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2-Hydroxy-4,6-dimethoxyacetophenone from Leaves of *Peperomia glabella*

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A 2-hidroxi-4,6-dimetoxiacetofenona foi isolada de folhas de *Peperomia glabella* (família Piperaceae). A substância cristaliza no grupo espacial $P\bar{1}$ com duas moléculas na unidade assimétrica. A análise estrutural revela uma rede bidimensional infinita no plano (011), estabilizada por ligações de hidrogênio inter-moleculares ao longo da direção [100] e interações de van der Waals ao longo da direção [011]. As moléculas apresentam fortes ligações de hidrogênio intra-moleculares [O1-HO1...O4 = 1,53(2) Å e O5-HO5...O8 = 1,38(2) Å]. A conformação molecular foi analisada usando o MOGUL, uma base de dados de geometria molecular derivada do CSD (Cambridge Structural Database).

The 2-hydroxy-4,6-dimethoxyacetophenone was isolated from the leaves of the *Peperomia glabella* (Piperaceae family). The molecule crystallizes in the space group $P\bar{1}$ with two independent molecules in the asymmetric unit. The structural analysis reveals an infinite two-dimensional network in the (011) plane, stabilized by intermolecular hydrogen bonds along [100] and van der Waals interactions along [011]. The molecules present strong intra-molecular hydrogen bonds [O1-HO1...O4 = 1.53(2) Å and O5-HO5...O8 = 1.38(2) Å]. The molecular conformation was analyzed using the MOGUL, a knowledge base of molecular geometry derived from the CSD (Cambridge Structural Database).

Keywords: *Peperomia glabella*, 2-hydroxy-4,6-dimethoxyacetophenone, X-ray diffraction

Introduction

Peperomia glabella (Piperaceae) is an epiphyte used in Venezuelan folk medicine as an antiasthmatic.[1] Piperaceae family comprises 14 genera and 1950 species.[2] Among these, *Piper* and *Peperomia* are the most abundant with approximately 700 and 600 species, respectively.[3] Phytochemical profile from genus *Piper* is characterized by occurrence of lignans and neolignans,[4,5] chromenes,[6-8] amides,[9,10] alkaloids,[11] Phenylpropanoids,[12] and cyclopentenedione derivatives.[13] Comparative study showed divergence of secondary metabolism in cell suspension cultures and differentiated plants of *P. cernuum* and *P.crassinervium*.[14] Compared with the genus *Piper*, few chemical investigations reported so far for *Peperomia* species have shown their common constituents as phenylpropanoids, benzopyrans, chromenes, and prenylated hydroquinones.[15-17] Additionally there are several nor/seco-compounds, e.g., the cyclobutane compound from *Peperomia pellucida* that seems to be produced by dimerisation of styryl phenol (a nor-phenylpropanoid).[18] *P. glabella* has been shown to contain one secolignan of butenolide skeleton.[19] In this work we wish to report the structure of the 2-hydroxy-4,6-dimethoxyacetophenone, (**1**), extracted from leaves of *Peperomia glabella*. Acetophenone derivatives have shown many interesting biological properties such as antinflammatory,[20,21] cytotoxic,[22] and choleretic[23] activities. This compound was previously isolated from *Artemisia maritima*,[24] *Artemisia gypsaceae*,[25] and *Plagiochila fasciculata* showing antifungal activities against *Trichophyton mentagrophytes*[26] from strain of *Trichoderma pseudokoningii* Rifai.[27] It is important to emphasize that (**1**) can be also obtained by synthetic route, from different starting compound, such as 1-hydroxy-3,5-dimethoxybenzene,[28, 29] 2,4,6-trihydroxiacetophenone,[30] and 1,3,5-trihydroxybenzene.[31]

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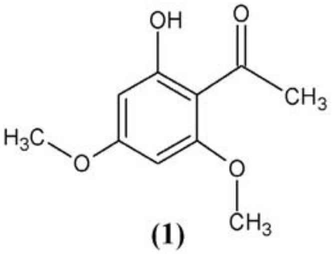

(1)

The aim of the present work is to determine unambiguously the molecular structure of (**1**) by X-ray diffraction (XRD) and its intra and inter-molecular geometry as well. To the best of our knowledge, this is the first occurrence of this class of compound in *Peperomia* species.

Experimental

General Considerations

The compound was isolated from leaves of samples of *Peperomia glabella*. All chemicals used during the extraction, purification and crystallization were of analytical or chromatography grade.

^{1}H and ^{13}C NMR spectra (4.9 T) were recorded on a Bruker AC-200 spectrometer operating at room temperature, using tetramethylsilane as an internal reference.

Plant material, extraction and isolation of 2-hydroxy-4,6-dimethoxyacetophenone

Peperomia glabella samples were collected at Lençóis (12° 45' 19.5" S 41° 30' 34.1" W) Bahia, Brazil. The leaves (8.20 g) were extracted four times with methanol (300 mL each time) at room temperature. This extract (2.07 g) was submitted to normal-phase silica gel column chromatography using increasing proportions of hexane:CH_2Cl_2. 2-hydroxy-4,6-dimethoxyacetophenone was obtained as solid white, 172 mg, crystallized from CH_3OH:CH_2Cl_2.

Identification of 2-hydroxy-4,6-dimethoxyacetophenone

The ^{1}H NMR spectrum of (**1**) showed two aromatic *meta* hydrogens at δ 6.05 and 5.93 (d, *J* 2.2 Hz). In addition, the acetophenone group was inferred from the methyl group at δ 2.60 and confirmed by ^{13}C NMR spectrum at δ 32.7 and by acetophenone carbonyl at δ 203.5. The additional substituents of the aromatic ring were defined as one quelated hydroxyl at δ 11.20 and two methoxyls observed at δ 3.85 (δ 55.4) and δ 3.81 (δ 55.4). The ^{13}C NMR spectrum (4.9 T) showed signals corresponding to four aromatic carbon quaternary atoms (δ 105.8; 167.5; 166.0; and 162.7); and two aromatic methyne (δ 90.6 and 93.0). Thus, compound (**1**) was identified as 2-hydroxy-4,6-dimethoxyacetophenone.[24]

X-ray Structure analysis of 2-hydroxy-4,6-dimethoxyacetophenone

A well-shaped single crystal of (**1**) was selected for the XRD experiments. The intensity data were collected at 150 K on an Enraf-Nonius Kappa-CCD diffractometer (95 mm CCD camera on k-goniostat) with graphite monochromated Mo Kα (λ = 0.71073 Å) radiation. The temperature was controlled using an Oxford Cryosystem low temperature device. Data collection (φ scans and ω scans with κ offsets) was made using the *COLLECT*;[32] integration and scaling of the reflections were performed with the HKL Denzo-Scalepack system of programs.[33] The final unit cell parameters were based on all reflections using HKL Scalepack.[33] The structure was solved using Direct Methods with SHELXS-97.[34] The model was refined by full-matrix least-squares procedures on F^2 using SHELXL-97.[34] H atoms of the phenyl and methyl groups were positioned stereochemically and were refined with fixed individual displacement parameters [$U_{iso}(H) = 1.2U_{eq}(C_{aromatic})$ or $1.5U_{eq}(C_{methoxy})$] using a riding model, with aromatic C-H distances of 0.95 Å and methyl C-H distances of 0.98 Å. The two hydroxyl H atoms were located by difference Fourier synthesis and were set as isotropic.

Data collections and experimental details for (**1**) are summarized in Table 1. The programs SHELXL-97, SHELXS-97, and ORTEP-3[35] were used within WinGX[36] to prepare materials for publication. The programs Mercury[37] and ORTEP-3 were used to prepare the molecular graphics.

Results and Discussion

Figure 1 shows an ORTEP-3[35] view of (**1**) with the atom numbering scheme. The structure crystallizes in $P\bar{1}$ with two independent molecules in the asymmetric unit (labelled as A and B in Figure 1). Comparison of these molecules by the method of Kabsch[38] showed them to be very similar with a root mean square deviation between homologous atoms of 0.024 Å. This fact suggested that the crystal could belong to a higher symmetric space group with just one molecule per asymmetric unit. Closer scrutiny, however, showed this is not the case because the affin transformation relating the two moieties did not coincide with any of those belonging to other space group. This symmetry was also carefully

Table 1. Crystal data, data collection details and structure refinement results of **1**

Empirical formula	$C_{10}H_{12}O_4$	
Formula weight	392.39	
Crystal system	Triclinic	
Space group	$P\bar{1}$ (No. 2)	
Unit cell dimensions (Å), º		
	α = 8.0551(4)	α = 70.590(3)
	β = 11.5505(6)	β= 77.218(3)
	γ = 11.7068(6)	γ = 75.733(3)
Volume (Å^3)	983.98(9)	
Z	4	
Density (calculated) (mg m^{-3})	1.122	
Absorption coefficient (mm^{-1})	0.103	
F(000)	416	
Crystal size (mm^3)	0.05 × 0.05 × 0.2	
θ range for data collection (deg)	2.95 to 25.00	
Index ranges	-9<=h<=9, -13<=k<=13, -13<=l<=13	
Reflection collected	19598	
Independent reflections	3461 [R(int) = 0.0775]	
Completeness to θ = 25.0º (%)	99.7	
Absorption correction	None	
Data/restraints/parameters	3461 / 0 / 260	
Goodness-of-fit on F^2	0.998	
Final *R* indexes [$I > 2\sigma(I)$]	R1 = 0.0486, wR2 = 0.1154	
R indexes (all data)	R1 = 0.0873, wR2 = 0.1380	
Extinction coefficient	0.036(8)	
Largest diff. peak and hole (e.Å^{-3})	0.205 and -0.202	

examined using PLATON,[39] and it was concluded that $P\bar{1}$ is in fact the correct space group.

The main geometric parameters are given in Table 2. The molecular conformation was analyzed using the MOGUL,[40] a knowledge base of molecular geometry derived from the Cambridge Structural Database (CSD)[41] that provides rapid access to information on the preferred values of bond lengths, valence angles and acyclic torsion angles. The Figure 2 shows an example of the graphical result of the query molecule studied here (molecule A). The resulting histogram is the C1-O1 bond length comparing with the C-O bond lengths in CSD entries containing similar structures. As emphasized by Bruno et al.,[40] comparison of the dimensions of a newly determined small-molecule crystal structure with bond lengths and angles of similar structures in the CSD is useful as a check against refinement errors and to highlight unusual geometrical features. This study showed that all bond lengths and bond angles are in agreement with the expected values for a good X-ray diffraction structure refinement. However, the MOGUL analysis has pointed out two interesting geometrical features due to resonance involving the moiety O3-C5-C6-C7-O4 (see Figure 1 and Table 2). It was observed that C5-O3 and C6-C7 is shorter than the average query values whereas the C5-C6 and C7-O4 is longer than the expected ones. It is important to emphasize that the same behaviour (not shown in Table 2) was observed to the molecule B present in the asymmetric unit.

Both molecules in the asymmetric unit are almost flat. The largest deviations from the least squares plane through the aromatic ring system A are -0.176(4) and 0.112(4) Å for C8 and C9 atoms, respectively. Similar results were observed to the molecule B: the largest

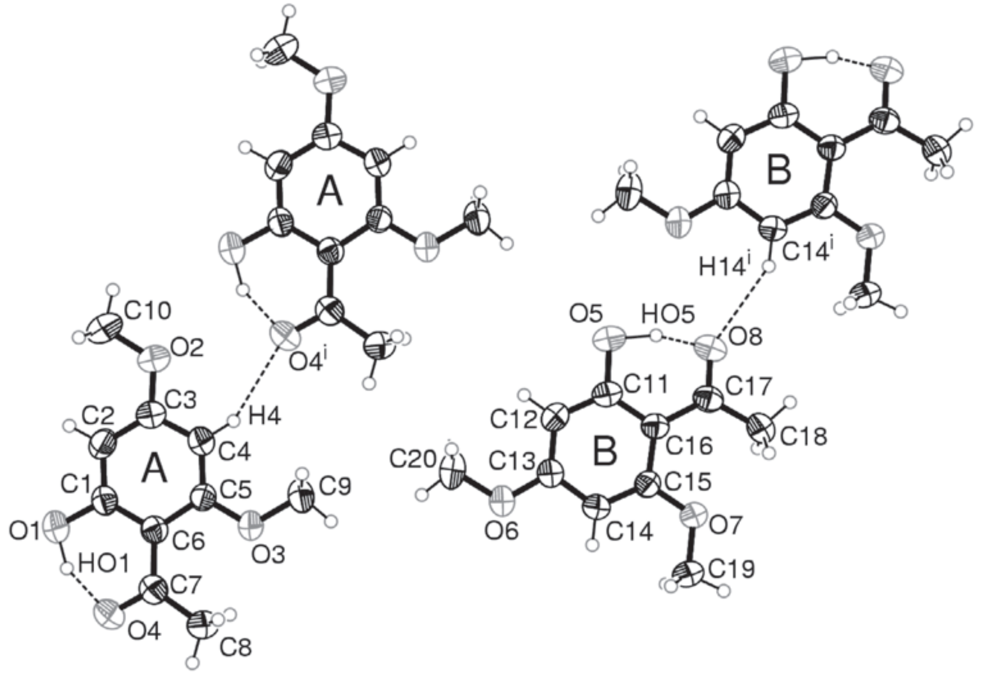

Figure 1. View of (**1**) with displacement ellipsoids for the non-hydrogen atoms shown at the 50% probability level. The H atoms are shown as spheres of arbitrary radii. Hydrogen bonds are indicated by dashed lines.

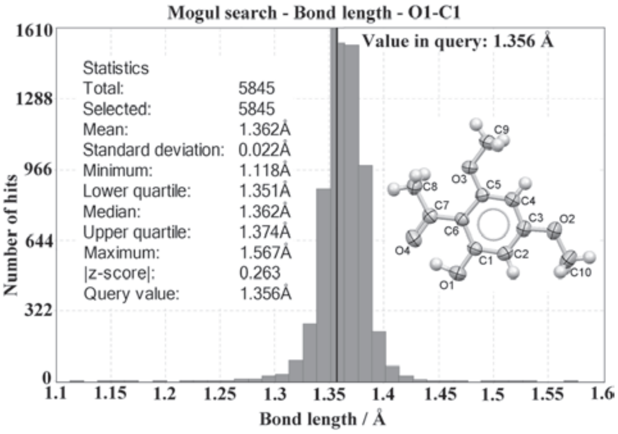

Figure 2. Histogram comparing the C1–O1 bond length with the C–O bond lengths in CSD entries containing structures similar to 2-hydroxy-4,6-dimethoxyacetophenone.

Table 2. Selected Bond lengths (Å) and angles (°) for compound (**1**) and MOGUL bond analysis

Geometry Type	Bond	Average query	Geometry Type	Angle	Average query
C1–O1	1.356(2)	1.36(2)	O1–C1–C2	116.4(2)	120(3)
C1–C2	1.384(3)	1.38(2)	O1–C1–C6	121.2(2)	121(2)
C1–C6	1.414(2)	1.41(2)	C2–C1–C6	122.3(2)	121(2)
C2–C3	1.384(3)	1.38(2)	C1–C2–C3	118.9(2)	119(2)
C3–O2	1.363(2)	1.37(3)	O2–C3–C2	124.1(2)	120(5)
C3–C4	1.388(3)	1.38(2)	O2–C3–C4	114.8(2)	120(5)
C4–C5	1.373(3)	1.38(2)	C2–C3–C4	121.1(2)	121(2)
C5–O3	1.351(2)	1.37(2)	C5–C4–C3	119.8(2)	118(2)
C5–C6	1.428(3)	1.40(2)	O3–C5–C4	122.6(2)	124(2)
C6–C7	1.455(3)	1.49(3)	O3–C5–C6	115.7(2)	116(2)
C7–O4	1.249(2)	1.22(3)	C4–C5–C6	121.6(2)	122(2)
C7–C8	1.493(3)	1.49(4)	C1–C6–C5	116.1(2)	117(1)
C9–O3	1.420(2)	1.42(4)	C1–C6–C7	119.6(2)	120(3)
C10–O2	1.425(2)	1.42(4)	C5–C6–C7	124.2(2)	122(2)
			O4–C7–C6	119.8(2)	120(2)
			O4–C7–C8	116.1(2)	120(2)
			C6–C7–C8	124.1(2)	120(3)
			C3–O2–C10	119.0(2)	118(3)
			C5–O3–C9	119.1(2)	118(2)

deviations were observed to the C18 (-0.173(4) Å) and C19 (0.120(4) Å) atoms. The least squares planes of the A and B molecules form an angle of 0.8(1)°. This result shows that the two moieties are in the same plane, which is also illustrated in Figures 3 and 4.

The molecules A and B exhibited strong intra-molecular hydrogen bonds involving O1-HO1...O4 and O5-HO5...O8, respectively (Table 3 and Figure 1). The weak intermolecular hydrogen bond between the aromatic hydrogen linked to C4 (molecule A) and the adjacent carboxyl oxygen O1 at x+1, y, z stabilizes the packing of the molecule A and gives rise to an infinite one dimensional chain parallel to the [100] direction (Table 3, Figures 1 and 3). The same interaction occur to the molecule B involving the aromatic hydrogen linked to C14 (molecule B) and the adjacent carboxyl oxygen O5 at x+1, y, z. The chains form a planar structure, connected by van der Waals interactions along the [011] direction. Therefore, the chains are linked

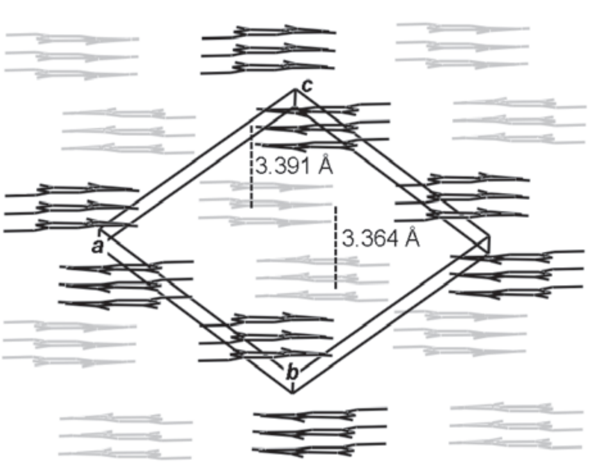

Figure 4. Packing of (**1**) projected onto bc plane. The separations between parallels infinite two-dimensional network parallel to the (011) plane are shown as dashed lines.

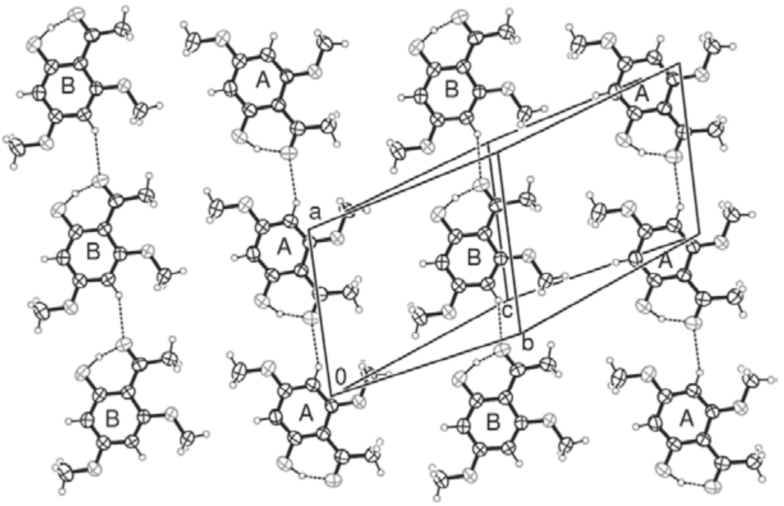

Figure 3. Packing of (**1**), showing the infinite two-dimensional network in the (011) plane. Hydrogen bonds are indicated by dashed lines.

Table 3. Hydrogen-bonding geometry (Å, º)

D–H...A	D–H	H...A	D...A	D–H...A
O1–HO1...O4	1.05 (3)	1.53 (2)	2.500 (3)	152 (3)
O5–HO5...O8	1.14 (2)	1.38 (2)	2.487 (3)	162 (2)
C4–H4...O4^{i}	0.93	2.44	3.302 (3)	153
C14–H14...O8^{i}	0.93	2.46	3.300 (3)	151

^{i}Symmetry code: 1 + x, y, z.

themselves, forming an infinite two-dimensional network parallel to the (011) plane. The stacking of these two-dimensional networks is shown in the Figure 4. It is also observed that double chains, which are related by the inversion symmetry, are formed along [100] direction either to molecule A or B. The distance between parallels two-dimensional networks is about 3.4 Å.

Acknowledgments

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Supplementary Information

^{1}H and ^{13}C NMR data for **1** are avaliable free of charge at http://jbcs.sbq.org.br, as PDF file.

Supplementary crystallographic data sets for (**1**) is available through the Cambridge Structural Data Base, deposition number CCDC 296321. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44123-336-033; e-mail: deposit@ccdc.cam.ac.uk or http:www.ccdc.ac.uk

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2-Hydroxy-4,6-dimethoxyacetophenone from Leaves of *Peperomia glabella*

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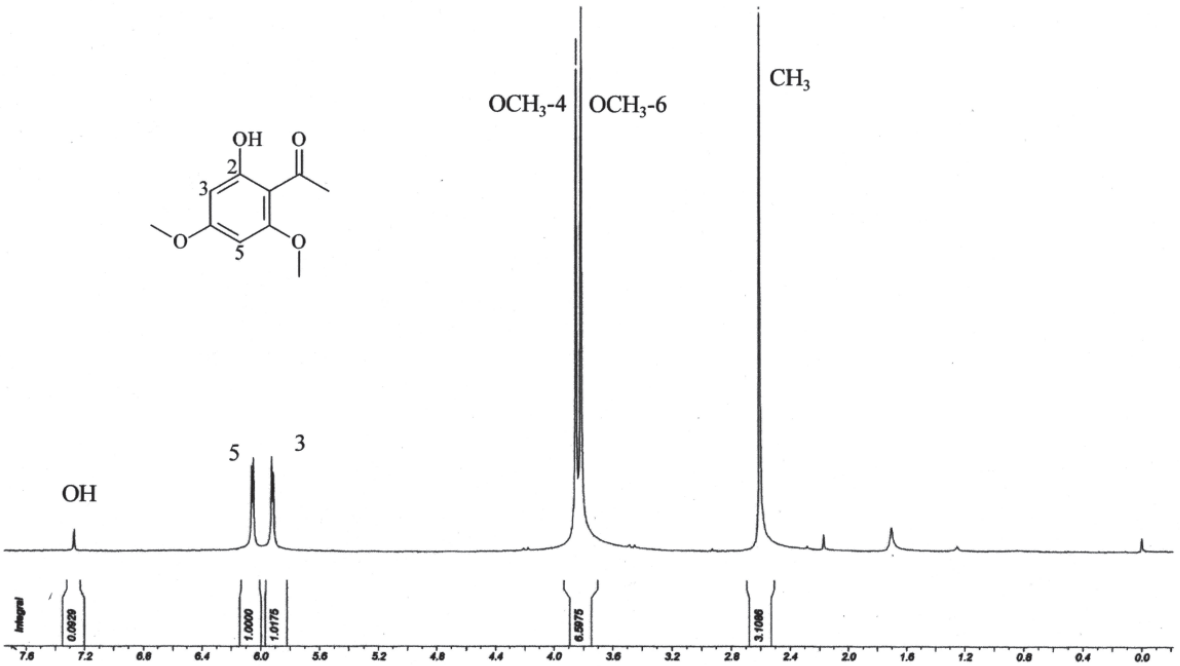

Figure S1. ^{1}H NMR spectra of (**1**) (4.9 T).

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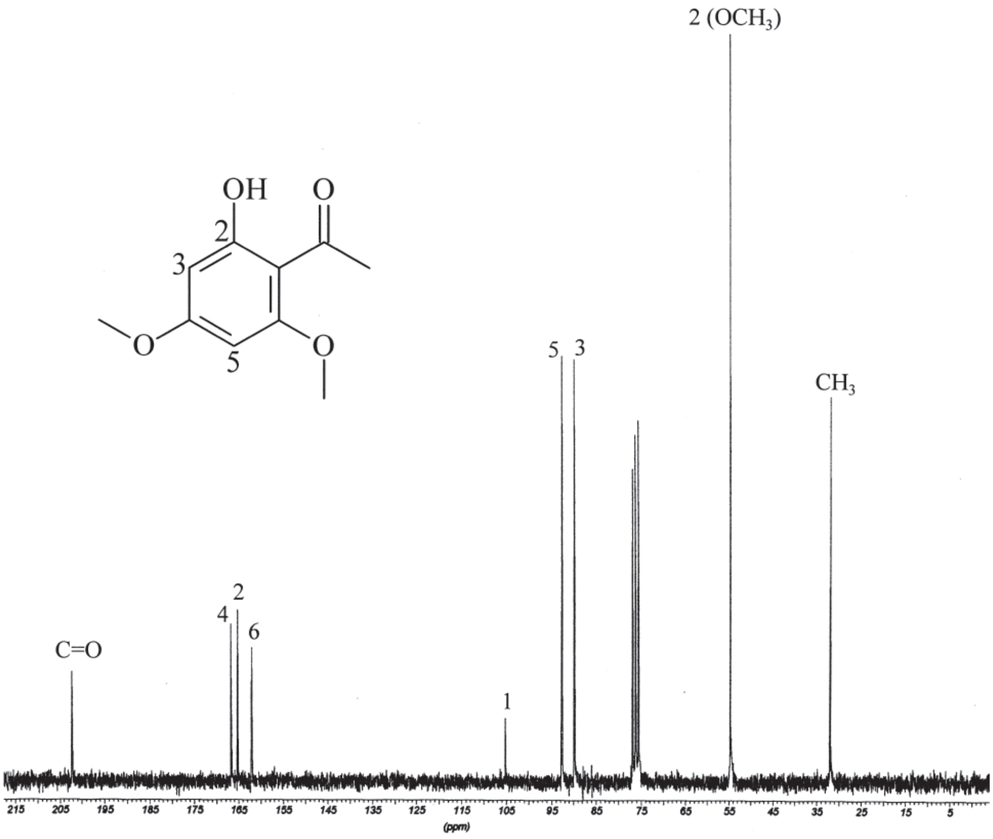

Figure S2. ^{13}C NMR spectra of (**1**) (4.9 T).