

Article

New Cyclic Diarylheptanoids from *Platycarya strobilacea*

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Abstract: Five new cyclic diarylheptanoids (platycary A–E, compounds 1–5) and three previously identified analogues (i.e., phttyearynol (compound 6), myricatomentogenin (compound 7), and juglanin D (compound 8)) were isolated from the stem bark of *Platycarya strobilacea*. The structures of these compounds were determined using NMR, HRESIMS, and electronic circular dichroism (ECD) data. The cytotoxicity of compounds 1–5 and their ability to inhibit nitric oxide (NO) production, as well as protect against the corticosterone-induced apoptosis of Pheochromocytoma (PC12) cells, were evaluated in vitro using the appropriate bioassays. Compounds 1 and 2 significantly inhibited the corticosterone-induced apoptosis of PC12 cells at a concentration of 20 μ M.

Keywords: cyclic diarylheptanoid; *Platycarya strobilacea*; Juglandaceae; corticosterone-induced apoptosis

1. Introduction

More than 500 diarylheptanoids, an important class of plant secondary metabolites with a aryl-C7-aryl skeleton (linear or cyclic type), have been isolated from a number of plant families, including the Aceraceae, Actinidiaceae, Betulaceae, Burseraceae, Casuarinaceae, Zingiberaceae Leguminosae, Myricaceae, and Juglandaceae [1]. Cyclic diarylheptanoids are further divided into *meta,meta*-bridged biphenyls and *meta,para*-bridged diphenyl ether heptanoids, many of which have beneficial biological activities such as anti-tumor, anti-inflammatory, estrogenic, anti-amyloidogenic, and anti-emetic activity [1,2]. Hence, the discovery of new natural diarylheptanoids and their phytochemical characterization is of considerable potential benefit to medical science. *Platycarya strobilacea* Sieb. et Zucc. (Juglandaceae) is a deciduous shrubby tree distributed in East Asia [3]. Previous phytochemical studies have found that this species contains large amounts of ellagitannins [4], flavonoids [5], and sesquiterpenoids [6,7], but apparently only one cyclic diarylheptanoid (i.e., platycarynol) [8]. Since a number of cyclic diarylheptanoids have been isolated from many species of Juglandaceae, in this paper we described the results of an extensive investigation of the stem bark of *P. strobilacea* in which eight cyclic diarylheptanoids, including five new ones (compounds 1–5), were isolated and identified. Furthermore, the anti-tumor cytotoxic activity of the five new isolates, and their ability to inhibit nitric oxide (NO) production and the corticosterone-induced apoptosis of PC12 cells, was evaluated in vitro.

2. Results and Discussion

A 95% EtOH extract of the stem bark of *P. strobilacea* was subjected to column chromatography (CC) over silica gel, Sephadex LH-20, and pre-TLC to afford compounds 1–8. The structures of the known compounds phttyearynol (6), myricatomentogenin (7), and juglanin D (8) were determined by spectral data analysis and comparison with published data (Figure 1) [8–10].

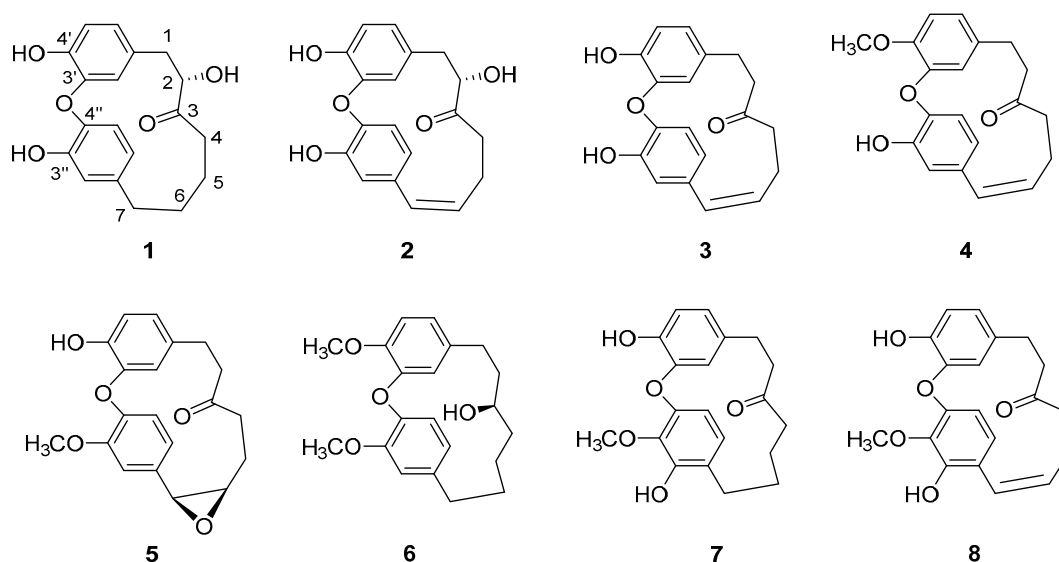


Figure 1. Structures of compounds 1–8.

Compound 1 was isolated as a white solid. Its molecular formula was assigned as $C_{19}H_{20}O_5$ by the HRESIMS (m/z 327.1234 $[M - H]^-$, calcd for $C_{19}H_{19}O_5$, 327.1232). The ^{13}C -NMR spectrum exhibited 19 carbon signals including characteristic peaks of a carbonyl group and 12 aromatic carbons (see the Supplementary Materials); the other carbons were identified using the HSQC spectrum as an oxymethine and five methylene (Tables 1 and 2). Detailed analysis using 2D NMR spectra revealed a heptanoid chain ($-1-CH_2-2-CH_2OH-3-(C=O)-4-CH_2-5-CH_2-6-CH_2-7-CH_2-$) moiety established by the $^1H-^1H$ COSY cross peaks of H-1/H-2, H-4/H-5, H-5/H-6, and H-6/H-7, as well as the Heteronuclear Multiple Bond Correlation (HMBC) cross peaks of H-1/C-3, H-2/C-3, H-2/C-4, and H-5/C-3. In the 1H -NMR spectrum, six aromatic proton signals at δ_H 6.57 (dd, $J = 8.1, 2.1$ Hz, H-6'), 5.72 (d, $J = 2.1$ Hz, H-2'), 6.72 (d, $J = 8.1$ Hz, H-5'), 6.82 (d, $J = 2.0$ Hz, H-2''), 6.77 (dd, $J = 8.2, 2.0$ Hz, H-6''), and 6.83 (d, $J = 8.2$ Hz, H-5'') revealed the presence of two 1,3,4-trisubstituted aromatic rings that were ABX coupling patterns. The chemical shift of H-2' at 5.72 ppm appeared highly upfield from other aromatic proton signals, and such a shielding effect is characteristic of biaryl-type cyclic diarylheptanoids that have an ether linkage between C-3' and C-4'' [2,8,11]. The above information suggests that compound 1 is 2-hydroxy-3',4''-epoxy-1-(4'-hydroxyphenyl)-7-(3''-hydroxyphenyl)-3-heptanone. The cross-peaks between H-1 and C-1', C-2', and C-6', and those between H-7 and C-1'', C-2'', and C-6'' in the HMBC spectrum confirmed the linkages of the heptanoid chain with two benzene rings. For the absolute configuration of the hydroxyl group at C-2, the theoretical calculations of electronic circular dichroism (ECD) for *R* and *S*-conformers were conducted in MeOH using TD-DFT at the B3LYP/6-31+g (d, p) level (performed using the Gaussian 09 program) [12]. The experimental ECD spectrum of compound 1 was compared with what was calculated using this method (Figure 2) and was determined to be a good match to the 2*S*-configuration. Moreover, the positive optical rotation ($(\alpha)_D^{25} + 143.33$ (c 0.06, MeOH)) of compound 1 was opposite to that of 2(*R*)-hydroxy-3',4''-epoxy-1-(4'-hydroxyphenyl)-7-(3''-methoxyphenyl)-3-heptanone ($(\alpha)_D^{25} - 81.13$ (c 0.03, MeOH)), a very similar structure previously isolated from the roots of *Juglans mandshurica* [11]. Therefore, the structure of compound 1 was determined (Figure 1) and named platycary A.

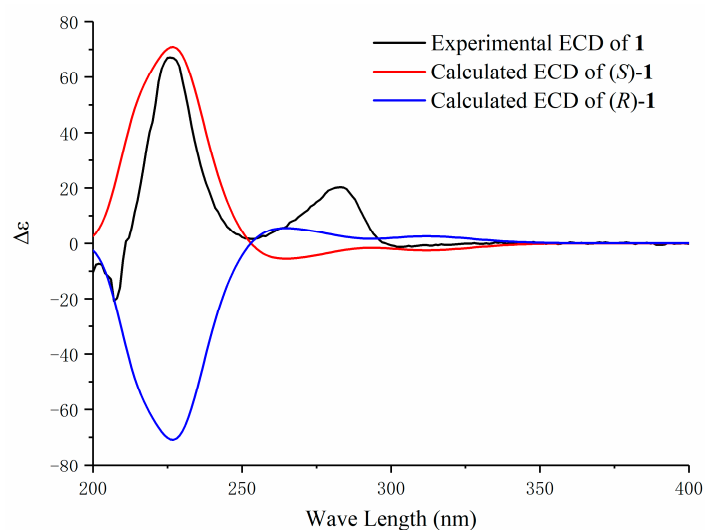


Figure 2. Experimental and calculated electronic circular dichroism (ECD) spectra of compound **1**.

Compound **2** was isolated as a white solid. Its molecular formula was assigned as $C_{19}H_{18}O_5$ by the HRESIMS (m/z 325.1073 $[M - H]^-$, calcd for $C_{19}H_{17}O_5$, 325.1076). Its ^{13}C -NMR spectrum exhibited a total of 19 carbon signals, including the characteristic peaks of a carbonyl group, a hydroxyl carbon, and 12 aromatic carbons as seen in compound **1**, and two groups of ABX patterns aromatic proton signals including the highly upfield H-2' (δ_H 5.57, br s), which was also observed in the 1H -NMR spectrum. These spectroscopic characteristics suggest that compound **2** is a biaryl-type cyclic diaryheptanoid. However, rather than the two methylene signals found in compound **1**, two additional *cis*-olefinic proton signals at δ_H 6.75 (d, $J = 11.2$ Hz, H-7) and 5.99 (dt, $J = 11.2, 7.2$ Hz, H-6), as well as the corresponding carbon signals at 132.2 and 133.2 ppm, were apparent in compound **2**. Further detailed analysis of compound **2** using 2D NMR spectra indicated a different heptanoid chain (-1-CH₂-2-CH₂OH-3-(C=O)-4-CH₂-5-CH₂-6-CH=7-CH-). The double bond at C-6 and C-7 was established by the 1H - 1H COSY correlations of H-4/H-5, H-5/H-6, H-6/H-7, and the HMBC correlations of H-6/C-1'' and H-7/C-1'', C-2'', C-6''. Moreover, the absolute configuration of C-2 was assigned to be *S* by comparison with ECD cotton effects (Figure 3). Finally, the structure of compound **2** was proposed and named platycary B.

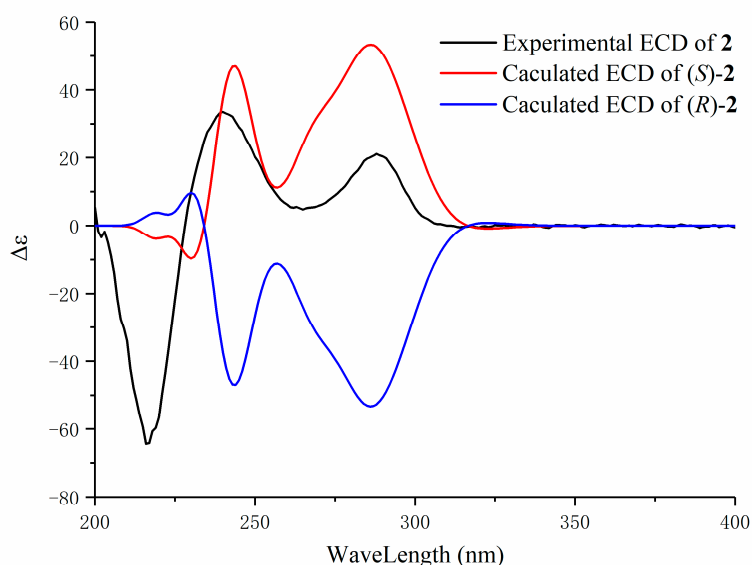


Figure 3. Experimental and calculated ECD spectra of compound **2**.

Compound **3** has the molecular formula $C_{19}H_{18}O_4$, determined from HRESIMS and NMR data. The 1H -NMR spectrum of compound **3** was very similar to that of compound **2**, with the same upfield aromatic signal of H-2' (δ_H 5.38, d) and the ABX coupling pattern due to two sets of 1,3,4-trisubstituted aromatic groups. However, in compound **3**, the hydroxyl carbon signal (δ_C 76.6, C-2 in compound **2**) of the heptanoid was replaced by a methylene signal (δ_C 40.8, C-2). Cross-peaks in the 1H - 1H COSY and HMBC spectra indicate connectivity from H-1 to H-7, creating a straight chain of the hept-6-en-3-one moiety. Moreover, the linkages of this chain to the two benzene rings were established by the HMBC cross-peaks of H-1/C-1', C-2', and C-6', as well as those H-7/C-1'', C-2'', and C-6''. Thus, the structure of compound **3** was determined (as shown in Figure 1) and named platycary C.

Compound **4** has the molecular formula $C_{20}H_{20}O_4$, determined from HRESIMS and NMR data. Its 1H and ^{13}C -NMR data (Tables 1 and 2) are quite similar to that of compound **3**, except for an additional methoxyl moiety (δ_C 56.1), and slight differences in the chemical shifts of C-3', C-4', and C-5' that hint to the linkage site of the methoxyl group. The HMBC correlations between $-OCH_3$ and C-4' further verified that the methoxyl group was located at C-4'. Therefore, the structure of compound **4** was proposed and named platycary D.

Table 1. The 1H -NMR (600 MHz) data of compounds 1–5, δ_H in ppm (coupling type, J in Hz).

No.	1 ^a	2 ^a	3 ^a	4 ^b	5 ^b
1	3.07 (dd, 15.1, 2.0)	3.18 (d, 15.8)	2.87 (m)	3.00 (m)	3.25 (m)
	2.82 (dd, 15.1, 7.6)	2.91 (dd, 15.8, 7.6)	2.80 (m)	2.85 (dd, 16.4, 8.3)	2.51 (dd, 16.1, 5.4)
2	3.98 (dd, 7.6, 2.0)	4.06 (dd, 7.7, 1.9)	2.35–2.39 (m)	2.40 (dd, 17.4, 9.6)	2.27 (dd, 17.7, 5.4)
				2.33 (dd, 16.8, 7.7)	2.46 (m)
4	2.12 (m)	2.36 (m)	2.18–2.24 (m)	2.22 (m)	2.40 (m)
	1.64 (m)	2.27 (m)		2.09 (m)	1.52 (dd, 19.0, 11.5)
5	1.46–1.56 (m)	2.55 (m)	2.38 (m)	2.52 (m)	2.06 (m)
		2.14 (m)	2.31 (m)	2.28 (m)	1.71 (m)
6	1.75 (m)	5.99 (dt, 11.2, 7.2)	5.97 (dt, 11.5, 7.3)	5.97 (dt, 11.2, 7.2)	3.26 (m, overlapped)
	1.60 (m)				
7	2.75 (m)	6.75 (d, 11.2)	6.71 (d, 11.5)	6.71 (d, 11.2)	4.18 (d, 4.3)
	2.55 (m)				
2'	5.72 (d, 2.1)	5.57 (br s)	5.38 (d, 2.0)	5.45 (d, 2.0)	5.16 (d, 2.2)
5'	6.72 (d, 8.1)	6.76 (overlapped)	6.73 (d, 8.1)	6.82 (d, 8.1)	6.84 (d, 8.3)
6'	6.57 (dd, 8.1, 2.1)	6.59 (dd, 8.2, 2.1)	6.57 (dd, 8.1, 2.0)	6.73 (dd, 8.1, 2.0)	6.63 (dd, 8.3, 2.2)
2''	6.82 (d, 2.0)	6.87 (d, 1.9)	6.83 (d, 1.9)	6.90 (d, 2.0)	6.97 (d, 1.7)
5''	6.83 (d, 8.2)	6.96 (d, 8.2)	6.92 (d, 8.1)	6.99 (d, 8.2)	7.06 (overlapped)
6''	6.77 (dd, 8.2, 2.0)	6.73 (overlapped)	6.74 (dd, 8.1, 1.9)	6.83 (dd, 8.2, 2.0)	7.06 (overlapped)
4'-OCH ₃				3.91 (s)	
3''-OCH ₃					3.72 (s, 3H)

^a Data were measured in CD₃OD; ^b Data were measured in CDCl₃.

Compound **5** was isolated as white needle-shaped crystals. Its molecular formula was deduced to be $C_{20}H_{20}O_5$ using HRESIMS (m/z 339.1232 [M – H][−], calcd for 339.1232). The 1H and ^{13}C -NMR spectra of compound **5** (Tables 1 and 2) exhibited characteristic signals of a carbonyl group, a methoxyl group, and two 1,3,4-trisubstituted phenyl groups (as were also apparent for compound **4**), while the difference between compound **5** and compound **4** was the heptanoid chain. Detailed analysis of the NMR data of compound **5** revealed two new signals at δ_C 55.9 and 56.2 ppm, which are typical indicators of epoxide functionality [13,14], whereas two olefinic carbons (δ_C 131.6 and 131.9) were present in compound **4**. The expected 6,7-epoxy-heptan-3-one moiety was established using 1H - 1H COSY and HMBC correlations. In addition, the linkage site of the methoxyl group was assigned to C-3'' by the HMBC correlation of $OCH_3/C-3''$. The relative stereochemistry of the epoxide was determined as *cis* based on the coupling constant between H-6 and H-7 ($J = 4.3$ Hz) (13,14), which was confirmed by a strong cross peak between H-6 and H-7 in the NOESY spectrum. Therefore, the structure of compound **5** was proposed and named platycary E.

Table 2. The ^{13}C -NMR (150 MHz) data of compounds **1–5**, δ_{C} in ppm.

NO.	1 ^a	2 ^a	3 ^a	4 ^b	5 ^b
1	38.5	37.9	27.7	26.7	26.7
2	77.3	76.6	40.8	39.9	40.0
3	215.5	214.3	211.4	208.5	207.3
4	42.7	39.0	42.9	42.1	37.9
5	20.8	20.4	20.0	18.8	20.9
6	28.6	132.2	132.4	131.6	56.2
7	36.8	133.2	133.1	131.9	55.9
1'	141.2	138.4	138.5	137.3	134.4
2'	119.6	118.4	118.4	116.5	110.8
3'	151.5	151.7	151.7	149.2	152.5
4'	144.1	144.1	143.3	141.3	144.0
5'	125.3	125.5	125.5	123.8	124.0
6'	122.8	121.7	121.6	121.3	119.6
1''	129.4	129.5	133.8	133.8	132.4
2''	116.6	115.7	113.5	112.9	111.6
3''	149.4	149.3	149.4	148.7	147.5
4''	145.6	145.2	144.6	146.4	143.0
5''	117.0	117.2	117.2	112.1	115.3
6''	124.9	124.6	122.9	122.5	122.4
4'-OCH ₃				56.1	
3''-OCH ₃					56.2

^a Data were measured in CD₃OD; ^b Data were measured in CDCl₃.

Previously, Jahng and Park (2018) summarized series of cyclic diaryl ether heptanoids and their biological properties. Some of these compounds showed cytotoxic activities against human cancer cell lines, nitric oxide (NO) production inhibitory activity, neuroprotective activity, radical scavenging activity, and osteogenic activity [2]. In view of the valuable pharmacological activities of cyclic diarylheptanoids, we tested the cytotoxic activity of compounds **1–5** against human cancer cell lines (including HL-60, A549, SMMC-7721, MCF-7, and SW480), and their ability to inhibit NO production in Lipopolysaccharide (LPS) activated murine macrophage RAW 264.7 cells and protective effect of corticosterone-induced apoptosis in Pheochromocytoma (PC12) cells. The results indicated that none of the five compounds showed cytotoxic activities (at 40 μM) or inhibited NO production (at 50 μM). However, compounds **1** and **2** significantly inhibited the corticosterone-induced apoptosis of PC12 cells at the concentration of 20 μM (Figure 4). The PC12 cell line is the most commonly used neuronal cell line for neuroscience research in vitro studies. A previous study indicated that corticosterone (CORT) at high concentrations induces cell injury and cell death in PC12 cells, and desipramine (DIM) can antagonize the neurotoxicity caused by CORT [15]. Our report indicated that compounds **1** and **2** are two potential cytoprotective agents for neurological diseases associated with corticosterone-induced neurotoxicity.

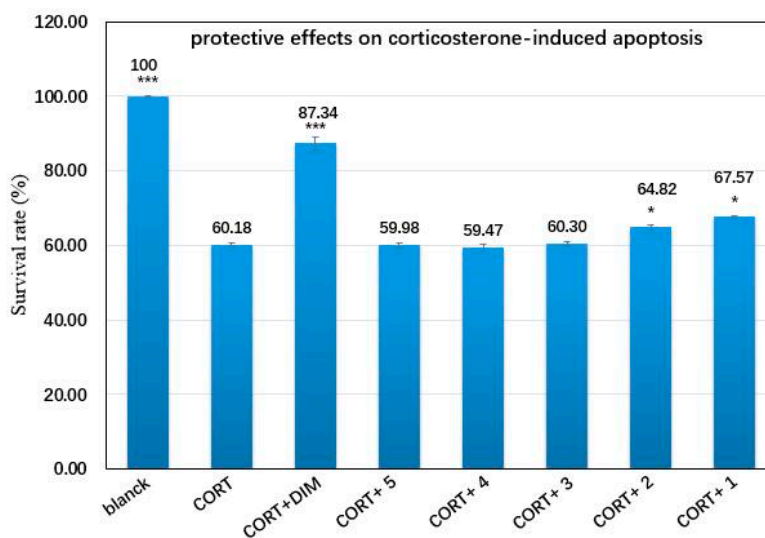


Figure 4. Protective effects of compounds 1–5 against corticosterone-induced apoptosis in PC12 cells. CORT = corticosterone, DIM = desipramine. Paired t-tests were used to evaluate the statistical significance of differences between different treatment groups and the model group (CORT). * Represents a *p*-value of < 0.05, *** represents a *p*-value of < 0.001.

3. Materials and Methods

3.1. General

Melting points were obtained on a SGW X-4 micro melting point apparatus (INESA Co., Shanghai, China). Optical rotations were measured on a SGW-533 automatic polarimeter (INESA Co., Shanghai, China). The 1D and 2D NMR spectra were measured with a Bruker DRX-600 instrument (Bruker BioS-pin GmbH Company, Rheinstetten, Germany) with TMS as the internal standard. ESIMS data were recorded on an API QSTAR mass spectrometer (Applied Biosystem/MSD Sciex, Concord, Ontario, Canada); HRESIMS were recorded on a Waters Xevo G2-XS QToF mass spectrometer (USA). ECD spectra were recorded on a JASCO J-810 circular dichroism (CD) spectropolarimeter (JASCO Co., Tokyo, Japan). Column chromatography was performed on silica gel 60 (100–200 mesh, Qingdao Marine Chemical Ltd., Qingdao, China), sephadex LH-20 (GE Healthcare, Uppsala, Sweden), and Develosil ODS (50 μ m, Nomura Chemical Co. Ltd., Osaka, Japan). The preparation of TLC was performed on HSGF254 plates (Jiangyou silicone Development Co., Ltd., Yantai, China).

3.2. Plant Material

The stem bark of *P. strobilacea* was collected from Cili county, Hunan Province, P.R. China (29°42' N and 111°13' E) in August 2018, and identified by Professor Zhang Dai-gui (Key Laboratory of Plant Resources Conservation and Utilization, Jishou University). A voucher specimen (zdg20180809) was deposited at the College of Plant Protection, Hunan Agricultural University.

3.3. Extraction and Isolation

Dried barks of *P. strobilacea* (12.5 kg) were powdered and extracted three times with EtOH (95% *v/v*) at room temperature, then concentrated under reduced pressure to obtain a crude residue (1.8 kg). The residue was suspended in H₂O (4 L) and then extracted with petroleum ether (PE) and EtOAc successively, to yield a PE-soluble fraction (35.0 g) and an EtOAc-soluble fraction (95.0 g). The EtOAc-soluble fraction was further subjected to silica gel CC (100–200 mesh) with elution of CHCl₃-MeOH (100:0 → 60:40, *v/v*) to give seven fractions (Fr. A–G). Fr.B (5.7 g) was decolorized on MCI gel (eluted with 90 % MeOH) and then chromatographed on an ODS-C18 column that eluted with acetone-H₂O (3:7 → 10:0, *v/v*) to afford 10 sub-fractions (B1–B10). After TLC detection, sub-fractions B5,

B6, B7, B9, and B10 with clear spots were further purified by Sephadex LH-20 column chromatography (eluted with MeOH). Compounds **5** (15.2 mg), **6** (23.7 mg) and **8** (10.8 mg) were obtained from sub-fractions B5, B6, and B10 by preparation TLC using CHCl₃-MeOH (95:5) as a developing solvent, respectively. Compounds **7** (20.5 mg) and **3** (117.8 mg) were obtained from sub-fractions B7 via methanol recrystallization, while compound **4** (50.8 mg) was yielded from sub-fraction B9 via recrystallization (CHCl₃-MeOH, 1:1 *v/v*). Similarly, Fr.C (6.4 g) was successively subjected on MCI gel and ODS-C18 column to afford 10 sub-fractions (C1–C10). Compounds **1** (27.9 mg) and **2** (8.0 mg) were obtained from sub-fractions C6 using methanol recrystallization and the prepared TLC using CHCl₃-MeOH (95:5) as a developing solvent.

3.4. Characterization of Compounds 1–5

Compound 1: white solid, m.p. 183 °C, (α)_D²⁵ +143.33 (*c* 0.06, MeOH); ECD data (MeOH): $\Delta\epsilon$ (nm) = −20.71 (207), +67.18 (226), +20.25 (283). ¹H-NMR (600 MHz, CD₃OD) and ¹³C-NMR (150 MHz, CD₃OD) spectroscopic data, see Tables 1 and 2; positive ion ESIMS *m/z*: 329 [M + H]⁺, negative ESIMS *m/z*: 327 [M − H][−], 363 [M + Cl][−] HRESIMS *m/z*: 327.1234 [M − H][−] (calcd for C₁₉H₁₉O₅, 327.1232).

Compound 2: white solid, m.p. 194 °C, (α)_D²⁵ +103.33 (*c* 0.12, MeOH); ECD data (MeOH): $\Delta\epsilon$ (nm) = −80.68 (218), +67.63 (240), +41 (288). ¹H-NMR (600 MHz, CD₃OD) and ¹³C-NMR (150 MHz, CD₃OD) spectroscopic data, see Tables 1 and 2; positive ion ESIMS *m/z*: 327 [M + H]⁺, negative ESIMS *m/z*: 325 [M − H][−], 361 [M + Cl][−] HRESIMS *m/z*: 325.1073 [M − H][−] (calcd for C₁₉H₁₇O₅, 325.1076).

Compound 3: colorless crystal, m.p. 135 °C; ¹H-NMR (600 MHz, CD₃OD) and ¹³C-NMR (150 MHz, CD₃OD) spectroscopic data, see Tables 1 and 2; positive ion ESIMS *m/z*: 311 [M + H]⁺, negative ESIMS *m/z*: 309 [M − H][−]; HRESIMS *m/z*: 309.1129 [M − H][−] (calcd for C₁₉H₁₇O₄, 309.1127).

Compound 4: colorless crystal, m.p. 119 °C; ¹H-NMR (600 MHz, CDCl₃) and ¹³C-NMR (150 MHz, CDCl₃) spectroscopic data (Tables 1 and 2); 325 [M + H]⁺, 347 [M + Na]⁺; negative ESIMS *m/z*: 323 [M − H][−], 359 [M + Cl][−]; HRESIMS *m/z*: 323.1280 [M − H][−] (calcd for C₂₀H₁₉O₄, 323.1283).

Compound 5: white needle-shaped crystal, m.p. 222 °C; ¹H-NMR (600 MHz, CDCl₃) and ¹³C-NMR (150 MHz, CDCl₃) spectroscopic data (Tables 1 and 2); 341 [M + H]⁺; negative ESIMS *m/z*: 339 [M − H][−], 375 [M + Cl][−]; HRESIMS *m/z*: 339.1232 [M − H][−] (calcd for C₂₀H₁₉O₅, 339.1232).

3.5. Determination of Biological Activity

The *in vitro* cytotoxicity of compounds **1–5** against human cancer cell lines (HL-60, A549, SMMC-7721, MCF-7, and SW480) was assayed using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) method, wherein Taxol was used as the positive control [16,17].

The inhibitory effects of compounds **1–5** on NO production were evaluated in LPS-activated murine macrophage RAW 264.7 cells, using a method modified from what had been previously reported [18]. RAW264.7 was purchased from the Chinese Academy of Sciences' Shanghai cell bank, and Dulbecco's modified Eagle's medium (DMEM) medium and fetal bovine serum were purchased from the Bi Company. Griess reagent, Lipopolysaccharide (LPS), and the comparator L-N^G-Monomethyl Arginine citrate (L-NMMA) were purchased from Sigma-Aldrich (Steinheim, Germany).

The protective effects of compounds **1–5** on corticosterone-induced apoptosis were evaluated using a previously reported method [19]. Briefly, differentiated PC12 cells were maintained in DMEM medium supplemented with 10% fetal bovine serum (FBS), penicillin (100 U/mL), and streptomycin (100 µg/mL), and were incubated at 5% CO₂ at 37 °C. Poorly differentiated PC12 cells were divided into the following groups: untreated, CORT (150 µmol/L), CORT (150 µmol/L) plus DIM (10 µmol/L) as the positive control, and CORT (150 µmol/L) plus one of the test compounds (20 µmol/L). Poorly differentiated PC12 cells were seeded into 96-well culture plates at a density of 1 × 10⁴ cells/well. After a 24 h culture, the wells were added as compounds, as previously described. Next, 48 h later,

MTS solution was added to each well. An absorbance was measured at 492 nm using a Thermo Multiskan FC. All data was expressed as mean \pm SD and paired t-tests implemented in SPSS 13.0 were used to evaluate the statistical significance of the differences between separate treatment groups and the control.

The above biological activities tests were conducted at the Natural Drug Activity Screening Center, Kunming Institute of Botany, Chinese Academy of Sciences.

4. Conclusions

Phytochemical investigation of the stem bark of *P. strobilacea* afforded five new cyclic diarylheptanoids (i.e., platycary A–E (compounds 1–5)) and three known ones: phttyearynol (compound 6), myricatomentogenin (compound 7), and juglanin D (compound 8). Biological activities of compounds 1–5 were evaluated using cytotoxicity, NO, and corticosterone-induced apoptosis assays. Compounds 1 and 2 exhibited significant protective effects against the corticosterone-induced apoptosis of PC12 cells at the concentration of 20 μ M, indicating that compounds 1 and 2 are two potential cytoprotective agents for neurological diseases. The identification of these new compounds significantly increases both the number of diarylheptanoids produced by *P. strobilacea* and the number of diarylheptanoids with potential medical value.

Supplementary Materials: The following are available online, Figures S1–S33 associated with the HRESIMS, 1 H-NMR, 13 C-NMR, and 2D NMR spectra of new compounds.

Author Contributions: G.-h.L. and R.-y.Z. were responsible for the collection of plant materials. H.-l.H. carried out the large-scale fermentation and extraction. J.X. and B.-l.L. isolated the compounds. L.Q. were responsible for biological activities. W.-b.D. carried out the structure elucidation and manuscript preparation. Y.-z.L. designed and supervised this research and the final revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Sample Availability: Samples of the compounds are not available from the authors.

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