

Article

The Occurrence of Flavonoids and Related Compounds in *Cedrus brevifolia* A. Henry ex Elwes & A. Henry Needles. Inhibitory Potencies on Lipoxygenase, Linoleic Acid Lipid Peroxidation and Antioxidant Activity

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Abstract: The phytochemical analysis of the polar extracts of *Cedrus brevifolia* needles yielded 20 compounds, namely from the methanol extract we isolated three flavonoids (1–3), one hydrolysable tannin (4), eleven phenolic derivatives (5–15) and one apocarotenoid (16), while from the methanol: water (5:1) extract we isolated four flavonoids (17–20). Chemical structures of all isolated compounds were determined by 1D, 2D-NMR (1 Dimension, 2 Dimensions Nuclear Magnetic Resonance) and UV-Vis (Ultraviolet-Visible) spectroscopy. Furthermore, the antioxidant potentials and the anti-inflammatory activities of both crude extracts and isolates were evaluated through DPPH radical scavenging capability, linoleic acid lipid peroxidation inhibition, and soybean LOX inhibition assays. This is the first report on the chemical profile of *C. brevifolia* needles. Catechin was the main compound derived from the methanol extract. According to our results, 4-O-β-D-glucopyranyl *trans*-p-coumaric acid and taxifolin were the most active ingredients.

Keywords: *C. brevifolia*; flavonoids; catechin; simple phenols; apocarotenoids; bioactivity, antioxidant; reducing power; total antioxidant capacity; reactive oxygen species

1. Introduction

Cedrus brevifolia (Pinaceae) is an important endemic tree of Cyprus flora with narrow distribution. It is well-differentiated from other species of the genus based on morphological and eco-physiological traits, such as short needles and slow growth, resistance to aphids, and the highest tolerance to drought in all cedar species [1]. In ancient times, Theophrastus (371–287 B.C.) was the first to mention the existence of *Cedrus* in Cyprus, Phoenicia and Syria as an important forest tree of that period [2]. Cedar wood has been highly appreciated since ancient times for building temples, palaces, and ships [2,3]. The Roman author and architect Marcus Vitruvius Pollio wrote that the material used for the roof of the Greek temple of Artemis in Ephesus was from *Cedrus* wood [4]. In ancient Egypt, it was known that cedar was very resistant to insects and pathogenic microorganisms, so they used its essential oil to mummify corpses [3].

In South-West Turkey the tar extract from *C. libani*, under the common name *katran*, is used internally and externally to heal wounds, fight parasites, and cure various diseases [3]. It is noteworthy that the tar extract has been proposed to be recognized for its therapeutic value by the French pharmacopoeia [5]. *C. brevifolia* bark is a source of compounds with antioxidant capacity and 15-lipoxygenase inhibitory activity [6]; *C. deodara* needles water extract exhibits antibacterial activity [7].

Taking in consideration the importance and uses of *Cedrus* species, this study was designed to investigate the chemical composition of the methanol and the aqueous methanol [MeOH:H₂O (5:1)] extracts prepared from needles of *C. brevifolia* and to evaluate their total antioxidant capacity and anti-inflammatory activity, as well as of the isolates.

2. Results

The methanol extract (6.5 g) yielded taxifolin (1) [8], astragalin (2) [9], isorhamnetin 3-O-β-D-glucoside (3) [10], (–)-catechin (4) [11], benzoate glucoside (5) [12], benzyl-β-D-glucoside (6) [13], benzyl-β-D-rutinoside (7) [14], 2-methoxy-phenyl-β-D-glucoside (8) [15], 3,4-dimethoxyphenyl-β-D-glucoside (9) [16], raspberry ketone (10) [17], p-anisic acid (11) [18], 4-hydroxybenzoic acid 4-O-β-D-glucoside (12) [19], p-coumaric acid (13, 6.0 mg) and its glucoside (14) [20,21], *trans*-vagoside (15) [22] and abscisic alcohol glucoside (16) [23]. The methanol:water (5:1) extract afforded kaempferol-3-O-β-rutinoside (17) [24], kaempferide-3-O-β-rutinoside (18) [25], tiliroside (19) [26], and syringetin 3-O-β-D-glucoside (20) [27] (Figure 1). Furthermore, both crude extracts and isolated compounds were examined for their inhibitory potency on lipoxygenase and lipid peroxidation, as well as for their antioxidant activity, in comparison to known antioxidants, e.g., caffeic acid, nor-dihydroguarectic acid (NDGA) and trolox. AAPH (2,2'-azobis (2-amidino-propane) dihydrochloride), DPPH (2,2-diphenyl-1-picrylhydrazyl) and soybean lipoxygenase (LOX) assays were used for the tests. This is the first report on the chemical profile of *C. brevifolia* needles. Catechin was the main compound derived from the methanol extract (See Supplementary Data, Table S1). According to our results of the in vitro tests, both extracts were found to possess potential antioxidant activity due to their high phenolic contents. Moreover, 4-O-β-D-glucopyranyl *trans*-p-coumaric acid and taxifolin were the most active ingredients (Figures 2–4, Table 1).

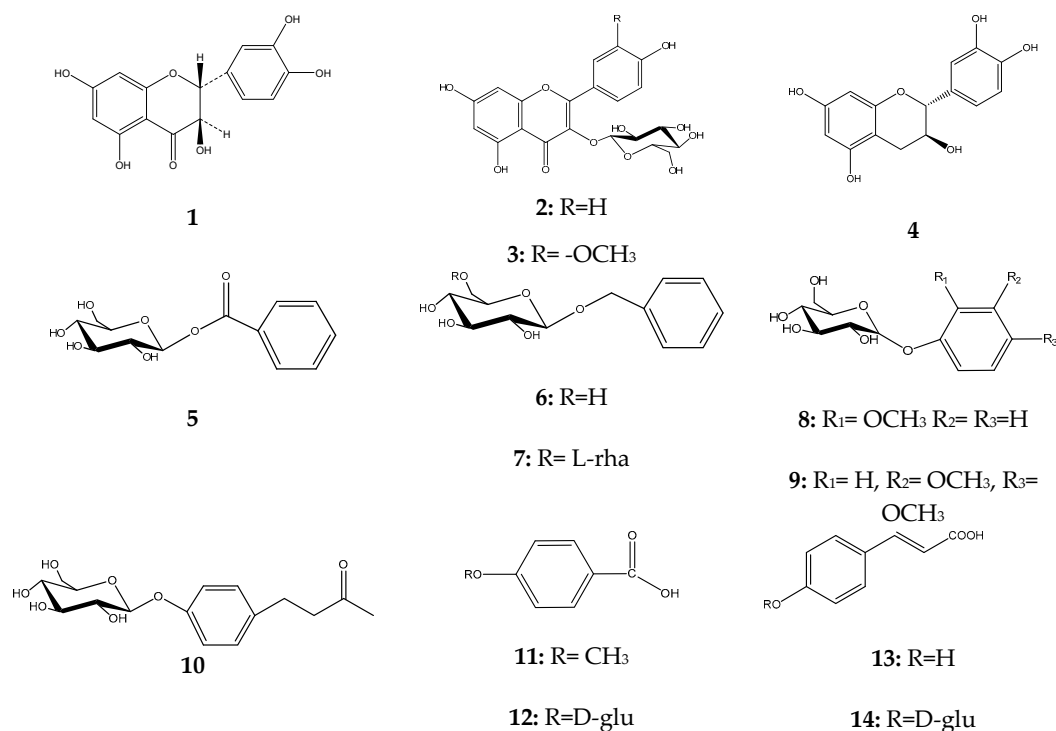


Figure 1. Cont.

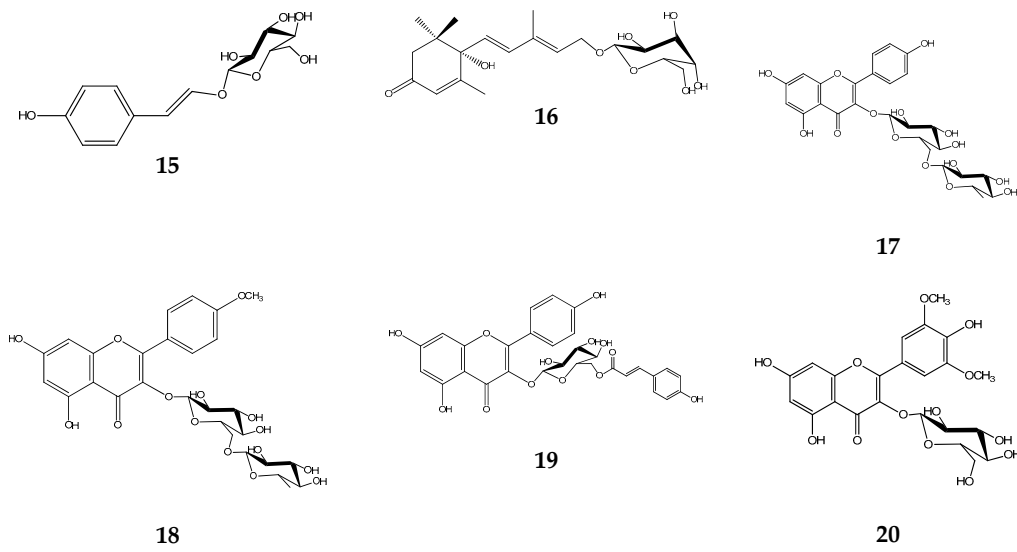


Figure 1. Structures of isolated compounds from *C. brevifolia* needles.

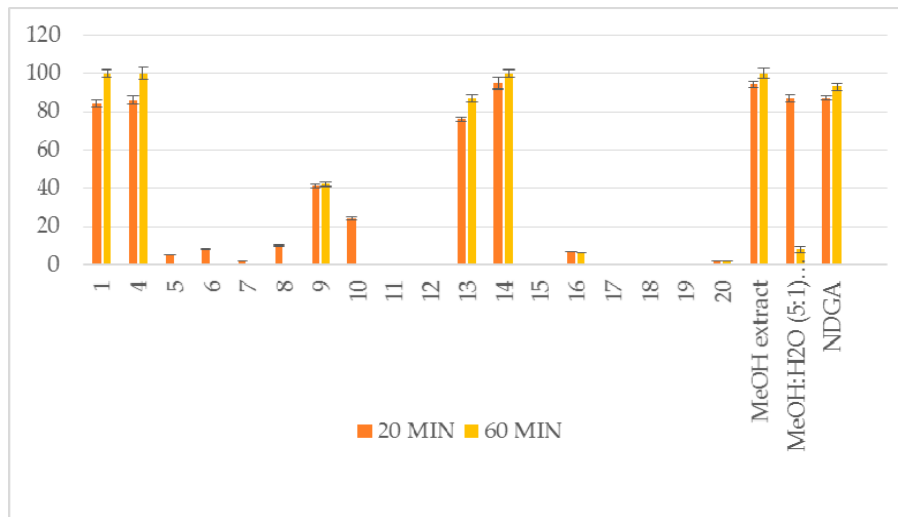


Figure 2. Reducing ability (RA %) at 0.1 mM. Interaction with DPPH.

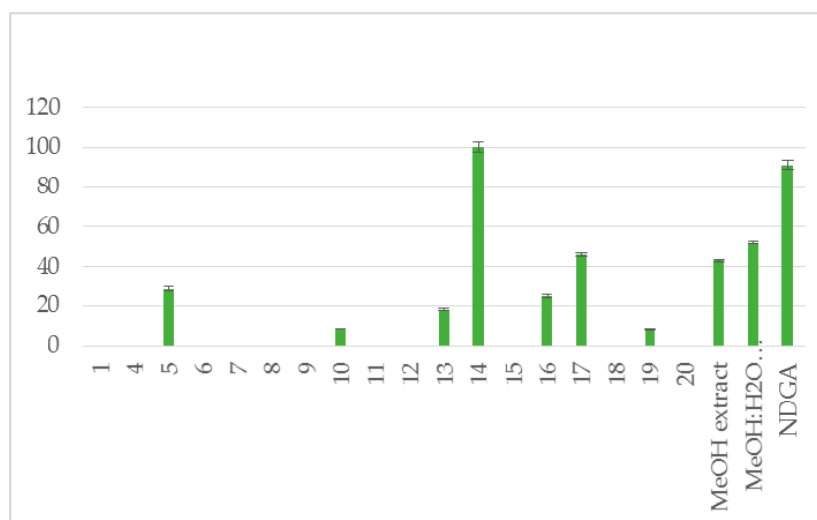


Figure 3. % Inhibition of soybean lipoxygenase (LOX) at 0.1 mM.

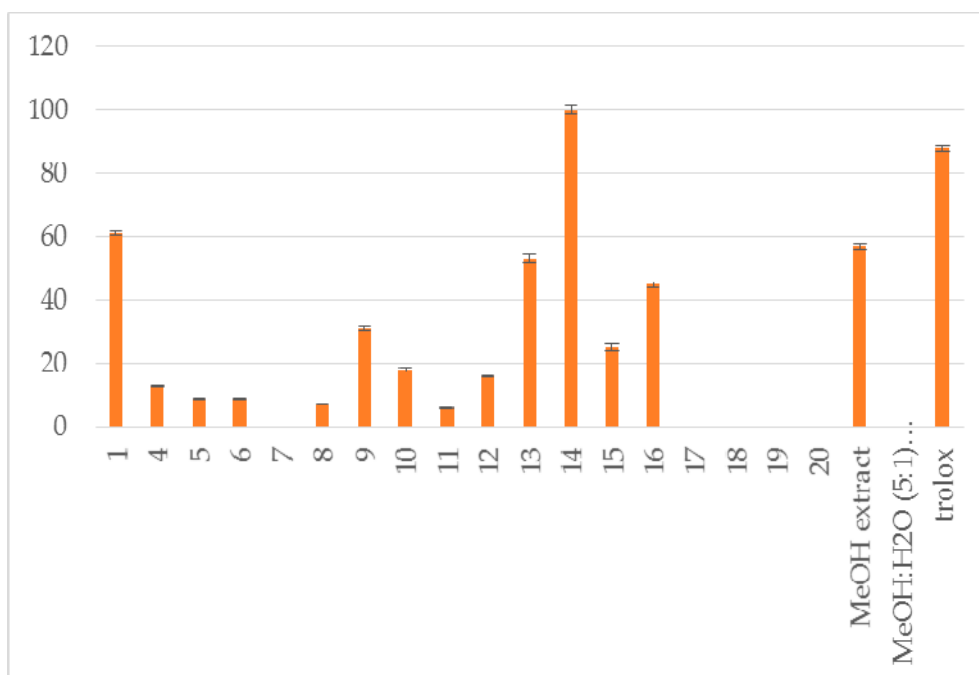


Figure 4. Percent inhibition of lipid peroxidation induced by AAPH at 0.1 mM.

Table 1. In vitro reducing ability (RA %) in DPPH assay, soybean lipoxygenase inhibition (% LOX inhbt) and anti-lipid peroxidation activity (A-LP %).

Compound	RA # % ± SD, DPPH, (20 min)	RA # % ± SD, DPPH, (60 min)	% LOX ± SD Inhbt @ (0.1 mM)	A-LP % ± SD @ (0.1 mM)
1	84 ± 1.8 *	100 ± 2.1 **	no	61 ± 0.6 **
4	86 ± 2.2 **	100 ± 3.1 **	no	13 ± 0.3 *
5	5 ± 0.1 *	no	29 ± 1.1 **	9 ± 0.1 *
6	8 ± 0.3 **	no	no	9 ± 0.1 *
7	2 ± 0.0 *	no	no	no
8	9.8 ± 0.4 *	no	no	7 ± 0.1 *
9	41 ± 1.0 **	42 ± 1.3 **	no	31 ± 0.7 *
10	24 ± 0.8 **	no	8.5 ± 0.1 **	18 ± 0.6 **
11	no	no	no	6 ± 0.1 *
12	no	no	no	16 ± 0.1 *
13	76 ± 1.1 **	87 ± 1.9 **	18 ± 0.6 **	53 ± 1.2 **
14	95 ± 3.2 **	100 ± 2.1 **	100 ± 2.5 **	100 ± 1.4 **
15	no	no	no	25 ± 1.0 *
16	7 ± 0.1 *	6 ± 0.0 *	25 ± 1.2 **	45 ± 0.9 **
17	nt #	nt #	46 ± 1.0 **	nt #
18	nt #	nt #	no	no
19	no	no	8 ± 0.3 *	no
20	2 ± 0.0 *	2 ± 0.0 *	no	no
MeOH extract	94 ± 1.9 **	100 ± 2.5 **	43 ± 0.4 *	57 ± 1.0 **
MeOH:H ₂ O (5:1) extract	87 ± 2.1 **	8 ± 1.8 **	52 ± 0.7 **	no
NDGA	87 ± 1.1 **	93 ± 1.8 **	91 ± 2.3 **	
trolox				88 ± 0.9 **

Final concentration 0.1mM; no: no activity under the experimental conditions; * $p < 0.05$; ** $p < 0.01$; nt #: not tested (The amount of the compounds was very small for the experiments to be performed. Thus, we decided for these compounds to test only their enzyme inhibitory activity for the sake of comparison); significant differences are relative to the solvent control.

3. Discussion

Overall, 20 compounds were isolated from *C. brevifolia* needles. The isolates were categorized as simple phenols, polyphenolic derivatives, and one apocarotenoid. Taking into account the phenolic nature of the isolates, we decided to evaluate their in vitro antioxidant activity using two different

antioxidant assays: (a) interaction with the stable free radical DPPH, as this method can be used for polar and nonpolar constituents [28], (b) interaction with the water-soluble azo compound AAPH in order to measure the radical-scavenging activity in vitro [29]. The antioxidant ability of the isolates was measured in comparison to positive controls, such as NDGA and trolox. The results are shown in Table 1 and Figures 2–4. The interaction, which indicates their radical scavenging ability in an iron-free system, was measured at 100 μ M after 20 and 60 min. In the DPPH assay, particularly effective antioxidants are the phenoxide anions from phenolic compounds like compounds 1, 4, 13 and 14, as well as nor-dihydroguarectic acid (NDGA), which was used as a reference. For these compounds it was observed an increase in their antioxidant activity after 60 min. Methanol and methanol: water extracts presented high reducing activity. This could be correlated to the presence of phenolic derivatives. The rest isolates did not present any interesting result. Due to low amounts, compounds 2 and 3 were not tested.

The % inhibition of lipid peroxidation given in Table 1 indicates three potent isolates, 1, 13 and 16. The methanol extract also exhibits anti lipid peroxidation activity.

We also decided to further evaluate the presented isolates and extracts for their ability to inhibit soybean LOX since most of the LOX inhibitors are antioxidants or free radical scavengers. Perusal of the % inhibition values (Table 1) shows that the most potent inhibitor is isolate 14 followed by 17 which seem to be less potent. It should to be noticed that both methanol extracts are almost equipotent. This inhibition is related to their antioxidant ability.

The investigation revealed that the polar extracts of *C. brevifolia* needles are abundant in phenolic compounds, which could explain its strong antioxidant activity.

4. Materials and Methods

4.1. Plant Material

C. brevifolia needles were collected on April 2013 from Cedar valley near Paphos (Cyprus) and authenticated by Mr. Konstantinos Nikolaou. A voucher specimen is kept at the Herbarium of Department of Forests, Cyprus, under the number: CYP 1467.

4.2. Equipment and Reagents

Optical rotation was recorded on a Perkin Elmer 341 polarimeter. The $[\alpha]_D$ values were obtained in methanol at 20 °C. UV spectra were recorded on a Shimadzu UV-160A spectrophotometer, according to [30] (1970). IR spectra were carried out by Perkin-Elmer Paragon 500 FT-IR spectrophotometer (PerkinElmer, Inc., Waltham, MA, USA). ^1H , ^{13}C and 2D-NMR spectra were recorded on a Bruker DRX 400 (Bruker BioSpin GmbH, Silberstetten, Germany), and on a Bruker AC 200 (50.3 MHz for ^{13}C -NMR) spectrometers at 295 K. Chemical shift are reported in ppm (δ) using the residual solvent signal (δ_{H} 3.31 in ^1H and δ_{C} 49.0 in ^{13}C , CD_3OD) as reference. Correlation spectroscopy (COSY); Heteronuclear Single Quantum Correlation (HSQC); Heteronuclear Multiple Bond Correlation (HMBC); Nuclear Overhauser Effect Spectroscopy (NOESY); Rotating-frame Overhauser Effect Spectroscopy (ROESY) experiments were performed using standard Bruker microprograms. Vacuum liquid chromatography (VLC) was performed on a silica gel (Merck: 43–63 μm) (Merck KGaA, Darmstadt, Germany) [31], column chromatography (CC) on silica gel 60H (SDS: 40–63 μm), Cellulose (Merck, Art. 2330) (Merck KGaA, Darmstadt, Germany) and Sephadex LH 20 (Pharmacia, Sweden). Gradient elution with the solvents mixtures indicated in each case. Semi-preparative RP_{18} -HPLC (Reversed Phase $_{18}$ -High Liquid Performance Chromatography) was performed on a HPLC system: PU-2080 pump Plus (JASCO, Tokyo, Japan); refractive index detector RID-10A (Shimadzu, Kyoto Japan); software: Clarity (JASCO, Tokyo, Japan), with Kromasil RP-18 columns (i.d.:10 mm, length: 250 mm, 10 μm); flow rate 1.5 mL/min. Prep. Thin Layer Chromatography plates pre coated with silica gel 60 (Merck, Art. 5721). Fractions monitoring to follow separation was performed by thin layer chromatography (TLC) on silica gel 60 F254 (Merck, Art. 5554) and cellulose (Merck Art. 5552). Compounds were

detected using UV absorbance (λ 254 and λ 365 nm). Vanillin/sulphuric acid reagent (vanillin 5% in $\text{H}_2\text{SO}_4/\text{MeOH}$ 1:1) and Neu's reagent [32] were used for detection at TLC chromatography. Analytical solvents were obtained from Panreac Quimica SA (Barcelona, Spain, Italy), while deuterated solvents were purchased from Merck, KGaA (Darmstadt, Germany). Medium-pressure liquid chromatographic (MPLC) separations were carried out using Büchi C-615 system & pump Büchi 688 with reverse phase column packed with SiO_2 . Desiccators were activated by anhydrous di-phosphorus pentoxide analytical reagent (a.r.) grade (Art. CL 00. 0631; Chem-Lab, N.V., Belgium).

4.3. Equipment and Reagents for In Vitro Experiments

Soybean lipoxygenase, sodium linoleate, 2,2-azobis (2-amidinopropane) dihydrochloride (AAPH), 1,1-diphenyl-2-picrylhydrazyl (DPPH) were obtained from Sigma Chemical, Co. (St. Louis, MO, USA). For the in vitro tests, UV-Vis spectra were obtained on a 554 double beam spectrophotometer Perkin-Elmer (Perkin-Elmer Corporation Ltd., Lane Beaconsfield, Bucks, UK).

4.4. Extraction and Chromatography

C. brevifolia needles (0.143 kg) were extracted successively with dichloromethane, methanol, and methanol: water 5:1, and concentrated to dryness to yield residues of 23.0 g and 18.3 g, respectively.

10 g of the MeOH extract was submitted to RP_{18} -MPLC (41.0 \times 4.0 cm) using a $\text{H}_2\text{O}:\text{MeOH}$ gradient system (100% $\text{H}_2\text{O} \rightarrow$ 100% MeOH; steps of 10% MeOH) to yield 11 fractions (A-K) of 500 mL each. Based on TLC results, combined fractions D and E (149.6 mg) were further applied to CC over silica gel eluted with mixtures of DM: MeOH: H_2O of increasing polarity (95:5:0.5 to 50:50:5) and gave 41 sub-fractions (D'A-D'L); subfraction D/L (6.0 mg) was identified as compound **13**; subfraction D/I (7.6 mg) was subjected to prep. TLC on silica gel with DM:MeOH: H_2O 7:3:0.3 and afforded compound **8** (4.0 mg). Fraction H (236.7mg) was subjected to repeated CC over Sephadex LH-20 (MeOH 100%) and silica gel (DM: MeOH: H_2O 95:5:0.5 to 50:50:5) and yielded compounds **11** (3.0 mg), **15** (2.8 mg). Fraction I (1.5 g) was submitted to CC over silica gel using mixtures of DM: MeOH: H_2O (100:0:0 to 0:0:100) and 15 fractions were obtained. Subfraction IF (9.1 mg; eluted with DM: MeOH: H_2O 80:20:2) was identified as compound **1** (9.1 mg); subfraction II (75.0 mg; eluted with DM: MeOH: H_2O 70:30:3) was subjected to prep. RP_{18} -HPLC (MeOH:AcOH 5% 4:6) and yielded compounds **2** (0.4 mg; Rt 40.4), **3** (0.5 mg; Rt 39.4), **5** (12.6 mg; Rt 14.8), **6** (3.8 mg; Rt 15.7), **9** (2.7 mg; Rt 9.39), **10** (8.4 mg; Rt 11.4), **12** (1.9 mg; Rt 43.6), **16** (3.4 mg; Rt 28.2); subfraction IJ (358.7 mg; eluted with DM: MeOH: H_2O 70:30:3) was subjected to CC over silica gel (EtOAc:MeOH: H_2O 100:0:0 to 70:30:3) and afforded compound **4** (19.0 mg); fraction IJK derived from the latter subfraction IJ (17.5 mg; eluted with EtOAc:MeOH: H_2O 90:10:1) was further fractionated by RP_{18} -HPLC (MeOH:AcOH 5% 4:6) and yielded compound **7** (2.8 mg; Rt 25.0); subfraction IL (259.6 mg) was submitted to CC over Cellulose (isocratic elution with AcOH: H_2O 15:85) and afforded compounds **4** (14.5 mg) and **14** (3.5 mg). Sub-fraction IK (142.0 mg) was subjected to CC over silica gel eluted with mixtures of increasing polarity of EtOAc/MeOH and yielded **4** (7.5 mg).

5.0 g of the methanol:water (5:1) extract also was submitted to RP_{18} -MPLC (41.0 \times 4.0 cm) using mixtures of decreasing polarity of $\text{H}_2\text{O}:\text{MeOH}$ (100:0 to 0:100; steps of 10%) and gave us 11 fractions (A-K). Fraction I (157.0 mg; eluted with $\text{H}_2\text{O}:\text{MeOH}$ 20:80) was subjected to CC over Sephadex LH-20 (MeOH 100%), and subfraction IF (70.5 mg) was further analyzed by RP_{18} -HPLC (MeOH:AcOH 5% 4:6) and yielded compound **20** (0.8 mg; Rt 14.0). Subfraction IE (44.0 mg) submitted to CC over silica gel (DM:MeOH 95:5 to 0:100) and yielded compound **17** (1.0 mg; eluted with DM: MeOH 80:20). Fraction J (256.0 mg; eluted with $\text{H}_2\text{O}:\text{MeOH}$ 10:90) was applied to CC over silica gel (DM:MeOH: H_2O 98:2:0.2 to 0:50:50); combined subfractions JK, JN (6.9 mg; eluted with DM:MeOH: H_2O 97:3:0.2 to 95:5:0.3) and subfraction JR (8.2 mg; eluted DM:MeOH: H_2O 85:15:0.6), were further fractionated by prep. TLC on silica gel (DM:MeOH: H_2O 8:2:0.2) and afforded compounds **19** (5.7 mg) and **18** (2.8 mg), respectively. All obtained extracts, fractions and isolated compounds were evaporated to dryness

in vacuum under low temperature, and then were put in activated desiccators with P₂O₅ until their weights had stabilized.

4.5. DPPH Radical Scavenging Activity

The reducing ability of *C. brevifolia* extracts and of the isolated compounds was determined using the method described by Pontiki et al. [33]. To an ethanolic solution of DPPH 1 mL from an 100 μM stock solution (freshly prepared), an equal volume of the extracts (stock solutions 5 mg/mL) and pure compounds (stock solutions 10 mM) dissolved in EtOH, were added separately. The mixture was shaken vigorously and incubated at room temperature for 20 and 60 min. Absorbance was measured spectrophotometrically at 517 nm. NDGA was used as reference substance. All tests were performed in triplicate and the averages of the results were calculated.

4.6. AAPH Induced Linoleic Acid Lipid Peroxidation Assay

The anti-lipid peroxidation activity of *C. brevifolia* extracts and isolated compounds were determined, as reported previously [33], i.e. 10 μL of the 16 mM sodium linoleate was added to the UV cuvette containing 0.93 mL of 0.05 M phosphate buffer, pH 7.4, which was previously pre-thermostated at 37 °C. The oxidation reaction was initiated under air by the addition of 50 μL of 40 mM AAPH solution. Oxidation was carried out in the presence of samples (10 μL) without an antioxidant, and lipid peroxidation was calculated in the presence of same level of EtOH at 234 nm.

4.7. Soybean LOX Inhibition

LOX inhibition of the extracts and isolates were determined by using the method described by Pontiki et al. [33]. The samples, dissolved in EtOH, were incubated at room temperature with sodium linoleate (100 μL) and 200 μL enzyme solution (1/9 × 10⁻⁴ w/v in saline). The transformation of sodium linoleate to 13-hydroperoxylinoleate sodium was measured spectrophotometrically at 234 nm and compared with the appropriate reference NDGA (nor-dihydroguaiaretic acid).

4.8. Statistics

Experiments were performed in triplicate. The results were expressed as mean ± standard deviation (SD). When needed statistical comparisons were made using the Kruskal Wallis test. Statistically significant difference was defined as $p < 0.05$.

The reducing abilities are given only as % inhibition since the majority of the tested compounds presented lower than 50% antioxidant ability at 100 μM. Considering the LOX inhibition as well as the anti-lipid peroxidation activity, only one and two compounds respectively exhibited high activities at 100 μM. Thus for the sake of comparison we did not determine the IC₅₀ values for them. The same concept was followed for the DPPH interaction results.

4.9. NMR Data of Compounds 1–20

The ¹H- and ¹³C-NMR data of these compounds (1–20) are listed as follows (see also Supplementary Material):

Compound 1: ¹H-NMR (400 MHz, CD₄O) δ_H: 6.95 *d* (1H, H-2', *J* = 1.8 Hz), 6.85 *dd* (1H, H-6', *J* = 8.0, 1.8 Hz), 6.80 *d* (1H, H-5', *J* = 8.0 Hz), 5.92 *d* (1H, H-8, *J* = 1.9 Hz), 5.88 *d* (1H, H-6, *J* = 1.9 Hz), 4.89 *d* (1H, H-2, *J* = 12.2 Hz), 4.50 *d* (1H, H-3, *J* = 12.2 Hz).

NOESY: nOe signals between H-2/H-3; H-3/H-6'.

Compound 2: ¹H-NMR (400 MHz, CD₄O) δ_H: 8.06 *d* (2H, H-2', H-6', *J* = 8.7 Hz) 6.90 *d* (2H, H-3', H-5', *J* = 8.7 Hz) 6.40 *s* (1H, H-8) 6.21 *s* (1H, H-6) 5.23 *d* (1H, H-1'', *J* = 7.8 Hz) 3.42–3.20 *m* (3H, H-2'', 3'', 4'', 5''), 3.69 *dd* (1H, H-6a'', *J* = 12.0, 5.8 Hz) 3.53 *dd* (1H, H-6b'' *J* = 12.0, 2.1 Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 161.0 (C-2) 100.0 (C-6) 94.4 (C-8) 158.4 (C-9) 104.0 (C-10) 123.0 (C-1') 131.9 (C-2',6') 159.2 (C-4') 115.1 (C-3',5') 103.7 (C-1'') 76.2 (C-2'') 78.1^a (C-3'') 71.3 (C-4'') 78.4^a (C-5'') 62.3 (C-6'').

^a: interchangeable signals.

Compound 3: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 7.93 *d* (1H, H-2', *J* = 2.0 Hz) 7.59 *dd* (1H, H-6', *J* = 8.6, 2.0 Hz) 6.89 *d* (1H, H-5', *J* = 2.0 Hz) 6.19 *d* (1H, H-6, *J* = 2.0 Hz) 6.38 *d* (1H, H-8, *J* = 2.0 Hz) 3.95 *s* (3H, OCH_3) 5.40 *d* (1H, H-1'', *J* = 7.8 Hz) 3.40–3.20 *m* (3H, H-2'',3'',4'',5'') 3.22 *dd* (1H, H-5'', *J* = 4.8, 3.0) 3.73 *dd* (1H, H-6a'', *J* = 12.0, 5.3 Hz) 3.52 *dd* (1H, H-6b'', *J* = 12.0, 1.8 Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 159.0 (C-2) 100.4 (C-6) 95.2 (C-8) 157.3 (C-9) 104.0 (C-10) 121.0 (C-1') 114.7 (C-2') 151.3 (3') 149.7 (C-4') 116.4 (C-5') 103.7 (C-1'') 123.8 (C-6') 103.7 (C-1'') 75.5 (C-2'') 78.0 (C-3'') 71.6 (C-4'') 78.2 (C-5'') 62.8 (C-6'').

Compound 4: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 6.82 *d* (1H, H-2', *J* = 1.9 Hz) 6.74 *d* (1H, H-5', *J* = 8.0 Hz) 6.71 *dd* (1H, H-6' *J* = 8.0, 1.9 Hz) 5.82 *d* (1H, H-6, *J* = 2.2 Hz) 5.94 *d* (1H, H-8, *J* = 2.2 Hz) 4.56 (1H, H-2, *J* = 7.7 Hz) 3.97 *ddq* (1H, H-3, *J* = 8.1, 7.7, 5.4 Hz) 2.84 *dd* (1H, H-4ax, *J* = 16.1, 5.4 Hz) 2.50 *dd* (1H, H-4eq, *J* = 16.1, 8.1 Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 82.8 (C-2) 68.8 (C-3) 28.4 (C-4) 157.6 (C-5) 95.5 (C-6) 157.8 (C-7) 96.3 (C-8) 156.9 (C-9) 100.8 (C-10) 132.4 (C-1') 115.3 (C-2') 146.4 (3',4') 116.0 (C-5') 119.9 (C-6').

Compound 5: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 8.10 *br d* (2H, H-2,6, *J* = 7.7 Hz) 7.50 *br t* (1H, H-3,5, *J* = 7.7 Hz) 7.63 (1H, H-4, *J* = 7.7 Hz). 5.73 *d* (1H, H-1', *J* = 7.6 Hz) 3.52 *dd* (1H, H-2', *J* = 7.6, *Hz) 3.49–3.43 *m* (3H, H-3',4',5'), 3.86 *dd* (1H, H-6a', *J* = 12.1, 2.1 Hz) 3.71 *dd* (1H, H-6b', *J* = 12.1, 5.1 Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 133.2 (C-1) 130.7 (C-2,6) 128.4 (C-3,5) 132.4 (C-4) 166.2 (C-7) 94.1 (C-1') 73.4 (C-2') 77.8^a (C-3') 71.3 (C-4') 78.4^a (C-5') 62.1 (C-6').

*: partially overlapped signal; ^a: interchangeable signals.

Compound 6: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 7.42 *br d* (2H, H-2,6, *J* = 7.3 Hz) 7.33 *br dd* (2H, H-3,5, *J* = 7.7, 7.3 Hz) 7.28 *br d* (1H, H-4, *J* = 7.3 Hz) 4.95 *d* (1H, H-7a, *J* = 11.8) 4.69 *d* (1H, H-7b, *J* = 11.8 Hz). 4.38 *d* (1H, H-1', *J* = 7.4 Hz) 3.43–3.31 *m* (3H, H-2',3',4',5') 3.91 *dd* (1H, H-6a', *J* = 2.1, 1.7 Hz) 3.70 *dd* (1H, H-6b', *J* = 11.7, 5.8 Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 138.9 (C-1) 128.9 (C-2,6) 128.9 (C-3,5) 128.4 (C-4) 71.4 (C-7) 103.0 (C-1') 74.9 (C-2') 78.0^a (C-3') 71.6 (C-4') 77.9^a (C-5') 62.4 (C-6').

^a: interchangeable signals.

Compound 7: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 7.42 *br d* (2H, H-2,6, *J* = 7.3 Hz) 7.33 *br dd* (2H, H-3,5, *J* = 7.7, 7.3 Hz) 7.28 *br d* (1H, H-4, *J* = 7.3 Hz) 4.87 *d* (1H, H-7a, *J* = 11.8) 4.64 *d* (1H, H-7b, *J* = 11.8 Hz) 4.32 *d* (1H, H-1', *J* = 7.9 Hz) 3.24 *dd* (1H, H-2', *J* = 8.5, 7.9) 3.70–3.20 *m** (3H, H-3',4',5'), 3.99 *dd* (1H, H-6a', *J* = 11.7, 1.7 Hz) 3.64 *dd* (1H, H-6b', *J* = 11.3, 5.9 Hz) 4.81 *d* (1H, H-1'', *J* = 1.7 Hz) 3.86 *dd* (1H, H-2'' *J* = 3.1, 1.7 Hz) 3.68 *m* (3H, H-3'', *J* = 9.5 3.1 Hz), 3.34 * (1H H-4'') 3.67 (1H H-5'') 1.27 *d* (3H H-6'', *J* = 6.2 Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 128.8 (C-2,6) 128.8 (C-3,5) 128.3 (C-4) 71.4 (C-7) 103.0 (C-1') 75.0 (C-2') 77.9^a (C-3') 71.3 (C-4') 77.4^a (C-5') 67.6 (C-6') 102.1 (C-1'') 72.2 (C-2'') 71.1 (C-3'') 73.7 (C-4'') 71.1 (C-5'') 17.9 (C-6'').

*: partially overlapped signals; ^a: interchangeable signals.

Compound 8: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 7.14 *br d* (1H, H-3, *J* = 8.2 Hz) 7.09–7.07 *m* (2H, H-4,5) 6.92 *dd* (1H, H-6, *J* = 8.2, 1.8 Hz). 4.89* (1H, H-1') 3.50 (1H, H-2') 3.82 ($-\text{OCH}_3$) 3.48 *m* (1H, H-3') 3.40 (1H, H-4') 3.91 *dd* (1H, H-6a', *J* = 11.7, 1.7 Hz) 3.70 *dd* (1H, H-6b', *J* = 11.7, 5.8 Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 117.0^a (C-3) 112.0 (C-4) 116.8^a (C-5) 120.2 (C-6) $-\text{OCH}_3$ (56.1) 102.2 (C-1') 74.5 (C-2') 77.5 (C-3') 71.0 (C-4') 78.0 (C-5') 62.0 (C-6').

*: partially overlapped by methanol-d₄ moisture; ^a: interchangeable signals.

Compound 9: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 6.83 *d* (1H, H-2, $J = 2.8$ Hz) 6.86 *d* (2H, H-5, $J = 8.8$ Hz) 6.67 *dd* (1H, H-6, $J = 8.8, 2.9$ Hz) 3.82 (-OCH₃-3), 3.79 (-OCH₃-4). 4.79 *d* (1H, H-1', $J = 7.5$ Hz) 3.46–3.35 *m* (4H, H-2', 3', 4', 5') 3.91 *dd* (1H, H-6a', $J = 11.7, 1.7$ Hz) 3.70 (1H, H-6b', $J = 11.7, 5.8$ Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 153.9 (C-1) 103.7 (C-2) 145.7 (C-3) 150.6 (C-4) 113.5 (C-5) 109.0 (C-6) –OCH₃ (56.1, 57.5) 103.1 (C-1') 74.9 (C-2') 77.4^a (C-3') 71.3 (C-4') 77.9^a (C-5') 62.2 (C-6').

^a: interchangeable signals.

Compound 10: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 7.11 *d* (2H, H-3,5, $J = 8.5$ Hz) 7.00 *d* (2H, H-2,6, $J = 8.5$ Hz) 2.80–2.76 *m* (2H, H-7,8) 2.10 *s* (–CH₃). 4.85 *d* (1H, H-1', $J = 7.8$ Hz) 3.43 (1H, H-2') 3.40–3.30 (2H, H-3', 4', 5') 3.88 *dd* (1H, H-6a', $J = 12.0, 1.8$ Hz) 3.69 (1H, H-6b', $J = 12.0, 5.0$ Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 157.3 (C-1) 117.5 (C-2,6) 129.0 (C-3,5) 135.3 (C-4) 29.68 (C-7) 45.6 (C-8) 29.63 (C-9 –CH₃) 210.3 (>C = 0) 102.0 (C-1') 74.6 (C-2') 77.8 (C-3') 71.0 (C-4') 77.7 (C-5') 62.0 (C-6').

Compound 11: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 7.96 *d* (2H, H-2,6, $J = 7.89$ Hz). 7.01 *d* (2H, H-3,5, $J = 7.04$ Hz) 3.88 *s* (–OCH₃).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 131.7 (C-2,6) 116.0 (C-3,5) 56.0 (–OCH₃).

Compound 12: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 8.06 *d* (2H, H-2,6, $J = 8.1$ Hz) 6.90 *d* (2H, H-3,5, $J = 8.1$ Hz). 4.96 *d* (1H, H-1', $J = 7.4$ Hz) 3.50–3.30 *m* (4H, H-2', 3', 4', 5') 3.91 *dd* (1H, H-6a', $J = 11.7, 1.7$ Hz) 3.70 (1H, H-6b', $J = 11.7, 5.8$ Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 132.0 (C-2,6) 116.2 (C-3,5) 101.0 (C-1') 75.0 (C-2') 78.0 (C-3') 71.8 (C-4') 78.0 (C-5') 62.3 (C-6').

Compound 13: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 7.44 *d* (2H, H-2,6, $J = 8.3$ Hz) 6.79 *d* (2H, H-3,5, $J = 8.3$ Hz) 7.56 *d* (1H, H-7, $J = 16.0$ Hz) 6.29 *d* (1H, H-8, $J = 16.0$ Hz).

$^{13}\text{C-NMR}$ (200 MHz CD_4O) δ_{C} : 131.4 (C-2,6) 124.3 (C-3,5) 146.7 (C-7) 115.4 (C-8).

Compound 14: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 7.54 *d* (2H, H-2,6, $J = 7.9$ Hz) 7.12 *dd* (2H, H-3,5, $J = 7.9$ Hz) 7.60 *d* (1H, H-7, $J = 16.2$ Hz) 6.37 *d* (1H, H-8, $J = 16.2$ Hz). 4.96 *d* (1H, H-1', $J = 7.2$ Hz) 3.70–3.41 *m* (4H, H-2', 3', 4', 5') 3.88 *dd* (1H, H-6a', $J = 12.1, 2.1$) 3.70 (1H, H-6b', $J = 12.1, 8.1$ Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 129.2 (C-1) 132.0 (C-2,6) 117.4 (C-3,5) 159.5 (C-4) 144.7 (C-7) 117.8 (C-8) 170.3 (C-9 –COOH) 101.2 (C-1') 74.4 (C-2') 77.5 (C-3') 70.7 (C-4') 78.0 (C-5') 62.2 (C-6').

Compound 15: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 7.48 *d* (2H, H-2,6, $J = 8.2$ Hz) 7.08 *d* (2H, H-3,5, $J = 8.2$ Hz) 7.37 *d* (1H, H-7, $J = 16.0$ Hz) 6.40 *d* (1H, H-8, $J = 16.0$ Hz). 4.94 *d* (1H, H-1') 3.55–3.28 *m* (4H, H-2', 3', 4', 5') 3.89 *dd* (1H, H-6a', $J = 11.8, 2.1$) 3.70 (1H, H-6b', $J = 11.8, 4.4$ Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 129.4 (C-2, 6) 117.6 (C-3, 5) 139.9 (C-4) 129.9 (C-7) 102.2 (C-1') 74.3 (C-2') 77.6 (C-3') 70.8 (C-4') 76.5 (C-5') 62.1 (C-6').

Compound 16: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 2.45 *d* (1H, H-2a, $J = 17.0$ Hz) 2.22 *d* (1H, H-2b, $J = 17.0$ Hz) 5.90 *tt* (1H, H-4, $J = 6.9, 1.2$ Hz) 5.91 *d* (1H, H-7, $J = 15.9$ Hz) 6.82 *d* (1H, H-8, $J = 15.9$ Hz) 1.89 *brs* (3H, H-10 CH₃) 1.07 *s* (3H, H-11 CH₃) 1.03 *s* (3H, H-12 CH₃) 1.90 *d* (3H, H-13 CH₃, 1.2 Hz) 5.63 *t* (1H, H-14, $J = 7.0$ Hz) 4.51 *dd* (1H, H-15a, $J = 12.3, 7.6$ Hz) 4.38 *dd* (1H, H-15b, $J = 12.3, 5.9$ Hz) 4.28 *d* (1H, H-1') 3.17 *t* (1H, H-2', $J = 8.0$ Hz) 3.27–3.35 *m* (4H, H-3', 4', 5') 3.88 *dd* (1H, H-6a', $J = 12.0, 1.7$) 3.68 (1H, H-6b', $J = 12.0, 5.7$ Hz).

$^{13}\text{C-NMR}$ (50.3 MHz CD_4O) δ_{C} : 42.7 (C-1) 49.6 (C-2) 200.0 (C-3 –C=O) 127.4 (C-4) 166.9 (C-5) 80.0 (C-6) 132.0 (C-7) 127.7 (C-8) 136.0 (C-9) 19.4 (C-10) 23.4 (C-11) 24.5 (C-12) 20.4 (C-13) 127.0 (C-14) 65.0 (C-15) 103.0 (C-1') 74.6 (C-2') 77.7 (C-3') 71.3 (C-4') 77.8 (C-5') 62.7 (C-6').

Compound 17: $^1\text{H-NMR}$ (400 MHz, CD_4O) δ_{H} : 8.07 *d* (2H, H-2', 6', $J = 8.7$ Hz) 6.90 *d* (2H, H-3', 5', $J = 8.7$ Hz) 6.34 *d* (1H, H-8, $J = 2.1$ Hz) 6.16 *d* (1H, H-6, $J = 2.1$ Hz) 5.06 *d* (1H, H-1'', $J = 7.8$ Hz) 3.44 *dd* (1H, H-2', $J = 7.9, 7.5$) 3.43–3.32 *m** (3H, H-3', 4', 5'), 3.88 *brd* (1H, H-6a', $J = 11.0, 1.7$ Hz) 3.64 *dd* (1H, H-6b', $J = 11.0, 5.9$ Hz) 4.52 *d* (1H, H-1'''' 1.7 Hz) 3.31* (1H, H-2''') 3.68 *m* (2H, H-3''', H-5''') 3.34* (1H H-4''')* 1.27 *d* (3H H-6''', $J = 6.2$ Hz).

^{13}C -NMR (50.3 MHz CD_4O) δ_{C} : 159.5 (C-2) 136.1 (C-3) 180.2 (C-4) 164.0 (C-5) 100.8 (C-6) 167.1 (C-7) 94.9 (C-8) 159.2 (C-9) 107.5 (C-10) 123.6 (C-1') 132.2 (C-2', 6') 117.0 (C-3', 5') 162.2 (C-4') 101.7 (C-1'') 76.7 (C-2'') 78.9 (C-3'') 72.0^a (C-4'') 78.0 (C-5'') 69.3 (C-6'') 102.9 (C-1''') 72.9^a (C-2''') 73.1 (C-3''') 74.3 (C-4''') 70.5 (C-5''') 18.6 (C-6''').

*: overlapped signals; ^a: interchangeable signals.

Compound 18: ^1H -NMR (400 MHz, CD_4O) δ_{H} : 8.04 *d* (2H, H-2', 6', *J* = 8.7 Hz) 6.82 *d* (2H, H-3', 5', *J* = 8.7 Hz) 6.33 *d* (1H, H-8, *J* = 2.1 Hz) 6.22 *d* (1H, H-6, *J* = 2.1 Hz) 3.94 (3H, $-\text{OCH}_3$) 5.84 *d* (1H, H-1'', *J* = 7.8 Hz) 3.24 *dd* (1H, H-2'', *J* = 8.5, 7.9) 3.43–3.32 *m*^a (3H, H-3'', 4'', 5''), 3.99 *dd* (1H, H-6a'', *J* = 11.7, 1.7 Hz) 3.64 *dd* (1H, H-6b'', *J* = 11.3, 5.9 Hz). 4.51 *d* (1H, H-1''', *J* = 1.7 Hz) 3.86 *dd* (1H, H-2''', *J* = 3.1, 1.7 Hz) 3.68 *m* (3H, H-3''', *J* = 9.5 3.1 Hz), 3.34^a (1H H-4''') 3.67 (1H H-5''') 1.27 *d* (3H H-6''', *J* = 6.2 Hz).

^{13}C -NMR (50.3 MHz CD_4O) δ_{C} : 128.8* (C-2', 6') 128.8 (C-3', 5') 128.3* (C-4') 71.4 (C-7) 103.0 (C-1'') 75.0 (C-2'') 77.9^b (C-3'') 71.3 (C-4'') 77.4^b (C-5'') 67.6 (C-6'') 102.1 (C-1''') 72.2 (C-2''') 71.1^a (C-3''') 73.7 (C-4''') 71.1^a (C-5''') 17.9 (C-6''').

^a, ^b: overlapped signals; *: interchanged signals.

Compound 19: δ (ppm) 7.98 *d* (2H, H-2', H-6', *J* = 8.8 Hz), 7.44 *d* (1H, H-7''', *J* = 15.6 Hz), 7.36 *d* (2H, H-2'' & H-6''', *J* = 9.2 Hz), 6.77 *d* (2H, d, H-3' & H-5', *J* = 8.8 Hz), 6.77 *d* (2H, H-3''' & H-5''', *J* = 9.2 Hz), 6.37 *d* (1H, H-8, *J* = 2.1 Hz), 6.14 *d* (1H, H-6, *J* = 2.1 Hz), 6.07 *d* (1H, H-8''', *J* = 15.6 Hz), 5.20 *d* (1H, H-1'', *J* = 7.6 Hz), 4.35 *dd* (1H, H-6''a, *J* = 12.6, 2.0 Hz), 4.21 *dd* (1H, H-6''b, *J* = 12.8, 6.8 Hz), 3.35–3.51 *m* (4H, H-2'', 3'', 4'', 5'') 159.5 (C-2) 137.0 (C-3) 179.4 (C-4) 162.7 (C-5) 99.7 (C-6) 165.8 (C-7) 94.9 (C-8) 158.3 (C-9) 105.7 (C-10) 123.4 (C-1') 132.2 (C-2', 6') 118.0 (C-3', 5') 161.4 (C-4') 104.1 (C-1'') 74.9 (C-2'') 77.9 (C-3'') 71.8 (C-4'') 75.2 (C-5'') 64.5 (C-6'') 123.2 (C-1''') 131.5 (C-2''', 6''') 117.2 (C-3''', 5''') 157.5 (C-4''') 147.5 (C-7''') 115.9 (C-8''') 168.7 (C-9''').

Compound 20: 7.53 *s* (2H, H-2, 6); 6.42 *d* (1H, H-8, *J* = 2 Hz), 6.21 *d* (1H, H-6, *J* = 2 Hz), 5.47 *d* (1H, H-1'', *J* = 8 Hz), 3.94 *s* (6H, $\text{OCH}_3 \times 2$ at C-3' and at C-5') 5.47 *d* (1H, H-1'', 7.8 Hz) 3.42–3.20 *m* (3H, H-2'', 3'', 4'', 5''), 3.74 *dd* (1H, H-6a'' 12.0, 5.8 Hz) 3.58 *dd* (1H, H-6b'' 12.0, 2.1 Hz).

^{13}C -NMR (50.3 MHz CD_4O) δ_{C} : 107.4 (C-2', 6') 99.6 (C-6) 94.4 (C-8) 56.5 ($-\text{OCH}_3$) 102.8 (C-1'') 76.2 (C-2'') 78.1^a (C-3'') 71.0 (C-4'') 77.3^a (C-5'') 62.2 (C-6'').

^a: overlapped signals.

Supplementary Materials: The following are available online at www.mdpi.com/2223-7747/7/1/1/s1.

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