Bioorganic & Medicinal Chemistry Letters 26 (2016) 730–733

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Bioactive lignan derivatives from the stems of *Firmiana simplex*

Kyeong Wan Woo [a], Won Se Suh [a], Lalita Subedi [b], Sun Yeou Kim [b,c], Aejung Kim [d], Kang Ro Lee [a,*]

[a] Natural Products Laboratory, School of Pharmacy, Sungkyunkwan University, 2066 Seobu-Ro, Jangan-ku, Suwon, Gyeonggi-do, Republic of Korea
[b] College of Pharmacy, Gachon University, #191 Hambakmoe-ro, Yeonsu-gu, Incheon 406-799, Republic of Korea
[c] Gachon Medical Research Institute, Gil Medical Center, Incheon, Republic of Korea
[d] The Graduate School of Alternative Medicine, Kyonggi University, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 25 September 2015
Revised 28 December 2015
Accepted 5 January 2016
Available online 6 January 2016

Keywords:
Firmiana simplex
Sterculiaceae
Lignan
Anti-neuroinflammatory effect

ABSTRACT

The $CHCl_3$ soluble fraction of the 80% MeOH extract of the stems of *Firmiana simplex* strongly inhibited nitric oxide production in lipopolysaccharide-activated BV-2 cells. A bioactivity-guided column chromatographic separation yielded two new lignans, firmianols A and B (**1**–**2**) together with seventeen known lignans (**3**–**19**). The structural elucidation of the new compounds was determined by spectroscopic methods, including 1D, 2D NMR and HR-FAB-MS. All isolated lignans were evaluated for their antineuroinflammatory effects on nitric oxide (NO) production in lipopolysaccharides (LPS)-activated murine microglia BV2 cells. Among the isolated, compounds **14** and **15** showed potent inhibitory activity against NO production (IC_{50} 1.05 and 0.929 μM, respectively) without cell toxicity in murine microglia BV-2 cells. Compounds **11**–**13** and **17** also exhibited strong inhibitory effects on NO production, with IC_{50} values ranging from 7.07 to 15.28 μM.

Neuroinflammation plays a central role in most neurodegenerative diseases such as Parkinson's disease, Alzheimer disease, multiple sclerosis, and stroke, and is mediated by microglial activation.[1] Microglia cells exist in the CNS and are the major targets of microgliosis following neurodegeneration.[2] Following microglial activation due to injury in the brain, excessive NO is produced, which initiates a cascade of neuroinflammatory responses.[3] Therefore, discovering neuroprotective drugs that inhibit NO production via activated microglia is crucial in treating neurodegenerative diseases.

In our continuing search for neuroinflammatory components from Korean medicinal plants,[4–8] the $CHCl_3$-soluble fraction of *Firmiana simplex* was found to strongly inhibit nitric oxide production in lipopolysaccharide-activated BV-2 cells.

F. simplex (Sterculiaceae) is a deciduous tree that is distributed in Korea and China.[9] It is called a Chinese parasol tree, which is characterized by large stems and leaves, and is popular as an ornamental plant.[10] *F. simplex* seeds have been used to treat diarrhea and stomach disorders.[11] Recently, Our earlier phytochemical investigation on *F. simplex* resulted in the isolation of cytotoxic triterpenes.[12] Using bioactivity-guided isolation techniques, nineteen lignan derivatives including two new lignans (**1**–**2**) were further isolated from the most active $CHCl_3$-soluble fraction (Fig. 1). In the present study, we report the isolation and structural elucidation of compounds **1**–**19** and their NO production activity.

Compound (**1**) was obtained as a colorless gum. The molecular formula of **1** was determined to be $C_{19}H_{18}O_6$ by the negative mode HR-FABMS data at *m*/*z* 341.1020 $[M-H]^-$ (calcd for $C_{19}H_{17}O_6$, 341.1020). The ^1H NMR spectrum (Table 1) of **1** showed signals of 1,3,4-trisubstitued-aromatic ring protons at δ_H 6.99 (1H, d, *J* = 1.5 Hz, H-2), 6.92 (1H, d, *J* = 7.5 Hz, H-6), and 6.81 (1H, dd, *J* = 7.5, 1.5 Hz, H-5), of 1,4-disubstitued-aromatic protons at δ_H 7.27 (2H, d, *J* = 9.0 Hz, H-2′, 6′) and 6.80 (2H, d, *J* = 9.0 Hz, H-3′, 5′) of dioxymethylene at 5.95 (2H, s, —OCH_2O—), of two oxygenated methines at 4.86 (1H, d, *J* = 5.5 Hz, H-7) and 4.69 (1H, s, H-7′), of four oxygenated methylenes at δ_H 4.46 (1H, t, *J* = 9.0 Hz, H-9a), 4.03 (1H, d, *J* = 9.0 Hz, H-9′a), 3.87 (1H, d, *J* = 9.0 Hz, H-9′b), and 3.78 (1H, dd, *J* = 8.5, 5.5 Hz, H-9b), of one methine proton at 3.00 (1H, dt, *J* = 7.5, 3.5 Hz, H-8).

The ^{13}C NMR spectrum (Table 2) revealed resonances for 19 carbons attributable to twelve aromatic carbons, one dioxymethylene carbon (δ_C 102.4), five oxygenated carbons (δ_C 92.7, 89.2, 87.5, 76.3, and 72.1), and one methine carbons (δ_C 62.6). The ^1H and ^{13}C NMR spectra of **1** were very close to those of (+)-beechenol, which was isolated from *Zanthoxylum beecheyanum*,[13] except that the proton and carbon signal of methine (H-8′) in (+)-beechenol were absent, and instead, the resonances of oxygenated carbon at δ_C 92.7 was present in **1**. The gross planar structure of **1** was confirmed by analysis of 2D NMR experiments (^1H–^1H COSY, HMQC, and HMBC) (Fig. 2).

* Corresponding author. Tel.: +82 31 290 7710; fax: +82 31 290 7730.
E-mail address: krlee@skku.edu (K.R. Lee).

http://dx.doi.org/10.1016/j.bmcl.2016.01.008
0960-894X/

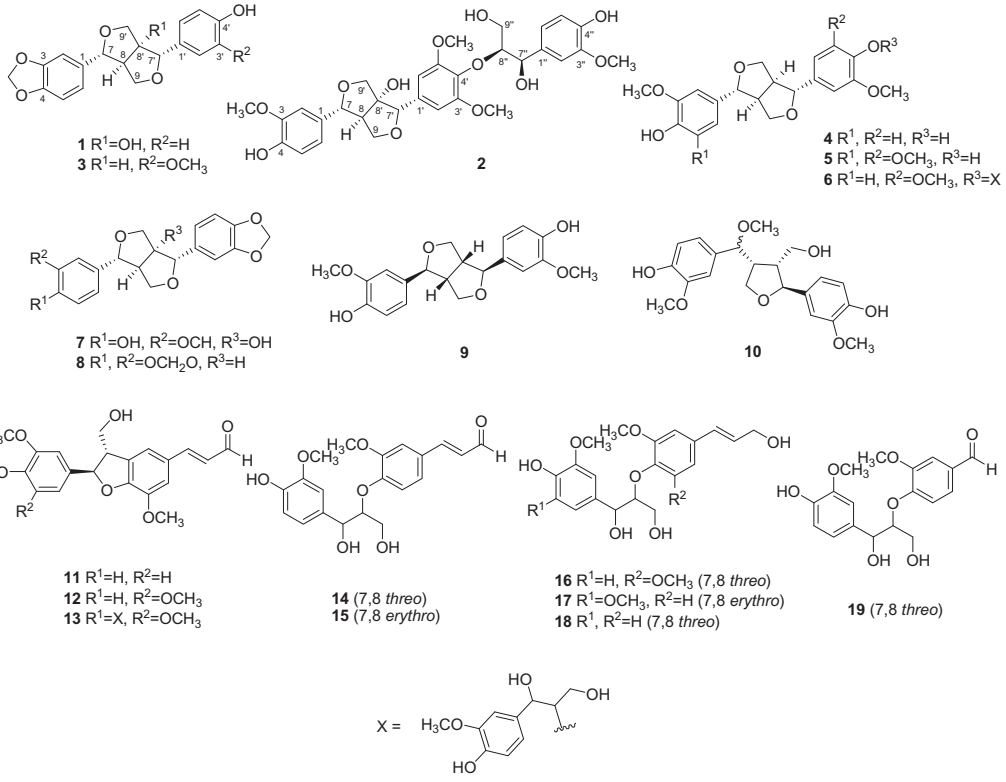

Figure 1. Chemical structures of compounds **1**–**19** from *F. simplex*.

Table 1
[1]H NMR data of compounds **1** and **2** (CD_3OD, 700 MHz, δ in ppm, J in Hz)[a]

Position	1		2	
	δ_H	HMBC	δ_H	HMBC
1	—		—	
2	6.99 (d, 2.0)	4, 6, 7	7.08 (d, 2.0)	4, 6, 7
3	—		—	
4	—		—	
5	6.81 (d, 9.0)	1, 3	6.80 (d, 8.0)	1, 3
6	6.92 (dd, 8.5, 1.5)	2, 3, 7	6.90 (dd, 8.0, 2.0)	2, 3, 7
7	4.86 (d, 5.5)	2, 6, 8, 9, 8′, 9′	4.8 (overlap)	2, 6, 8, 9, 8′, 9′
8	3.00 dt (7.5, 5.5)	1, 8′	3.07 m	1, 8′
9a	4.46 (t, 9.0)	7, 8, 7′, 8′	4.51 (t, 9.0)	7, 8, 7′, 8′
9b	3.78 (dd, 8.5, 5.5)		3.81 (dd, 9.0, 6.0)	
1′	—		—	
2′	7.27 (d, 9.0)	2′, 3′, 4′, 7′	6.80 s	4′, 6′, 7′
3′	6.80 (d, 9.0)	1′, 3′, 4′	—	
4′	—		—	
5′	6.80 (d, 9.0)	1′, 3′, 4′	—	
6′	7.27 (d, 9.0)	2′, 3′, 4′, 7′	6.80 s	2′, 4′, 7′
7′	4.69 s	8, 9, 2′, 8′, 9′	4.75 s	9, 1′, 2′, 8′, 9′
8′	—		—	
9′a	4.03 (d, 9.0)	7, 8, 7′, 8′	4.14 (d, 9.0)	7, 8, 7′, 8′
9′b	3.87 (d, 9.0)		3.91 (d, 9.0)	
1″			—	
2″			7.03 br s	4″, 6″, 7″
3″			—	
4″			—	
5″			6.77 (d, 8.0)	1″, 3″
6″			6.82 (overlap)	2″, 4″, 7″
7″			4.97 (d, 5.0)	1″, 2″, 6″, 8″, 9″
8″			4.24 m	4′
9″a			3.90 m	7″
9″b			3.58 (dd, 12.0, 3.5)	
3-OCH_3			3.88 s	3
3′-OCH_3			3.87 s	3′
3″-OCH_3			3.86 s	3″
-OCH_2O-	5.95 s	3	—	

[a] Assignments were based on HMQC, and HMBC experiments.

The configuration of **1** was determined on the basis of the NOESY correlations [H-7/H-9b, H-8/H-9a, H-9b/H-7′, H-7′/H-9′a] (Fig. 3) and positive optical rotation value ($[\alpha]_D^{25}$ +18.0, CH_3OH) in comparison to (+)-syringaresinol.[14] Thus, the structure of **1** was established to be (+)-8′-hydroxybeechenol, and was named firmianol A.

Compound (**2**) was obtained as a colorless gum. The molecular formula of **2** was determined to be $C_{31}H_{35}O_{12}$ by the positive mode HR-FABMS data at m/z 623.2100 $[M+Na]^+$ (calcd for $C_{31}H_{35}O_{12}Na$, 623.2099). Its NMR spectra were analogous to those of (+)-1-hydroxypinoresinol, which was isolated from *Saussurea pulchella*,[15]

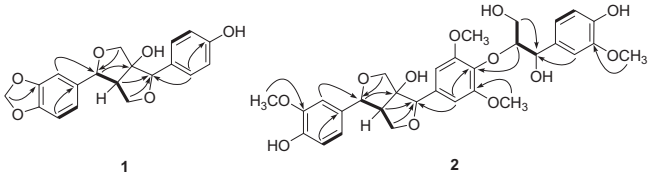

Figure 2. Key COSY (bold line) and HMBC (arrow) correlations of **1** and **2**.