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•Research article•

Bioactive neolignans and lignans from the roots of *Paeonia lactiflora*

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[ABSTRACT] Two new neolignans and one new lignan (**1**–**3**) were obtained from the roots of *Paeonia lactiflora*. Their structures were unambiguously elucidated based on extensive spectroscopic analysis, single-crystal X-ray crystallography, and the calculated and experimental electronic circular dichroism (ECD) spectra. Compound **1** was a racemic mixture and successfully resolved into the anticipated enantiomers *via* chiral-phase HPLC. Compound **3** demonstrated moderate inhibitory activity against human carboxylesterase 2A1 (hCES2A1) with an IC_{50} value of 7.28 ± 0.94 μmol·L^{-1}.

[KEY WORDS] *Paeonia lactiflora*; Neolignan; Lignan; Human carboxylesterase 2A1
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Introduction

Lignans and neolignans are typically dimeric phenylpropanoids with a variety of structural types and widely distributed in nature. Most of lignans and neolignans are optically active and exhibit anticancer, antimitotic, and antiviral activity, specifically inhibitory effects on certain enzymes [1-4].

Paeonia lactiflora is an evergreen herb belonging to the Ranunculaceae family. Its dried roots and skin-free roots (named "*Chi shao*" and "*Bai shao*" in Chinese, respectively) are two important traditional Chinese medicines (TCMs) for the treatment of cardiovascular, extravastated blood, stagnated blood, and female genital diseases [5]. Chemical and pharmacological studies showed that the cage-like monoterpenoids were the characteristic chemotaxonomic makers and key active constituents of *P. lactiflora* [6-9]. To date, only several lignans and neolignans have been reported from the *Paeonia* species [10-12]. As our ongoing research for diverse chemical and biological natural products from TCMs, a series of terpenoids and aromatic derivatives of *P. lactiflora* were investigated [13-16]. In the present study, we continued to investigate the bioactive constituents of *P. lactiflora*, resulting in the discovery of two new neolignans and one new lignan (**1**–**3**) (Fig. 1). The structure and absolute configuration of **1**–**3** were determined based on extensive analysis of NMR spectroscopic data and single-crystal X-ray crystallography analysis, as well as the calculated and experimental electronic circular dichroism (ECD) spectra. Compound **1** was a racemic mixture and successfully resolved into the anticipated enantiomers through chiral-phase HPLC. Herein, we report the isolation, structure elucidation, and biological activity of **1**–**3**.

Results and Discussion

Compound **1** was obtained as white powder with $[\alpha]_D^{20}$ −5.7 (*c* 0.39, MeOH). The molecular formula of $C_{20}H_{24}O_6$ was determined on the basis of HR-ESI-MS at *m/z* 361.1642 $[M + H]^+$ (Calcd. for $C_{20}H_{25}O_6$, *m/z* 361.1646) combined with the NMR data (Table 1). The ^{1}H NMR spectrum of **1**

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[Δ]These authors contributed equally to this work.
These authors have no conflict of interest to declare.

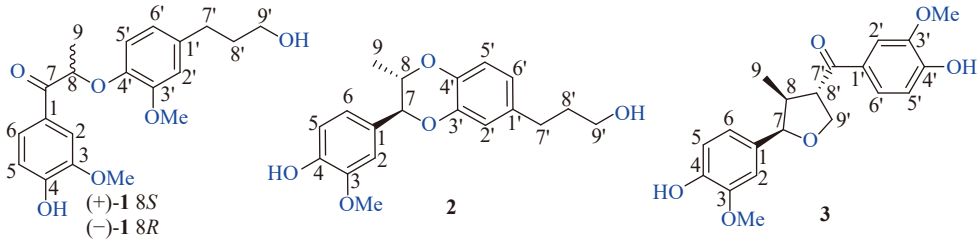

Fig. 1 Structures of compounds 1–3

Table 1 The ^{1}H (600 MHz) and ^{13}C NMR (150 MHz) data of compounds 1–3 [a]

No.	**1** (CD_3OD)		**2** (CD_3OD)		**3** (CD_3OD)	
	δ_H (mult, *J*, Hz)	δ_C	δ_H (mult, *J*, Hz)	δ_C	δ_H (mult, *J*, Hz)	δ_C
1		127.8		130.2		132.2
2	7.62 d (2.4)	112.6	6.96 d (1.2)	112.0	6.86 d (1.8)	116.0
3		149.2		149.2		148.7
4		153.8		148.3		146.7
5	6.87 d (8.4)	116.0	6.84 d (7.8)	116.2	6.85 d (8.4)	111.1
6	7.68 dd (8.4, 1.8)	125.2	6.85 dd (7.8, 1.8)	121.7	6.73 dd (8.4, 1.8)	120.0
7		199.6	4.54 d (7.8)	82.3	4.99 d (6.0)	84.8
8	5.57 q (6.6)	78.4	4.08 m	75.3	2.73 m	43.8
9	1.59 d (6.6)	19.4	1.12 d (6.6)	17.6	0.74 d (7.2)	15.8
1′		138.0		136.4		132.2
2′	6.83 d (2.4)	114.1	6.74 d (1.8)	117.6	7.56 d (1.8)	112.1
3′		151.3		145.3		149.3
4′		146.4		143.0		155.3
5′	6.73 d (8.4)	117.6	6.78 d (8.4)	117.5	6.77 d (8.4)	115.9
6′	6.63 dd (8.4, 2.4)	121.5	6.68 dd (7.8, 1.8)	122.3	7.58 dd (8.4, 2.4)	125.1
7′	2.59 t (7.8)	32.6	2.58 t (7.8)	32.4		200.2
8′	1.78 m	35.5	1.79 m	35.6	3.95 m	54.3
9′	3.53 t (6.6)	62.2	3.55 t (6.6)	62.2	4.43 t (8.4) 4.05 dd (8.4, 6.0)	70.4
OMe-3	3.88 s	56.4	3.87 s	56.5	3.85 s	55.4
OMe-3′	3.79 s	56.3			3.91 s	55.4

[a] NMR data (δ) were measured at 600 MHz for ^{1}H, and 150 MHz for ^{13}C. Proton coupling constants (*J*) in Hz are given in parentheses. The assignments were based on ^{1}H-^{1}H COSY, HSQC, and HMBC experiments.

showed two aromatic rings with ABX mutually coupling systems at δ_H 7.62 (1H, d, *J* = 2.4 Hz, H-2), 6.87 (1H, d, *J* = 8.4 Hz, H-5), 7.68 (1H, dd, *J* = 8.4, 1.8 Hz, H-6), 6.83 (1H, d, *J* = 2.4 Hz, H-2′), 6.73 (1H, d, *J* = 8.4 Hz, H-5′), and 6.63 (1H, dd, *J* = 8.4, 2.4 Hz, H-6′). In addition, based on the ^{1}H-^{1}H COSY spectrum, its ^{1}H NMR spectrum displayed resonances assignable to 1′-hydroxypropyl unit at δ_H 2.59 (2H, t, *J* = 7.8 Hz, H_2-7′), 1.78 (2H, m, H_2-8′), and 3.53 (2H, t, *J* = 6.6 Hz, H_2-9′), and 1-substitued oxethyl group at δ_H 5.57 (1H, q, *J* = 6.6 Hz, H-8) and 1.59 (d, *J* = 6.6, H_3-9). The ^{13}C NMR spectrum of **1** showed 20 carbon signals, which were classified as 12 olefinic carbons, one methyl, three methylenes (including one oxygenated), one oxygenated methine, one carbonyl, and two methoxy carbons with the aid of HSQC spectrum. In the HMBC spectrum of **1**, long range cross-peaks of H-2/C-7, H-6/C-7, H-8/C-1, H_3-9/C-7, H_2-7′/C-2′, H_2-7′/C-6′, and H_2-7′/C-9′, together with their chemical shifts, confirmed the presence of 3,4,8-trisubstituted propiophenone and 3′,4′-disubstituted phenylpropanol units. HMBC correlations of C-3 with H-2, H-5, and the methoxy at δ_H 3.88 and of C-3′ with H-2′, H-5′, and the methoxy at δ_H 3.79 located the two methoxy groups at C-3 and C-3′, respectively (Fig. 2). Finally, a correlation from H-8 to C-4′ was observed in the HMBC spectrum of **1**, completing the planar structure of **1** as 4,9′-di-

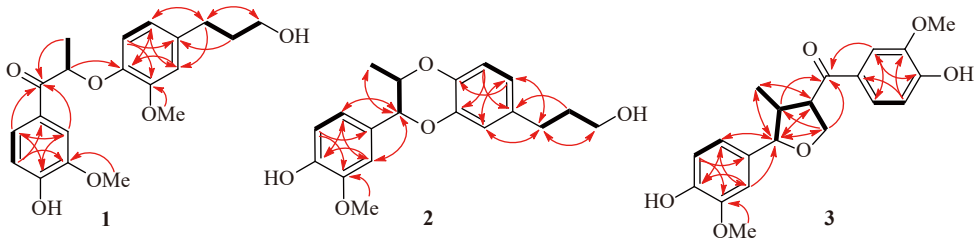

Fig. 2 Key ^{1}H-^{1}H COSY (bold lines) and HMBC (red arrows) correlations of compounds 1–3

hydroxy-3,3′-dimethoxy-8,4′-oxyneolignan-7-one. As compound **1** possessed only one chiral center, its small $[\alpha]_D^{20}$ value and no Cotton effects in the ECD spectrum (Fig. S4, Supplementary Materials) suggested that compound **1** was a racemic mixture. Subsequently, **1** was successfully separated into enantiomers (+)-**1** and (−)-**1** with the aid of chiral-phase HPLC (Chiralpak IB N-3 chiral column, MeCN/H_2O/TFA, 25 : 75 : 0.1) (Fig. S1, Supplementary Materials), which displayed mirror images of each other in their ECD spectra. Their absolute configuration was established through comparison of the experimental and theoretical ECD spectra predicted using the time-dependent density functional theory (TDDFT) (Supporting Information). The experimental and theoretically calculated ECD spectra for (+)-**1** and (−)-**1**, respectively, matched well as shown in Fig. 3. Therefore, the *S* and *R* configuration were assigned to (+)-**1** and (−)-**1**, respectively.

Compound **2** was obtained as colorless solid, and its molecular formula $C_{19}H_{22}O_5$ was established by HR-ESI-MS at *m/z* 331.1539 $[M + H]^+$ (Calcd. for $C_{19}H_{23}O_5$, *m/z* 331.1540) . Compared with the molecular formula of **1**, **2** was less of 30Da than **1**. The side by side comparison of the ^{1}H and ^{13}C NMR (Table 1) data between **2** and **1** revealed that signals attributed to the 7-keone and one methoxy group in **1** were absent in **2**, and instead, signals assignable to another oxymethine appeared in **2** at δ_H 4.54 and δ_C 82.3 (C-7), respectively. These observations suggested that **2** was an 8,4′:7,3′-diepoxyneolignan or 8,3′:7,4′-diepoxyneolignan. Although no HMBC correlations for H-7/C-3′ and H-8/C-4′ or H-7/C-4′ and H-8/C-3′ were observed (Fig. 2), the 8,3′:7,4′-diepoxy linkage were secured by the X-ray crystallographic analysis of **2** using the anomalous scattering of Cu Kα radiation. The ORTEP diagram with 7*S*,8*S* configuration shown in Fig. 4 was fully consistent with the large coupling constant of H-7 ($J_{7,8}$ = 7.8 Hz) due to a *trans* relationship between H-7 and H-8. Therefore, the structure of **2** was elucidated as (−)-(7*S*,8*S*)-4,9′-dihydroxy-3-methoxy -8,4′:7,3′-diepoxyneolignan.

Compound **3** was assigned the molecular formula of $C_{20}H_{22}O_6$ by the HR-ESI-MS at *m/z* 359.1488 $[M + H]^+$ (Calcd. for $C_{20}H_{23}O_6$, *m/z* 359.1489). Analysis of the 1D and 2D NMR data (Fig. 2) of **3** revealed that **3** possessed the completely identical planar structure to forsythialan C [17]. According to the ^{1}H NMR data, there were significant differences in H-7, H-8, H_3-9, H-8′, and H_2-9′ between **3** and forsythialan C. The NOESY correlations of H_3-9/H-2, H_3-9/H-6, H_3-9/H-8′, H-7/H-2′, and H-7/H-6′ indicated that H-7, H-8, and the benzophenone group, opposite the phenyl moiety and H-8′, were on the same side of the tetrahydrofuran ring (Fig. 5). On the basis of these data, **3** was the C-7 epimer of forsythialan C and named as *rel*-7*S*,8*R*,8′*R*-forsythialan C.

All the isolates were evaluated for their inhibitory activities against human carboxylesterase 2A1 (hCE2A1). Only compound **3** demonstrated moderate inhibitory activity with an IC_{50} value of 7.28 ± 0.94 μmol·L^{-1}. However, compounds **1**–**3** were inactive when tested for inhibitory effects against acetaminophen-induced HepG2 cell injury at 10 μmol·L^{-1}.

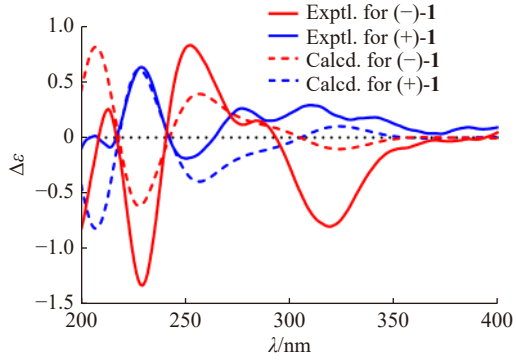

Fig. 3 Comparison of the experimental and the calculated ECD curves of compounds (+)-1 and (−)-1

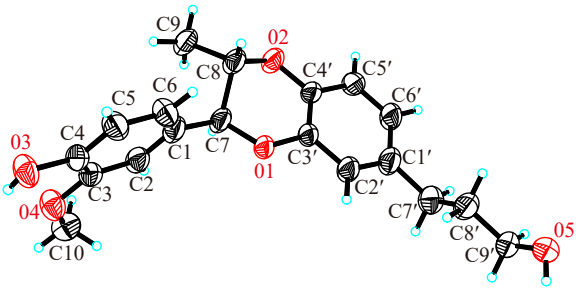

Fig. 4 ORTEP drawing of 2 depicting its absolute configuration

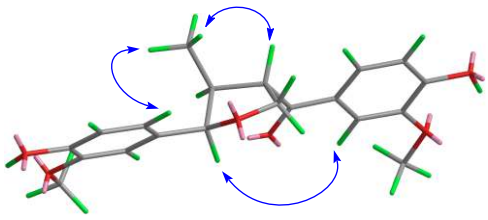

Fig. 5 Key NOESY (blue arrows) correlations of compound 3

Experimental

General experimental procedures

Optical rotation values were measured on a Rudolph Research Autopol III automatic polarimeter. UV spectra were measured on a Cary 300 spectrometer. ECD spectra were recorded on a JASCO J-815 spectrometer. IR spectra were obtained on a Nicolet Impact 400 FT-IR spectrophotometer. The NMR experiments were conducted on a Bruker spectrometer (600 MHz for ^{1}H or 150 MHz for ^{13}C) equipped with an inverse detection probe. ESIMS and HR-ESIMS data were obtained on a Q-Trap LC/MS/MS (Turbo ionspray source) and an Agilent 6520 Accurate-Mass Q-TOFL CMS spectrometers (Agilent Technologies, Ltd., Santa Clara, CA, USA), respectively. Column chromatography (CC) was performed using MCI gel (CHP20P), silica gel (200−300 mesh, Qingdao Marine Chemical Inc., China), and Sephadex LH-20 (Pharmacia Biotech AB, Uppsala Sweden). HPLC separation was conducted on Waters HPLC equipment, including a Waters 600 pump, a Waters 600 controller, and Waters 2487 dual λ absorbance, as well as GRACE semipreparative (250 mm × 10 mm) and preparative (250 mm × 19 mm) RP C_{18} (5 μm) columns, and Chiralpak IB-N3 (250 mm × 4.6 mm, 3 μm) column for resolution of enantiomers.

Plant material

P. lactiflora roots were collected in Chifeng, Inner Mongolia Autonomous Region, during September 2014 and identified by Prof. LI Min-Hui at Baotou Medical College [14].

Extraction and isolation

Dried and powdered roots of *P. lactiflora* (50 kg) were extracted by ultrasonication using deionized water (150 L, 3 × 1 h) followed by 95% EtOH (120 L, 2 × 1 h) at ambient temperature. Removal of the solvent from the 95% EtOH extract under reduced pressure afforded a crude residue, which was suspended in H_2O, and partitioned with EtOAc to yield EtOAc-(580 g) and H_2O (105 g)-soluble extracts [13]. The EtOAc extract was separated by CC over silica gel (100–200 mesh, 3 kg, 15 mm × 80 cm) eluting with PE/acetone solvent mixtures (50 ∶ 1, 30 ∶ 1, 20 ∶ 1, 10 ∶ 1, and 8 ∶ 1) and then CH_2Cl_2/MeOH solvent mixtures (20 ∶ 1, 10 ∶ 1, 8 ∶ 1, 5 ∶ 1, 2 ∶ 1, and 1 ∶ 1) to give ten subfractions (A–J). Fraction A was chromatographed by MPLC over reversed–phase C_{18} silica gel using gradient elution (MeOH/H_2O, 80 ∶ 20→100 ∶ 0) to give six fractions (A1–A6). A2 was purified by semipreparative HPLC to afford **2** [RP C_{18}, 5 μm, 250 mm × 10 mm, 230 nm, MeCN/H_2O (44 ∶ 56), 2.0 mL·min^{-1}, t_R = 19.0 min, 1.2 mg]. Fraction C was chromatographed by MPLC over RP C_{18} silica gel using MeOH/H_2O gradient (15 ∶ 85→100 ∶ 0) to give five subfractions (C1–C5). C4 was subjected to CC over silica gel eluted with CH_2Cl_2/MeOH (100 ∶ 1, 50 ∶ 1, and 0 ∶ 1) to obtain two subfractions (C41–C42). C42 were isolated by semipreparative HPLC to give **1** [RP C_{18}, 5 μm, 250 mm × 10 mm, 230 nm, MeOH/H_2O (60 ∶ 40), 2.0 mL·min^{-1}, t_R = 12.5 min, 8.2 mg] and **3** [RP C_{18}, 5 μm, 250 mm × 10 mm, 230 nm, MeOH/H_2O (61 ∶ 39), 2.0 mL·min^{-1}, t_R = 26.0 min, 1.5 mg]. The enantiomers of **1** were separated by HPLC using a Chiralpak IB N-3 chiral column to yeild (+)-**1** [(3 μm, 250 mm × 4.6 mm, 280 nm, CH_3CN/H_2O/TFA (25 ∶ 75 ∶ 0.1), t_R = 49.3 min, 0.9 mg)] and (−)-**1** [(3 μm, 250 mm × 4.6 mm, 280 nm, CH_3CN/H_2O/TFA (25 ∶ 75 ∶ 0.1), t_R = 47.0 min, 0.5 mg)].

*4,9′-Dihydroxy-3,3′-dimethoxy-8,4′-oxyneolignan-7-one (**1**)*

White powder; $[\alpha]_D^{20}$ −5.7 (*c* 0.39, MeOH); UV (MeOH) λ_{max} nm (logε): 204 (1.03), 230 (0.51), 280 (0.29), 309 (0.22); IR(KBr) υ_{max} 3384, 2936, 2851, 1678, 1590, 1513, 1462, 1425, 1378, 1270, 1225, 1202, 1142, 1084, 1034, 1008, 948, 880, 862, 825, 788, 754, 724, 634, 560 cm^{-1}; HR-ESI-MS *m/z* 361.1642 $[M + H]^+$ (Calcd. for $C_{20}H_{25}O_6$, *m/z* 361.1646); ^{1}H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) data, see Table 1.

*(+)-(S)-4,9′-Dihydroxy-3,3′-dimethoxy-8,4′-oxyneolignan-7-one [(+)**1**]*: $[\alpha]_D^{20}$ +16.1 (*c* 0.82, CH_3CN); ECD (CH_3CN) 277 (Δε + 0.267), 250 (Δε −0.19), 229 (Δε + 0.64).

*(−)-(R)-4,9′-Dihydroxy-3,3′-dimethoxy-8,4′-oxyneolignan-7-one [(−)**1**]*: $[\alpha]_D^{20}$ −16.3 (*c* 0.49, CH_3CN); ECD (CH_3CN) 285 (Δε + 0.15), 252 (Δε + 0.83), 229 (Δε −1.33).

*(−)-(7S,8S)-4,9′-Dihydroxy-3-methoxy -8,4′:7,3′-diepoxyneolignan (**2**)*

Colorless solid; $[\alpha]_D^{20}$ −8.2 (*c* 0.05, MeOH); UV (MeOH) λ_{max} nm (logε): 206 (1.34), 227 (0.32), 283 (0.13); IR(KBr) υ_{max} 3360, 2923, 2853, 1680, 1603, 1508, 1454, 1380, 1275, 1209, 1143, 1032, 846, 802, 725, 601, 520 cm^{-1}; HR-ESI-MS *m/z* 331.1539 $[M + H]^+$ (Calcd. for $C_{19}H_{23}O_5$, *m/z* 331.1540); ^{1}H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) data, see Table 1.

*rel-(7S,8R,8′R)-Forsythialan C (**3**)*

White powder; $[\alpha]_D^{20}$ −12.3 (*c* 0.07, MeOH); UV (MeOH) λ_{max} nm (logε): 203 (0.53), 230 (0.22), 279 (0.13), 307 (0.08); IR(KBr) υ_{max} 3300, 2961, 2930, 1651, 1523, 1454, 1396, 1260, 1235, 1077, 966, 801, 647 cm^{-1}; HR-ESI-MS *m/z* 359.1488 $[M + H]^+$ (calcd for $C_{20}H_{23}O_6$, *m/z* 359.1489); ^{1}H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) data, see Table 1.

ECD calculations

See Supplementary Materials.

Enzyme inhibition assays

The inhibitory effects against human carboxylesterase 2 A1 (hCE2A1) were investigated using fluorescein diacetate (FD) as the probe substrate, while loperamide (LPA) was used as a positive control [18]. Briefly, the incubation mixture with a total volume of 200 μL consisted of HLMs (at a final concentration of 2 μg·mL^{-1}), 0.1 mol·L^{-1} phosphate buffer (pH 7.4), and each inhibitor. After 10 min pre-incubation at 37 °C, the reaction started by the addition of FD (at a final concentration of 10 μmol·L^{-1}, near the K_m value of FD in HLMs), with a final concentration of DMSO at 1% (*V*/*V*, without loss of the catalytic activity). FD hydrolysis with or without inhibitors were performed at 37 ℃ for 20 min and then terminated by adding an equal volume of ice-cold acetonitrile. FD and its hydrolytic metabolite fluorescein were

further analyzed by Synergy H[1] Multi-Mode Reader (Biotek, USA). The excitation wavelength of fluorescein was set at 480 nm, while the emission wavelength was 520 nm. The gain value was set at 60. The residual activities of hCE2 were calculated with the following equation: the residual activity (%) = (the florescence intensity in the presence of inhibitor)/the florescence intensity in negative control (without any inhibitor) × 100%. All assays were conducted in triplicate, and the data were shown as mean ± SD.

Protective effect of acetaminophen-induced HepG2 cell injury

See Ref. 19.

Supplementary Materials

Supplementray information can be acquired by e-mail to corresponding author.

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