by these compounds at 50 μmol L^{-1}, respectively.

Conclusion

Supplementary information

Supplementary data including ^1H, ^{13}C NMR (DEPT), HMQC, HMBC, COSY, ROSEY and MS for compound **1** are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgements

This work was supported by Special Fund for Agro-scientific Research in the Public Interest (201303117), the Fundamental Scientific Research Funds for CATAS (1630052013001; ITBB110301) and National Support Science and Technology Subject (2013BAI11B04). The authors are grateful to Professor You-Wei Wang, School of Pharmaceutical Sciences, Wuhan University, People's Republic of China, for identification of the plants. The authors also thank the members of the analytical group

of the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, for the measurement of all the spectra.

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Submitted: February 20, 2013
Published online: August 9, 2013

J. Braz. Chem. Soc., Vol. 24, No. 9, S1-S5, 2013.
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0103 - 5053 $6.00+0.00

Supplementary Information

Phenolic Compounds from the Roots of *Valeriana officinalis* var. *latifolia*

Peng-Cheng Wang,[a] Xin-Hui Ran,[a] Huai-Rong Luo,[a] Qing-Yun Ma,[b] Yu-Qing Liu,[a] Jun Zhou*,[a] and You-Xing Zhao*,[b]

[a]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, People's Republic of China

[b]Key Laboratory of Biology and Genetic Resources of Tropical Crops, Ministry of Agriculture, Institute of Tropical Bioscience and Biotechnology, Chinese Academy of Tropical Agriculture Sciences, Haikou 571101, People's Republic of China

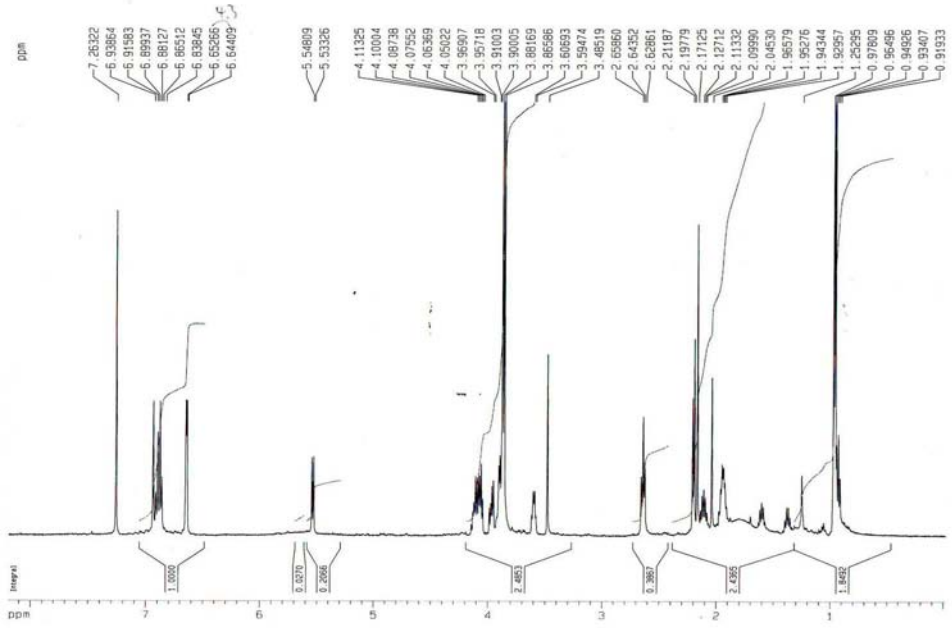

Figure S1. ^{1}H NMR spectrum (500 MHz) of compound **1** in $CDCl_3$.

*e-mail: zhoujun3264@yahoo.com.cn, zhaoyouxing@itbb.org.cn

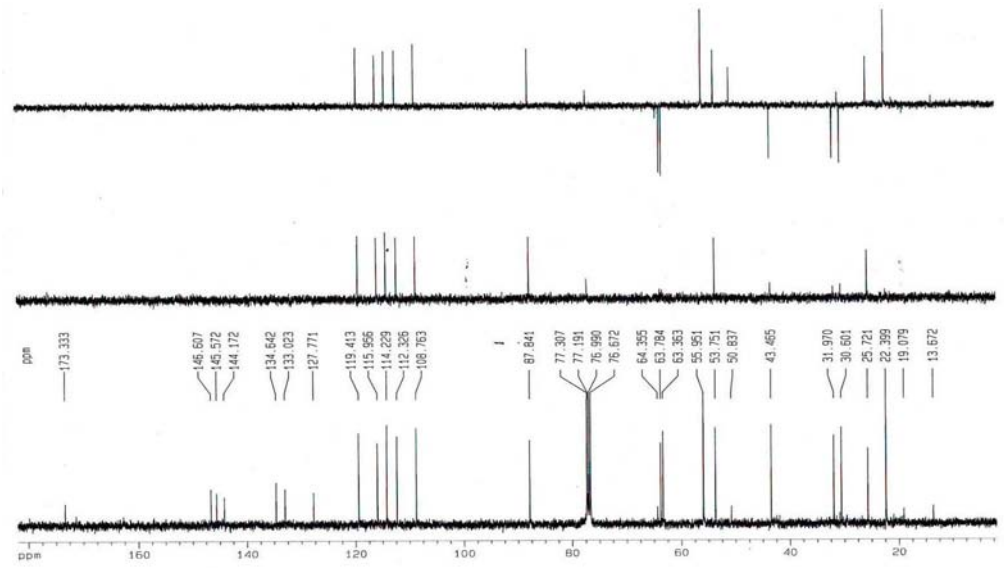

Figure S2. ^{13}C NMR and DEPT spectra (100 MHz) of compound **1** in $CDCl_3$.

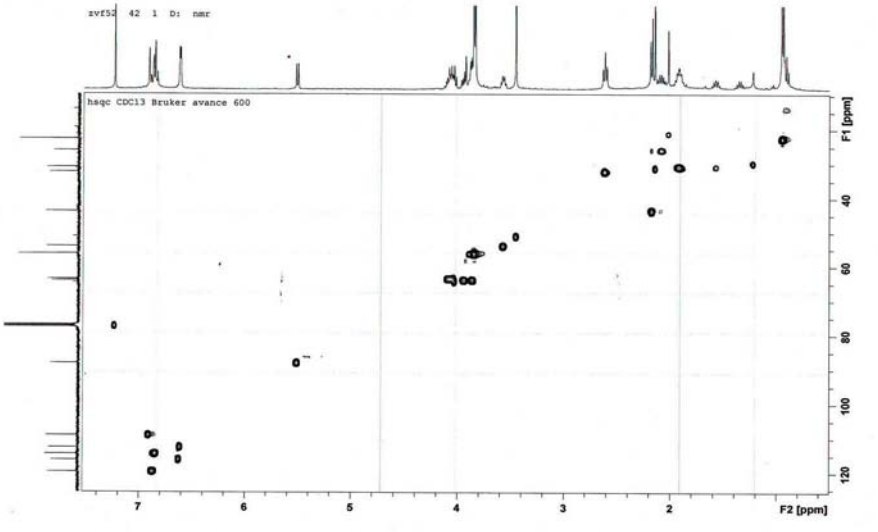

Figure S3. HSQC spectrum of compound **1** in $CDCl_3$.

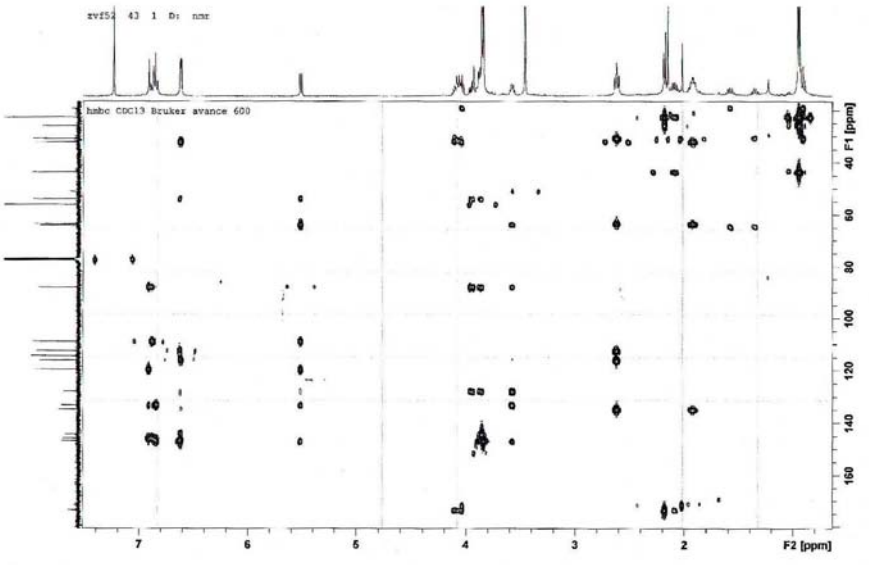

Figure S4. HMBC spectrum of compound **1** in $CDCl_3$.

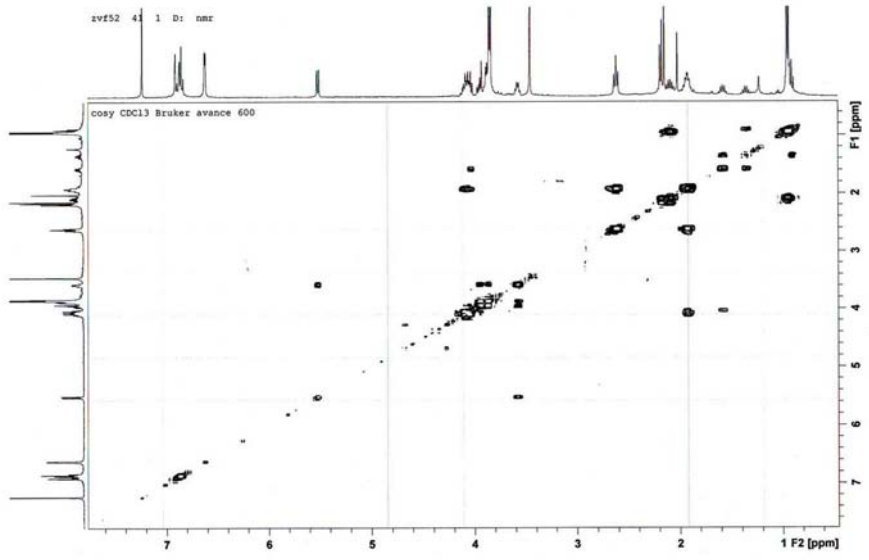

Figure S5. ^1H-^1H COSY spectrum (600 MHz) of compound **1** in $CDCl_3$.

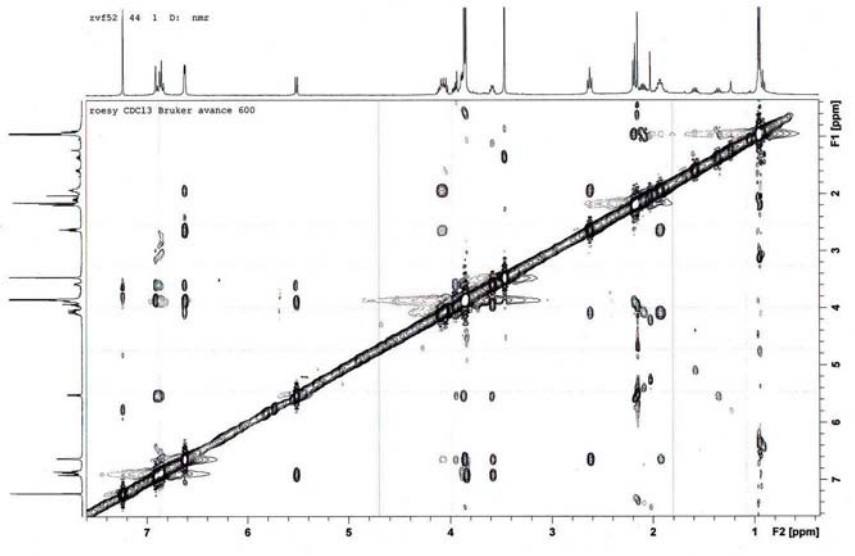

Figure S6. ROESY spectrum of compound **1** in $CDCl_3$.

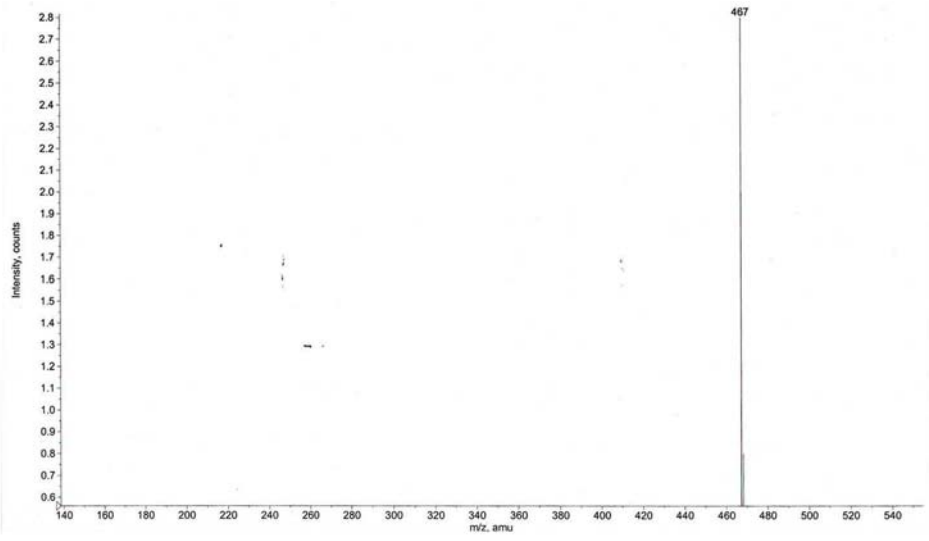

Figure S7. (+)-ESI-MS spectrum of compound **1**.

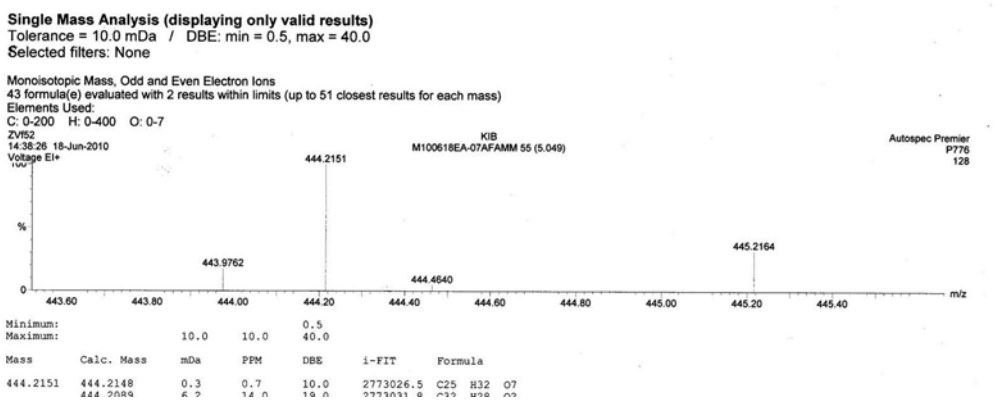

Figure S8. HREI-MS spectrum of compound **1**.