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Two new amide glycosides with anti-inflammatory activity from the leaves of *Streblus ilicifolius* (Vidal) Corner

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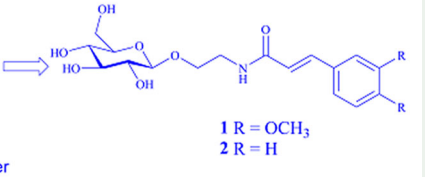
ABSTRACT

Two new amide glycosides, streblusoamides A (**1**) and B (**2**), along with 11 known compounds (**3**–**13**) were isolated from the leaves of *Streblus ilicifolius*. The structures of the isolates were elucidated by spectroscopic methods. All of the isolates were tested for inhibition of NO production in lipopolysaccharide (LPS)-induced RAW 264.7 cells to investigate their anti-inflammatory effects. The results revealed that compounds **1**, **5** and **6** moderately inhibited the release of NO production with IC_{50} values ranging from 50.90 μM to 64.79 μM.

Streblus ilicifolius (Vidal) Corner



1 R = OCH_3
2 R = H

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Streblus ilicifolius (Vidal) Corner; amide glycoside; anti-inflammatory activity

1. Introduction

The genus *Streblus* is a small deciduous shrub belonging to the family of Moraceae. It includes 20 species and mainly distributed in South China and South Asia. Previous phytochemical investigations on the genus *Streblus* led to the isolation of phenylpropanoids (Li et al. 2012; Li et al. 2012, 2012, 2012, 2013;Li et al. 2014; He et al. 2016; Nie et al. 2016; He et al. 2017), benzofurans (He et al. 2017), flavonoids (Li et al. 2012, 2012, 2012), steroids (Prakash et al. 1992; Shivendra et al. 2015; Ren et al. 2017; Miao

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et al. 2018) and terpenes (Li et al. 2012; Vidhu et al. 2012; Shivendra et al. 2015; Vidhu et al. 2015; Verma et al. 2016). Extracts of the genus *Streblus* have been reported to possess the effects of anti-inflammatory (Sripanidkulchai et al. 2009; Chen et al. 2011; Huang et al. 2012), antibacterial (Taweechaisupapong et al. 2000; 2005; Li et al. 2012; Huang et al. 2012; Neekhra et al. 2019), anti-hepatitis virus (Li et al. 2012, Li et al. 2012), anti-tumor (Alamgir et al. 2013; He et al. 2016), and anti-oxidation (Zhu et al. 2010; Prasansuklab et al. 2018; Neekhra et al. 2019).

In our previous researches, the investigations of plants of the genus *Streblus* resulted in the isolation of a lot of phenylpropanoids and lignans (Li et al. 2012, 2012, 2012, 2013; Li 2014; He et al. 2016; Zhang et al. 2019). *Streblus ilicifolius* (Vidal) Corner, a species of *Streblus,* distributes mainly in southern China (Zhang et al. 1998). It was reported that the wood extract of *S. ilicifolius* showed the potential of antityrosinase and antimicrobial activities (Sukanya et al. 2016). As part of an ongoing project to assess the bioactive metabolites from the plants of the genus *Streblus*, we carried out a phytochemical investigation on *S. ilicifolius* with anti-inflammatory activity. Two new amide glycosides, streblusoamides A (**1**) and B (**2**), along with 11 known compounds, were isolated from the leaves of the plant. Herein, the isolation, purification and determination of these isolates, the assay used to determine the anti-inflammatory activities of the constituents are described.

2. Results and discussion

Phytochemical investigation of the 75% EtOH extract of the leaves of *S. ilicifolius* using sequential column chromatography over silica gel, RP-C_{18} silica, Sephadex LH-20, along with semipreparative HPLC to afford two new amide glycosides, streblusoamides A (**1**) and B (**2**), together with 11 known compounds (**3**–**13**). The structures of the known compounds were identified as adenine (**3**) (Chen et al. 2002), (-)-isolariciresinol 3α-*O*-*β*-D-glucopyranoside (**4**) (Wang et al. 1998), moracin M 6-*β*-D-glucopyranoside (**5**) (Piao et al. 2009), moracin M 3′-(*β*-D-glucopyranoside) (**6**) (Cao et al. 2018), 5,5′-dimethoxylariciresinol-4′-*O*-*β*-D-glucoside (**7**) (Kiem et al. 2008), 5,5′-dimethoxylariciresinol-4-*O*-*β*-D-glucoside (**8**) (Yan et al. 2017), lariciresinol-4-*O*-*β*-D-glucopyranoside (**9**) (Li et al. 2005), kaempferol-7-*O*-*β*-D-glucoside (**10**) (Yang et al. 2013), benzyl-*O*-glucopyranoside (**11**) (Ni et al. 2020), 4-(1,2,3-trihydroxypropyl)-2,6-dimethoxyphenyl-1-*O*-*β*-D-glucopyranoside (**12**) (Li et al. 2005) and prenyl glucoside (**13**) (Ly et al. 2002) (Figure 1).

Compound **1** was isolated as colorless, amorphous powder. In the UV spectrum, the absorption maxima were exhibited at 285 and 318 nm. The IR spectrum displayed characteristic absorption bands for amino (3362 cm^{-1}), acylamino (1657 cm^{-1}), phenyl group (1599, 1546, 1514 cm^{-1}). It has a molecular formula of $C_{19}H_{27}NO_9$ with 7 degrees of unsaturation based on the positive-ion HRESIMS peak at *m/z* 436.1582 (calcd for $C_{19}H_{27}NO_9Na$, 436.1584) and NMR data (Supplementary material Table S1; Figure S2). The ^{1}H NMR spectrum of **1** showed signals attributed to a 1,3,4-substituted phenyl moiety [δ_H 7.15 (d, $J = 2.0$ Hz, H-2), 7.11 (dd, $J = 8.3$, 2.0 Hz, H-6), 6.94 (d, $J = 8.3$ Hz, H-5)], a *trans*-vinyl [δ_H 7.45 (d, $J = 15.7$ Hz, H-7), 6.51 (d, $J = 15.7$ Hz, H-8)], an oxygenated methylene [δ_H 3.95 (ddd, $J = 10.6$, 6.6, 4.0, H-11a), 3.73 (ddd, $J = 10.6$, 6.8, 4.0, H-11b)], a methylene [δ_H 3.55 (ddd, $J = 14.2$, 6.6, 4.0, H-10a), 3.48 (ddd, $J = 14.2$,

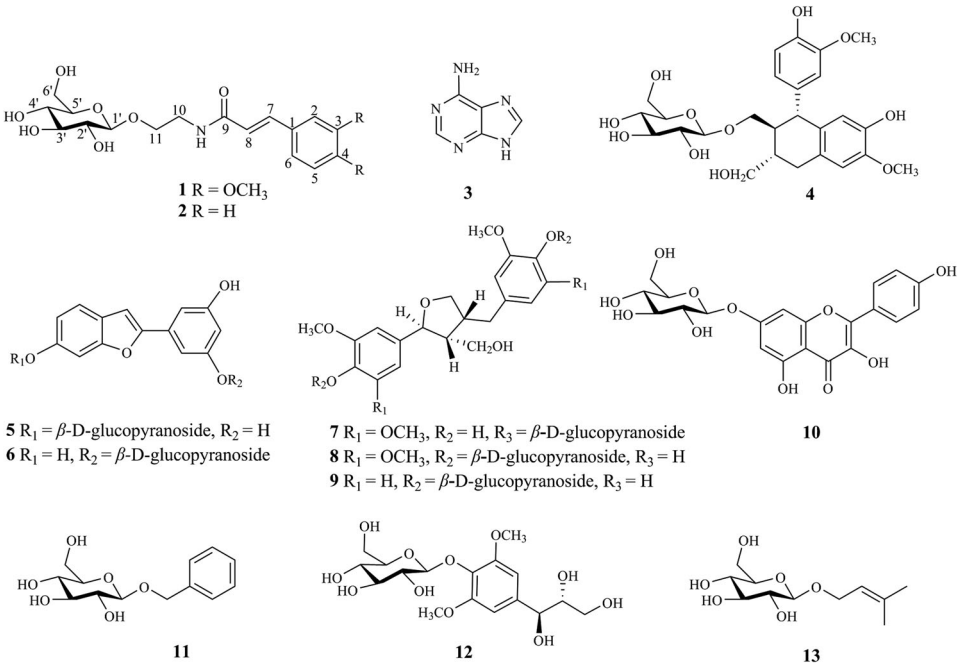

Figure 1. Structures of compounds **1–13**.

6.8, 4.0, H-10b)], an anomeric sugar proton [δ_H 4.28 (d, $J = 7.8$ Hz, H-1′), and two methoxy protons [δ_H 3.83 (s, 4-OCH_3), 3.84 (s, 3-OCH_3)] (Supplementary material Table S1; Figure S3). The ^{13}C NMR data, assigned with the aid of the HSQC spectrum, displayed 19 carbon resonances, including an amide carbonyl [δ_C 169.1 (C-9)], eight aromatic/olefinic carbons [δ_C 152.2 (C-4), 150.7 (C-3), 141.9 (C-7), 129.3 (C-1), 123.3 (C-6), 119.6 (C-8), 112.7 (C-5), 111.2 (C-2)], an oxygenated methylene carbon [δ_C 69.8 (C-11)], a methylene carbon [δ_C 40.9 (C-10)], a glucopyranosyl moiety (δ_C 104.6, C-1′; 75.1, C-2′; 78.0, C-3′; 71.6, C-4′; 78.0, C-5′; 62.7, C-6′), and two oxygenated methyl carbons (δ_C 56.4 and 56.4) (Supplementary material Table S1; Figures S4-S5). These spectroscopic data indicated that compound **1** has a *trans*-cinnamoyl moiety (Zhao et al. 2016), an ethoxyl group and a glucopyranosyl group. In the HMBC spectrum of **1** (Supplementary material Figures S1 and S6), the correlations of H-7 [δ_H 7.45 d (15.7)] to C-2 (δ_C 111.2), C-6 (δ_C 123.3) and C-9 (δ_C 169.1), and H-8 [δ_H 6.51 d (15.7)] to C-1 (δ_C 129.4) and C-9 (δ_C 169.1) confirmed that C-1 was linked to C-7, which proved the presence of a cinnamoyl moiety. Furthermore, the HMBC correlation of H-10 to C-9 revealed the linkage of the ethoxy moiety and *trans*-cinnamoyl moiety by an amide bond. Moreover, The HMBC correlation from H-1′ [δ_H 4.28 d (7.8)] to C-11 (δ_C 69.8) showed that the sugar unit was attached to position C-11. In addition, glucose (Glc) and its relative configuration were identified in the acid hydrolysis solution of **1** by comparing with the authentic sample by performing TLC and HPLC test (see Experimental Section). The coupling constant of $J_{1'/2'} = 7.8$ Hz of the anomeric proton suggested that the sugar unit was β-oriented. The HMBC correlations of the methoxy protons 4-OCH_3 (δ_H 3.83) to C-4 (δ_C 152.2) and 3-OCH_3 (δ_H 3.84) to C-3 (δ_C 150.7) suggested that the two methoxy groups were located at C-3 and C-4, respectively.

Therefore, compound **1** was established as (*E*)-(3,4-dimethoxy)-cinnamoyl-ethyl-*O*-β-D-glucopyranoside and named streblusoamide A (Figure 1).

Compound **2** was obtained as colorless, amorphous powder. Its molecular formula $C_{17}H_{23}NO_7$ was determined by the positive-ion HRESIMS peak at *m/z*, 376.1369 $[M+Na]^+$ (calcd for $C_{17}H_{23}NO_7Na$, 376.1372) (Supplementary material Figure S7), which is 60 Da less than that of **1**, suggesting that **2** possesses two less methoxy groups than **1**. In the UV spectrum, the absorption maxima was exhibited at 270 nm. The IR spectrum of **2** displayed prominent absorption maxima at 3353, 1658, 1616, 1578, 1546 and 1066 cm^{-1}, indicating the presence of amino, acylamino and phenyl functionalities. Compound **2** had identical NMR (Supplementary material Table S1; Figures S8-S9) data to those of **1**, as revealed by comparison of their MS and NMR signals, indicating that **2** was an analogue of **1**. The differences existed in the ^1H and ^{13}C NMR data of the phenyl groups and methoxy groups between **2** and **1** (Supplementary material Table S1; Figures S8-S9). The ^1H NMR signals of **2** showed five phenyl proton peaks at δ_H 7.37 (m, H-2, 6), 7.56 (m, H-3, 5) and 7.36 (m, H-4), suggesting the presence of an one-substituted phenyl moiety in **2** (Supplementary material Table S1; Figure S8). Moreover, the ^{13}C NMR signals of phenyl carbons were changed from δ_C 129.3 (C-1), 152.2 (C-2), 112.7 (C-3), 123.3 (C-4), 150.7 (C-5), 111.2 (C-6) in **1** to δ_C 136.3 (C-1), 130.0 (C-2, 6), 128.8 (C-3, 5), 130.8 (C-4) in **2**, respectively (Supplementary material Table S1). Comparison of their ^1H and ^{13}C NMR data (Supplementary material Table S1) showed that two hydrogen atoms [δ_H 7.56 (1H, m), δ_C 128.8] and [δ_H 7.36 (1H, m), δ_C 130.8] were situated at C-3 and C-4 in **2** instead of two methoxy groups at C-3 and C-4 in **1**. In the HMBC spectrum of **2** (Supplementary material Figures S1 and S11), the correlations of H-7 [δ_H 7.54 d (15.8)] to C-1 (δ_C 131.3), C-2/6 (δ_C 130.0), C-8 (δ_C 121.8) and C-9 (δ_C 168.1), and H-8 [δ_H 6.65 d (15.8)] to C-1 (δ_C 136.3) and C-9 (δ_C 168.1) suggested that C-1 was linked to C-7, which proved the presence of a cinnamoyl moiety. In addition, the sugar moiety was determined as a D-glucose based on the ^1H-NMR and ^{13}C-NMR data (Supplementary material Table S1), acid hydrolysis and TLC and HPLC test with an authentic sample (see Experimental Section). The coupling constant of $J_{1'/2'} = 7.7$ Hz of the anomeric proton revealed that the glucoside unit was β-oriented. Therefore, compound **2** was determined to be (*E*)-cinnamoyl-ethyl-*O*-β-D-glucopyranoside and named streblusoside B (Figure 1).

All the isolates were subjected to an anti-inflammatory assay *in vitro* against RAW 264.7 cells (Supplementary material Table S2). Cell viability was measured by a MTT assay. At the effective concentration, all the compounds showed no obvious cytotoxicity to the RAW264.7 cells. The results showed that compounds **1**, **5** and **6** had moderate inhibitory activities with IC_{50} values ranging from 50.90 μM to 64.79 μM, and **1**, **5** and **6** were weaker than the positive control, dexamethasone, with an IC_{50} value of 44.99 μM. The other compounds showed no effects to the release of NO production.

3. Experimental

3.1. General

The optical rotations were obtained using an ADP440+ polarimeter. HRESIMS were carried out on a Waters/Micromass Q-TOF-Ultima (Waters, Milford, MA, USA) mass spectrometer. NMR spectra were performed on a Bruker Advance 400 MHz

spectrometer and 600 MHz spectrometer. Semi-preparative HPLC was performed using a Waters 2695 HPLC system, and samples were separated on a Waters SunFire-C_{18} column (5 μm, i.d. 10 mm $\times$ 250 mm). Analytical HPLC was conducted on a Waters 2695 instrument (Waters Corporation, Milford, Massachusetts MA, USA) using Waters 2424 ELSD as detector and D-glucose was analyzed as sugar standard (Sigma) by HPLC on a GH0525046C18AQ column (5 μm, 4.6 $\times$ 250 mm, Sil Green). Optical rotations were measured on an ADP440+ polarimeter (λ 589 nm, path length 1.0 cm).

3.2. Plant material

The leave of *S. ilicifolius* was collected in August 2018 from Lingshui, a city of Hainan province, China, and was authenticated by Prof. Guodong Li, College of Traditional Chinese Medicine, Yunnan University of Chinese Medicine. A voucher specimen has been deposited in the Natural Products Laboratory of Guangxi Normal University, registration No. ZFC201906025e.

3.3. Extraction and isolation

The air-dried leaves (10 kg) of *S. ilicifolius* were refluxed with 75% EtOH (2 h $\times$ 3) to generate a crude extract (0.75 kg). The crude extract was suspended in water and successively partitioned with different solvents into EtOAc (Fraction A, 143 g) and *n*-BuOH (Fraction B, 500 g) fractions. The *n*-BuOH extract was applied to a silica gel CC, eluting with a CH_2Cl_2-MeOH (100:0-0:100, v/v) to give five fractions (Fr.B.1-Fr.B.5). Fr. B.2 (16.7 g) was subjected to a RP-18 column using a step gradient of H_2O-MeOH (95:5 $\rightarrow$ 0:100, v/v) to afford eight fractions (Fr.B.2.1-Fr.B.2.8). Fr.B.2.1 (4.0 g) was chromatographed over Sephadex LH-20 column, eluting with CH_2Cl_2-MeOH (1:1) to give five fractions (Fr.B.2.1.1-Fr.B.2.1.5). Fr.B.2.1.4 (111 mg) was purified by semi-preparative HPLC (H_2O-MeOH, 93:7, v/v) to yield compound **3** (4.0 mg). Compounds **11** (5.1 mg) and **13** (1.1 mg) were achieved from Fr.B.2.1.2 by Sephadex LH-20 column and then purified by semi-preparative HPLC (H_2O-MeOH, 85:15, v/v). Fr.B.3 (93 g) was loaded onto a RP-C_{18} column with a gradient of H_2O-MeOH (95:5 $\rightarrow$ 0:100, v/v) to afford eight subfractions Fr.B.3.1-Fr.B.3.8. Fr.B.3.3 (7.97 g) was separated by the Sephadex LH-20 column eluted with CH_2Cl_2-MeOH (1:1) and the semi-preparative HPLC (H_2O-MeOH, 85:15, v/v) to afford compounds **4** (13.2 mg), **5** (7.2 mg), **6** (10.3 mg), **7** (6.7 mg), **8** (4.0 mg), **9** (4.2 mg), **10** (4.2 mg), and **12** (2.8 mg), respectively. Compounds **1** (2.1 mg) and **2** (38.1 mg) were obtained from Fr.B.3.4 by MCI column chromatography with a gradient of H_2O-MeOH (95:5 $\rightarrow$ 0:100, v/v), silica gel column chromatography using a step gradient of CH_2Cl_2-MeOH (100:0-0:100, v/v) and the semi-preparative HPLC (H_2O-MeOH, 85:15, v/v), respectively.

3.3.1. (E)-(3,4-dimethoxy)-cinnamoyl-ethyl-O-β-D-glucopyranoside (streblusoside A) (1)

Colorless amorphous powder, [α] $-$ 7.59 (c 0.12, MeOH); UV (MeOH): λ_{max} (nm) = 285 and 318; IR (KBr): ν_{max} = 3362, 1657, 1599, 1546, 1514, 1463, 1382, 1262, 1024 cm^{-1}. HRESIMS *m/z* 436.1582 $[M + Na]^+$, calcd for $C_{19}H_{27}NO_9Na$, 436.1584; ^1H NMR (600 MHz,

CD_3OD) δ 7.45 (d, $J = 15.7$ Hz, H-7), 7.15 (d, $J = 2.0$ Hz, H-2), 7.11 (dd, $J = 8.3$, 2.0 Hz, H-6), 6.94 (d, $J = 8.3$ Hz, H-5), 6.51 (d, $J = 15.7$ Hz, H-8), 4.28 (d, $J = 7.8$ Hz, H-1′), 3.95 (ddd, $J = 10.6$, 6.7, 3.9 Hz, H-11a), 3.84 (s, 3-OCH_3), 3.83 (s, 4-OCH_3), 3.85 (m, H-6′a), 3.73 (ddd, $J = 10.6$, 6.7, 3.7 Hz, H-11b), 3.65 (m, H-6′b), 3.55 (m, H-10a), 3.48 (m, H-10b), 3.35 (m, H-5′), 3.28 (m, H-4′), 3.25 (m, H-3′), 3.19 (m, H-2′); ^{13}C NMR (150 MHz, CD_3OD) δ 169.1 (C-9), 152.2 (C-4), 150.7 (C-3), 141.9 (C-7), 129.3 (C-1), 123.3 (C-6), 119.6 (C-8), 112.7 (C-5), 111.2 (C-2), 104.6 (C-1′), 78.0 (C-3′), 78.0 (C-5′), 75.1 (C-2′), 71.6 (C-4′), 69.8 (C-11), 62.7 (C-6′), 56.4 (3-OCH_3), 56.4 (4-OCH_3), 40.9 (C-10).

3.3.2. (E)-cinnamoyl-ethyl-O-β-D-glucopyranoside (streblusoside B) (2)

Colorless amorphous powder, [α] − 32.88 (c 0.04, MeOH); UV (MeOH): λ_{max} (nm) = 270; IR (KBr): ν_{max} = 3353, 1658, 1616, 1578, 1546, 1450, 1341, 1286, 1037 cm^{-1}. HRESIMS *m/z* 376.1369 $[M + Na]^+$, calcd for $C_{17}H_{23}NO_7Na$, 376.1372; ^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (m, H-3,5), 7.56 (m, H-7), 7.37 (m, H-2, 6), 7.36 (m, H-4), 6.65 (d, $J = 15.8$ Hz, H-8), 4.30 (d, $J = 7.7$ Hz, H-1′), 3.97 (ddd, $J = 10.5$, 6.4, 4.0 Hz, H-11a), 3.88 (dd, $J = 11.9$, 1.6 Hz, H-6′a), 3.74 (ddd, $J = 10.7$, 6.8, 3.9 Hz, H-11b), 3.67 (m, H-6′b), 3.58 (ddd, $J = 14.2$, 6.4, 3.9 Hz, H-10a), 3.50 (ddd, $J = 14.2$, 6.8, 4.0 Hz, H-10b), 3.34 (m, H-5′), 3.30 (m, H-4′), 3.28 (m, H-3′), 3.21 (m, H-2′); ^{13}C NMR (100 MHz, CD_3OD) δ 168.7 (C-9), 141.9 (C-7), 136.3 (C-1), 130.8 (C-4), 130.0 (C-2, 6), 128.8 (C-3,5), 121.8 (C-8), 104.6 (C-1′), 78.0 (C-3′), 78.0 (C-5′), 75.1 (C-2′), 71.6 (C-4′), 69.8 (C-11), 62.7 (C-6′), 40.9 (C-10).

3.4. Hydrolyses of compounds 1 and 2

Acidic hydrolyses of compounds **1** and **2** were carried out according to the method described previously (He et al. 2017). The sugar moieties were determined by comparing the R_f values of the products by TLC on silica gel with authentic samples as reference and EtOAc-pyridine-EtOH-H_2O (8:1:1:2) as mobile phase. The R_f values were 0.39 (D-glucose). The sugar moiety from **1** and **2** was identified as D-glucose based on the comparison of the retention time of an authentic sample (t_R: D-glucose 15.32 min) by HPLC on a GH0525046C18AQ column (5 μm, 4.6 × 250 mm, Sil Green) using formic acid: water = 0.5: 100 (v/v) as mobile phase (Figure S16 and S17).

3.5. Anti-inflammatory assay

The anti-inflammatory effects of compounds (**1**-**13**) were examined on the production of nitric oxide (NO) in LPS-stimulated cells using a method according to our previously described method (Zhang et al. 2018). The macrophage cell line was RAW 264.7, Cells (5×10^5 cells/mL) were grown in DMEM and cultured in 96-well plates at 37 °C. Cells were pretreated with or without test compounds for 2 h, then incubated with LPS for 24 h. NO production was determined by measuring the nitrite concentration using the Griess reagent. Results are expressed as the means ± SD, n = 3.

4. Conclusion

Two new amide glycosides, streblusoamides A (**1**) and B (**2**), together with 11 known compounds, were isolated from *S. ilicifolius*. Their structures were determined by extensive spectroscopic analyses and comparison with literature data. The results revealed that compounds **1**, **5** and **6** showed moderate inhibitory activities.

Supporting material

All spectral data associated with this research article are provided as supplementary file.

Disclosure statement

No potential conflict of interest was reported by the authors.

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