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A cytotoxic decahydronaphthalenylpropenal derivative and tetrahydrofuran lignans from the stems of *Cameraria latifolia*

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Abstract

A new decahydronaphthalenylpropenal derivative, (+)-camerarialdehyde (**1**), a new tetrahydrofuran lignan, (–)-diepiolivil (**2**), and two known lignans were isolated from a methanol-soluble extract of the stems of *Cameraria latifolia*, which was obtained from a repository donated to IHVR by Merck Research Laboratories. The structures of compounds **1** and **2** were determined by interpretation of their spectroscopic data, with the absolute configuration of **1** being established by analysis of its CD spectrum. The absolute configuration of the 1,3-diol moiety of **2** was proposed from the CD spectrum induced with dimolybdenum tetraacetate in DMSO solution. All compounds isolated were evaluated against HT-29 human colon cancer cells, and compound **1** was found to show cytotoxicity toward this cell line.

Keywords

Cameraria latifolia; decahydronaphthalenylpropenal derivative; tetrahydrofuran lignans; CD spectrum induced by dimolybdenum tetraacetate

Cameraria is a genus of plants in the family Apocynaceae, for which the previous chemical and biological investigations have been very limited. There are no prior reports on the constituents and their biological activities of the species *Cameraria latifolia* L. As an extension of a search for new natural product anticancer agents from diverse organisms,¹ a small-scale sample of a dichloromethane partition of methanol-soluble extract of *C. latifolia* stems,² obtained from a repository donated to the Natural Products Discovery Institute (NPDI), Institute for Hepatitis and Virus Research (IHVR) by Merck Research Laboratories, Rahway, NJ, USA, was found to be cytotoxic toward the HT-29 human colon cancer cell line (IC₅₀, 15.2 μg/mL) and selected for further investigation. Using column chromatography guided by cytotoxicity to HT-29 cells,^{3,4} a new decahydronaphthalenylpropenal derivative, (+)-camerarialdehyde (**1**),⁵ and a new

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Supplementary data

Supplementary data including the MS and NMR spectra of (+)-camerarialdehyde (**1**) and (–)-diepiolivil (**2**) associated with this article can be found in the online version at <http://dx.doi.org/tetlet>.

tetrahydrofuran lignan, (–)-diepiolivil (**2**),⁶ were characterized structurally (Figure 1). Also isolated and identified were the known tetrahydrofuran lignans, (+)-pinoresinol⁷ $\{[\alpha]^{20}_D +76.6$ (c 0.03, MeOH)}, and (+)-syringaresinol⁸ $\{[\alpha]^{20}_D +15.0$ (c 0.02, MeOH)}.

Compound **1** was isolated as a colorless optically active gum $\{[\alpha]^{20}_D +60.0$ (c 0.02, MeOH)}. An ion peak $[M + Na]^+$ observed in the HRESIMS at m/z 257.1525 (calcd for $C_{15}H_{22}O_2Na$, 257.1517) indicated five degrees of unsaturation for this molecule. Consistent with this molecular formula, the ^1H NMR spectrum of **1** showed a singlet at δ_H 9.54 (H-14) for an aldehyde proton, four singlets at δ_H 4.57 (H-11a), δ_H 5.04 (H-11b), δ_H 6.00 (H-15a), and 6.31 (H-15b) for two vinyl groups, a singlet at δ_H 0.75 (H-12) for a tertiary methyl group, a double doublet at δ_H 4.05 (H-7) for an oxygenated methine proton, and several multiplets over the range δ_H 1.25 to 2.58 for 12 methylene and methine protons (Table 1).⁹ The ^{13}C NMR spectrum of **1** showed 15 resolved signals classified as a formyl group, two vinyl groups, a tertiary methyl group, five methylene groups, and three methine and a quaternary carbon, for which the connectivity was established by interpretation of HMBC spectroscopic data (Figure 2). Three signals at δ_C 155.0 (C-13), 194.8 (C-14), and 133.3 (C-15) and two signals at δ_C 152.7 (C-6) and 102.5 (C-11), appearing in the ^{13}C NMR spectrum (Table 1) were assigned to a propenal moiety and a vinyl group, respectively.^{10,11} Based on these two residues and five degrees of unsaturation of **1** indicated by mass spectrometry, a bicyclic system could be proposed for **1**. A six-membered ring including C-5 to C-10 was suggested by the ^1H - ^1H COSY sequence H-7/H₂-8/H₂-9 and HMBC correlations between H-9, H-11, and H-12/C-5 and H-5/C-7. Another six-membered ring comprising C-1 to C-5 and C-10 was implied by the second ^1H - ^1H COSY sequence H-1/H₂-2/H₂-3/H₂-4/H-5 and a HMBC correlation between H-12/C-5. The propenal residue could be located at the C-1 position, as indicated by HMBC correlations between H-14 and H-15/C-1 (Figure 2), and the vinyl group was assigned at the C-6 position, as supported by HMBC correlations between H-11/C-5 and C-7 (Figure 2). In addition, the IR (ν_{max} 3443 cm^{-1}) and ^1H [δ_H 4.05 dd (10.7, 5.2)] and ^{13}C (δ_C 73.4) NMR spectra of **1** all supported the presence of a hydroxy group, which was assigned at the C-7 position, as evidenced by HMBC correlations between H-5/C-7 and H-7/C-8 (Figure 2). Therefore, the planar structure of **1** was assigned as 2-decahydro-[(1-methylene-2-hydroxy-10-methyl)-naphthalenyl]-propenal.¹¹

The relative configuration of **1** was established by analysis of its NOESY correlations (Figure 2), and the absolute configuration at the C-5 chiral center of **1** was determined by analysis of the CD spectrum. A previous study demonstrated that (+)- and (–)-cadinene, containing a decalin ring, showed opposite Cotton effects (CEs) in their CD spectra obtained in hexane.¹² (–)-Cadinene exhibited a strong negative CE at 203 nm and a positive CE at 188 nm in the CD spectrum, while (+)-cadinene showed the opposite CE profile at these same wavelengths.¹² Consistent with the CE values of (+)-cadinene, compound **1** showed a strong positive CE value around 197 nm (a positive CE appeared over the range of 205 nm to 190 nm), and a negative CE value occurred at 183 nm in the CD spectrum measured in MeOH, indicating a 5*R* configuration. This inference was based on the consideration that the CE values reported for (+) and (–)-cadinene might arise from a $\pi \rightarrow \pi^*$ transition of a terminal carbon-carbon double bond, and these indicate the absolute configuration at the C-5 and C-10 positions of (+)- and (–)-cadinene.¹² The NOESY correlations observed for **1** between H-1/H-5, H-5/H-7, H-4a/H-7, H-4a/H-11a, and H-11a/H-12 were consistent with 1*S*, 5*R*, 7*S*, and 10*R* configurations. Thus, **1** was proposed as 2-[(2*S*,4*aR*,5*S*,8*aR*)-decahydro-(1-methylene-2-hydroxy-10-methyl)-naphthalenyl]-propenal, which has been accorded the trivial name, camerarialdehyde (**1**). A positive CE value at 250.5 and a negative CE value at 223.0 nm observed in the CD spectrum of **1** might be regarded as an indication of exciton coupling arising from $n \rightarrow \pi$ and $\pi \rightarrow \pi^*$ transitions of the propenal and vinyl groups for the 1*S* and 7*S* configurations of **1**.

Compound **2** was isolated as an amorphous colorless optically active powder $\{[\alpha]_D^{20} - 53.5$ (c 0.15, MeOH) $\}$ with the molecular formula of $C_{20}H_{24}O_7$ established by positive-ion sodiated HRESIMS (m/z 399.1410, calcd for $C_{20}H_{24}O_7Na$, 399.1420), and indicating nine degrees of unsaturation. In the IR spectrum (ν_{max} , cm^{-1}), **2** showed bands characteristic of hydroxy group (3405) and aromatic (1604, 1516, 1464) absorptions,¹³ consistent with UV absorptions at 280 and 230 nm.¹⁴ The ^{13}C NMR spectrum of **2** showed 20 resolved signals for two benzyl groups, two methoxy groups, two oxygenated methylene carbons, a methine and a quaternary carbons (Table 2). Consistent with the ^{13}C NMR signals, the ^1H NMR spectrum of **2** showed six signals for two 1,3,4-trisubstituted aromatic rings, a signal for two methoxy groups, and several signals for saturated methylene and methine groups (Table 2). These observations indicated that **2** contains three ring systems, which were assigned as two benzene rings and a furan ring, based on the NMR data of **2**. A 4-hydroxy-3-methoxyphenyl group could be proposed as being linked at the C-7 position, as implied by the HMBC correlations between the protons of one of the methoxy groups and C-3, H-2/C-4, H-5/C-3, and H-7/C-1, C-2, C-6, and C-8 (Table 2). Another 4-hydroxy-3-methoxyphenyl group was assigned at the C-7' position, as indicated by the HMBC correlations between the protons of the second methoxy group and C-3', H-2'/C-4' and C-6', and H-7'/C-1', C-2', C-6', and C-9' (Table 2). A furan ring was proposed to include C-8, C-9, C-7', C-8', based on HMBC correlations between H-7/C-8, H-9/C-8 and C-7', and H-8'/C-8, C-1', C-7', and C-9'. A hydroxy group was assigned at the C-8 position by the HMBC correlations observed between H-7, H-9, and H-8'/C-8, and another hydroxy group was assigned at the C-9' position by cross correlations observed between H-7'/C-1', C-2', C-6', and C-9' in the 2D HMBC NMR spectrum of **2**. The planar structural determination for **2** was confirmed by comparison of its NMR data with those of (–)-*trans*-3,4-divanillyltetrahydrofuran,¹⁴ 3-(α ,4-dihydroxy-3-methoxybenzyl)-4-(4-hydroxy-3-ethoxybenzyl)tetrahydrofuran,^{15,16} and olivil.¹⁷

The CD spectrum of olivil has been reported in the literature.^{18,19} Comparison of the spectroscopic data with those of olivil¹⁷ indicated that compound **2** might be an epimer of olivil. The absolute configuration of vicinal diol groups has been determined successfully by a simple and reliable CD method employing dimolybdenum tetraacetate $[Mo_2(OAc)_4]$, namely, Sznatzke's method.^{20,21} The in situ complexation of the chiral ligands, vicinal diols with $[Mo_2(OAc)_4]$ results in a series of bands from 260 to 500 nm apparent in the induced CD spectrum, and the sign of the band at 310 nm may be related to the absolute configuration of the 1,2-diols.^{20,21} As extended examples of Sznatzke's method, some 1,3-diols have been found to give complexes with $[Mo_2(OAc)_4]$ and to show induced CEs in their CD spectra, although the shape of their induced CD curves of 1,3-diols is different from those of 1,2-diols.^{22,23} For the complexation of 1,3-diols and $[Mo_2(OAc)_4]$ to lead to an ICD spectrum, the *syn*-parallel orientation of the hydroxy groups of the 1,3-diol moiety is required, and the sign of the CE around 400 nm in the ICD relates the chirality of the 1,3-diol moiety.^{22,23} Following procedures reported in the literature,^{22,23} the CD spectrum of **2** induced by $[Mo_2(OAc)_4]$ in a DMSO solution was recorded between 200 to 500 nm immediately after mixing both agents (Figures 3A and 3B), and the time of evolution of the ICD spectra of **2** was investigated (Figure 3C) from 10 to 50 min after being mixed. The ICD spectrum of **2** showed that the CE at 400 nm can be induced by complexation of **2** and $[Mo_2(OAc)_4]$, with this phenomenon being completed in 10 min and persisting for 50 min (Figure 3C). The strong positive CE observed around 310 nm (Figure 3B) and relatively weak negative CE band at 400 nm (Figure 3B) in the ICD spectra of **2** indicated that hydroxy group at the C-8 position and hydroxymethyl group at the C-8' position are *cis*.²⁴ According to the empirical sector rule on the basis of the sign of the CE around 400 nm from ICD of 1,3-diols,²² the negative Cotton effect at 400 nm observed in the ICD of **2** and the projection of the sector rule (Figure 3D) indicated a 8*S* and 8'*S* absolute configuration

for **2**. In turn, the NOESY correlations between H-7'/H-7a and H-9b and H-8'/H-7b and H-9a (Figure 2) suggested an 7' *R* configuration for **2**. Thus, compound **2** was determined as (2*R*,3*S*,4*S*)-4-(4-hydroxy-3-methoxyphenyl)-4-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyltetrahydrofuran. It is a C-7' and C-8' epimer of (–)-olivil, and has been given a trivial name, (–)-diepiolivil (**2**). Negative Cotton effects at 234.5 and 205.0 nm observed in the CD spectrum of **2** (Figure 3E) might be regarded as an indication of exciton coupling arising from a benzene ring at C-7' for **2**, as supported by its UV absorptions at 280, 230, and 206 nm (Figure 3F).

Compounds **1**, **2**, (+)-pinoresinol, and (+)-syringaresinol were tested in terms of their cytotoxicity against the HT-29 human colon cancer cell line,²⁵ using paclitaxel as a positive control. Of these, only compound **1** showed cytotoxicity toward HT-29 cells, with an IC₅₀ value of 4.7 μg/mL (20.1 μM). Compound **2** was inactive (IC₅₀ > 5 μg/mL) against HT-29 cells, consistent with a previous report that the presence of benzylic hydroxy groups decreases the resultant cytotoxicity of tetrahydrofuran lignans for cancer cell lines.²⁶

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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2. *Plant Material*: A stem sample of *Cameraria latifolia* L. was collected and identified by Dr. Hans T. Beck in Dade County, Florida (20° 40' N, 80° 15' W) in June 1991. A herbarium specimen was deposited at the New York Botanical Garden under accession number HB 01119.
3. *General Experimental Procedures*: Specific rotation values were obtained on a Perkin-Elmer model 343 polarimeter. UV spectra were recorded on a Hitachi U2910 UV spectrophotometer. CD measurements were performed using a JASCO J-810 spectropolarimeter. IR spectra were recorded on a Nicolet 6700 FT-IR spectrometer. ¹H and ¹³C, DEPT, HSQC, HMBC, NOESY, and COSY NMR spectra were recorded on Bruker Avance DRX-400 or 800 MHz NMR spectrometers at room temperature. ESIMS and HRESIMS were measured in the positive-ion mode on a Q-TOF mass spectrometer. Column chromatography was conducted using silica gel (65 × 250 or 230 × 400 mesh, Sorbent Technologies, Atlanta, GA). Analytical and preparative TLC systems were performed on precoated silica gel 60 F254 plates (Sorbent Technologies, Atlanta, GA). Sephadex LH-20 was purchased from Amersham Biosciences, Uppsala, Sweden. For visualization of TLC plates, sulfuric acid reagent was used. All procedures were carried out using anhydrous solvents purchased from commercial sources without further purification.
4. *Extraction and Isolation Procedures*: The ground dried stems of *Cameraria latifolia* were extracted exhaustively with methanol at room temperature. The solvent was evaporated in vacuo. The resultant dried methanol extract was suspended in 10% H₂O in MeOH and partitioned with *n*-hexane three times. The spent aqueous layer was concentrated under a vacuum to approximately 50% aqueous methanol and extracted twice with equal volumes of methylene chloride. Then, the aqueous layer was passed through PVP after a brief evaporation process to remove any residual

methylene chloride and the resin was washed extensively with methanol. A part of methylene chloride extract (800 mg) was separated chromatographically into six fractions, and fraction 6 was found to be cytotoxic, which was chromatographed over a silica gel column, eluted with a gradient mixture of *n*-hexane–acetone (10:1→1:1), and then purified by passage over a Sephadex LH-20 column, eluted with CH₂Cl₂–MeOH (1:1), affording (+)-camerarialdehyde (**1**, 2.0 mg), (–)-diepiolivil (**2**, 8.0 mg), (+)-pinoresinol (1.0 mg), and (+)-syringaresinol (1.0 mg).

5. *Selected data for 1*: Colorless gum; $[\alpha]_D^{20}$ +60.0 (*c* 0.02, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 230 (3.20), 202 (3.60) nm; CD (MeOH, nm) $\lambda_{\max}$ ($\Delta\epsilon$) 250.5 (+0.56), 223.0 (–0.64), 197.0 (+20.14), 183.0 (–9.81), 179.0 (+3.26); IR (dried film) $\nu_{\max}$ 3443, 2918, 2849, 1733, 1556, 1450, 1162, 1021, 852 cm^{–1}; ¹H and ¹³C NMR data, see Table 1; positive-ion sodiated HRESIMS *m/z* 257.1525, calcd for C₁₅H₂₂O₂Na, 257.1517.
6. *Selected data for 2*: Amorphous colorless powder. $[\alpha]_D^{20}$ –53.5 (*c* 0.15, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 280 (3.89), 230 (4.23), 206 (4.62) nm; CD (MeOH, nm) $\lambda_{\max}$ ($\Delta\epsilon$) 234.5 (–4.83), 205.0 (–6.52), 200.0 (+11.07); IR (dried film) $\nu_{\max}$ 3405, 1604, 1516, 1464, 1273, 1034, 754 cm^{–1}; ¹H and ¹³C NMR data, see Table 2; positive-ion sodiated HRESIMS *m/z* 399.1410, calcd for C₂₀H₂₄O₇Na, 399.1420.
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Figure 1.
Structures of (+)-camerarialdehyde (1) and (–)-diepiolivil (2) isolated from *Cameraria latifolia*.

Figure 2. COSY and key HMBC and NOESY 2D NMR correlations of (+)-cameradehyde (**1**) and partial NOESY 2D NMR correlations of (-)-diepiolivil (**2**). Molecular models of **1** and **2** were obtained from Chem3D Pro 12.0 program, and the NOESY 2D NMR spectrum was measured on a machine of Bruker DRX 800 MHz NMR spectrometer.

Figure 3.

A. Induced CD (ICD) spectrum from (370–500 nm) of (–)-diepiolivil (**2**), 2.0 mM, in a solution of dimolybdenum tetraacetate, 2.4 mM, in DMSO (green line) and CD spectra of dimolybdenum tetraacetate, 2.4 mM, in DMSO (blue line) and **2**, 2.0 mM, in DMSO (red line). B. Induced CD (ICD) spectrum (307–370 nm) of (–)-epiolivil (**2**), 2.0 mM, in a solution of dimolybdenum tetraacetate, 2.4 mM, in DMSO (green line) and CD spectra of dimolybdenum tetraacetate, 2.4 mM, in DMSO (red line) and **2**, 2.0 mM, in DMSO (blue line). C. Time evolution of ICD spectra of **2**, 2.0 mM, in a solution of dimolybdenum tetraacetate, 2.4 mM, in DMSO. Time $t = 10$ (1), $t = 20$ (2), $t = 30$ (3), $t = 40$ (4), $t = 50$ (5) corresponds to about 10, 20, 30, 40, and 50 min after the mixing **2** and $[\text{Mo}_2(\text{OAc})_4]$. ICD spectra (Figures 3A–3C) were measured between 200 and 500 nm at room temperature with a JASCO J-810 spectropolarimeter, using DMSO solution in a cell of 0.5 cm pathlength. D. Projection of the sector rule for **2** (carbon atoms C-8 and C-9' are located behind the oxygen atoms). E. CD spectra of **2**, 0.1 mM, in a MeOH solution. CD spectra were measured between 400 and 200 nm at room temperature with a JASCO J-810 spectropolarimeter, using MeOH solution in a cell of 0.5 cm pathlength and corrected by subtracting a spectrum of the appropriate solution in the absence of the samples recorded under identical conditions. F. UV spectra of **2**, 0.1 mM, in MeOH. UV spectrum was recorded with a Hitachi U2910 UV spectrophotometer in the range 190–500 nm in MeOH solution using cells of 1 cm pathlength with MeOH as the reference solvent. $[\text{Mo}_2(\text{OAc})_4]$ (Sigma-Aldrich), DMSO (Sigma Aldrich, anhydrous 99.9%), and MeOH (Fisher Scientific, HPLC grade) were commercially available and used without further purification.

Table 1¹H and ¹³C NMR spectroscopic data for (+)-camerarialdehyde (**1**) in CDCl₃

Position	$\delta_{\text{C}}(\text{mult.})^a$	$\delta_{\text{H}}(\text{mult., J, Hz})^b$
1	36.2 CH	2.58 m
2	26.9 CH ₂	1.59 overlap
3	29.5 CH ₂	1.25 overlap
4	39.8 CH ₂	1.38 (H _a) m 1.49 (H _b) t (4.3)
5	48.1 CH	1.86 br d (11.5)
6	152.7 C	
7	73.4 CH	4.05 dd (10.7, 5.2)
8	32.9 CH ₂	1.53 (H _a) overlap 2.02 (H _b) m
9	40.6 CH ₂	1.32 (H _a) m 1.59 (H _b) overlap
10	35.8 C	
11	102.5 CH ₂	4.57 (H _a) s 5.04 (H _b) s
12	16.5 CH ₃	0.75 s
13	155.0 C	
14	194.8 CH	9.54 s
15	133.3 CH ₂	6.00 (H _a) s 6.31 (H _b) s

^aRecorded at 100.6 MHz and referenced to residual CHCl₃ at δ 77.16.⁹ CH₃, CH₂, CH, and C multiplicities were determined by DEPT 90, DEPT 135, and HSQC experiments.

^bRecorded at 400.1 MHz and referenced to residual CHCl₃ at δ 7.26.⁹ s = singlet, br d = broad doublet, dd = double doublet, t = triplet, tt = triple triplet, m = multiplet. *J* values presented in Hz and omitted if the signals overlapped as multiplets. The overlapped signals assigned by ¹H-¹H COSY, HSQC, and HMBC spectra are presented without designating multiplicity.

Table 2

NMR spectroscopic data for (–)-diepiolivil (**2**) in CDCl₃

Position	$\delta_{\text{C}}(\text{mult.})^a$	$\delta_{\text{H}}(\text{mult., J, Hz})^b$	COSY (H→H) ^c	HMBC (H→C) ^d	NOESY (H→H) ^e
1	128.3 C				
2	112.9 CH	6.81 d (1.6)		3, 4, 7	7a, 7b, 9a, 9b
3	146.6 C				
4	144.8 C				
5	114.2 CH	6.89 overlap	6	3	
6	123.0 CH	6.79 dd (8.0, 1.6)	5		7a, 7b, 9a, 9b
7	39.3 CH ₂	2.96 (H _a) d (13.7)	7b	1, 2, 6, 8	2, 9'a, 9'b, 7', 8'
		3.08 (H _b) d (13.7)	7a		2, 9'a, 9'b, 8', 9b
8	81.4 C				
9	77.1 CH ₂	3.69 (H _a) d (8.8)	9b	8, 7'	2, 8'
		3.91 (H _b) overlap	9a		2, 6, 7'
1'	133.9 C				
2'	108.8 CH	7.01 s		1', 3', 4', 6', 7'	7', 8'
3'	146.9 C				
4'	145.5 C				
5'	114.6 CH	6.89 (H _a) overlap			
6'	119.6 CH	6.81 (H _b) overlap			7', 8'
7'	83.3 CH	4.71 d (8.0)	8'	1', 2', 6', 9'	7a, 9b, 2', 6', 8', 9'a, 9'b
8'	59.1 CH	2.52 m	7', 9'a, 9'b	8, 1', 7', 9'	7b, 9a, 2', 6', 9'a, 9'b
9'	60.8 CH ₂	3.84 (H _a) dd (10.8, 5.6)	8' 8'	7'	7a, 7b, 7', 8', 7a, 7b, 7', 8',
		3.98 (H _b) dd (10.8, 7.6)			
OCH ₃ -3/3'	56.0 CH ₃	3.91 s		3/3'	

^aRecorded at 100.6 MHz and referenced to residual CHCl₃ at δ 77.16.⁹ CH₃, CH₂, CH, and C multiplicities were determined by DEPT 90 and DEPT 135 and HSQC experiments.

^bRecorded at 400.1 MHz and referenced to residual CHCl₃ at δ 7.26.⁹ s = singlet, d = doublet, dd = double doublet, m = multiple. *J* values are presented in Hz and omitted if the signals overlapped as multiplets. The overlapped signals assigned by ¹H-¹H COSY, HSQC, and HMBC spectra are presented without designating multiplicity.

^cRecorded at 400.1 MHz and referenced to residual CHCl₃ at δ 7.26 with a proton showing a COSY correlation to the indicated proton.

^dRecorded at 400.1 MHz with a proton showing a HMBC correlation to the indicated carbon.

^eRecorded at 800.1 MHz and referenced to residual CHCl₃ at δ 7.26 ppm with a proton showing a NOESY correlation to the indicated proton.