

Article

Anti-inflammatory Lignans from the Fruits of *Acanthopanax sessiliflorus*

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Abstract: A new lignan, named acanthosessilin A (**1**), as well as eight known lignan and lignan glycosides **2–9** were isolated from an ethanolic extract of *Acanthopanax sessiliflorus* fruits. The chemical structures were determined by spectroscopic methods, including HR-EIMS, 1D NMR (¹H, ¹³C, DEPT), 2D NMR (gCOSY, gHSQC, gHMBC, NOESY), and IR spectroscopy. All isolated compounds were tested for the ability to inhibit LPS-induced nitric oxide production in RAW264.7 macrophages.

Keywords: *Acanthopanax sessiliflorus*; lignan; acanthosessilin A; nitric oxide

1. Introduction

Acanthopanax sessiliflorus (Rupr. et Maxim) Seem, belonging to the Araliaceae family, is widely distributed in Korea, China, and Japan. The bark and twigs of *Acanthopanax* species are traditionally used in Korea as anti-rheumatoid arthritis, anti-inflammatory, and anti-diabetic drugs and are recognized to have ginseng-like activities [1,2]. Previous studies on its phytochemicals resulted in the isolation of lignans from the leaves and roots of *Acanthopanax* species [3–5], and eleutheroside E has been identified as a major compound in the fruits of *Acanthopanax* species [6]. Lignans are thought to

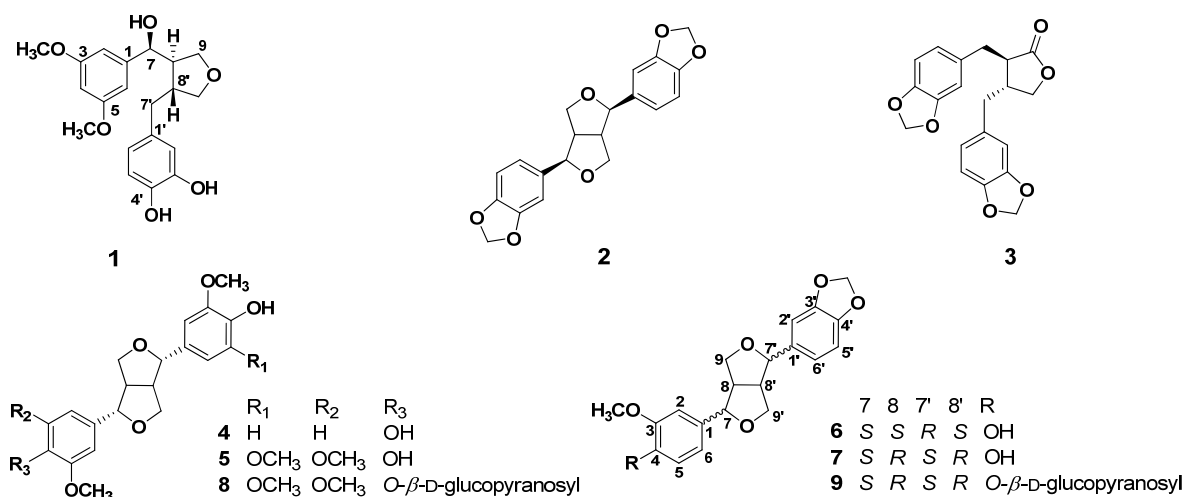
be the major active constituents of these plants and are believed to play essential roles in the treatment of diseases [7,8]. However, most phytochemical and pharmacological studies have mainly focused on the leaves, bark, and roots of *Acanthopanax* species, and only a few reports have investigated the fruits. *Acanthopanax* species are native medicinal plants and the fruits of *Acanthopanax* species have been used as a remedy to “wipe out evil wind” in traditional medicine [9]. To further investigate the bioactive constituents derived in the fruits of these species, the present phytochemical study was initiated.

We report herein on the isolation of a new 3,4-dibenzylfuran lignan (**1**) from the fruits of *A. sessiliflorus*, together with eight known compounds **2–9**, and the structural determination of these substances using extensive spectroscopic methods. Several previous studies have provided evidence for the anti-inflammatory effects of extracts and components from *Acanthopanax* species [10–12]. Therefore, isolated compounds **1–9** were evaluated for anti-inflammatory activities through the measurement of nitrite, a soluble oxidation product of nitric oxide (NO), in lipopolysaccharide (LPS)-induced RAW 254.7 macrophage cells.

2. Results and Discussion

A 70% ethanolic extract of dried *A. sessiliflorus* fruits was suspended in H₂O and extracted with EtOAc. The EtOAc soluble fraction was concentrated under reduced pressure to produce a residue that was subjected to multiple chromatographic steps using Sephadex LH-20, silica gel, and reversed-phase C18, yielding compounds **1–9** (Figure 1).

Figure 1. Chemical structures of isolated compounds **1–9**.



Compound **1**, obtained as colorless crystals from methanol, exhibited a UV absorption maximum at 282 nm. The molecular formula was determined to be C₂₀H₂₄O₆ from the molecular ion peak [M]⁺ at *m/z* 360.1552 (calcd for C₂₀H₂₄O₆, 360.1572) in the HR-EIMS. IR absorption bands at 3,430, 1,648, and 1512 cm^{−1} were characteristic of hydroxyl and aromatic groups. The ¹H-NMR spectrum showed three aromatic proton signals with *J*₄ coupling at δ_H 6.90 (1H, d, *J* = 3.2 Hz, H-4), 6.76 (1H, overlapped, H-2), and 6.75 (1H, overlapped, H-6), which were assigned to a 1,3,5-trisubstituted benzene moiety. Three other aromatic proton signals at δ_H 6.78 (1H, d, *J* = 2.0 Hz, H-2'), 6.70 (1H, d, *J* = 8.0 Hz, H-6'), and 6.63 (1H, dd, *J* = 8.0, 2.0 Hz, H-5') corresponded to another 1,2,4-trisubstituted

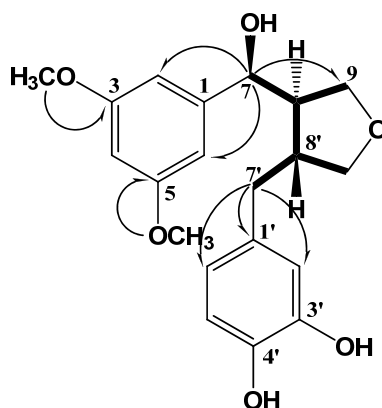
benzene moiety. A doublet oxygenated methine proton signal at δ_H 4.74 (1H, J = 6.8 Hz), assigned to H-7, and two oxygenated methyl proton signals at δ_H 3.82 (3H) and 3.83 (3H) for two methoxy groups were observed. Two oxygenated methylene proton signals were observed at δ_H 3.97 (1H, dd, J = 8.4, 6.8 Hz), 3.71 (1H, dd, J = 8.4, 6.8 Hz), 3.82 (1H, overlapped), and 3.62 (1H, dd, J = 10.8, 6.4 Hz), which were assigned to H-9a, H-9b, H-9'a, and H-9'b, respectively. In the high magnetic field, two methine proton signals at δ_H 2.34 (1H, m, H-8) and 2.72 (1H, m, H-8'), and two methylene proton signals at δ_H 2.92 (1H, dd, J = 13.2, 4.8 Hz, H-7'a) and 2.48 (1H, dd, J = 13.2, 11.6 Hz, H-7'b) were observed, suggesting the presence of a furan moiety. The ^{13}C -NMR spectrum showed twenty carbon signals, including two methoxy carbon signals [δ_C 56.3 (OMe-3,5)], confirming **1** to be a lignan. The multiplicity of each carbon was determined using a DEPT experiment. In the aromatic region, six olefin methine carbon signals [δ_C 122.1 (C-6'), 119.8 (C-5'), 116.1 (C-2), 115.9 (C-6), 113.3 (C-2'), and 110.6 (C-4)], two carbonated quaternary carbon signals [δ_C 135.7 (C-1) and 133.5 (C-1')] and four oxygenated quaternary carbon signals [δ_C 149.0 (C-3, 5), 147.0 (C-4'), and 145.7 (C-3')] due to the 1,3,5-tri- and 1,2,4-trisubstituted benzene moieties were observed. The oxygenated methine carbon signal at δ_C 84.0 (C-7) shifted downfield due to attached to heteroatom (–OH). Also, two oxygenated methylene carbon signals [δ_C 73.4 (C-9') and 60.4 (C-9)] and two methoxy carbon signals [δ_C 56.3 (3, 5-OMe)] were observed. In the high magnetic field, two methine carbon signals [δ_C 54.0 (C-8) and 43.8 (C-8')] and a methylene carbon signal [δ_C 33.6 (C-7')] were observed. With further analysis of the HSQC and DEPT 135 spectra of **1**, the proton and carbon NMR signals could be assigned (Table 1). The correlations in the ^1H – ^1H COSY spectrum indicated key connectives of H-8 (δ_H 2.34) with H-7 (δ_H 4.74), H-8' (δ_H 2.72), H-9a (δ_H 3.97), and H-9b (δ_H 3.71) and H-8' (δ_H 2.72) with H-7'b (δ_H 2.48), H-9'a (δ_H 3.82), and H-9'b (δ_H 3.62) (Figure 2). In the HMBC spectrum, the long-range correlations of the two aromatic rings with the tetrahydrofuran ring were indicated by cross peaks between H-7 (δ_H 4.74) and C-2 (δ_C 116.1), C-6 (δ_C 115.9), and C-9 (δ_C 60.4) and between H-7' (δ_H 2.92, 2.48) and C-1' (δ_C 133.5), C-2' (δ_C 113.3), and C-6' (δ_C 122.1) (Figure 2). In addition, the long-range correlations between the proton signals of methoxy (δ_H 3.82, 3.83) and the oxygenated quaternary carbon signals of C-3, 5 (δ_C 149.0) were also identified. The relative stereochemistry of H-8 and H-8' **1** was identified as *trans* from the lack of NOE effect between H-8 and H-8'. The coupling constant of 6.8 Hz between H-7 and H-8, as well as the optical rotation of **1** ($[\alpha]_D^{25} = -43.5^\circ$) suggested an *S* configuration at C-7 [13]. A lignan with 7*S* and 8*R* configuration of similar structure, (3*R*,4*R*)-4-[(*S*)-(hydroxy)(4-hydroxy-3-methoxyphenyl)methyl]-3-(4-hydroxy-3-methoxybenzyl)tetrahydrofuran ($[\alpha]_D^{20} = -49^\circ$), supported the above, as reported in the literature [14]. The ^{13}C -NMR spectra (C-7, C-8, C-7', C-8') and NOESY experiment of **1** was very similar to (+) tripterygiol except for the optical rotation ($[\alpha]_D^{25} = +48.3^\circ$) and were comparable to the *epi*-THF lignan [15]. This indicates that the H-8 and H-8' are present in (7*S*,8*R*)-configuration.

Finally, the structure of **1** was determined to be 3-(3',4'-dihydroxybenzyl)-4-[(7*S*),7-hydroxy-3,5-dimethoxybenzyl]tetrahydrofuran, and named acanthosessilin A. Comparisons of NMR and MS data for the known compounds **2**–**9** with reported values led to their identification as (–)-sesamin (**2**) [16], (–)-hinokinin (**3**) [3], (+)-syringaresinol (**4**) [16], (+)-pinioresinol (**5**) [17], (+)-piperitol (**6**) [18], (+)-xanthoxylol (**7**) [19], acanthoside B (**8**) [20], and simlexoside (**9**) [21], respectively (Figure 1). Compounds **1**, **6**, **7**, and **9** were isolated from the genus *Acanthopanax* for the first time. In addition, compounds **3** and **5** were also isolated from this plant for the first time.

Table 1. ^1H - (400 MHz) and ^{13}C -NMR (100 MHz) data of compound **1** (in CD_3OD , δ in ppm, J in Hz) ^a.

No.	δ_{H}	δ_{C}	No.	δ_{H}	δ_{C}
1		135.7	1'		133.5
2	6.76 (1H, overlapped)	116.1	2'	6.78 (1H, d, $J = 2.0$ Hz)	113.3
3		149.0	3'		145.7
4	6.90 (1H, d, $J = 3.2$ Hz)	110.6	4'		147.0
5		149.0	5'	6.70 (1H, d, $J = 8.0$ Hz)	119.8
6	6.75 (1H, overlapped)	115.9	6'	6.63 (1H, dd, $J = 8.0, 2.0$ Hz)	122.1
7	4.74 (1H, d, $J = 6.8$)	84.0	7'	2.92 (1H, dd, $J = 13.2, 4.8$ Hz, H-7'a) 2.48 (1H, dd, $J = 13.2, 11.6$ Hz, H-7'b)	33.6
8	2.34 (1H, <i>m</i>)	54.0	8'	2.72 (1H, <i>m</i>)	43.8
9	3.97 (1H, dd, $J = 8.4, 6.8$, H-9a) 3.71 (1H, dd, $J = 8.4, 6.8$, H-9b)	60.4	9'	3.82 (1H, overlapped, H-9'a) 3.62 (1H, dd, 10.8, 6.4 Hz, H-9'b)	73.4
3-OCH ₃	3.83 (3H, s)	56.3			
5-OCH ₃	3.82 (3H, s)	56.3			

^a Assignments were confirmed by DEPT, ^1H - ^1H COSY, HSQC, and HMBC.

Figure 2. Key ^1H - ^1H COSY (bold dash) and HMBC (arrow) correlations of compound **1**.

Previous studies have already reported on the anti-inflammatory effects of components from *A. sessiliflorus* [11,12]. Since NO is known to play an important role in the inflammatory process, inhibitors of NO production are considered as potential anti-inflammatory agents [22]. Thus, we also investigated the inhibitory effects of compounds (**1–9**) on NO production by using the Griess reaction to measure nitrite, a soluble oxidation product of NO, in the culture medium of LPS-induced RAW 264.7 macrophages. As shown in Table 2, compounds **3–7** moderately inhibited NO production with IC_{50} values of 21.56, 17.75, 10.34, 22.30, and 27.57 μM , respectively. Compounds **1**, **2**, **8**, and **9** also decreased NO production with IC_{50} values in the range of 49.94 to 65.07 μM . Some cell toxicity was observed in cells treated with compounds **3** and **9**, whereas other compounds had no influence on cell viability.

Table 2. Inhibitory effects of compounds 1–9 against LPS-Induced NO production in RAW 264.7 macrophage cells.

Compound	IC ₅₀ (μM) ^a	Cell viability (%) ^b
1	49.94 ± 6.56	84.81 ± 2.71
2	38.92 ± 2.86	95.52 ± 2.01
3	21.56 ± 1.19	50.21 ± 1.55
4	17.75 ± 1.15	80.21 ± 1.11
5	10.34 ± 2.37	81.50 ± 3.32
6	22.30 ± 1.10	84.11 ± 2.46
7	21.57 ± 1.28	88.43 ± 3.71
8	65.07 ± 8.02	82.42 ± 1.27
9	53.00 ± 2.75	54.52 ± 2.21
Aminoguanidine ^c	6.51 ± 1.15	84.61 ± 2.50

^a IC₅₀ value of each compound was defined as the concentration (μM) that caused 50% inhibition of NO production in LPS-activated RAW 264.7 macrophage cells. Cells were pretreated for 1 h with compounds before stimulation with LPS (1 μg/mL) for 24 h; ^b Cell viability indicates mean maximum inhibitory effect, at a concentration of 100 μM, expressed as a percentage inhibition of nitrite production induced by LPS (1 μg/mL) in the presence of vehicle; ^c Positive control. The results are averages of three independent experiments, and the data are expressed as mean ± SD.

3. Experimental

3.1. General

Melting points were obtained using a Fisher-Johns Melting Point Apparatus with a microscope. Ultraviolet spectra were measured on a Shimadzu model UV-1601 spectrophotometer. CD spectra were obtained with a JASCO 715 spectropolarimeter. Optical rotations were measured on a JASCO P-1010 digital polarimeter. ¹H-, ¹³C-, and 2D-NMR spectra were recorded on a Varian Unity Inova AS 400 FT-NMR instrument, and chemical shifts were given in δ (ppm) based on tetramethylsilane (TMS) as an internal standard. IR spectra were run on a Perkin Elmer Spectrum One FT-IR spectrometer. EIMS and HR-EIMS spectra were obtained using a JEOL JMS-700 mass spectrometer (Tokyo, Japan). Silica gel 60 (Merck, 230–400 mesh), LiChroprep RP-18 (Merck, 40–63 μm), and Sephadex LH-20 (Amersham Pharmacia Biotech., Uppsala, Sweden) were used for column chromatography (CC). Pre-coated silica gel plates (Merck, Kieselgel 60 F₂₅₄, 0.25 mm) and pre-coated RP-18 F_{254s} plates (Merck) were used for analytical thin-layer chromatography analyses. Spots were visualized by spraying with 10% aqueous H₂SO₄ solution followed by heating.

3.2. Plant Material

The fruits of *A. sessiliflorus* were provided by the Jeongseon Agricultural Extension Center, Jeongseon, Korea in August 2009 and were identified by Prof. Dae-Keun Kim, College of Pharmacy, Woo Suk University, Jeonju, Korea. A voucher specimen (KHU090809) was reserved at the Laboratory of Natural Products Chemistry, Kyung Hee University, Yongin, Korea.

3.3. Extraction and Isolation

The air-dried fruits of *A. sessiliflorus* (10 kg) were powdered and extracted three times with 36 L of aqueous 70% EtOH at room temperature for 24 h. After concentration *in vacuo*, the EtOH extract (2,012 g) was suspended in H₂O (3 L) and then partitioned with EtOAc (3 L $\times$ 3) followed by concentration to give the EtOAc fraction (E, 118 g). Fraction E (100 g) was subjected to a silica gel CC (15 $\times$ 21 cm) using a gradient of CH₂Cl₃–MeOH (15:1 $\rightarrow$ 10:1 $\rightarrow$ 5:1 $\rightarrow$ 3:1 $\rightarrow$ 1:1, 2.8 L each) to yield 14 fractions (E1 to E14). Fraction E1 [4.3 g, elution volume/total volume (Ve/Vt) 0.01–0.07] was subjected to the silica gel CC [5 $\times$ 10 cm, *n*-hexane–EtOAc (6:1, 4.5 L)] to give compound **2** [486 mg, Ve/Vt 0.43–0.60, (silica F_{254s}) R_f 0.55, *n*-hexane–EtOAc (2:1)]. Subfraction E1-17 (500 mg, Ve/Vt 0.48–0.77) was separated by CC [RP-18 (3.5 $\times$ 4 cm), acetone–H₂O (2:1, 1.5 L)] to give compound **3** [22.7 mg, Ve/Vt 0.40–0.45, TLC (RP-18 F_{254s}) R_f 0.55, acetone–H₂O (1:1)]. Fraction E3 [36.3 g, Ve/Vt 0.15–0.33] was subjected to the silica gel CC [6 $\times$ 16 cm, CHCl₃–EtOAc (7:1, 5.5 L)] to give five subfractions (E3-1 to E3-5). CC [silica gel (3.5 $\times$ 16 cm), *n*-hexane–EtOAc (1:1, 3 L)] of subfraction E3-3 (1.80 g, Ve/Vt 0.34–0.53) gave 19 subfractions (E3-3-1 to E3-3-19). Subfraction E3-3-13 (80 mg, Ve/Vt 0.36–0.51) was separated by CC [RP-18 (3.5 $\times$ 5.5 cm), acetone–MeOH–H₂O (1:1:3, 1.5 L)] to give compound **1** [11 mg, Ve/Vt 0.22–0.33, TLC (RP-18 F_{254s}) R_f 0.55, acetone–MeOH–H₂O (1:2:1)]. Fraction E8 (8.98 g, Ve/Vt 0.59–0.67) was fractionated using silica gel CC [4 $\times$ 12 cm, CHCl₃–MeOH–H₂O (16:3:1 $\rightarrow$ 13:3:1, each 3.7 L)] and yielded nine subfractions (E8-1 to E8-9). Subfraction E8-4 (1.85 g, Ve/Vt 0.45–0.58) was purified using CC [RP-18 (3.5 $\times$ 6.5 cm), MeOH–H₂O (3:1, 1.2 L)] to give compound **4** [55 mg, Ve/Vt 0.56–0.70, TLC (RP-18 F_{254s}) R_f 0.40, MeOH–H₂O (5:1)]. Subfraction E8-5 (1.22 g, Ve/Vt 0.59–0.68) was fractionated using a Sephadex LH 20 CC [3 $\times$ 50 cm, MeOH–H₂O (4:1, 1.8 L)] and yielded five subfractions (E8-5-1 to E8-5-5). Purification of subfraction E8-5-4 (222 mg, Ve/Vt 0.75–0.88) using CC [RP-18 (3 $\times$ 10 cm), EtOH–H₂O (1:3, 0.5 L)] yielded compound **8** [44 mg, Ve/Vt 0.33–0.50, TLC (RP-18 F_{254s}) R_f 0.70, EtOH–H₂O (1:1)]. Subfraction E8-5-5 (146 mg, Ve/Vt 0.89–1.00) was separated by CC [RP-18 (30 $\times$ 10 cm), MeOH–H₂O (3:1, 1 L)] to give compound **9** [20 mg, Ve/Vt 0.49–0.60, TLC (RP-18 F_{254s}) R_f 0.50, MeOH–H₂O (5:1)]. Fraction E9 (5.80 g, Ve/Vt 0.68–0.72) was fractionated using silica gel CC [5 $\times$ 18 cm, CH₂Cl₃–EtOH–H₂O (16:3:1 $\rightarrow$ 13:3:1 $\rightarrow$ 10:3:1, each 3.2 L)] and yielded four subfractions (E9-1 to E9-4). Subfraction E9-4 (2.45 g, Ve/Vt 0.75–1.00) was chromatographed over RP-18 (5 $\times$ 5.5 cm) and eluted with MeOH–H₂O (1:1 $\rightarrow$ 3:1, each 1.8 L) to give twenty subfractions (E9-4-1 to E9-4-20). Subfraction E9-4-1 (282 mg, Ve/Vt 0.01–0.12) was purified over silica gel CC (4 $\times$ 12 cm) and eluted with CHCl₃–MeOH–H₂O (14:3:1, 2 L) to give compound **10** [40 mg, Ve/Vt 0.22–0.32, TLC (silica F₂₅₄) R_f 0.65, CHCl₃–MeOH–H₂O (14:3:1)]. Subfraction E9-4-6 (190 mg, Ve/Vt 0.55–0.64) was separated by CC [RP-18 (30 $\times$ 10 cm), acetone–H₂O (1:1, 1.5 L)] to give compound **6** [20 mg, Ve/Vt 0.49–0.60, TLC (RP-18 F_{254s}) R_f 0.55, acetone–H₂O (2:1)] and compound **7** [11 mg, Ve/Vt 0.66–0.71, TLC (RP-18 F_{254s}) R_f 0.50, acetone–H₂O (2:1)].

3.4. Spectroscopic Data

Acanthosessilin A (**1**). Colorless crystals, m.p.: 123–125 °C; [α]_D²⁵ −43.5° (*c* = 0.5, MeOH); CD (*c* = 2.50 $\times$ 10^{−3} M, MeOH) $\lambda_{\max}$ nm ($\Delta\epsilon$): −0.42 (217), −0.49 (236); UV $\lambda_{\max}$ (MeOH) nm: 280; IR

(CaF₂ window) cm⁻¹: 3430, 1648, 1512, 1245; EIMS *m/z*: 360 [M]⁺; HR-EIMS *m/z*: 360.1552 [M]⁺ (calcd for C₂₀H₂₄O₆, 360.1572); ¹H- and ¹³C-NMR data, see Table 1.

3.5. Measurement of NO Production and Cell Viability

Assays for NO production and cell viability were carried out as previously described [23]. Briefly, RAW 264.7 macrophages were harvested and seeded in 96-well plates (1 × 10⁴ cells/well) for measurement of NO production. The plates were pretreated with various concentrations of samples for 30 min and incubated with LPS (1 µg/mL) for 24 h. The amount of NO was determined by the nitrite concentration in cultured RAW264.7 macrophage supernatants using the Griess reagent. The cell viability was evaluated by MTT reduction.

4. Conclusions

The new compound 3-(3',4'-dihydroxybenzyl)-4-[(7*S*),7-hydroxy-3,5-dimethoxybenzyl]tetrahydrofuran, named acanthosessilin A (1), was isolated from *Acanthopanax sessiliflorus*, together with eight known lignans. According to previous investigations on *Acanthopanax* species, we have evaluated the inhibitory activities of all compounds against LPS-induced NO production in RAW264.7 macrophages. All compounds moderately inhibited NO production with IC₅₀ values in the range of 10.34 to 65.07 µM. The results provide a potential explanation for the use of this plant as a herbal medicine in the treatment of inflammatory diseases, and they may be potentially useful in developing new anti-inflammatory agents.

Supplementary Materials

¹H-NMR, ¹³C-NMR, EIMS, and HR-EIMS spectra of **1** are available as supporting data, which can be accessed at: <http://www.mdpi.com/1420-3049/18/1/41/s1>.

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Sample Availability: Samples of the compounds **1–9** are available from the authors.

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