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Furofuran lignan glucosides from the leaves of *Vitex negundo* var. *cannabifolia*

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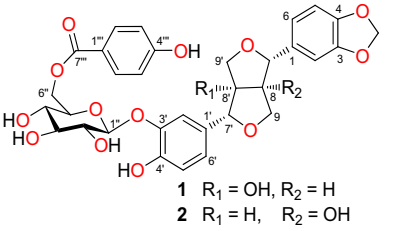
ABSTRACT

Two new furofuran lignan glucosides, cannabilignin (**1**) and isocannabilignin (**2**), together with four known compounds (**3**–**6**), were isolated from the leaves of *Vitex negundo* var. *cannabifolia*. The structures of the isolates were elucidated by analysis of spectroscopic data. Compound **3** exhibited weak inhibition of nitric oxide production in lipopolysaccharide-stimulated BV-2 microglial cells with IC_{50} value of 69.1 ± 5.8 μM.



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KEYWORDS
Verbenaceae; *Vitex negundo* var. *cannabifolia*; lignan glucoside

1. Introduction

Vitex negundo L. var. *cannabifolia*, is a shrub or small tree, mainly growing in Yangzi River basin of China (Pei & Chen 1982). Different parts of this plant are used in traditional Chinese medicine for the treatment of various diseases. Its fruits have been used to treat cough, asthma, analgesia, diarrhoea, and beriberi (The Editorial Committee of the Administration Bureau of Traditional Chinese Medicine 1999); the roots are utilised for the treatment of colds, headache, toothache, malaria, and rheumatic arthralgia, while the leaves are used to treat cough, asthma, and chronic bronchitis (The State Pharmacopoeia Commission of People's Republic of China's 2010). Phytochemical investigations indicated the presence of diterpenoids, irioid glycosides, lignans, phenolic glycosides, flavonoids, and triterpenoids in this plant (Taguchi 1976; Yamasaki et al. 2008; Ling et al. 2010; Chen et al. 2012; Li et al. 2014,

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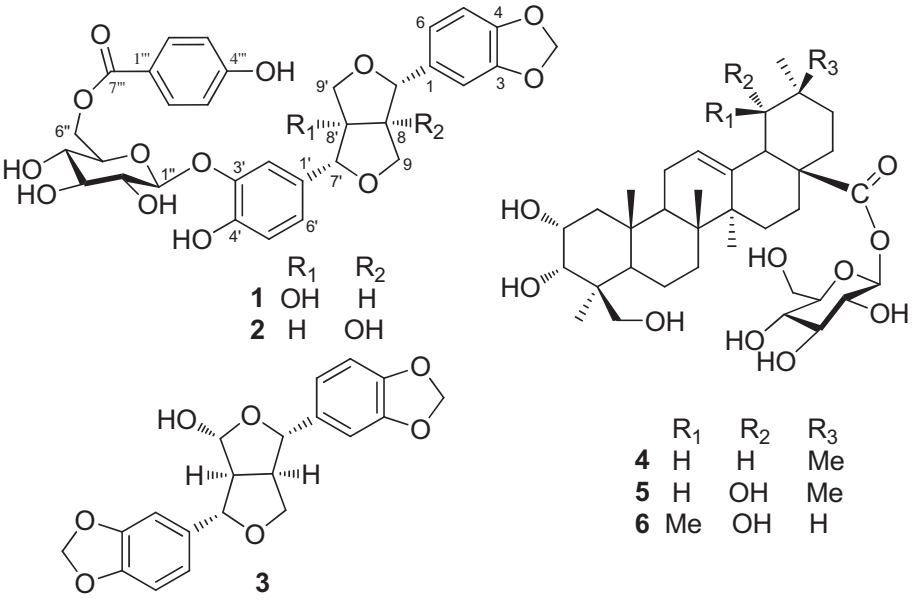

Figure 1. Structures of compounds **1**–**6**.

2015; Lou et al. 2014; Fang et al. 2016). Our group recently reported the isolation of six new and eight known polyoxygenated triterpenoids, which showed anti-inflammatory activity (Li et al. 2014). In our ongoing investigation of anti-inflammatory agents from *V. negundo* var. *cannabifolia*, two new furofuran lignan glucosides, cannabilignin (**1**) and isocannabilignin (**2**), along with four known compounds (**3**–**6**) (Figure 1) were isolated from the 95% EtOH extract of the leaves of *V. negundo* var. *cannabifolia*. Herein, the isolation and structural elucidation of the isolates as well as their inhibitory effects on LPS-stimulated nitric oxide (NO) production in BV-2 microglial cells are described.

2. Results and discussion

Cannabilignin (**1**) was obtained as a colourless gum, $[\alpha]_D^{21}$ –34 (*c* 0.1, MeOH). Its molecular formula was determined as $C_{32}H_{32}O_{14}$ by the ^{13}C NMR data and a deprotonated ion at *m/z* 639.1744 $[M - H]^-$ in the negative-ion HR-ESI-MS, indicating 17 indices of hydrogen deficiency. The IR spectrum indicated the presence of hydroxy (3427 cm^{-1}) and ester carbonyl (1695 cm^{-1}) functionalities. The ^1H NMR spectrum of **1** exhibited proton signals of two sets of ABX coupling systems [δ_H 6.92 (1H, d, *J* = 2.0 Hz, H-2), 6.87 (1H, dd, *J* = 8.0, 2.0 Hz, H-6), 6.78 (1H, d, *J* = 8.0 Hz, H-5); 7.09 (1H, d, *J* = 1.5 Hz, H-2′), 7.01 (1H, dd, *J* = 8.0, 1.5 Hz, H-6′), 6.83 (1H, d, *J* = 8.0 Hz, H-5′)], one methylenedioxy group [δ_H 5.93 (2H, s, $-OCH_2O-$)], two oxygenated methylenes [δ_H 4.35 (1H, dd, *J* = 8.5, 8.5 Hz, H-9*α*), 3.66 (1H, m, H-9*β*); 3.87 (1H, d, *J* = 9.5 Hz, H-9′*β*), 3.79 (1H, d, *J* = 9.5 Hz, H-9′*α*)], and two oxygenated methines [δ_H 4.67 (1H, d, *J* = 6.0 Hz, H-7), 4.44 (1H, br s, H-7′)]. These data together with the characteristic chemical shifts of 18 carbon signals at δ_C 149.4, 148.7, 148.3, 146.2, 136.3, 129.5, 124.3, 120.9, 118.2, 116.8, 109.0, 107.8, 92.8, 88.6, 87.6, 76.6, 71.9, 62.7 in the ^{13}C NMR spectrum indicated that **1** was an 8′-hydroxyfurofuran lignan derivative (Gu et al. 2004). In addition, the resonances attributable to a glucosyl moiety

[δ_C 104.3 (C-1″), 77.4 (C-3″), 76.0 (C-5″), 74.8 (C-2″), 71.7 (C-4″), 64.9 (C-6″); δ_H 4.81 (1H, d, J = 7.5 Hz, H-1″), 4.75 (1H, dd, J = 12.0, 2.0 Hz, H-6″a), 4.39 (1H, dd, J = 12.0, 7.0 Hz, H-6″b), 3.74 (1H, m, H-5″), 3.53 (1H, m, H-2″), 3.51 (1H, m, H-3″), 3.46 (1H, m, H-4″)] as well as a *p*-hydroxybenzoyl moiety [δ_C 167.9 (C-7‴), 163.6 (C-4‴), 133.0 (C-2‴, 6‴), 122.2 (C-1‴), 116.4 (C-3‴, 5‴); δ_H 7.91 (2H, d, J = 9.0 Hz, H-2‴, 6‴), 6.85 (2H, d, J = 9.0 Hz, H-3‴, 5‴)] were observed in the NMR spectra. The ^{1}H and ^{13}C NMR data of **1** were closely related to those of (1*R*,2*S*,5*R*,6*R*)-1-hydroxy-2-(3,4-dihydroxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0] octane (Luo et al. 2014), except for the presence of an additional 6-*O*-(*p*-hydroxybenzoyl)-glucosyl unit at C-3′ in **1**. This deduction was supported by the HMBC correlations from the anomeric proton (δ_H 4.81) to C-3′ (δ_C 146.2) and from H_2-6″ (δ_H 4.75, 4.39) to the carbonyl carbon (δ_C 167.9). Other HMBC correlations permitted further confirmation of the planar molecular structure of **1** (Figure S19, supplementary material). In the NOESY spectrum, NOE correlations of H-7′/H-9′β, H-7′/H-9β, H-7/H-9′β, and H-7/H-9β indicated that H-7 and H-7′ are β-orientated. In turn, NOEs of H-8/H-9α, H-8/H-2, and H-8/H-6 suggested the α-orientation of H-8. Compound **1** was hydrolysed with 2.0 M trifluoroacetic acid (CF_3COOH) to produce D-glucose, which was identified by HPLC analysis using an optical rotation detector (Yoshikawa et al. 2006). Moreover, the β-configuration was prompted by the large coupling constant of the anomeric proton (δ_H 4.81, d, J = 7.5 Hz). The ECD spectrum of **1** showed negative Cotton effects at 223 and 273 nm, which indicated that the absolute configuration of **1** was 7*S*,7′*R*,8*R*,8′*S* (Gu et al. 2004). Therefore, the structure of cannabilignin (**1**) was established as shown.

Compound **2** (isocannabilignin) was obtained as a colourless gum, $[\alpha]_D^{21}$ −18 (*c* 0.1, MeOH). Its IR spectrum exhibited absorption bands for hydroxy (3431 cm^{-1}) and ester carbonyl (1699 cm^{-1}) groups. The molecular formula $C_{32}H_{32}O_{14}$ of **2** was determined to be the same as that of **1** from the ^{13}C NMR and negative-ion HR-ESI-MS data (*m/z* 639.1725 [M − H]$^-$). Analysis of the ^{1}H and ^{13}C NMR spectroscopic data of **2** showed a close structural resemblance to **1**. The major difference was that a hydroxy group was located at C-8 in **2** rather than C-8′ in **1**. This assignment was supported by the HMBC correlations from H-8′ to C-1′ and C-8; from H-2 to C-3, C-4, C-6, and C-7; from H-6 to C-2, C-4, C-5, and C-7; from methylenedioxy protons to C-3 and C-4; from H-2′ to C-3′, C-4′, C-6′, and C-7′; from H-6′ to C-2′, C-4′, C-5′, and C-7′; from H-1″ to C-3′; from H_2-6″ to C-7‴; and from H-2‴ and H-6‴ to C-7‴. In the NOESY spectrum, NOE correlations of H-7′/H-9′β, H-7′/H-9β, H-7/H-9′β, H-7/H-9β, and H-8′/H-9′α, H-8′/H-2′, and H-8′/H-6′ suggested the β-orientations of H-7 and H-7′, as well as α-orientation of H-8′. In the ECD spectrum, negative Cotton effects at 232 and 279 nm indicated that the absolute configuration of **2** was 7*R*,7′*S*,8*S*,8′*R* (Gu et al. 2004).

The remaining four known compounds were identified as 9*R*-hydroxy-*d*-sesamin (**3**) (Ye et al. 2002), vulgarsaponin A (**4**) (Xiao et al. 2016), 2α,3α,19α,24-tetrahydroxyolea-12-en-28-oic acid β-D-glucopyranosyl ester (**5**) (Ono et al. 2009), and 2α,3α,19α,24 -tetrahydroxy-urs-12-en-28-oic acid β-D-glucopyranosyl ester (**6**) (Ono et al. 2009), by comparing their spectroscopic and physical data with those reported in literature.

Compounds **1**–**6** were evaluated for their inhibitory effects on the NO production in LPS-activated BV-2 microglial cells using the Griess assay (Li et al. 2012; Huang et al. 2015). Indomethacin (IC_{50} = 15.4 ± 1.3 μM) was used as a positive control. Only compound **3** showed weak inhibition against NO production with IC_{50} value of 69.1 ± 5.8 μM.

3. Experimental

3.1. General experimental procedures

Optical rotations were obtained on a Rudolph Autopol IV automatic polarimeter. IR spectra were recorded on a Thermo Nicolet Nexus 470 FT-IR spectrophotometer with KBr pellets. UV spectra were measured on a UV-2401PC spectrometer. ECD spectrum was acquired on a Jasco J-810 CD spectrophotometer. The HR-ESI-MS data were recorded on an LCMS-IT-TOF system, fitted with a Prominence UFLC system and an ESI interface (Shimadzu, Kyoto, Japan). The NMR spectra were recorded on a Varian INOVA-500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Silica gel (200–300 mesh, Qingdao Marine Chemical Inc, Qingdao, China), LiChroprep RP-C_{18} gel (40–63 μm, Merck, Germany), and Sephadex LH-20 (Pharmacia) were used for open column chromatography. Semi-preparative HPLC was performed on a Waters 2535 pump system (Waters Corporation, Milford, MA, USA), equipped with a 2998 photodiode array detector monitoring at 198 and 254 nm. A semi-preparative RP-HPLC column (Grace Prevail C_{18}, 250 × 10 mm, 5 μm) was employed for the isolation. TLC was performed using GF_{254} plates, sprayed with vanillin reagent, prepared by mixing 1 g of vanillin with 100 mL of concentrated H_2SO_4, and heated until optimal colour development. All purified compounds submitted for bioassay were at least 95% pure as judged by HPLC and supported by ^{1}H NMR analysis.

3.2. Plant material

The leaves of *V. negundo* var. *cannabifolia* were collected in Xinyang, Henan Province, People's Republic of China, in September 2012, and plant authentication was performed by Prof. Peng-Fei Tu. A voucher specimen (JLI-VNC-201209) is deposited in the Modern Research Center for Traditional Chinese Medicine, Beijing University of Chinese Medicine.

3.3. Extraction and isolation

The leaves of *V. negundo* var. *cannabifolia* (10 kg) were refluxed with 95% EtOH three times (each 100 L, 2 h). After removal of the solvent under reduced pressure, the residue (3.6 kg) was suspended in H_2O (5 L) and partitioned with petroleum ether (4 × 5 L), EtOAc (4 × 5 L), and *n*-BuOH (4 × 5 L), successively. The EtOAc extract (290 g) was subjected to silica gel column chromatography (CC, 10 × 80 cm) eluting with a stepwise gradient of CH_2Cl_2–MeOH (from 20:1 to 1:1) to afford fractions A–L. Fraction B (4.7 g) was subjected to silica gel CC (3 × 47 cm) using petroleum ether–EtOAc (from 7:1 to 1:1) as the mobile phase to give 12 subfractions, B1–B12. Subfraction B2 (675 mg) was purified on a Sephadex LH-20 CC (2 × 110 cm) eluting with CH_2Cl_2–MeOH (1:1) to afford **3** [68.4 mg; TLC, *Rf* = 0.57 (petroleum ether–EtOAc, 2:1)]. Fraction H (4.3 g) was subjected to silica gel CC (3 × 45 cm) to give nine subfractions, H1–H9. Fraction H6 (900 mg) was chromatographed on Sephadex LH-20 CC (2.5 × 110 cm) eluting with CH_2Cl_2–MeOH (1:1) to yield 12 portions (H6a-H6l). H6f (50 mg) was purified by semi-preparative RP-C_{18} HPLC (25% CH_3CN, 3.0 mL/min) to produce **2** (5.2 mg, t_R = 24.0 min) and **1** (5.5 mg, t_R = 26.5 min). Fraction *J* (3.9 g) was chromatographed over silica gel CC (3 × 43 cm) with gradient elution of CH_2Cl_2–MeOH (from 20:1 to 0:1) to produce subfractions J1–J9. Fraction J7 (579 mg) was subjected to Sephadex LH-20 CC (2 × 110 cm) eluting with MeOH to yield J7a–J7h. Compound **4** [5.5 mg; TLC, *Rf* = 0.67 (CH_2Cl_2–MeOH,

4:1)] was obtained from subfraction J7a via ODS CC (1.5 × 19 cm) with gradient elution of MeOH–H_2O (from 55 to 100%). Subfraction J7a was purified by semi-preparative RP-C_{18} HPLC (24% CH_3CN, 3.0 mL/min) to give **5** (5.5 mg, t_R = 13.8 min) and **6** (6.3 mg, t_R = 14.5 min).

Cannabilignin (**1**): colourless gum; $[\alpha]_D^{21}$ −34 (*c* 0.1, MeOH); HR-ESI-MS: *m/z* 639.1744 $[M - H]^-$ (Calcd for $C_{32}H_{31}O_{14}$, 639.1719). UV λ_{max}^{MeOH} (log ε) 207 (2.50), 230 (2.09), 259 (2.10) nm; ECD (*c* 0.781 mM, MeOH), λ_{max} ($\Delta\varepsilon$) 223 (−0.46), 273 (−0.77) nm; IR (KBr) ν_{max}: 3427, 1695, 1656, 1634, 1609, 1515, 1444, 1384, 1278, 1167, 1065 cm^{-1}. ^1H NMR (500 MHz, methanol-d_4): δ 7.91 (2H, d, *J* = 9.0 Hz, H-2‴, H-6‴), 7.09 (1H, d, *J* = 1.5 Hz, H-2′), 7.01 (1H, dd, *J* = 8.0, 1.5 Hz, H-6′), 6.92 (1H, d, *J* = 2.0 Hz, H-2), 6.87 (1H, dd *J* = 8.0, 2.0 Hz, H-6), 6.85 (1H, d, *J* = 9.0 Hz, H-3‴, H-5‴), 6.83 (1H, d, *J* = 8.0 Hz, H-5′), 6.78 (1H, d, *J* = 8.0 Hz, H-5), 5.93 (2H, s, –OCH_2O–), 4.81 (1H, d, *J* = 7.5 Hz, H-1″), 4.75 (1H, dd, *J* = 12.0, 2.0 Hz, H-6″a), 4.67 (1H, d, *J* = 6.0 Hz, H-7), 4.44 (1H, br s, H-7′), 4.39 (1H, dd, *J* = 12.0, 7.0 Hz, H-6″b), 4.35 (1H, dd, *J* = 8.5, 8.5 Hz, H-9*α*), 3.87 (1H, d, *J* = 9.5 Hz, H-9′*β*), 3.79 (1H, d, *J* = 9.5 Hz, H-9′*α*), 3.74 (1H, m, H-5″), 3.66 (1H, m, H-9*β*), 3.53 (1H, m, H-2″), 3.51 (1H, m, H-3″), 3.46 (1H, m, H-4″), 2.90 (1H, m, H-8); ^{13}C NMR (125 MHz, methanol-d_4): δ 167.9 (C-7‴), 163.6 (C-4‴), 149.4 (C-4), 148.7 (C-3), 148.3 (C-4′), 146.2 (C-3′), 136.3 (C-1), 133.0 (C-2‴, C-6‴), 129.5 (C-1′), 124.3 (C-6′), 122.2 (C-1‴), 120.9 (C-6), 118.2 (C-2′), 116.8 (C-5′), 116.4 (C-3‴, C-5‴), 109.0 (C-5), 107.8 (C-2), 104.3 (C-1″), 102.4 (–OCH_2O–), 92.8 (C-8′), 88.6 (C-7′), 87.6 (C-7), 77.4 (C-3″), 76.6 (C-9′), 76.0 (C-5″), 74.8 (C-2″), 71.9 (C-9), 71.7 (C-4″), 64.9 (C-6″), 62.7 (C-8).

Isocannabilignin (**2**): colourless gum; $[\alpha]_D^{21}$ −18 (*c* 0.1, MeOH); HR-ESI-MS: *m/z* 639.1725 $[M - H]^-$ (Calcd for $C_{32}H_{31}O_{14}$, 639.1719). UV λ_{max}^{MeOH} (log ε) 206 (2.50), 232 (2.00), 259 (2.03) nm; ECD (*c* 1.563 mM, MeOH), λ_{max} ($\Delta\varepsilon$) 232 (−1.12), 279 (−1.55) nm; IR (KBr) ν_{max}: 3431, 1699, 1653, 1634, 1609, 1515, 1446, 1385, 1280, 1168, 1064 cm^{-1}. ^1H NMR (500 MHz, methanol-d_4): δ 7.91 (2H, d, *J* = 8.5 Hz, H-2‴, H-6‴), 7.17 (1H, d, *J* = 2.0 Hz, H-2′), 7.01 (1H, dd, *J* = 8.5, 2.0 Hz, H-6′), 6.93 (1H, d, *J* = 1.5 Hz, H-2), 6.85 (1H, overlapped, H-5′), 6.85 (1H, d, *J* = 8.5 Hz, H-3‴, H-5‴), 6.84 (1H, overlapped, H-6), 6.78 (1H, d, *J* = 7.5 Hz, H-5), 5.92 (2H, s, –OCH_2O–), 4.81 (1H, overlapped, H-1″), 4.74 (1H, dd, *J* = 12.0, 1.5 Hz, H-6″a), 4.59 (1H, d, *J* = 5.0 Hz, H-7′), 4.55 (1H, s, H-7), 4.39 (1H, dd, *J* = 12.0, 7.0 Hz, H-6″b), 4.33 (1H, dd, *J* = 9.0, 9.0 Hz, H-9′*α*), 3.91 (1H, d, *J* = 9.5 Hz, H-9*β*), 3.77 (1H, d, *J* = 9.5 Hz, H-9*α*), 3.75 (1H, m, H-5″), 3.58 (1H, m, H-9′*β*), 3.52 (1H, m, H-2″), 3.49 (1H, m, H-3″), 3.47 (1H, m, H-4″), 2.93 (1H, m, H-8′); ^{13}C NMR (125 MHz, methanol-d_4): δ 168.0 (C-7‴), 163.6 (C-4‴), 148.8 (C-3), 148.7 (C-4), 148.1 (C-4′), 146.5 (C-3′), 134.1 (C-1′), 133.0 (C-2‴, C-6‴), 131.7 (C-1), 123.0 (C-6′), 122.2 (C-6), 122.0 (C-1‴), 117.3 (C-5′), 117.2 (C-2′), 116.3 (C-3‴, C-5‴), 109.4 (C-2), 108.6 (C-5), 104.2 (C-1″), 102.2 (–OCH_2O–), 92.8 (C-8), 89.1 (C-7), 87.3 (C-7′), 77.4 (C-3″), 76.0 (C-5″), 75.9 (C-9), 74.8 (C-2″), 72.1 (C-9′), 71.8 (C-4″), 64.9 (C-6″), 62.4 (C-8′).

3.4. Hydrolysis of compounds 1 and 2

Each compound (2.0 mg) was dissolved in 2.0 M trifluoroacetic acid (2.0 mL) and heated at 90 °C for 2 h in a sealed tube. After cooling, the reaction mixture was extracted with EtOAc. After repeated evaporation to dryness of the aqueous layer with MeOH until neutral, the residue was dissolved in water (0.5 mL) and subjected to HPLC analysis under the following conditions, respectively: HPLC column, Hypersil-APS2 (250 × 4.6 mm, 5 µm); detection, CHIRALYSER–MP optical rotation detector; mobile phase, CH_3CN–H_2O (85:15, v/v); flow rate 1.0 mL/min. Identification of D-glucose was carried out by comparison of its retention time and optical rotation with those of authentic D-glucose (t_R = 13.4 min, positive optical rotation).

3.5. Cell culture and measurement of NO production

BV-2 microglial cells were purchased from Peking Union Medical College (PUMC) Cell Bank (Beijing, People's Republic of China). Cell maintenance, experimental procedures, and data determination for the inhibition of NO production are the same as previously described (Li et al. 2012; Huang et al. 2015). Indomethacin (IC_{50} = 15.4 ± 1.3 μM) was used as a positive control.

4. Conclusion

Two new furofuran lignan glucosides, cannabilignin (**1**) and isocannabilignin (**2**), together with four known compounds were obtained from the leaves of *V. negundo* var. *cannabifolia*. Compound **4** was obtained from this plant for the first time, whereas compounds **5** and **6** were firstly isolated from the *Vitex* genus. Compound **3** showed weak inhibition against NO production in LPS-stimulated BV-2 microglial cells with IC_{50} value of 69.1 ± 5.8 μM.

Supplementary material

Supplementary material relating to this article is available online, alongside Figures S1–S20.

Disclosure statement

No potential conflict of interest was reported by the authors.

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