https://dx.doi.org/10.21577/0103-5053.20230019

J. Braz. Chem. Soc., Vol. 34, No. 8, 1071-1077, 2023

Article

Warminins A, B and C, Three New Furofuran Lignans from *Aristolochia warmingii* Mast. (Aristolochiaceae)

Camila L. Cunha,[a] Paulo Vinícius G. de Antonio,[a] Maria do Carmo G. Lustosa,[a] Állefe B. Cruz,[b] Juliana C. Holzbach,[b] Douglas H. Pereira[b] and Isabele R. Nascimento*[,a]

[a]*Instituto de Química, Universidade Estadual Paulista (Unesp), 14800-060 Araraquara-SP, Brazil*

[b] *Colegiado de Ciências Exatas e Biotecnológicas, Universidade Federal do Tocantins (UFT), 77402-970 Gurupi-TO, Brazil*

The genus *Aristolochia* stands out as the most representative of the Aristolochiaceae plant family, with approximately 550 species distributed around the world, many of which have little or no studies reported in the literature. Investigation of the acetone extract from leaves of *Aristolochia warmingii* Mast. resulted in the isolation and identification of twenty-three compounds, mostly lignans and neolignans, including the new furofuran lignans warminin A (**1**), warminin B (**2**) and warminin C (**3**). The structures of the compounds were established by comprehensive spectroscopic and spectrometric analyses. A large amount of (−)-epieudesmin (**4**) was isolated from the extract, which suggests that *A. warmingii* could be a potential source of this compound. The hexane, acetone, ethanol, and ethanol Soxhlet extracts, in addition to fourteen of the isolated compounds, were evaluated for their ability to inhibit the formation of advanced glycation end products (AGEs), but they did not show significant activities.

Keywords: Aristolochiaceae, *Aristolochia warmingii*, furofuran lignans, neolignans, epieudesmin

Introduction

Aristolochiaceae traditionally comprises four genera (*Aristolochia* L., *Asarum* L., *Saruma* Oliv., and *Thottea* Rottb.) with approximately 600 species. *Aristolochia* stands out as the most representative genus of the family, with about 550 species distributed around the world, mainly in tropical and subtropical regions.[1,2] In Brazil, 84 species of *Aristolochia* are recorded, 37 of which are endemic.[3]

Although *Aristolochia* species are used in traditional medicine, mainly as abortifacients, emmenagogues, sedatives, anti-malarial, analgesics, anti-cancers, anti-inflammatories, and snake anti-venom,[4] recent studies have highlighted the danger of using these plants. This is because these plants are highly nephrotoxic and carcinogenic to humans, mainly due to the presence of aristolochic acids, nitrophenanthrenic carboxylic acids, which are considered chemotaxonomic markers of the genus *Aristolochia*.[5,6]

In addition to aristolochic acids, *Aristolochia* species produce other secondary metabolites, such as lignoids, alkaloids, flavonoids, phenolic derivatives, terpenoids, and fatty acids.[4,7]

Recent studies showed that several compounds with antioxidant properties inhibited the formation of AGEs (advanced glycation end products), which are related in the development of chronic illnesses, such as diabetes, cardiovascular and neurodegenerative diseases, atherosclerosis, cataracts, Alzheimer's, and cancer.[8]

Continuing the chemical studies of plants belonging to the genus *Aristolochia*, we report the isolation and structural elucidation of 23 compounds from the leaves of the unstudied species *Aristolochia warmingii* Mast., including three new furofuran lignans (**1**-**3**). Organic extracts and compounds were also evaluated for anti-glycation activity.

Experimental

Chromatographic analysis

The fractionation of the extract and samples were performed by column chromatography (CC) using a glass column with a diameter of 2.5 cm and a length of 36.0 cm, packed with silica gel 60 Å (40-63 μm, Sigma-Aldrich,

*e-mail: isabele.nascimento@unesp.br
Editor handled this article: Paulo Cezar Vieira

Buchs, Switzerland). Thin-layer chromatography (TLC) was performed using silica gel plates (2-25 μm, 60 Å, Sigma-Aldrich, Milwaukee, USA) with glass support. The chromatoplates were revealed using sublimated iodine and ultraviolet (UV) radiation at 254 and 365 nm. In high performance liquid chromatography (HPLC), the analyzed samples were previously subjected to a clean-up procedure using solid phase with Macherey-Nagel C18 reverse phase cartridges (3.0 mL; 500 mg, Chromabond, Düren, Germany) and, subsequently, filtered through a microfilter of polyvinylidene difluoride (PVDF) (13 mm; 0.22 μm, Exacta, San Prospero, Italia). The analyses were performed using JASCO (Tokyo, Japan) liquid chromatograph with LC-Net II/ADC controller, PU-2086 Plus pump, AS-2055 Plus automatic injector, and MD-2018 Plus photodiode array detector. The analytical mode used a C18 ODS column (Zorbax RX-C18, 4.6 × 250 mm, 5 μm, Agilent, Santa Clara, USA), while in the semi-preparative mode a C18 ODS column (Zorbax RX-C18, 9.4 × 250 mm, 5 μm, Agilent, Santa Clara, USA) was employed. Ultrapure water was obtained from Millipore's Direct-Q 3 UV system (minimum resistivity 18.2 MΩ cm at 25 °C, Molsheim, France). The solvents (chromatographic grade) used in the extracts preparation, in the chromatographic processes and in fraction partitions were purchased from Chromasolv (Muskegon, USA), Supelco (Darmstadt, Germany), J.T.Baker (Phillipsburg, USA), M.Tedia (Fairfield, USA), and Panreac (Barcelona, Spain).

Physical data

The one-dimensional (^{1}H, ^{13}C and nuclear overhauser effect spectroscopy (NOESY)) and two-dimensional (heteronuclear single quantum coherence spectroscopy (HSQC) and heteronuclear multiple bond correlation (HMBC)) nuclear magnetic resonance (NMR) spectra were acquired on a Bruker (Rheinstetten, Germany) spectrometer, model Avance III HD 600 (14.1 T), with a frequency of 600 MHz for the core of ^{1}H and 151 MHz for ^{13}C, with a 5 mm cryogenic probe, reverse detection and three acquisition channels (^{1}H, ^{13}C and ^{15}N) at 23 °C. The deuterated solvents ($CDCl_3$, CD_3OD (with purity ≥ 99.8% for D) and dimethyl sulfoxide (DMSO-d_6, D, 99.9%)) were purchased from Sigma-Aldrich (Milwaukee, USA) and CIL (Andover, USA). The absorption spectra in the infrared region were obtained in a Bruker (Bremen, Germany) Vertex 70 Fourier-Transform (FT-IR) spectrophotometer, DLaTGS detector and reading range from 400 to 4000 cm^{-1}. The electronic circular dichroism (ECD) spectra were obtained using a JASCO (Tokyo, Japan) J-815 spectropolarimeter. For the measurements, a 1.0 mm cuvette was used, and the scan was carried out from 190 to 400 nm. The measurements of specific optical rotation $[\alpha]_D$ were obtained in a digital PerkinElmer (Waltham, USA) 341 LC polarimeter, with sodium filter (589 nm) and quartz cell with an optical path of 1.00 dm. High-resolution mass spectra (HRMS) were obtained on an ESI-QqTOF-MS Bruker (Bremen, Germany) Maxis Impact mass spectrometer.

Plant material

The plant was collected in Monte Alegre, GO, Brazil, in February 2016, and identified as *Aristolochia warmingii* Mast. by Dr Joelcio Freitas. The botanical material was registered at Conselho de Gestão do Patrimônio Genético (CGEN/SisGen), Brazil, under the number A3486D8. A specimen of voucher (MBML 50515) was deposited in the herbarium of the Museum of Biology Prof Mello Leitão, Santa Teresa, ES, Brazil. The leaves were dried at 45 ºC for 24 h. After drying, the material was ground with the aid of a knife mill.

Extraction and isolation

The ground leaves (168.67 g) were subjected to successive extractions at room temperature with organic solvents: hexane, acetone and ethanol (3 × ca. 400 mL, three days with manual shaking every 24 h for two minutes). The remaining material was extracted until exhaustion with ethanol in a Soxhlet apparatus. Four extracts were obtained, after evaporation of solvents: hexane (5.99 g), acetone (8.00 g), ethanol (14.19 g), and ethanol Soxhlet (26.02 g).

A portion of the acetone extract (6.0 g) was fractionated by CC using a gradient of hexane (Hex)/ethyl acetate (EtOAc)/methanol (MeOH) (Hex → Hex:EtOAc (100:0 to 50:50, v/v) → EtOAc → EtOAc:MeOH (100:0 to 50:50, v/v) → MeOH) as eluent, which resulted in 29 fractions (ca. 100 mL each).

The analysis of fractions 11, 12 and 8 by 1D and 2D NMR allowed the identification of **4** (1,282.0 mg), **5** (307.0 mg) and **6** (255.0), respectively. Fraction 5 was purified by preparative TLC, using $CHCl_3$:MeOH (97:3), resulting in the isolation of **7** (8.2 mg). Fraction 9 was subjected to HPLC (C18, H_2O/MeOH 45 → 75% MeOH in 12 min, flow rate 2.5 mL min^{-1}, detection at λ = 250 nm) on a semi-preparative scale, which resulted in the isolation and identification of **8** + **20** (88.5 mg), **12** (0.4 mg) and **13** (0.5 mg). Separation of fraction 13 was performed by HPLC (C18, H_2O/MeOH 20 → 100% MeOH in 40 min, flow rate 2.5 mL min^{-1}, detection at λ = 274 nm) on a semi-preparative scale, yielding the compounds **1** (2.3 mg),

2 (7.2 mg), **3** (0.5 mg), **9** (0.6 mg), **10** (0.9 mg), **11** (1.4 mg), and **14** (1.0 mg). Fraction 14 was submitted to HPLC (C18, H_2O/MeOH 20 → 100% MeOH in 12 min, flow rate 2.5 mL min^{-1}, detection at λ = 274 nm) on a semi-preparative scale, resulting in the isolation of **15** (26.0 mg), **16** (5.1 mg) and **18** (4.0 mg). Fraction 19 was eluted by HPLC (C18, H_2O/MeOH 5 → 100% MeOH in 60 min, flow rate 2.5 mL min^{-1}, detection at λ = 274 nm) on a semi-preparative scale, giving **21** (1.8 mg). The fraction 20 was subjected to HPLC (C18, H_2O/MeOH 20 → 100% MeOH in 40 min, flow rate 2.5 mL min^{-1}, detection at λ = 274 nm) on a semi-preparative scale, giving **17** (7.4 mg) and **19** (1.5 mg). Precipitates formed in MeOH were separated from fractions 22 and 26 and identified as **22** (2.2 mg) and **23** (3.0 mg), respectively.

Anti-glycation activity

The anti-glycating activity was performed according to the methodology described by Fraige *et al.*[9] using the bovine serum albumin (BSA) assay with methylglyoxal (MGO). A solution of 1 mg mL^{-1} BSA was prepared in sodium phosphate buffer solution (10 mmol L^{-1}, pH 7.4). A solution of 1 mg mL^{-1} of sample was prepared in 500 µL of water and 500 µL of DMSO. To the BSA solution, the MGO reagent (5 mmol L^{-1}) and the samples (150 µg mL^{-1}) were added. Then, they were incubated at 37 °C, under agitation at 150 rpm, for 72 h. An aminoguanidine solution (10 mmol L^{-1}) was used as a positive control. After incubation, samples were transferred to 96-well plates and fluorescence reading was performed at maximum excitation of 370 nm and maximum emission of 440 nm. The percentage of inhibition of AGE formation is calculated using the equation $[(FL_{CN} - FL_{bCN}) - (FL_S\ FL_{bS})]/(FL_{CN} - FL_{bCN}) \times 100$, where FL_{CN} and FL_{bCN} are the fluorescence intensities of the negative control mixture and its blank, respectively, and FL_S and FL_{bS} are the fluorescence intensities of the sample and its blank, respectively.

Warminin A ((–)-(7*R*,7'*S*,8*S*,8'*S*)-4,5-dihydroxy-3,3',4'-trimethoxy-7,9':7',9-diepoxylignan, **1**)

$[\alpha]_D^{25}$ –61.0 (*c* 0.10, $CHCl_3$); UV-Vis (MeOH) λ / nm 220, 280; IR (ATR) ν / cm^{-1} 3397, 2928, 2843, 1616, 1512, 1448, 1267; ^1H and ^{13}C NMR data, see Table 1; HRMS (ESI) *m/z*, calcd. for $C_{21}H_{23}O_7$ $[M - H]^-$: 387.1444, found: 387.1443 $[M - H]^-$, error 0.26 ppm.

Warminin B ((–)-(7*R*,7'*S*,8*S*,8'*S*)-4-hydroxy-3,3',4',5-tetramethoxy-7,9':7',9-diepoxylignan, **2**)

$[\alpha]_D^{25}$ –151.0 (*c* 0.10, $CHCl_3$); UV-Vis (MeOH) λ / nm 220, 275; IR (ATR) ν / cm^{-1} 3393, 2947, 2830, 1616, 1506, 1454, 1241; ^1H and ^{13}C NMR data, see Table 1; HRMS (ESI) *m/z*, calcd. for $C_{22}H_{25}O_7$ $[M - H]^-$: 401.1600, found: 401.1596 $[M - H]^-$, error 1.00 ppm.

Warminin C ((–)-(7*R*,7'*S*,8*S*,8'*S*)-3',4,4'-trimethoxy-3,5'-dihydroxy-7,9':7',9-diepoxylignan, **3**)

$[\alpha]_D^{25}$ –7.5 (*c* 0.08, $CHCl_3$); UV-Vis (MeOH) λ / nm 220, 280; IR (ATR) ν / cm^{-1} 3419, 2918, 2843, 1725, 1512; ^1H and ^{13}C NMR data, see Table 1.

Results and Discussion

The phytochemical investigation of the acetone extract of *A. warmingii* leaves led to the isolation and identification of 23 compounds, of which three are being described for the first time (**1-3**). The structures were elucidated through the analysis of their spectroscopic data and comparison with values reported in the literature. Among the isolated compounds, there were fourteen furofuran lignans (**1**-**14**), four dihydrobenzofuran neolignans (**15**-**18**), one dihydrobenzofuran bisnorneolignan (**19**), one dibenzylbutyrolactone lignan (**20**), one C_6C_2 derivative (**21**), one imidazole derivative (**22**), and one cyclitol (**23**) (Figure 1).

The known compounds were identified as (–)-epieudesmin (**4**),[10] (–)-phillygenin (**5**),[11] (–)-fargesin (**6**),[11] (–)-episesamin (**7**),[12] xanthoxylol (**8**),[13] (–)-medioresinol (**9**),[14] (–)-pinoresinol (**10**),[15] (–)-eudesmin (**11**),[16] (–)-kobusin (**12**),[17] (–)-piperitol (**13**),[13] (–)-de-4'-*O*-methylmagnolin (**14**),[18] (–)-*trans*-dehydrodiconiferyl alcohol (**15**),[19] (*E*)-3-[(2*S*,3*R*)-2,3-dihydro-3-hydroxymethyl-7-methoxy-2-(3',4'-dimethoxyphenyl)-1-benzo[*b*]furan-5-yl]-2-propen-l-ol (**16**),[20] (–)-*trans*-dehydrodiconiferyl alcohol-4-β-*D*-glucoside (**17**),[21] (–)-*cis*-dehydrodiconiferyl alcohol (**18**),[22] ficusal (**19**),[23] kusunokinin (**20**),[11] 2-(3,4-dihydroxy)-phenyl-ethyl-β-*D*-glucopyranoside (**21**),[24] (+)-allantoin (**22**),[25] and sequoyitol (**23**).[26]

Compound **1** was obtained as a brownish yellow oil, with molecular formula $C_{21}H_{24}O_7$ determined by ESI-QqTOF-MS, on negative mode, consistent with peak *m/z* 387.1443 $[M - H]^-$ (mass calculated for $C_{21}H_{23}O_7$, 387.1444), corresponding to 10 unsaturation degrees. The UV spectrum of **1** showed bands of maximum absorption at 230 and 280 nm. The ^{13}C NMR spectrum of **1** showed 21 carbon signals referring to two benzene rings (δ_C 101.0-148.9), two benzyl carbinolic (δ_C 82.2, 87.8), two oxymethylenes (δ_C 69.8, 71.2), three aromatic methoxyls (δ_C 2 × 56.0, 56.3), and two aliphatic methines (δ_C 50.2, 54.6). The ^1H NMR spectrum indicated the presence of one 1,3,4,5-tetrasubstituted aromatic ring (δ_H 6.53 (d,

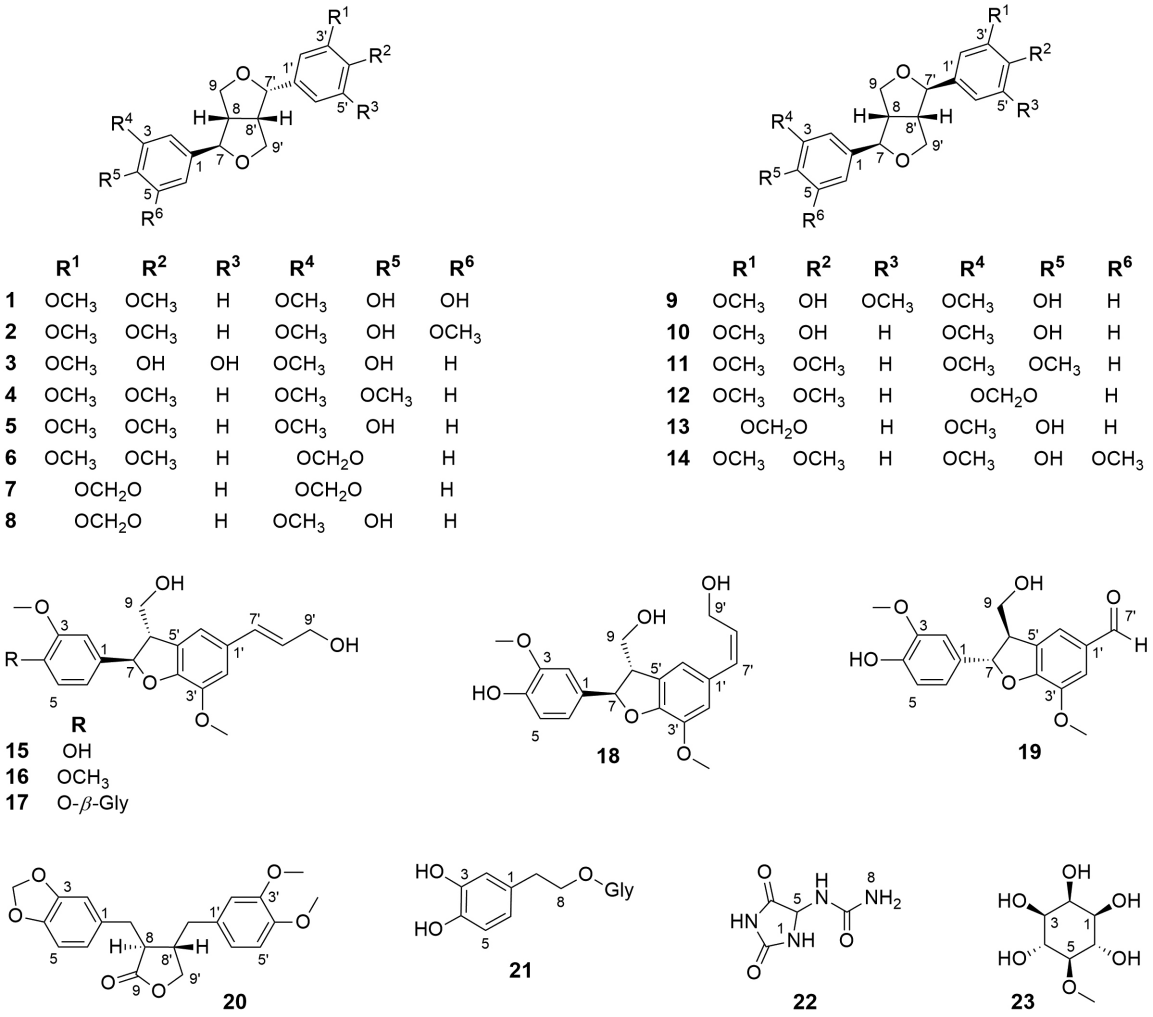

Figure 1. Chemical constituents isolated from the acetone extract of *A. warmingii* leaves.

J 1.7 Hz), 6.59 (d, *J* 1.7 Hz)) and one 1,3,4-trisubstituted aromatic ring (δ_H 6.93 (br s), 6.85 (d, *J* 8.4 Hz), 6.86 (dd, *J* 8.4 and 1.3 Hz)). Additional NMR experiments, such as HSQC and HMBC, contributed to the complete assignment of all proton signals and their corresponding carbons of **1** (Table 1).

The furofuran skeleton of the structure of **1** was determined based on the observed correlations in the HMBC contour map of H-7 (δ_H 4.40) with C-9 (δ_C 71.2), H-7' (δ_H 4.87) with C-9' (δ_C 69.8), H-8 (δ_H ca. 2.89) with C-1 (δ_C 133.2), C-7' (δ_C 82.2) and C-9' (δ_C 69.8), and H-8' (δ_H ca. 3.31) with C-1' (δ_C 131.0), C-7 (δ_C 87.8) and C-9 (δ_C 71.2) (Figure 2). The correlations of the methoxy hydrogens at δ_H 3.88 with C-3 (δ_C 147.2) and C-4' (δ_C 148.1), as well as the hydrogens at δ_H 3.91 with C-3' (δ_C 148.9), indicated the position of the methoxy groups in each aromatic ring. The NOESY correlation between the methoxy hydrogens at δ_H 3.91 and H-2' (δ_H 6.93) also confirmed the proposed arrangement (Supplementary Information section, Figure S6). The location of hydroxyl groups was supported by the correlations in the HMBC contour map between the broad simplet at δ_H 5.42 (2H) with the carbons C-4 (δ_C 132.0) and C-5 (δ_C 144.0). The HMBC correlations of H-7 (δ_H 4.40) with C-1 (δ_C 133.2), C-2 (δ_C 101.0) and C-6 (δ_C 106.7), and of H-7' (δ_H 4.87) with C-1' (δ_C 131.0), C-2' (δ_C 109.0) and C-6' (δ_C 117.8), confirmed the position of each aromatic ring in the furofuran skeleton (Figure 2).

In nature, lignans with the tetrahydrofurofuran skeleton always have their rings joined in *cis* configuration due to the high torsional stress inherent to the bicyclic system of the tetrahydrofurofuran ring. Recently, Shao *et al.*[27] proposed an efficient method for determining the relative configuration of C-7/C-8 and C7'/C-8' of furofuran lignans by ^{1}H NMR. This proposal was based on the chemical shift differences of the diastereotopic methylene hydrogen pairs 2H-9 and 2H-9' ($\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$) for each of the three configuration types: (*i*) for H-7/H-8 *trans*, H-7'/H-8' *trans*, with $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'}$ = 0.30-0.40; (*ii*) for H-7/H-8 *trans*, H-7'/H-8' *cis*, with $\Delta\delta_{H\text{-}9}$ = 0.25-0.36 and $\Delta\delta_{H\text{-}9'}$ > 0.50;

Table 1. NMR data for compounds **1**, **2** and **3** (14.1 T, *J* in Hz, $CDCl_3$)

Position	Warminin A (**1**)		Warminin B (**2**)		Warminin C (**3**)	
	δ_C[a] / ppm	δ_H / ppm	δ_C[a] / ppm	δ_H / ppm	δ_C[a] / ppm	δ_H / ppm
1	133.2	–	132.3	–	132.9	–
2	101.0	6.53 (d, *J* 1.7)	102.9	6.60 (br s)	108.5	6.91 (d, *J* 1.8)
3	147.2	–	147.2	–	146.7	–
4	132.0	–	134.4	–	145.2	–
5	144.0	–	147.2	–	114.2	6.89 (d, *J* 8.1)
6	106.7	6.59 (d, *J* 1.7)	102.9	6.60 (br s)	119.2	6.84 (dd, *J* 8.1, 1.8)
7	87.8	4.40 (d, *J* 7.0)	88.1	4.41 (d, *J* 7.2)	87.8	4.41 (d, *J* 7.2)
8	54.6	2.87-2.91 (m)	54.8	2.89-2.92 (m)	54.5	2.87-2.90 (m)
9	71.2	3.82-3.85 (m) 4.13 (d, *J* 9.6)	71.1	3.83-3.87 (m) 4.14 (d, *J* 9.5)	70.9	3.83 (dd, *J* 9.4, 6.2) 4.11 (d, *J* 9.4)
1’	131.0	–	131.0	–	131.0	–
2’	109.0	6.93 (br s)	109.0	6.93 (br s)	100.6	6.58 (d, *J* 1.1)
3’	148.9	–	148.9	–	146.7	–
4’	148.1	–	148.1	–	[b]	–
5’	111.1	6.85 (d, *J* 8.4)	111.1	6.85 (d, *J* 8.4)	143.6	–
6’	117.8	6.86 (dd, *J* 8.4, 1.3)	117.8	6.87 (dd, *J* 8.4, 1.5)	105.9	6.53 (d, *J* 1.1)
7’	82.2	4.87 (d, *J* 5.5)	82.2	4.88 (d, *J* 5.8)	82.0	4.82 (d, *J* 5.3)
8’	50.2	3.29-3.34 (m)	50.2	3.30-3.38 (m)	50.0	3.29-3.35 (m)
9’	69.8	3.29-3.34 (m) 3.82-3.85 (m)	69.9	3.30-3.38 (m) 3.83-3.87 (m)	69.8	3.29-3.35 (m) 3.87-3.88 (m)
CH_3O-3	56.0	3.88 (s)	56.4	3.90 (s)	56.0	3.90 (s)
CH_3O-5	–	–	56.4	3.90 (s)	–	–
CH_3O-3’	56.3	3.91 (s)	56.0	3.91 (s)	56.0	3.90 (s)
CH_3O-4’	56.0	3.88 (s)	56.0	3.88 (s)	–	–
HO-4	–	5.42 (s)	–	5.52 (s)	–	5.58 (s)
HO-5	–	5.42 (s)	–	–	–	–
HO-5’	–	–	–	–	–	5.32 (s)

[a]Assignments based on HMQC and HMBC experiments; [b]value not observed.

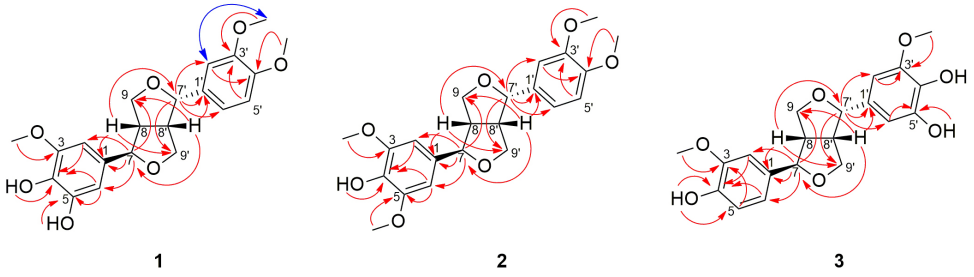

Figure 2. Selected HMBC (⟶) and NOESY (⟷) correlations for compounds **1**, **2** and **3**.

and (*iii*) for H-7/H-8 *cis*, H-7’/H-8’ *cis*, with $\Delta\delta_{H\text{-}9}$ and $\Delta\delta_{H\text{-}9'} < 0.2$. Based on this, the relative configuration of **1** was determined as H-7/H-8 *trans* and H-7’/H-8’ *cis* type ($\Delta\delta_{H\text{-}9} = 0.30$, $\Delta\delta_{H\text{-}9'} = 0.52$). After comparing the ECD (negative Cotton effect at 235 nm) and optical activity ($[\alpha]_D^{25}$ −61.0 (*c* 0.10, $CHCl_3$)) data of **1** with furofuran lignans of the same relative configuration described in the literature,[27,28] it was possible to suggest the absolute configuration as (−)-(7*R*,7’*S*,8*S*,8’*S*). Compound **1** is being described for the first time in the literature and has been named as warminin A.

Compound **2** was obtained as a brownish yellow oil, with molecular formula $C_{22}H_{26}O_7$, established from the peak *m/z* 401.1596 $[M - H]^-$ (mass calculated for $C_{22}H_{25}O_7$,

401.1600), obtained in negative mode by ESI-QqTOF-MS. Compound **2** showed bands of maximum absorption on the UV spectrum at 232 and 275 nm. The ^{1}H and ^{13}C NMR spectra of compound **2** were very similar to those obtained from **1**, showing signals of one additional methoxyl group (Table 1). The position of the four aromatic methoxy groups in the benzene rings were determined based on the correlations observed in the HMBC contour map between δ_H 3.90 with C-3 (δ_C 147.2) and C-5 (δ_C 147.2), δ_H 3.91 with C-3' (δ_C 148.9) and δ_H 3.88 with C-4' (δ_C 148.1) (Figure 2). In the same way as for **1**, the identity and substitution pattern of the chemical structure of **2** were established by analyzing the correlations observed in the HMBC spectrum. Considering the value of optical rotation ($[\alpha]_D^{25}$ −151.0 (*c* 0.1; $CHCl_3$)), as well as the ECD data (negative Cotton effect at 230 nm), it was possible to suggest the absolute configuration for compound **2** as being (−)-(7*R*,7'*S*,8*S*,8'*S*) and naming it as warminin B.

Compound **3** was obtained as a brownish yellow oil. The ^{1}H and ^{13}C NMR data of **3** were very similar to those of compounds **1** and **2** (Table 1). In the ^{1}H NMR spectrum, it was observed signals for one 1,3,4-trisubstituted (δ_H 6.91 (d, *J* 1.8 Hz), 6.89 (*d*, *J* 8.1 Hz), 6.84 (dd, *J* 8.1 and 1.8 Hz)) and one 1,3,4,5-tetrasubstituted phenyl rings (δ_H 6.58 (d, *J* 1.1 Hz) and 6.53 (d, *J* 1.1 Hz)). The two methoxyl aromatic groups at δ_H 3.90 showed long-range connectivity with C-3 (δ_C 146.7) and C-3' (δ_C 146.7) in the HMBC spectrum. Two simplets at δ_H 5.58 and δ_H 5.32 with established correlations with C-4 (δ_C 145.2) and C-5' (δ_C 143.6), respectively, suggested the presence of the hydroxyl groups in the structure. As for compounds **1** and **2**, the absolute configuration of **3** was established as (−)-(7*R*,7'*S*,8*S*,8'*S*) based on the ECD curve and optical activity value ($[\alpha]_D^{25}$ −10.0) and named as warminin C.

The study of the acetone extract of leaves of *A. warmingii* showed that this species produced a wide variety of lignans with different degrees of oxidation in the aromatic rings, especially those of the furofuran type. Fourteen furofuran lignans were isolated and identified, which three of them are being described for the first time in the literature (**1**-**3**). Another noteworthy fact was the high amount of (−)-epieudesmin (**4**) isolated from *A. warmingii*, representing more than 21% by mass of the acetone extract. Epieudesmin stands out for having anti-inflammatory,[29,30] antitrypanosomal[31] and antifungal[32] activities, for being active against breast tumor cells,[33] and for inhibiting α-glycosidase.[34] The species *A. warmingii* appears to be a promising source of this compound.

The anti-glycation activity of compounds **4-7**, **11**, **12**, **15**-**17**, and **19-23**, as well as the hexane, acetone, ethanol, and ethanol Soxhlet extracts, was evaluated with respect to the ability to inhibit the AGEs formation. Unfortunately, the samples did not show significant activities.

Conclusions

The phytochemical study of acetone extract from leaves of *A. warmingii* led to the isolation of 23 compounds, mostly lignans (**1**-**14**) and neolignans (**15**-**20**), including three new furofuran lignans (**1**-**3**). *A. warmingii* demonstrated as a source of epieudesmin which represents 21% of the acetone extract.

Supplementary Information

Supplementary information (1D and 2D NMR, HRMS, FTIR, and ECD spectra of compounds **1**-**3**) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

The authors thank Dr Joelcio Freitas for plant identification, and FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo), CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) and CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, finance code 001) for financial support.

Author Contributions

Camila L. Cunha and Paulo Vinícius G. de Antonio were responsible for the investigation, data curation, formal analysis, writing the original draft, writing-review and editing; Maria do Carmo G. Lustosa, Juliana C. Holzbach, Douglas H. Pereira, and Állefe B. Cruz for formal analysis, validation, writing-review, resources and software; Isabele R. Nascimento for conceptualization, data curation, funding acquisition, resources, supervision, writing-review and editing.

References

1. Freitas, J.; Doweld, A. B.; *Phytotaxa* **2021**, *500*, 59. [Crossref]
2. Fernandes, J. M.; Silva, D. F.; Lopes, C. R. A. S.; de Almeida, A. A. S. D.; Braga, J. M. A.; Freitas, J.; González, F.; *Res. Soc. Dev.* **2021**, *10*, e518101018676. [Crossref]
3. Aristolochiaceae, https://floradobrasil.jbrj.gov.br/FB54, accessed in January 2023.
4. Lerma-Herrera, M. A.; Beiza-Granados, L.; Ochoa-Zarzosa, A.; López-Meza, J. E.; Navarro-Santos, P.; Herrera-Bucio, R.; Aviña-Verduzco, J.; García-Gutiérrez, H. A.; *Molecules* **2022**, *27*, 3937. [Crossref]
5. Lukinich-Gruia, A. T.; Nortier, J.; Pavlović, N. M.; Milovanović,

D.; Popović, M.; Drăghia, L. P.; Păunescu, V.; Tatu, C. A.; *Chemosphere* **2022**, *297*, 134111. [Crossref]
6. Han, J.; Xian, Z.; Zhang, Y.; Liu, J.; Liang, A.; *Front. Pharmacol.* **2019**, *10*, 648. [Crossref]
7. Kuo, P. C.; Li, Y. C.; Wu, T. S.; *J. Tradit. Complementary Med.* **2012**, *2*, 249. [Crossref]
8. Song, Q.; Liu, J.; Dong, L.; Wang, X.; Zhang, X.; *Biomed. Pharmacother.* **2021**, *140*, 111750. [Crossref]
9. Fraige, K.; Dametto, A. C.; Zeraik, M. L.; de Freitas, L.; Saraiva, A. C.; Medeiros, A. I.; Castro-Gamboa, I.; Cavalheiro, A. J.; Silva, D. H. S.; Lopes, N. P.; Bolzani, V. S.; *Phytochem. Anal.* **2018**, *29*, 196. [Crossref]
10. Pelter, A.; Ward, R. S.; Venkata Rao, E.; Sastry, K. V.; *Tetrahedron* **1976**, *32*, 2783. [Crossref]
11. Messiano, G. B.; Vieira, L.; Machado, M. B.; Lopes, L. M. X.; de Bortoli, S. A.; Zukerman-Schpector, J.; *J. Agric. Food Chem.* **2008**, *56*, 2655. [Crossref]
12. Zhang, F.; Chu, C. H.; Xu, Q.; Fu, S. P.; Hu, J. H.; Xiao, H. Bin; Liang, X. M.; *J. Asian Nat. Prod. Res.* **2005**, *7*, 1. [Crossref]
13. Takaku, N.; Choi, D. H.; Mikame, K.; Okunishi, T.; Suzuki, S.; Ohashi, H.; Umezawa, T.; Shimada, M.; *J. Wood Sci.* **2001**, *47*, 476. [Crossref]
14. Sribuhom, T.; Sriphana, U.; Thongsri, Y.; Yenjai, C.; *Phytochem. Lett.* **2015**, *11*, 80. [Crossref]
15. Yamauchi, S.; Ichikawa, H.; Nishiwaki, H.; Shuto, Y.; *J. Agric. Food Chem.* **2015**, *63*, 5224. [Crossref]
16. Seo, Y.; *Biotechnol. Bioprocess Eng.* **2010**, *15*, 400. [Crossref]
17. Santhanam, R. K.; Ahmad, S.; Abas, F.; Ismail, I. S.; Rukayadi, Y.; Akhtar, M. T.; Shaari, K.; *Molecules* **2016**, *21*, 652. [Crossref]
18. Miyazawa, M.; Kasahara, H.; Kameoka, H.; *Phytochemistry* **1993**, *32*, 1421. [Crossref]
19. Han, H.-Y.; Wang, X.-H.; Wang, N.-L.; Ling, M.-T.; Wong, Y.-C.; Yao, X.-S.; *J. Agric. Food Chem.* **2008**, *56*, 6928. [Crossref]
20. Yuen, M. S. M.; Xue, F.; Mak, T. C. W.; Wong, H. N. C.; *Tetrahedron* **1998**, *54*, 12429. [Crossref]
21. Pereira, C.; Barreto Jr., C. B.; Kuster, R. M.; Simas, N. K.; Sakuragui, C. M.; Porzel, A.; Wessjohann, L.; *Quim. Nova* **2012**, *35*, 1123. [Crossref]
22. Fiorentino, A.; DellaGreca, M.; D'Abrosca, B.; Oriano, P.; Golino, A.; Izzo, A.; Zarrelli, A.; Monaco, P.; *Biochem. Syst. Ecol.* **2007**, *35*, 392. [Crossref]
23. Li, Y.-C.; Kuo, Y.-H.; *Chem. Pharm. Bull.* **2000**, *48*, 1862. [Crossref]
24. Della Greca, M.; Ferrara, M.; Fiorentino, A.; Monaco, P.; Previtera, L.; *Phytochemistry* **1998**, *49*, 1299. [Crossref]
25. Holzbach, J. C.; Lopes, L. M. X.; *Molecules* **2010**, *15*, 9462. [Crossref]
26. Sultana, N.; Hartley, T. G.; Waterman, P. G.; *Phytochemistry* **1999**, *50*, 1249. [Crossref]
27. Shao, S.-Y.; Yang, Y.-N.; Feng, Z.-M.; Jiang, J.-S.; Zhang, P.-C.; *J. Nat. Prod.* **2018**, *81*, 1023. [Crossref]
28. Samizu, K.; Ogasawara, K.; *Chem. Lett.* **1995**, *24*, 543. [Crossref]
29. Wu, X.-Y.; Xiong, J.; Liu, X.-H.; Hu, J.-F.; *Chem. Biodiversity* **2016**, *13*, 1030. [Crossref]
30. Wu, H.; Liu, T.; Zhang, Z.; Wang, W.; Zhu, W.; Li, L.; Li, Y.; Chen, X.; *Ind. Crops Prod.* **2018**, *125*, 416. [Crossref]
31. Sartorelli, P.; Carvalho, C. S.; Reimão, J. Q.; Lorenzi, H.; Tempone, A. G.; *Planta Med.* **2010**, *76*, 1454. [Crossref]
32. Cavin, A.; Potterat, O.; Wolfender, J.-L.; Hostettmann, K.; Dyatmyko, W.; *J. Nat. Prod.* **1998**, *61*, 1497. [Crossref]
33. Aimaiti, S.; Saito, Y.; Fukuyoshi, S.; Goto, M.; Miyake, K.; Newman, D. J.; O'Keefe, B. R.; Lee, K.-H.; Nakagawa-Goto, K.; *Molecules* **2019**, *24*, 4005. [Crossref]
34. Rayanil, K.; Sutassanawichanna, W.; Suntornwat, O.; Tuntiwachwuttikul, P.; *Nat. Prod. Res.* **2016**, *30*, 2675. [Crossref]

Submitted: September 12, 2022
Published online: February 10, 2023