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RESEARCH ARTICLE

Phenolic constituents from *Parakmeria yunnanensis* and their anti-HIV-1 activity

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Abstract Three new phenolic compounds, yunnanensins A–C (**1–3**), together with fourteen known ones (**4–17**), were isolated from the leaves and stems of *Parakmeria yunnanensis*. The structures of new compounds were established on the basis of extensive spectroscopic analyses. Several compounds showed weak anti-HIV-1 activity.

Keywords *Parakmeria yunnanensis* · Yunnanensins A–C · Phenolic constituents · Anti-HIV-1

Introduction

Plants of the family Magnoliaceae, containing more than 250 species, are mainly distributed in southeastern Asia. Modern phytochemical and pharmacological studies have shown that this family is rich in different types of lignans and some of them possess various beneficial pharmacological activities such as cytotoxicity (Youn et al. 2007), muscle relaxation (Watanabe et al. 1975), central depressant effect (Watanabe et al. 1983), antigastric ulcer (Watanabe 1986), vasorelaxant (Teng et al. 1990), antiallergic (Bae et al. 1999), antibacterial (Namba et al. 1982), anti-diabetes mellitus (Sohn et al. 2007) and neurotrophic activities (Fukuyama et al. 1992).

Structural and biological diversity of lignans in Magnoliaceae family prompted us to investigate chemically on *Parakmeria yunnanensis*, a plant distributed in Yunnan, Guizhou and Guangxi provinces of China. Previous study on this plant revealed the occurrence of lignans and flavones (Cheng et al. 2001). Our study of this plant led to the isolation of three new compounds, yunnanensins A–C (**1–3**), along with fourteen known ones identified as 4′-*o*-*β*-D-glucopyranoside lariciresinol (**4**) (Baderschneider and Winterhalter 2001), (−)-syringaresinol-4-*β*-*o*-D-glucopyranoside (**5**) (Kinjo et al. 1991), (−)-episyringaresinol (**6**) (Kunitomo et al. 1975), (−)-syringaresinol (**7**) (Sharp et al. 2001), (−)-epipinoresinol (**8**) (Thieme and Winkler 1969), (+)-lirioresinol C (**9**) (Chang et al. 1998), (−)-pinoresinol (**10**) (Nabeta et al. 1991), (+)-anhydrosecoisolariciresinol (**11**) (Ono et al. 2000), (1*S*, 2*R*, 3*R*)-1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-6-methoxy-3-acetate-2,3-naphthalenedimethanol (**12**) (Yamamoto et al. 2004), isoshonanin (**13**) (Bernini et al. 2009), (+)-isolariciresinol (**14**) (Yamamoto et al. 2004), 1,2-bis(4-hydroxy-3-methoxyphenyl)-1-propanone (**15**) (Lundquist and Miksche 1965), 1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)-1,3-propanediol (**16**) and 2-methoxy-4-[3-methyl-5-(1-propenyl)-2-benzofuranyl]-phenol (**17**) (Cheng et al. 2001), respectively. Compounds **3–17** were evaluated

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Table 1 ^{1}H and ^{13}C NMR spectroscopic assignments of **1** and **2**

No.	**1**[a,b,c]		**2**[a,b,d]	
	δ_H	δ_C	δ_H	δ_C
1	–	135.9, s	–	139.8, s
2	6.56 (br s)	111.3, d	6.99 (d, 1.5)	111.3, d
3	–	143.7, s	–	147.0, s
4	–	146.6, s	–	151.0, s
5	6.84 (d, 8.0)	114.4, d	7.06 (d, 8.3)	118.1, d
6	6.62 (overlap)	122.2, d	6.87 (d, 8.3, 1.5)	119.3, d
7	3.80 (overlap)	47.2, d	3.46 (overlap)	83.8, d
8	1.99 (m)	43.5, d	2.36 (m)	54.1, d
9α	4.06 (dd, 11.6, 3.8)	63.5, t	3.75 (dd, 9.1, 6.4)	60.5, t
9β	3.95 (dd, 11.6, 4.1)	–	4.00 (dd,9.1, 4.2)	–
1′	–	126.9, s	–	133.5, s
2′	–	132.2, s	6.79 (d, 1.3)	113.3, d
3′	6.31 (s)	115.3, d	–	149.0, s
4′	–	143.7, s	–	145.8, s
5′	–	144.9, s	6.71 (d, 8.0)	116.2, d
6′	6.61 (s)	110.1, d	6.64 (dd, 8.0, 1.3)	122.1, d
7′α	2.81 (m, 2H)	32.7, t	2.52 (dd, 13.0, 11.4)	33.6, t
7′β	–	–	2.90 (dd, 13.0, 4.9)	–
8′	2.26 (m)	35.5, d	2.73 (m)	43.8, d
9′	4.22 (dd, 11.2, 4.5)	66.6, t	3.67 (m)	73.6, t
	4.08 (dd, 11.2, 2.9)		3.88 (m)	
OMe	3.82 (s) (OMe-3)	55.9, q	3.86 (s) (OMe-3)	56.7, q
OMe	3.86 (s) (OMe-5′)	55.9, q	3.83 (s) (OMe-3′)	56.3, q
			–	–
1″	–	–	4.86 (d, 7.3)	102.7, d
2″	–	–	3.59 (m)	75.3, d
3″	–	–	3.46 (overlap)	77.7, d
4″	–	–	3.49 (overlap)	74.9, d
5″	–	–	3.37 (overlap)	71.6, d
6″	–	–	4.36 (dd, 13.0, 1.8)	64.6, t
			4.25 (dd, 13.0, 6.4)	
OAc	2.07 (s)	171.0, s OAc-9′)	2.01 (s)	172.6, s
	2.05 (s)	20.9, q (OAc-9′)		20.7, q
		171.1, s (OAc-9)		
		20.9, q (OAc-9)		

[a] Recorded at 400 MHz
[b] Recorded at 100 MHz
[c] Recorded in CD3OD
[d] Recorded in $CDCl_3$

for their in vitro anti-HIV-1 activity. Herein, the isolation, structural elucidation and biological activity of these compounds were presented.

Materials and methods

General experimental procedures

Optical rotations were measured with a JASCO DIP-370 digital polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. A BioRad FtS–135 spectrophotometer was used for scanning IR spectroscopy with KBr pellets, whereas CD spectra were recorded on a JASCO J-810 spectropolarimeter. 1D and 2D NMR spectra were recorded on Bruker AM-400, DRX-500 and BRUKER AVANCE III-600 MHz spectrometers. Unless otherwise specified, chemical shifts (δ) were expressed in ppm with reference to the solvent signals. High-resolution electrospray-ionization (HRESIMS) spectra were performed on a VG Autospec-3000 spectrometer. Column chromatography was performed using silica gel (200–300 mesh, Qing-dao Marine Chemical, Inc., Qingdao, China), Lichroprep RP-18 gel (40–63 μm, Merck,

Table 2 ^{1}H and ^{13}C NMR spectroscopic assignments of **3**

No.	**3**[a,b,c]		No.	**3**[a,b,c]	
	δ_H	δ_C		δ_H	δ_C
1		126.5 s	8		76.0, s
2	6.67 (d, 1.7)	112.7, d	9	2.63 (d, 16.2)	42.8, t
				2.94 (d, 16.2)	
3		146.2, s	10		171.2, s
4		144.8, s	11		174.8, s
5	6.75 (d, 8.0 Hz)	114.0, d	OMe-3	3.79 (s)	55.8, q
6	6.56 (dd, 8.0, 1.7)	122.8, d	OMe-10	3.69 (s)	52.8, q
7	2.79 (d, 13.7)	44.9, t	OMe-11	3.60 (s)	51.9, q
	2.90 (d, 13.7)				

[a] Recorded at 400 MHz

[b] Recorded at 100 MHz

[c] Recorded in $CDCl_3$

Darmstadt, Germany), and Sephadex LH-20 (Pharmacia). Semi-preparative HPLC was performed on an Agilent 1100 liquid chromatograph with a Zorbax SB-C_{18}, 9.4 mm × 25 cm, column. Fractions were monitored by TLC and spots were visualized by heating the silica gel plates sprayed with 10 % H_2SO_4 in EtOH.

Plant material

The leaves and stems of *P. yunnanensis* were collected in Kunming Botanic Garden, Yunnan Province, People's Republic of China, in August 2010. The specimen was identified by Prof. Xun Gong and a voucher specimen (No. KIB 2010-08-11) has been deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and isolation

The plant material of *P. yunnanensis* (12.5 kg) was grounded and exhaustively extracted with 70 % aqueous Me_2CO at room temperature. The solvent was evaporated in vacuo, and the crude extract was dissolved in H_2O and partitioned with EtOAc. The EtOAc portion (310.0 g) was chromatographed on a silica gel column eluting with $CHCl_3$–Me_2CO (1:0, 9:1, 8:2, 2:1, 1:1, and 0:1) to afford fractions **I**–**VI**. Fraction **II** was repeatedly chromatographed on RP-18, silica gel (200–300 mesh) and Sephadex LH-20, and finally by semi-preparative HPLC to yield compounds **4** (4.0 mg), **7** (0.7 mg), **9** (11.0 mg), **12** (3.0 mg), and **18** (26.0 mg). Fraction **III** was chromatographed on RP-18 eluting with CH_3OH–H_2O (20:80–100:0) and then chromatographed on silica gel, Sephadex LH-20 and finally by semi-preparative HPLC to yield compound **1** (1.5 mg), **8** (10.2 mg), **10** (2.6 mg), **11** (5.6 mg), **13** (6.0 mg), **14** (8.0 mg), **15** (12.6 mg), **16** (3.6 mg), and **17** (0.8 mg). Fraction **V** was chromatographed on reversed phase eluting with CH_3OH–H_2O(10:90–100:0) and then chromatographed on silica gel, Sephadex LH-20 and finally by semi-preparative HPLC to yield compounds **2** (1.2 mg), **3** (4.0 mg), **5** (37.6 mg), and **6** (5.6 mg).

Yunnanensin A (**1**)

Yellowish oil; $[\alpha]_D^{23}$ −6.8 (*c* 0.75, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 284 (2.40), 203 (3.31) nm; IR (KBr) ν_{max} 3442,

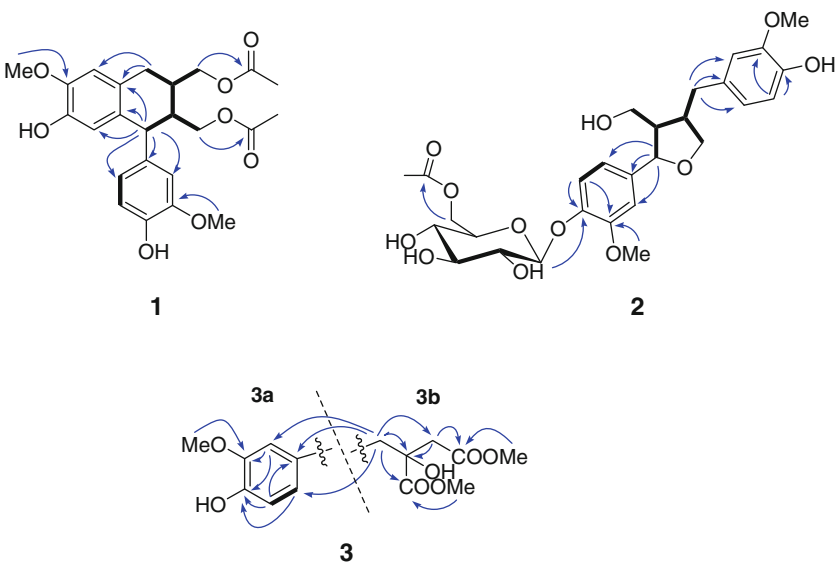

Fig. 1 Key HMBC (H→C) and ^{1}H-^{1}H COSY (*thick black line*) correlations of **1**–**3**

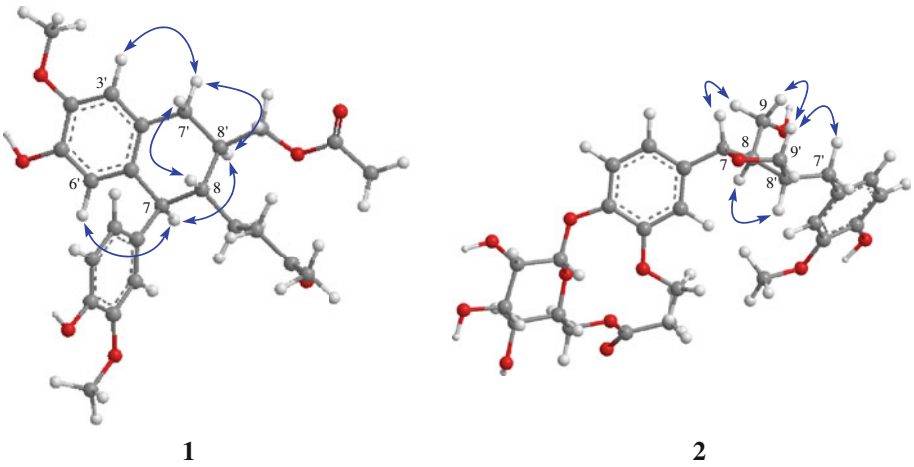

Fig. 2 Selected ROESY (H↔H) correlations of **1** and **2**

1 **2**

2926, 1730, 1632, 1515, 1384, 1250 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; Negative HRESIMS *m/z* 443.1713 $[M-H]^-$(calcd. 443.1705).

Yunnanensin B (**2**)

Yellowish oil; $[\alpha]_D^{23}$ −15.7 (*c* 1.39, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 279 (2.73), 226 (3.18), 202 (3.78) nm; IR (KBr) ν_{max} 3432, 2923, 2853, 1732, 1633, 1515, 1456, 1271 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; Negative HRESIMS *m/z* 563.2124 $[M-H]^-$ (calcd. 563.2128).

Yunnanensin C (**3**)

Yellowish oil; $[\alpha]_D^{23}$ −15.1 (*c* 0.70, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 281 (2.28), 228 (2.60), 202 (3.14) nm; IR (KBr) ν_{max} 3439, 2928, 1730, 1631, 1516, 1489, 1445, 1250, 1127 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; Negative HRESIMS *m/z* 297.0969 $[M-H]^-$ (calcd. 297.0974).

Anti-HIV-1 assay

Cytotoxicity against C8166 cells (CC_{50}) was assessed using the MTT method, and anti-HIV-1 activity was evaluated by the inhibition assay for the cytopathic effects of HIV-1_{IIIB} (EC_{50}) (Wang et al. 2009). Zidovudine (AZT) was used as the positive control in this assay.

Results and discussion

Yunnanensin A (**1**), obtained as yellow oils, has a molecular formula of $C_{24}H_{28}O_8$ based on a pseudomolecular ion peak at *m/z* 443.1713 $[M-H]^-$ in its negative HRESIMS spectrum as well as ^{1}H, ^{13}C NMR data, requiring eleven unsaturations. The ^{1}H NMR spectrum showed a 1,3,4-trisubstituted aromatic ring system [δ_H 6.62 (overlap, H-6), 6.84 (d, J = 8.0, H-5), and 6.56 (br s, H-2)], an 1′,3′,4′,6′-tetrasubstituted aromatic ring [δ_H 6.31 (1H, s, H-3′) and 6.61 (overlap, H-6′)], four methyl groups [two methoxy ones at δ_H 3.82 (s), δ_H 3.86 (s) and two acetyl methyl groups at δ_H 2.07 (s), δ_H 2.05 (s)] and other signals (between δ_H 2.81–4.22). The ^{13}C NMR and DEPT spectroscopic data displayed signals comprising of seven aromatic quaternary carbons (four oxy-quaternary ones), eight methines (five aromatic ones), one methylene carbon, two oxy-methylenes, two methoxy carbons, two acetyl groups (including two methyl carbons and two carbonyl carbons) (Table 1). Comparison of the ^{1}H and ^{13}C NMR (DEPT) spectroscopic data of **1** with those of known compound burseligan (Jutiviboonsuk et al. 2005) indicated that **1** was structurally similar with that of burseligan except for the observation of the additional signals contributed by two acetyl groups in **1** (δ_H 2.07, 2.05 and δ_C 20.9, 171.0, 20.9, 171.1). The key HMBC and ^{1}H-^{1}H COSY correlations of **1** also supported the above deductions (Fig. 1). The relative configurations of **1** were established on the basis of ROESY spectrum. The key ROESY correlations between H-7 and H-8′ revealed that H-7 and H-8′ were cofacial and arbitrarily defined as having a β-configuration. The correlations between H-7′α and H-8 indicated that they were on the same side, and they were thus assigned the α-configuration (Fig. 2). The absolute configuration of **1** was determined by examination of the circular dichroism (CD) spectrum of compound **1**. The CD spectrum of **1** showed a negative cotton effect at 292 nm ($\Delta\varepsilon$ − 4.3 mdeg), suggesting the 7*S* configuration (Dhal et al. 1994; Trinh Thi Thanh et al. 2012; Sun et al. 2011; Zhao et al. 2003). Thus, the absolute stereochemistry was identified as 7*S*, 8*R*, and 8′*R*.

Yunnanensin B (**2**) gave a pseudomolecular ion peak in its negative HRESIMS spectrum at *m/z* 563.2124 $[M-H]^-$, indicative of the molecular formula $C_{28}H_{36}O_{12}$ and equating to eleven double-bond equivalents unsaturations. The ^{1}H NMR spectrum showed the presence of two 1,3,4-

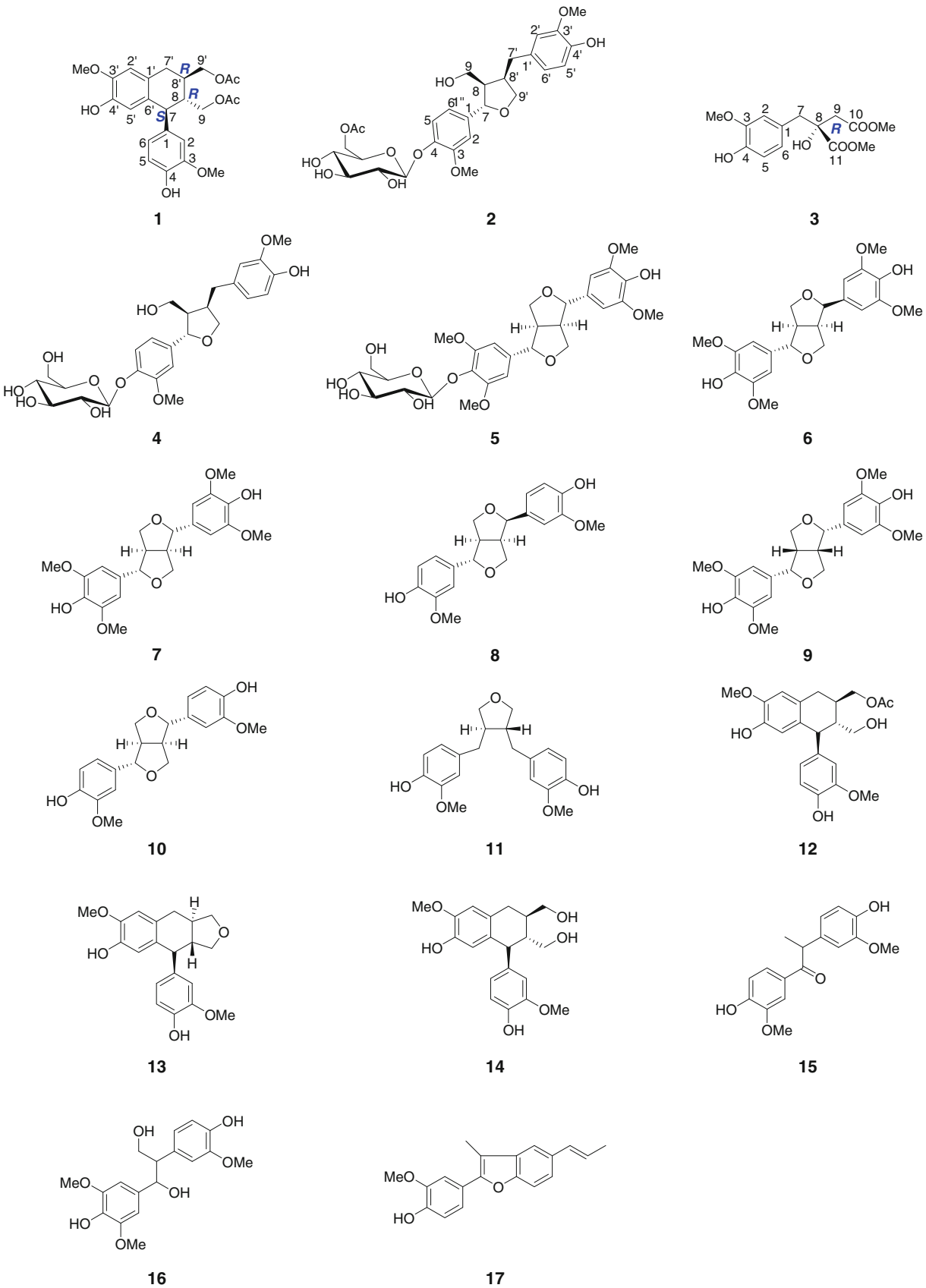

Fig. 3 Structures of compounds **1**–**17**

Table 3 Anti-HIV-1 activities of **3–17**

Compound	CC_{50} (μg ml^{-1})	EC_{50} (μg ml^{-1})	TI (CC_{50}/EC_{50})
3	>200	>200	–
4	>200	>200	–
5	>200	>200	–
6	>200	>200	–
7	>200	83.0	>2.410
8	>200	>200	–
9	>200	>200	–
10	>200	>200	–
11	>200	>200	–
12	>200	100.7	>1.987
13	>200	82.0	>2.438
14	>200	>200	–
15	>200	87.1	>2.295
16	>200	>200	–
17	92.858	23.591	3.936
Positive control AZT	1,317.41	1.35 ng ml^{-1}	975,859

CC_{50} concentration causing 50 % cellular cytotoxicity, *EC_{50}* 50 % effective concentration, *TI* therapeutic index

trisubstituted aromatic rings at δ_H 6.79 (d, $J = 1.3$, H-2′), 6.71 (d, $J = 8.0$, H-5′), 6.64 (dd, $J = 8.0$, 1.3, H-6′), 6.99 (d, $J = 1.5$, H-2), 7.06 (d, $J = 8.3$, H-5), and 6.87 (dd, $J = 8.3$, 1.5, H-6), two methoxy groups at δ_H 3.86 (s) and 3.83 (s), and one glucopyranosyl unit [δ_H 4.86 (d, $J = 7.3$, H-1″)]. The J value (7.3 Hz) of the anomeric H-atom established the *β*-configuration of the glucose moiety. In addition, the ^{13}C NMR and DEPT spectra indicated the occurrence of three methines [including an *O*-bearing one at δ_C 83.8 (C-7)] and three methylenes [including two *O*-bearing ones at δ_C 73.6 (C-9′) and 60.5 (C-9)]. These NMR features resembled those of 4-(*β*-D-glucopyranosyloxy)-9′-hydroxy-3,3′,4′-trimethoxy-7′,9-epoxylignan (Sugiyama and Kikuchi 1993), except for an additional signals arising from an acetyl group at δ_H 2.01 (s, 3H) and δ_C 20.7 and δ_C 172.6 in **2**. The downfield chemical shift at C-6″ (δ_C 64.6) and upfield chemical shift at C-5″ (δ_C 71.6) suggested that the additional acetyl group was linked to C-6″ of **2**, which was further confirmed by the long-range correlation of H-6″ (δ_H 4.25, 4.36) with the C-atom signal of the acetyl group at δ_C 172.6 observed in the HMBC experiment (Fig. 1). Moreover, the ROESY correlations of H-1″ (δ_H 4.86) with H-5 (δ_H 7.06), of the methoxy H-atoms (δ_H 3.83) with H-2′ (δ_H 6.79), and of the methoxy H-atoms (δ_H 3.86) and H-2 (δ_H 6.99), revealed the locations of the glucosyl moiety at C-4, and the two methoxy groups at C-3 and C-3′, respectively (Fig. 1). Other HMBC correlations confirmed the planar structure of **2**. The relative stereochemistry of **2** was fixed by the performance of a ROESY experiment (Fig. 2). The ROESY cross-peaks of H-7/H-9, H-9′/H-9, and H-9′/H-7′ indicated that H-7, H-9 and H-7′ were on the same side and arbitrarily assigned as *β*-configuration, while the correlation between H-8 and H-8′ suggested that they were α-oriented.

Yunnanensin C (**3**) was assigned the molecular formula, $C_{14}H_{18}O_7$, which was established on the basis of the spectra of ^{13}C NMR and DEPT and further confirmed by the pseudomolecular ion peak at *m/z* 333.0897 $[M-H]^-$ in the negative HRESIMS spectrum, corresponding to six unsaturation degrees. The ^1H NMR spectrum of **3** displayed signals due to one set of ABC-type aromatic systems at δ_H 6.67 (d, $J = 1.7$ Hz, H-2), 6.75 (d, $J = 8.0$ Hz, H-5), and 6.56 (dd, $J = 8.0$, 1.7 Hz, H-6), three methoxy groups at δ_H 3.60 (s, OMe-10), 3.69 (s, OMe-11), and 3.79 (s, OMe-3) and also displayed other signals (δ_H 2.63–2.94, 4H). The ^{13}C NMR and DEPT spectra of **3** exhibited the presence of fourteen carbons, consisting of eight sp^2 ones (two ester groups at δ_C 171.2 and 174.8 and six aromatic carbons including two oxygenated ones), two methylene carbons and three oxygenated methine carbons. Detailed analyses of ^1H-^1H COSY, HMBC and ROESY spectra of **3** showed that the aromatic methoxyl and hydroxyl groups should be located at C-3 and C-4 in the benzene ring which were deduced by the HMBC correlations of H-2 (δ_H 6.67) with C-3 (δ_C 146.2), C-4 (δ_C 144.8), and C-6 (δ_C 122.8), of H-5 (δ_H 6.75) with C-1 (δ_C 126.5), C-3 (146.2), and C-4 (144.8), and of H-6 (δ_H 6.56) with C-1 (δ_C 126.5) and C-4 (δ_C 144.8), together with the ^1H-^1H COSY correlation of H-5 (δ_H 6.75) with H-6 (δ_H 6.56). This deduction was further confirmed by the ROESY correlation of OMe-3 (δ_H 3.79) with H-2 (δ_H 6.67). Thus, the partial structure **3a** was established as shown (Fig. 1).

In the HMBC spectrum, both the proton signals at δ_H 2.70/2.90 (d, H-7, 2H) and δ_H 2.63/2.94 (d, H-9, 2H) showed correlations with C-8 (δ_C 76.0) and C-11 (δ_C 174.8), and proton signals at δ_H 2.63/2.94 (d, H-9, 2H) showed the correlation with C-10 (δ_C 171.2). In addition, two methoxyl groups located at C-10 and C-11 were deduced by the HMBC correlations from proton signals at δ_H 3.60 (s, OMe-10) and 3.69 (s, OMe-11) to C-10 and C-11, respectively. Above evidence led to the establishment of another partial structure **3b** (Fig. 3). Furthermore, fragments **3a** and **3b** were joined together by the connection of C-1–C-7 deduced by the HMBC corrections of H-7 (δ_H 2.70 and 2.90, d, 2H) with C-1, C-2 and C-6.

Since only one chiral center in compound **3**, its absolute configuration can be determined by comparison its ORD data with those of its analogues. In our work, the absolute configuration of **3** was determined by comparison of the ORD data of **3** with that of a structural similar compound, eucomic acid, which displayed a negative specific rotation

indicative of *R* configuration of the chiral center (Heller and Tamm 1974). Compound **3** also gave a negative rotation ($[\alpha]_D^{23}$ −15.1 (*c* 0.70, CH_3OH)), which was in accordance with published data (Heller and Tamm 1974; Koizumi et al. 1976; Ishii et al. 1979; Tovar-Gijón et al. 2006; Okada et al. 2009). Based on the above evidence, the absolute configuration of the chiral center at C-8 was also determined to be *R*. Consequently, the structure of **3** was established.

The anti-HIV activity was indicated as potencies of the compounds **3–17** in preventing the cytopathic effects of HIV-1 in C8166 cells with cytotoxicity measured in parallel with the determination of antiviral activity using AZT as a positive control (EC_{50} = 1.35 ng ml^{-1} and CC_{50} = 1,317.41 μg ml^{-1}) (Wang et al. 2009). The results were listed in Table 3. Among the tested isolates, compound **17** showed weak anti-HIV-1 activity with an EC_{50} value of 23.6 μg ml^{-1} and TI value of 3.9.

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