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Two new monoterpenoid glycosides from *Glechoma longituba*

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Chemical study on the constituents of the whole plant of *Glechoma longituba* (Labiatae) led to the isolation of two new pinane-type monoterpenoid glycosides, characterised as 2α-pinan-3-one-2-*O*-β-glucopyranoside (**1**) and 5α-pinan-3-one-5-*O*-β-glucopyranoside (**2**) along with 13 known compounds. Their structures were elucidated on the basis of spectroscopic analysis and chemical methods.

Keywords: *Glechoma longituba*; Labiatae; Monoterpenoid glycoside; 2α-Pinan-3-one-2-*O*-β-glucopyranoside; 5α-Pinan-3-one-5-*O*-β-glucopyranoside

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1. Introduction

Glechoma longituba (Nakai) Kupr. (Labiatae) is distributed extensively in China except for the northwest and Inner Mongolia region. The aerial part of *Glechoma longituba* (Nakai) Kupr. has been used in China as a medicinal herb with the effect of clearing away heat, detoxicating and invigorating the circulation of blood [1]. Previous phytochemical study revealed the existence of triterpenoids [2,3], sesquiterpenoids [4], caffeic acid and its derivatives [5–7] from the genus *Glechoma*. In order to know more about the constituents of this medicinal plant, systematic chemical investigation was made on the whole plant of *Glechoma longituba* (Nakai) Kupr. We herein report the isolation and structural identification of two new pinane-type monoterpenoid glucosides characterised as 2α-pinan-3-one-2-*O*-β-glucopyranoside (**1**) and 5α-pinan-3-one-5-*O*-β-glucopyranoside (**2**). Besides the two new compounds, 13 known compounds were also isolated and identified as (1*S*,2*S*,3*R*)-2,3-pinanediol (**3**) [8], 1α,5β-guai-10(14)-ene-4α,6β-diol (**4**) [9], 1α,5β-guaiane-4α,6β,10α-triol (**5**) [9], 1β,10α,4β,5α-diepoxy-7αH-germacran-6β-ol (**6**) [10], rosmarinic acid (**7**) [11], methyl rosmarinate (**8**) [12], apigenin-7-*O*-β-D-glucopyranoside (**9**) [13], luteolin-7-*O*-β-D-glucopyranoside (**10**) [13], 4-allyl-2,6-dimethoxyphenol-1-*O*-β-D-glucopyranoside (**11**) [14], 4-allyl-2-methoxyphenol-1-*O*-β-D-glucopyranoside (**12**) [15], (6*R*,9*R*)-3-oxo-α-ionol-9-*O*-β-D-glucopyranoside (**13**) [15], apigenin (**14**) [16], and luteolin (**15**) [17], respectively (figure 1).

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2. Results and discussion

Compound **1** was obtained as a white amorphous powder with molecular formula $C_{16}H_{26}O_7$ deduced from HRESI-MS and NMR analysis. The IR spectrum of **1** showed the presence of carbonyl function ($1710\,cm^{-1}$) and hydroxyl groups ($3350–3560\,cm^{-1}$) in the molecule.

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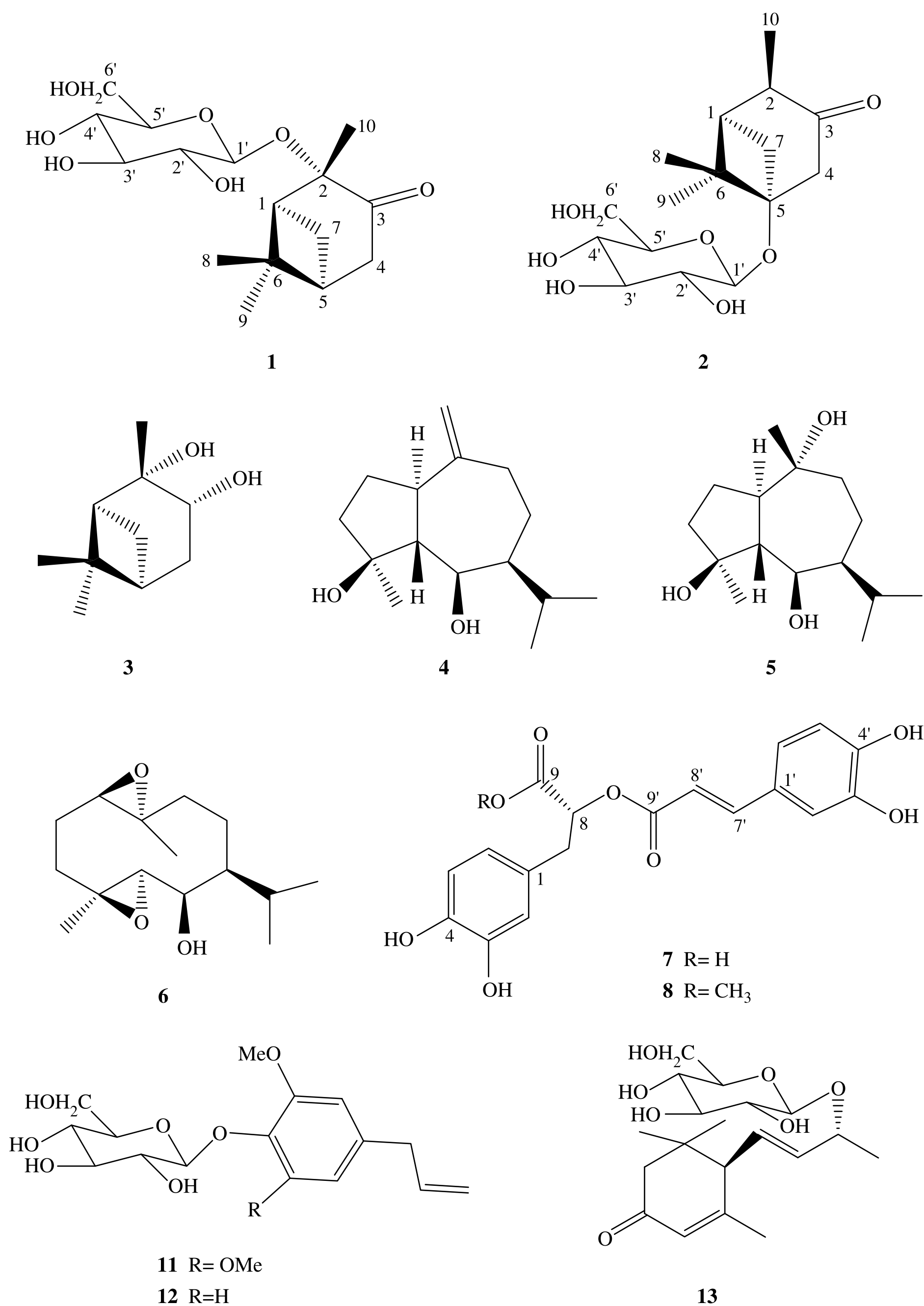

Figure 1. Structures of compounds **1**–**8** and **11**–**13**.

Enzymatic hydrolysis of **1** revealed glucose as its sugar component by co-TLC with authentic sample. The ^{1}H NMR spectrum of **1** showed the presence of three methyl groups at δ 0.71 (3H, s), 1.21 (3H, s), and 1.30 (3H, s); one anomeric proton signal of β-glucopyranosyl moiety at δ 4.20 (1H, d, 8.0 Hz). The ^{13}C NMR spectrum of **1** displayed 16 carbon signals separated by DEPT experiment into three methyls, three methylenes, seven methines, and three quaternary carbons. Analysis of the ^{1}H–^{1}H COSY (figure 2) and HMQC spectra of **1** led to the fragment -CH(1)-CH$_2$(7)-CH(5)-CH$_2$(4) in its structure. The planar structural skeleton of **1** was further established on the basis of its HMBC spectrum (figure 2), in which, ^{1}H–^{13}C long-range correlation signals were observed at H-1/C-2, C-3, C-6, C-9, C-10; H-4β/C-3, C-6, C-7; H-5/C-1; H-7α and H-7β/C-1, C-2, C-4; H$_3$-8/C-1, C-5, C-9; H$_3$-10/C-1, C-2, C-3; H$_3$-9/C-1, C-5, C-8; and H-1′/C-2. The relative configuration of **1** was determined from its ROESY spectrum (figure 3), in which, NOE correlation signals were found between H-1 (2.10) and H-5 (2.02), H-4α (2.82) and H-7α (1.90), H-7β (2.30) and H$_3$-9 (1.30), H$_3$-8 (0.71) and H-4β (2.42), and between H$_3$-10 (1.21) and H$_3$-8 (0.71). The cross-peak between H-4β (2.42) and H$_3$-10 (1.21) was not observed in its ROESY spectrum, which indicated that both of these groups were in equatorial orientation and the conformation of the ring (composed by C1, C2, C3, C4, C5 and C6) was in boat orientation in agreement with that of the Dreiding model. Therefore, **1** was determined to be 2α-pinan-3-one-2-*O*-β-glucopyranoside, which is a new compound.

Compound **2** was obtained as a colourless gum with molecular formula $C_{16}H_{26}O_7$ deduced from HRESI-MS and NMR analysis. The IR spectrum of **2** showed the presence of carbonyl function (1712 cm^{-1}) and hydroxyl groups (3350–3550 cm^{-1}) in the molecule. Enzymatic hydrolysis of **2** revealed glucose as its sugar moiety. The ^{1}H NMR spectrum of **2** exhibited three methyl groups at δ 0.78 (3H, s), 1.08 (3H, d, 7.4 Hz), and 1.20 (3H, s); and one anomeric proton signal of β-glucopyranosyl moiety at δ 4.20 (1H, d, 7.9 Hz). The ^{13}C NMR spectrum of **2** displayed 16 carbon signals separated by DEPT experiment into three methyls, three methylenes, seven methines, and three quaternary carbons. Analysis of the ^{1}H–^{1}H COSY (figure 2) and HMQC spectra of **2** led to the following fragments CH$_3$(10)-CH(2) and CH(1)-CH$_2$(7). The cross-peak between H-1 and H-2 in the ^{1}H–^{1}H COSY spectrum was not observed. Analysis of the 3D-structure of **2** generated from the Dreiding model indicated the dihedral angle between H-1 and H-2 to be around 90°, which conformed to $^3J_{1,2} \approx 0$ Hz.

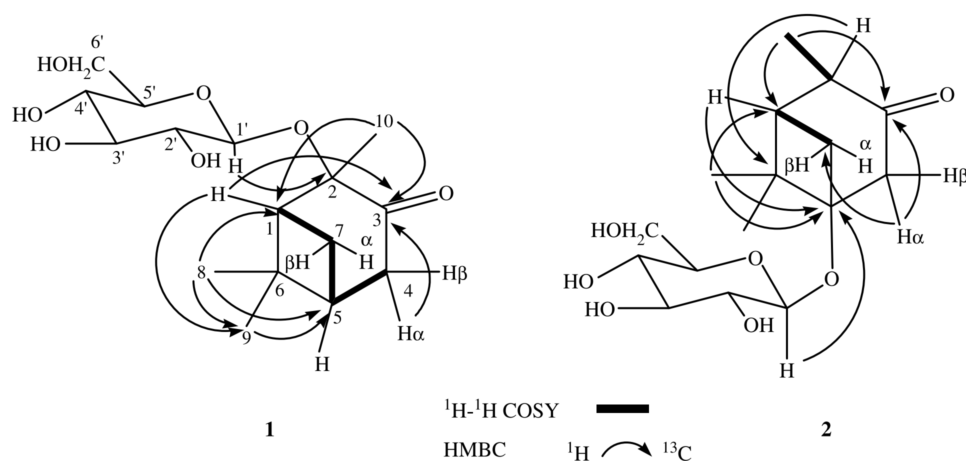

Figure 2. ^{1}H–^{1}H COSY and key HMBC correlations of **1** and **2**.

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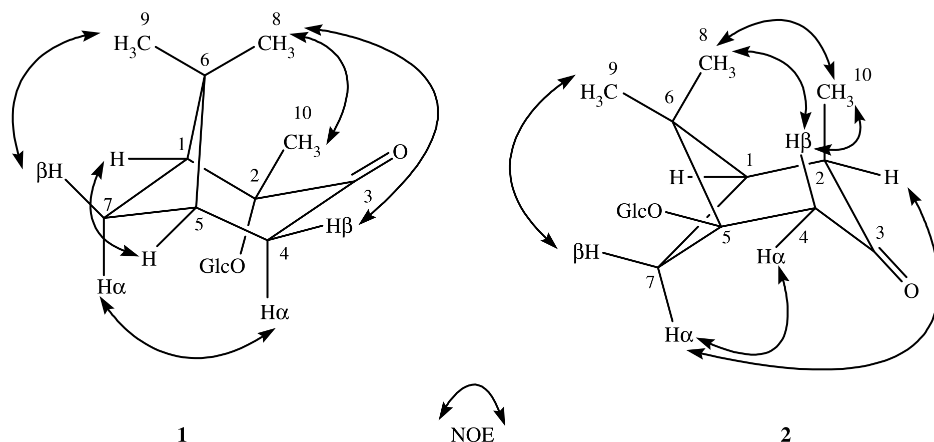

Figure 3. Main NOE correlations in the ROESY spectrum of **1** and **2**.

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The planar structural skeleton of **2** was established on the basis of its HMBC spectrum (figure 2), in which, the HMBC correlations were observed at H-1/C-3, C-5, C-6, C-7, C-9, C-10; H-2/C-1, C-3, C-7, C-10; H-4β/C-3, C-5, C-7; H-7α/C-1, C-2, C-4, C-5, C-6; H_3-8/C-1, C-5, C-7, C-9; H_3-9/C-1, C-5, C-6, C-8; H_3-10/C-1, C-2, C-3; and H-1′/C-5. The relative configuration of **2** was determined from its ROESY spectrum (figure 3), in which, NOE correlations were found between H-2α (2.32) and H-7α (1.66), H-4α (2.83) and H-7α (1.66), H-7β (2.55) and H_3-9 (1.20), and between H_3-10β (1.08) and H_3-8 (0.78), H-4β (2.55). The correlation between H-4β (2.55) and H_3-10β (1.08) could be observed in its ROESY spectrum compared with that of **1**, which indicated that H-4β and H_3-10β were in axial orientation and the conformation of the ring (composed by C1, C2, C3, C4, C5, and C6) was in chair orientation according to Dreiding model analysis. Therefore, **2** was determined to be 5α-pinan-3-one-5-*O*-β-glucopyranoside which is also a new compound.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured with Perkin–Elmer 241MC or 341 polarimeters. UV spectra were recorded with a Beckman DU-7 spectrometer. IR spectra were recorded using a Perkin–Elmer 577 spectrometer. LRESI-MS were measured using a Finnigan LCQ-DECA instrument, and HRESI-MS data were obtained on a Mariner spectrometer. The NMR experiments were run on a Bruker AM 400 spectrometer with TMS as internal standard. Preparative HPLC was carried out using a Varian SD-1 instrument equipped with a Merck NW25 C_{18} column (10 μm, 20 mm × 250 mm) and ProStar 320 UV/Vis Detector. Column chromatographic separations were carried out using silica gel H60 (300–400 mesh), zcx-II (100–200 mesh) (Qingdao Haiyang Chemical Group Corp., Qingdao, China), macroporous resin D101 (Huazhen Polymer Co. Ltd, Shanghai, China) as packing materials. Lobar column chromatography was carried out using Lichroprep Si60 (40–63 μm) (Merck, Germany) equipped with a LabAlliance Series I pump (LabAlliance Co., USA). HSGF254 silica gel TLC plates (Yantai Chemical Industrial Institute, Yantai, China) and RP-18 WF_{254} TLC plates (Merck) were used for analytical TLC.

3.2 Plant material

The whole plant of *Glechoma longituba* was collected in the suburb of Guangzhou, Guangdong province, China, in May 2003, and identified by Professor Zexian Li of South China Institute of Botany, Chinese Academy of Sciences. A voucher specimen (No. 060713SIMM) is deposited in the herbarium of Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

3.3 Extraction and isolation

Air-dried and powered whole plant (3.0 kg) of *Glechoma longituba* was extracted with 95% EtOH three times, each for 3 days at room temperature. The extract was concentrated to dryness *in vacuo* and then suspended in 20% EtOH overnight. After filtration of the precipitated chlorophyll and removal of EtOH from the filtrate *in vacuo*, the aqueous residue (500 ml) was partitioned with $CHCl_3$ and *n*-butanol (500 ml × 3), successively, yielding $CHCl_3$ extract (4.8 g) and *n*-butanol extract (22.1 g), respectively. The $CHCl_3$ extract (4.8 g) was subjected to VLC over silica gel H60 using petroleum ether/acetone gradient (20:1, 10:1, 8:1, 6:1, 4:1, and 2:1, each 500 ml) as eluent. Combination of the eluent by TLC evidence yielded five fractions (C1–C5). Fraction C1 (102 mg) was further purified by preparative HPLC with CH_3OH/H_2O (20–80% in 60 min) as eluent to afford compounds **3** (30.3 mg) and **4** (10.1 mg); Fraction C2 (1.0 g) was subjected to preparative HPLC eluting with CH_3OH/H_2O (20–80% in 60 min) and further purified by using normal phase Lobar column eluted with petroleum ether/acetone (6:1) to give compound **5** (12.2 mg); Fraction C3 (1.2 g) was separated by preparative HPLC eluting with CH_3OH/H_2O (20–80% in 60 min) and by using Lobar column with petroleum ether/acetone (5:1) to afford compound **6** (33.3 mg). The *n*-butanol extract (22.1 g) was separated into four fractions (B1–B4) through column chromatography over macroporous resin D101 eluted with $EtOH/H_2O$ gradient (1:9, 3:7, 3:2, and 9:1, each 800 ml). Fraction B2 (8.0 g) was chromatographed by preparative HPLC eluting with CH_3OH/H_2O (20–80% in 60 min) to give two subfractions (B2A and B2B). Fraction B2A was subjected to preparative TLC using $CHCl_3/CH_3OH/H_2O$ (3:1:0.1) as developing solvent to afford compounds **7** (118.2 mg), **8** (44.2 mg), **9** (5.5 mg), and **10** (3.5 mg). Fraction B2B was subjected to preparative HPLC eluting with CH_3OH/H_2O (20–80% in 60 min) and preparative TLC using $CHCl_3/CH_3OH/H_2O$ (5:1:0.1) to afford compounds **1** (17.1 mg), **2** (14.2 mg), **11** (11.4 mg), **12** (40.3 mg), **13** (11.2 mg), **14** (6.3 mg), and **15** (3.2 mg).

3.3.1 2α-Pinan-3-one-2-*O*-β-glucopyranoside (1). White amorphous powder; $[\alpha]_D^{24}$ + 4.0 (*c* 0.25, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3560–3350, 2987, 2921, 1710, 1413, 1371, 1064, 1020. ^1H NMR and ^{13}C NMR spectral data: see table 1. LRESI-MS: *m/z* 353.2 $[M + Na]^+$; HRESI-MS: *m/z* 353.1568 $[M + Na]^+$ (calcd for $C_{16}H_{26}O_7Na$, 353.1576) and 369.1322 $[M + K]^+$ (calcd for $C_{16}H_{26}O_7K$, 369.1316).

3.3.2 5α-Pinan-3-one-5-*O*-β-glucopyranoside (2). Colourless gum; $[\alpha]_D^{24}$ −1.0 (*c* 0.20, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3550–3350, 2973, 2935, 2879, 1712, 1456, 1373, 1076, 1035. ^1H NMR and ^{13}C NMR spectral data: see table 1. LRESI-MS: *m/z* 369.2 $[M + K]^+$; HRESI-MS: *m/z* 369.1328 $[M + K]^+$ (calcd for $C_{16}H_{26}O_7K$, 369.1316).

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Table 1. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectral data of **1** and **2** (DMSO-d_6).

	1		*2*	
No.	δ_C	δ_H *(Hz)*	δ_C	δ_H *(Hz)*
1	49.9 (d)	2.10 (1H, dd, 6.2, 5.6)	37.4 (d)	1.88 (1H, dd, 7.5, 1.8)
2	80.9 (s)		48.3 (d)	2.32 (1H, q, 7.4)
3	209.9 (s)		213.4 (s)	
4α	43.8 (t)	2.82 (1H, m)	49.8 (d)	2.83 (1H, d, 18.6)
4β		2.42 (1H, br d, 18.3)		2.55 (1H, m)
5	38.6 (d)	2.02 (1H, m)	77.3 (s)	
6	38.3 (s)		43.6 (s)	
7α	28.4 (t)	1.90 (1H, d, 10.9)	38.3 (t)	1.66 (1H, d, 9.4)
7β		2.30 (1H, m)		2.55 (1H, m)
8	22.3 (q)	0.71 (3H, s)	19.7 (q)	0.78 (3H, s)
9	27.4 (q)	1.30 (3H, s)	22.7 (q)	1.20 (3H, s)
10	22.8 (q)	1.21 (3H, s)	16.3 (q)	1.08 (3H, d, 7.4)
1′	95.7 (d)	4.20 (1H, d, 8.0)	98.1 (d)	4.20 (1H, d, 7.9)
2′	72.8 (d)	2.85 (1H,dd, 8.2, 9.0)	73.4 (d)	2.92 (1H, dd, 8.5, 7.9)
3′	77.0 (d)	3.08 (1H, dd, 9.0, 8.4)	76.7 (d)	3.12 (1H, dd, 8.5, 8.6)
4′	70.1 (d)	3.01 (1H, dd, 9.6, 8.4)	70.1 (d)	3.00 (1H, dd, 8.6, 9.3)
5′	76.3 (d)	2.79 (1H, m)	76.7 (d)	3.07 (1H, m)
6′	60.9 (t)	3.34 (1H, dd, 11.7, 5.3)	61.1 (t)	3.36 (1H, dd, 11.7, 6.1)
		3.52 (1H, m)		3.65 (1H, dd, 11.7, 1.4)

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3.4 Enzymatic hydrolysis of 1 and 2

Compounds **1** and **2** (each 1 mg) were dissolved in 0.5 ml H_2O together with β-cellulase (1 mg), respectively. After keeping at 37°C for 3 days, the aqueous solution and authentic sugar samples were analysed by co-TLC, and glucose was identified in the aqueous solution (EtOAc/MeOH/H_2O/HOAc, 13:3:3:4, R_f 0.46).

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