Bioorganic & Medicinal Chemistry Letters 26 (2016) 3342–3345

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

# Two pairs of farnesyl phenolic enantiomers as natural nitric oxide inhibitors from *Ganoderma sinense*

Meng Wang [a], Fei Wang [a], Feng Xu [a], Li-Qin Ding [b], Qian Zhang [c], Hui-Xiang Li [c], Feng Zhao [c], Li-Qing Wang [a], Li-Han Zhu [a], Li-Xia Chen [a,*], Feng Qiu [a,b,*]

[a] *Department of Natural Products Chemistry, School of Traditional Chinese Materia Medica, Key Laboratory of Structure-Based Drug Design & Discovery, Ministry of Education, Shenyang Pharmaceutical University, Shenyang 110016, People's Republic of China*
[b] *School of Chinese Materia Medica and Tianjin State Key Laboratory of Modern Chinese Medicine, Tianjin University of Traditional Chinese Medicine, 312 Anshanxi Road, Nankai District, Tianjin 300193, People's Republic of China*
[c] *School of Pharmacy, Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Yantai University, Yantai 264005, People's Republic of China*

ARTICLE INFO

*Article history:*
Received 8 March 2016
Revised 2 May 2016
Accepted 12 May 2016
Available online 12 May 2016

*Keywords:*
*Ganoderma sinense*
Farnesyl phenol
NO inhibitory activity

ABSTRACT

Four new farnesyl phenolic compounds, ganosinensols A–D (**1**–**4**) were isolated from the 95% EtOH extract of the fruiting bodies of *Ganoderma sinense*. Two pairs of enantiomers, **1**/**2**, and **3**/**4** were isolated by HPLC using a Daicel Chiralpak IE column. Their structures were elucidated from extensive spectroscopic analyses and comparison with literature data. The absolute configurations of **1**–**4** were assigned by ECD spectra. All of these isolated compounds showed potent inhibitory activity against LPS-induced nitric oxide production in RAW 264.7 macrophages, with $IC_{50}$ values from 1.15 to 2.26 μM.

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Lingzhi (*Ganoderma*) has been used as a folk medicine for thousands of years and is a well-known traditional medicine in China. *Ganoderma* contains more than 100 species, with wide distribution in China. *Ganoderma sinense* is recorded in Chinese pharmacopoeia together with *Ganoderma lucidum* for the treatment of asthma and hypertension.[1] Recent studies showed that the mushrooms of *Ganoderma* possess anti-inflammatory,[2,3] immune regulation,[4,5] hepatoprotective,[6] antitumor[7–9] and other pharmacological effects. Previous phytochemical investigations have shown that *Ganoderma* contains a variety of chemical components, including polysaccharides, triterpenes, sterols, and so on.[10]

Nitric oxide (NO) is produced from L-arginine by nitric oxide synthase (NOS) and plays an important role in the inflammatory process. The overproduction of NO can cause various inflammatory diseases, such as arthritis, bowel diseases, and allergic rhinitis.[11–13] Therefore, regulation of the NO production is significant for the cure of inflammation. It is reported that the extract of the mushrooms of *Ganoderma* showed remarkable anti-inflammatory activity.[2,3,14] In our continuous program to find bioactive compounds with potential inhibitory activity against NO production from the natural sources,[15,16] the EtOAc fraction from EtOH extract of *G. sinense* was found to show inhibitory effect. The chemical constituents from EtOAc fraction of *G. sinense* were investigated. Four new farnesyl phenolic compounds (**1**–**4**) were isolated and their inhibitory effects on NO production in lipopolysaccharide-stimulated RAW 264.7 macrophages were evaluated. Herein, structural elucidation, chiral HPLC separation, absolute configuration assignments, and NO inhibitory activity of these compounds are described. Furthermore, a possible biogenetic pathway for compounds **1** and **2** is proposed (Scheme 1).

The fruiting bodies of *G. sinense*[17] were cut into pieces and extracted with 95% EtOH, and the extract was successively partitioned with cyclohexane, EtOAc, and *n*-BuOH. The EtOAc extract was subjected to silica gel, Sephadex LH-20, ODS open column chromatography (CC), and preparative HPLC[18] to yield four new farnesyl phenols (**1**–**4**) (Fig. 1).

Compounds **1** and **2**[19] were isolated as yellow oil (MeOH), and possessed a molecular formula of $C_{30}H_{32}O_8$ according to the $^{13}C$ NMR and HRESIMS data at *m*/*z* 543.1999 $[M+Na]^+$ (calcd 543.1995). The $^1H$, $^{13}C$ NMR (Table 1), and HSQC spectra suggested the presence of a 1,2,4-trisubstituted dihydroxybenzene structure [$\delta_H$ 6.69 (1H, d, $J$ = 8.4 Hz), 6.57 (1H, dd, $J$ = 8.4, 2.8 Hz), 6.35 (1H, d, $J$ = 2.8 Hz)], a *p*-substituted hydroxybenzene structure [$\delta_H$ 7.55 (2H, d, $J$ = 8.4 Hz), 6.78 (2H, d, $J$ = 8.4 Hz)], one methyl group, six methylene groups (two oxygenated), one oxygenated tertiary carbon, eight $sp^2$ carbons, and two ester carbonyl carbons.

* Corresponding authors. Tel.: +86 24 23986515 (L.X.C.), +86 22 59596223 (F.Q.).
*E-mail addresses:* syzyclx@163.com (L.-X. Chen), fengqiu20070118@163.com (F. Qiu).

http://dx.doi.org/10.1016/j.bmcl.2016.05.037
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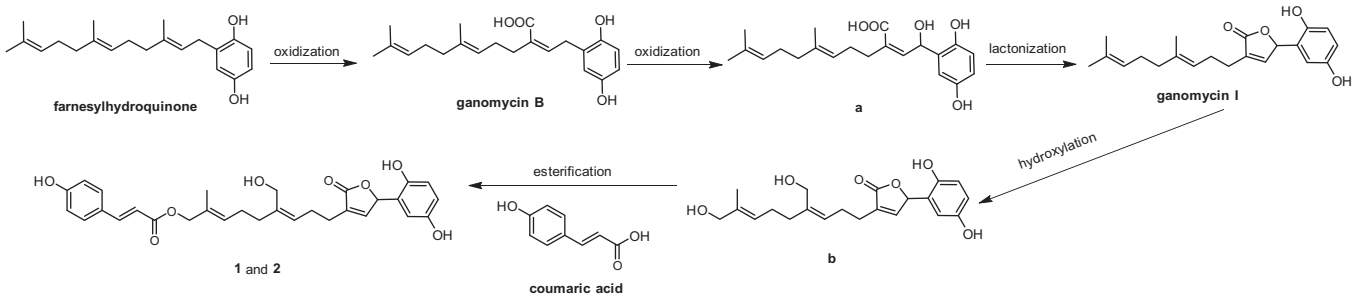


**Scheme 1.** Plausible biogenetic pathway for compounds **1** and **2**.

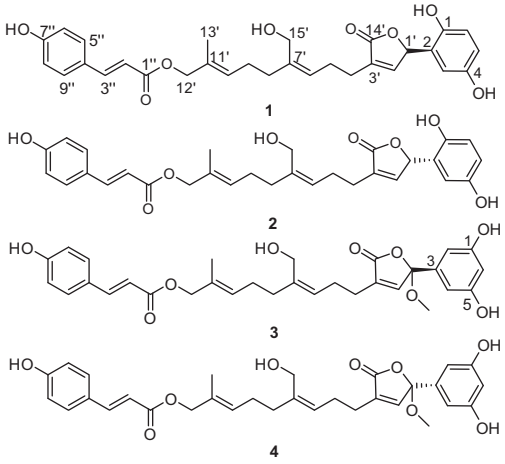


**Figure 1.** Structures of compounds **1**–**4**.

Comparison of the $^{1}H$ and $^{13}C$ NMR data of **1** and **2** with those of fornicin B, which was previously isolated from *Ganoderma fornicatum*,[20] indicated differences at C-1′/C-12′/C-15′. The absence of a methyl group at $\delta_C$ 25.8/$\delta_H$ 1.63 and the existence of a methene at $\delta_C$ 69.0/$\delta_H$ 4.50 and an *E*-*p*-coumaric acid [$\delta_C$ 166.4, 159.9, 144.7, 130.3, 125.0, 115.8, 114.1/$\delta_H$ 7.57 (1H, d, *J* = 16.0 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 6.78 (2H, d, *J* = 8.4 Hz), 6.40 (1H, d, *J* = 16.0 Hz)][21] in **1** and **2**, suggested that C-12′ is attached to *E*-*p*-coumaric acid and forms one ester. The long-range correlations (Fig. 2) of $H_2$-12′ ($\delta_H$ 4.50) with C-1″/C-10′/C-11′/C-13′, and $H_3$-13′ ($\delta_H$ 1.61) with C-10′/C-11′/C-12′ ($\delta_C$ 69.0), confirmed the above speculation. The appearance of two oxygenated carbons at $\delta_C$ 77.4/58.0 and the missing of three carbons (two oxygenated) at $\delta_C$ 107.6 (C-1′)/56.9 (1′-$OCH_3$)/16.1 (C-15′) in **1** and **2**, revealed the absence of a methoxy group and the existence of a hydroxy group at C-15′. This deduction was further supported by the HMBC correlations (Fig. 2) of $H_2$-15′ ($\delta_H$ 3.92) with C-6′/C-7′/C-8′, and H-1′ ($\delta_H$ 6.16) with C-2′/C-2/C-3. The *E* configurations of $\Delta^{6',7}$ and $\Delta^{10',11'}$ double bonds were assigned according to the NOESY correlations (Fig. 2) of H-6′ with H-8′, and H-10′ with H-12′.

The optical rotation data ($[\alpha]^{20}_D$ −2) of the mix of **1** and **2** inferred that it was likely a racemic mixture. Further separation of the enantiomers was performed on a Chiralpak IE liquid chromatography column to yield **1** (2.0 mg, $t_R$ = 10.0 min) and **2** (1.9 mg, $t_R$ = 14.0 min) (*n*–hexane/isopropanol, 65:35) (Fig. 3). The ECD spectra and optical rotation values of **1** and **2** showed their enantiomeric relationship. The absolute configuration of C-1′ in **1** was established using the ECD method developed for the determination of the absolute configuration of 5-substituted 2-(5*H*)-furanones.[22–24] The ECD spectrum of **1** showed negative

**Table 1**
$^{1}H$ and $^{13}C$ NMR spectroscopic data for compounds **1**–**4**[a]

| Position | **1** and **2**[b] | | **3** and **4**[c] | |
|---|---|---|---|---|
| | $\delta_C$ | $\delta_H$ (*J* in Hz) | $\delta_C$ | $\delta_H$ (*J* in Hz) |
| 1 | 147.3 | | 151.4 | |
| 2 | 121.8 | | 118.4 | 6.68, br s |
| 3 | 112.2 | 6.35, d (2.8) | 123.6 | |
| 4 | 150.0 | | 118.4 | 6.68, br s |
| 5 | 116.1 | 6.57, dd (8.4, 2.8) | 149.4 | |
| 6 | 116.3 | 6.69, d (8.4) | 114.8 | 6.93, br s |
| 1′ | 77.4 | 6.16, br s | 108.7 | |
| 2′ | 149.5 | 7.42, br s | 148.5 | 7.40, s |
| 3′ | 131.2 | | 135.8 | |
| 4′ | 25.0 | 2.26, br s | 26.3 | 2.34, br s |
| 5′ | 25.0 | 2.26, br s | 26.5 | 2.34, br s |
| 6′ | 124.6 | 5.18, t (6.8) | 127.5 | 5.24, br t (6.6) |
| 7′ | 139.9 | | 140.9 | |
| 8′ | 34.0 | 2.08, br s | 35.5 | 2.10, br s |
| 9′ | 26.0 | 2.08, br s | 27.5 | 2.10, br s |
| 10’ | 128.5 | 5.46, t (6.8) | 130.3 | 5.46, br s |
| 11′ | 130.1 | | 131.8 | |
| 12′ | 69.0 | 4.50, s | 71.2 | 4.55, s |
| 13′ | 13.8 | 1.61, s | 14.3 | 1.67, s |
| 14′ | 173.8 | | 173.5 | |
| 15′a | 58.0 | 3.92, s | 60.0 | 4.00, d (12.0) |
| 15′b | | | | 3.95, d (12.0) |
| 1″ | 166.4 | | 169.3 | |
| 2″ | 114.1 | 6.40, d (16.0) | 115.4 | 6.33, d (16.2) |
| 3″ | 144.7 | 7.57, d (16.0) | 146.7 | 7.61, d (16.2) |
| 4″ | 125.0 | | 127.3 | |
| 5″9″ | 130.3 | 7.55, d (8.4) | 131.3 | 7.45, d (7.2) |
| 6″8″ | 115.8 | 6.78, d (8.4) | 117.0 | 6.80, d (7.2) |
| 7″ | 159.9 | | 161.4 | |
| $OCH_3$ | | | 52.4 | 3.26, s |

[a] The assignments were based on HSQC and HMBC experiments; $^{13}C$ NMR, 100 MHz.
[b] Measured in DMSO-$d_6$; $^{1}H$ NMR, 400 MHz.
[c] Measured in $CD_3OD$; $^{1}H$ NMR, 600 MHz.

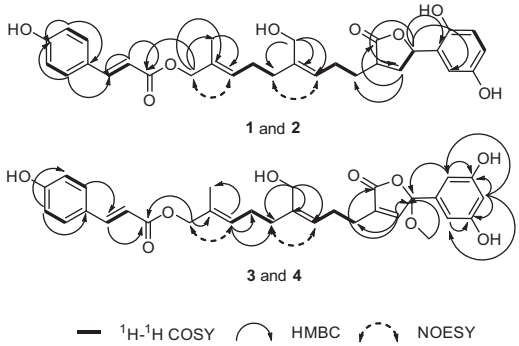


**Figure 2.** Key $^{1}H$–$^{1}H$ COSY, HMBC and NOESY correlations of **1**–**4**.

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