Four ionones and ionone glycosides from the whole plant of *Rehmannia piasezkii*

Jie Zhou, Guo-Ru Shi, Wan-Qi Zhang, Ruo-Yun Chen, Yan-Fei Liu and De-Quan Yu

State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

**ABSTRACT**

Four new ionones and ionone glycosides (1–4) were isolated from the whole plant of *Rehmannia piasezkii* Maxim. Their planar structures as well as absolute configuration were confirmed via spectroscopic analysis, ECD calculation, and X-ray crystallography. Compounds 1–4 were tested for their cytotoxicity against five human tumor cell lines and ability to inhibit LPS-activated NO production in the BV2 cell line.

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1. Introduction

*Rehmannia piasezkii* Maxim. is one of the *Rehmannia* (Scrophulariaceae) six species, mainly distributed in Hubei province in mainland China and has been used as a folk medicine for traumatic burns and sores. However, the chemical and pharmacological study of this plant has not yet been carried out thoroughly. Previous phytochemical studies on *R. glutinosa*, *R. chingii*, and *R. henryi* have led to the isolation and identification of iridoid glycosides, ionone glycosides, and phenethyl alcohol glycosides [1–8]. Many of the compounds exhibited anti-inflammatory and hepatoprotective activities. As part of ongoing research on *Rehmannia* species, further phytochemical investigation was carried out on the whole plant of *R. piasezkii*. In the article, four new ionones and ionone glycosides were isolated from the water extract of the whole plant of *R. piasezkii*. Herein, we describe the isolation, structural elucidation, and biological evaluation of the isolated compounds.

2. Results and discussion

Compound 1, obtained as colorless crystals from MeOH, possessed a molecular formula of C_{13}H_{26}O_{4} by HRESIMS at m/z 269.1725 [M + Na]^+ , indicating one indice of
hydrogen deficiency. The \( ^1H \) NMR spectrum showed four methyl protons at \( \delta_H 0.97 \) (3H, s, H-11), 1.17 (3H, d, \( J = 6.6 \) Hz, H-10), 1.18 (3H, s, H-12), and 1.24 (3H, s, H-13), four methylenes, two oxygenated methine protons at \( \delta_H 3.98 \) (1H, tt, \( J = 10.2, 3.6 \) Hz, H-3) and \( \delta_H 3.67-3.72 \) (1H, m, H-9). The \( ^13C \) NMR data (Table 1) exhibited 13 carbon resonances, and were assigned by HSQC spectrum to four methyls at \( \delta_C 23.6 \) (C-12), 25.6 (C-10), 27.6 (C-13), and 28.4 (C-11), four methylenes at \( \delta_C 27.3 \) (C-7), 46.7 (C-4), and 47.4 (C-2), two oxygenated methines at \( \delta_C 65.2 \) (C-3) and 69.8 (C-9), two oxygenated tertiary carbons at \( \delta_C 77.3 \) (C-6) and 79.0 (C-5), and one quaternary carbon at \( \delta_C 41.9 \) (C-1). The planar structure of 1 was confirmed by 2D NMR analysis (Figure 1). The \(^1H–^1H\) COSY correlations implied two proton spin systems of H-2/H3-11 and H2-7/H2-8/H-9/H3-10. The HMBC correlations (Figure 2) from H3-11 and H3-12 to C-1, C-2, and C-6 indicated the linkage of C-2, C-6, C-11, and C-12 to the quaternary carbon C-1. The correlations from H3-13 to C-4, C-5, and C-6, and from H2-7 to C-6 constructed the connections of C-4, C-6, C-13 to C-5 and C-7–C-8–C-9–C-10. Thus, compound 1 was determined to be a norcarotenoid as shown (Figure 1).

ROESY correlations and the coupling constant analyses of H-3 was assigned the relative configuration. The coupling constants of H-3 were \( J = 10.2 \) and 3.6 Hz, indicating that the H-3 occupied an axial position according to the typical ax–ax and ax–eq coupling constants. ROESY correlations of H-3/H3-12 and H2-7 implied that these protons were \( \alpha \)-oriented. The cross-peaks of H-4/H3-11 and H3-13 indicated the protons were \( \beta \)-oriented. The absolute configuration of 1 was confirmed as 3S, 5R, 6R, 9S by single-crystal X-ray diffraction analysis with a Flack parameter of \(-0.06(9)\) (Figure 3). Therefore, piasezkiiosine A was characterized as shown.

For compound 2, its molecular formula was determined as C\(_{13}\)H\(_{24}\)O\(_4\) from the HRESIMS (m/z 267.1565 [M + Na]+), which is 2 mass less than compound 1, requiring an extra index of hydrogen deficiency. The IR spectrum showed absorption at 1712 cm\(^{-1}\) and 1573 cm\(^{-1}\) due to double-bond functionality. The \( ^13C \) NMR spectrum exhibited two olefinic carbons (\( \delta_C 135.8, 131.4 \)), two methylenes (\( \delta_C 27.7, 35.9 \)), two methines (\( \delta_C 74.8, 69.6 \)), three hydrogen free carbons (\( \delta_C 44.4, 75.4, 81.5 \)), and four methyl carbons (\( \delta_C 24.1, 22.8, 17.7, 26.8 \)). Analysis of the \(^1H–^1H\) COSY correlations (Figure 2) of H2-3 (\( \delta_H 1.92-1.93 \) and 1.50-1.51)/H-2 (\( \delta_H 3.72 \)) and H-4 (\( \delta_H 1.92-1.93 \) and 1.50-1.51), and H-9 (\( \delta_H 4.34-4.36 \))/H-8 (\( \delta_H 5.74 \)) and H3-10 (\( \delta_H 1.27 \)), combined with the HMBC cross-peaks of H3-11 (\( \delta_H 0.93 \))/C-1, C-2, and C-6, H3-12 (\( \delta_H 1.10 \))/C-1, C-2, and C-6, H-7 (\( \delta_H 6.11 \))/C-5, C-6, and C-8, and H3-13 (\( \delta_H 1.04 \))/C-5 and C-6 revealed the planar structure of 2. The coupling constants of H-2 were \( J = 11.4 \) and 5.6 Hz, indicating that H-2 occupied an axial position according to the typical ax–ax and ax–eq coupling constants, and ROESY correlations of H-2/H3-11 and H3-13 suggested H-2, H3-11, and H3-13 are all \( \beta \)-oriented. And the configuration of HO-9 was determined by the results of Mosher’s experiment. The results of \( \Delta \delta \) \( R-S \) (H-7 and H-8) > 0 and \( \Delta \delta \) \( R-S \) (H-10) < 0 indicated the configuration of C-9 was S (Figure 4). Herein, piasezkiiosine B was characterized as shown.

Compound 3 gave a molecular formula of C\(_{19}\)H\(_{34}\)O\(_9\) by HRESIMS at m/z 429.2092 [M + Na]+, 162 mass units higher than that of 2, in accordance with the presence of a glucopyranose. Its NMR data were similar to those of 2 except for evidence of the
Table 1. $^1$H and $^{13}$C NMR spectral data of compounds 1–4.

| Position | $\Delta$C | $\delta_{^1}$H | $\delta_{^{13}}$C | $\Delta$C | $\delta_{^1}$H | $\delta_{^{13}}$C | $\Delta$C | $\delta_{^1}$H | $\delta_{^{13}}$C |
|----------|------------|----------------|----------------|------------|----------------|----------------|------------|----------------|----------------|
| 1        | 41.9       | 44.4           | 44.6           | 47.9       |                |                |
| 2        | 47.4       | $\alpha$ 1.63-1.64 m | 74.8 | 3.72 dd (11.4, 5.6) | 74.8 | 3.74 dd (12.6, 4.8) | 28.6 | $\alpha$ 1.85 td (13.2, 4.2) |                |
|          |            | $\beta$ 1.36 ddd (10.8, 4.2, 2.4) |        |            |                |                |
| 3        | 65.2       | 3.98 tt (10.2, 3.6) | 27.7 | $\alpha$ 1.92-1.93 m | 27.3 | $\alpha$ 1.42 ddd (12.0, 7.8, 3.6) | 19.0 | $\alpha$ 2.03-2.05 m |                |
|          |            |                |                | $\beta$ 1.50-1.51 m | $\beta$ 2.12 dt (12.0, 5.4) | $\beta$ 1.35-1.37 m |
| 4        | 46.7       | $\alpha$ 1.74 dd (4.8, 3.6) | 35.9 | $\alpha$ 1.92-1.93 m | 31.8 | 1.77-1.78 m | 33.0 | 1.67-1.69 m |                |
|          |            | $\beta$ 1.66-1.67 m |                | $\beta$ 1.50-1.51 m |                |                |
| 5        | 79.0       |                | 75.4 |                | 83.3 |                | 81.7 |                |                |
| 6        | 77.3       |                | 81.5 |                | 81.1 |                | 82.2 |                |                |
| 7        | 27.3       | a 1.89-1.90 m | 131.4 | 6.11 dd (15.6, 1.8) | 132.2 | 6.24 dd (16.2, 1.2) | 81.2 | 4.75 d (7.8) |                |
|          |            | b 1.68-1.69 m |                |                |                |                |
| 8        | 35.8       | 1.68-1.69 m | 135.8 | 5.74 dd (15.6, 6.6) | 135.1 | 5.68 dd (16.2, 6.0) | 129.7 | 5.70 ddd (15.6, 7.8, 1.8) |                |
| 9        | 69.8       | 3.67-3.72 m | 69.6 | 4.34-4.36 m | 69.6 | 4.33-4.37 m | 131.9 | 5.90 ddd (15.6, 6.6, 1.2) |                |
| 10       | 25.6       | 1.17 d (6.6) | 24.1 | 1.27d (6.6) | 24.2 | 1.27 d (6.6) | 18.3 | 1.74 dd (6.6, 1.8) |                |
| 11       | 28.4       | 0.97 s | 22.8 | 0.93 s | 22.9 | 0.90 s | 24.4 | 1.43 s |                |
| 12       | 23.6       | 1.18 s | 17.7 | 1.10 s | 18.1 | 1.06 s | 80.1 | 1.38 br d (6.0) |                |
| 13       | 27.6       | 1.24 s | 26.8 | 1.04 s | 21.9 | 1.15 s | 22.5 | 1.26 s |                |
| $1'$     |            |                | 98.1 | 4.45 d (7.8) | 98.3 | 4.45 d (7.8) |                |                |
| $2'$     |            |                | 75.5 | 3.18-3.20 m | 75.3 | 3.18 ddd (9.0, 7.8) |                |                |
| $3'$     |            |                | 79.2 | 3.34 t (9.0) | 79.1 | 3.34-3.36 m |                |                |
| $4'$     |            |                | 71.8 | 3.27 t (9.6) | 71.6 | 3.30-3.32 m |                |                |
| $5'$     |            |                | 77.4 | 3.20 t (9.0) | 77.3 | 3.20-3.22 m |                |                |
| $6'$     |            |                | 62.8 | a 3.80 dd (12.0, 2.4) | 62.9 | a 3.80 dd (12.0, 2.4) |                |                |
|          |            |                | b 3.60 dd (12.0, 6.0) | b 3.66 dd (12.0, 5.4) |                |                |

$^a$ $^1$H NMR ($\delta$) recorded at 600 MHz in CD$_3$OD, $^{13}$C NMR ($\delta$) recorded at 150 MHz in CD$_3$OD.
presence of the glucopyranose at C-5 in 3. This was confirmed by HMBC correlations from H-1' to C-5. Acid hydrolysis of 3 afforded d-glucose, which was identified by TLC comparison and measurement of optical rotation value. The β-anomeric configuration for glucosyl unit was judged from its large $J_{H_1, H_2}$ coupling constant ($J = 7.8$ Hz). Thus, the structure of piasezkiinoside A was characterized as shown.

Compound 4 gave a molecular formula as $C_{19}H_{32}O_{8}$ established by HRESIMS at $m/z$ 411.1984 [M+Na]$^+$, attributed to four indices of hydrogen deficiency. The $^{13}$C NMR spectrum showed 19 carbon signals including 6 for a glucopyranosyl unit and remaining 13 for an ionone skeleton. The planar structure was assigned by $^1$H–$^1$H COSY and HMBC spectra. The proton spin systems of H$_2$-2/H$_2$-3/H$_2$-4 and H-7/H-8/H-9/H$_3$-10 in $^1$H–$^1$H COSY spectrum, together with the HMBC correlations from H$_2$-12 and H$_3$-11 to C-1, C-2, and C-6, H$_3$-13 to C-4, C-5, and C-6, besides the cross-peaks of H$_2$-12/C-7 and H-7/C-12 indicated an extra ether bridge between C-7

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

**Figure 2.** The $^1$H–$^1$H COSY and key HMBC correlaitons of 1–4.

**Figure 3.** The ORTEP drawing of 1.
and C-12. And the glucopyranosyl was located at C-5 based on the HMBC correlation from H-1’ to C-5. The sugar was confirmed as α-glucose by comparison with an authentic sample and by measuring its optical rotation. In ROESY spectrum, correlations of H3-11/H-2β, H-7, H-12β, and H3-13, indicated these protons were all β-oriented. The CD spectrum of 4 exhibited similar Cotton effect (negative at 227 nm) to that of frehmaglutin D [3], indicating that the asymmetric centers at C-1, C-5, C-6 and C-7 were 1R, 5R, 6S, 7R configurations. Therefore, piasezkiionoside B (4) was characterized as shown.

Compounds 1–4 were tested for their cytotoxicity against five tumor cell lines, (HCT-116, U251, HGC27, HepG2 and MCF7). However, all were inactive for all cell lines used (IC50 > 10 μM). These compounds were evaluated for their inhibitory activity against lipopolysaccharide (LPS)-induced nitric oxide (NO) production in murine microglia BV2 cells, and all were inactive (cell viability < 60%).

3. Experimental

3.1. General experimental procedures

Optical rotations were measured with a JASCO P-2000 polarimeter, and UV spectra with a JASCO V-650 spectrophotometer (JASCO Corporation, Tokyo, Japan). IR spectra were recorded on a Nicolet 5700 spectrometer (Thermo Electron Scientific Instruments Corp., Madison, USA) by an FT-IR microscope transmission method. NMR measurements were performed on Bruker AV600 IIIHD spectrometers using TMS as an internal reference (Bruker Biospin Corporation, Fallanden, Switzerland), and chemical shifts are expressed in ppm with reference to the CD3OD (δH 3.31/δC 49.0) signals. HRESIMS were obtained using an Agilent 1100 series LC/MSD ion trap mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). ECD spectra were recorded on JASCO J-815 spectropolarimeter. The crystallographic data were recorded on a XtaLAB Synergy R HyPix diffractometer (Rigaku Americas Corporation, Poland). Silica gel (200–300 mesh, Qingdao Marine Chemical Factory, Qingdao, China), amino silica gel (NH MB100-40/75 Fuji Silysia Chemical, Tokyo, Japan), Sephadex LH-20 (GE, Sweden), and ODS (50 μm, YMC, Kyoto, Japan) were used for column chromatography. Analytical thin-layer chromatography (TLC) was carried out with GF254 plates (Qingdao Marine Chemical Factory). Spots were visualized by spraying with 10% H2SO4 in 95% EtOH followed by heating.

3.2. Plant material

Whole plants of *Rehmannia piasezkii* Maxim were collected in Hubei Province, China, in July 2019, and identified by associate Professor Lin Ma (Institute of Materia
Medica, Chinese Academy of Medical Sciences & Peking Union Medical College). A voucher specimen (ID – S – 2982) has been deposited at the Herbarium of Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing.

3.3. Extraction and isolation

The whole plants of *R. piasezkii* (15.0 kg) was extracted with H$_2$O (2 × 100 L) under reflux (1 h each). The combined extracts were concentrated under reduced pressure to dryness (1.5 kg). The residue was suspended in H$_2$O and applied to a Diaion HP20 column eluted gradiently with EtOH/H$_2$O (0:100, 10:90, 50:50, 95:5, v/v, each 10 L) to afford four main fractions (Frs. A–D) based on TLC analysis.

Fraction B (304.6 g) was separated using a reversed-phase C$_{18}$ silica gel column (20 × 45 cm), to provide twelve subfractions (B1–B12). B7 (6.7 g) was fractioned over silica gel (CH$_2$Cl$_2$/MeOH, 10:1, 5:1, 2:1, 1:1, 1:5, 1:10) to afford five subfractions (B7a–B7e).

**3.3.1. Piasezkiiosine A (1)**

Colorless crystal, mp 72.1–73.2°C, [α]$_D^{20}$ -9.4 (c 0.25, MeOH); UV (MeOH) $\lambda_{max}$ (log ε) 204.0 (2.91) nm; IR $\nu_{max}$ 3383, 2965, 2925, 1462, 1374, 1041, 929, 861 cm$^{-1}$; $^1$H NMR (methanol-d$_4$, 600 MHz) and 13C NMR (methanol-d$_4$, 150 MHz) spectral data see Table 1; (+)HRESIMS: m/z 269.1725 [M + Na]$^+$ (calcd for C$_{13}$H$_{26}$O$_4$Na, 269.1723).

**3.3.2. Piasezkiiosine B (2)**

White amorphous powder, [α]$_D^{20}$ -4.9 (c 0.25, MeOH); UV (MeOH) $\lambda_{max}$ (log ε) 203.2 (3.50) nm; IR $\nu_{max}$ 3380, 2926, 1712, 1573, 1371, 1063, 1046, 983, 938, 874 cm$^{-1}$; $^1$H NMR (methanol-d$_4$, 600 MHz) and 13C NMR (methanol-d$_4$, 150 MHz) spectral data see Table 1; (+)HRESIMS: m/z 267.1565 [M + Na]$^+$ (calcd for C$_{13}$H$_{24}$O$_4$Na, 267.1566).

**3.3.3. Piasezkiionoside A (3)**

White amorphous powder, [α]$_D^{20}$ -56.1 (c 0.65, MeOH); UV (MeOH) $\lambda_{max}$ (log ε) 202.6 (3.88), 226.2 (3.42), 276.4 (2.59) nm; IR $\nu_{max}$ 3349, 2926, 1455, 1417, 1374, 1080, 1046, 938 cm$^{-1}$; $^1$H NMR (methanol-d$_4$, 600 MHz) and 13C NMR (methanol-d$_4$, 150 MHz) spectral data see Table 1; (+)HRESIMS: m/z 267.1565 [M + Na]$^+$ (calcd for C$_{13}$H$_{24}$O$_4$Na, 267.1566).
150 MHz) spectral data see Table 1; (+)HRESIMS: m/z 429.2092 [M + Na]⁺ (calcd for C₁₉H₃₄O₉Na, 429.2095).

3.3.4. Piasezkiionoside B (4)
White amorphous powder, [α]D²⁰ +36.4 (c 1.20, MeOH); UV (MeOH) λmax (log ε) 203.8 (3.88), 274.4 (2.90) nm; CD (MeCN): Δε 227 nm − 0.21; IR νmax 3396, 2932, 1716, 1454, 1375, 1077, 1034, 988 cm⁻¹;¹H NMR (methanol-d₄, 600 MHz) and ¹³C NMR (methanol-d₄, 150 MHz) spectral data see Table 1; (+)HRESIMS: m/z 411.1984 [M + Na]⁺ (calcd for C₁₉H₃₂O₈Na, 411.1989).

3.4. X-ray crystallographic analysis of piasezkiiosine A (1) (MeOH)
Crystal data for compound 1: C₁₃H₂₆O₄, M = 246.34, orthorhombic, T = 293(2) K, λ = 1.54184 Å, colorless crystal (crystallized from MeOH at room temperature), size 0.25 × 0.17 × 0.13 mm³, a = 7.56950(10) Å, b = 11.47630(10) Å, c = 15.9873(2) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 1388.81(3), space group P2₁2₁2₁, Z = 4, Dc = 1.178 g/cm³, μ (Cu Kα) = 0.692 mm⁻¹, F (000) = 544.0 reflections and 2498 independent reflections (Rint = 0.0268) were collected in the θ range of (9.486° ≤ 2θ ≤ 144.268°) with index ranges of −9 ≤ h ≤ 9, −10 ≤ k ≤ 14, −13 ≤ l ≤ 19, completeness θmax = 98%, data/restraints/parameters 2498/0/163. Largest difference peak and hole = 0.17 and −0.11 e Å⁻³. The final R1 value was 0.0319 (I > 2σ(I)). The final wR2 value was 0.0776 (I > 2σ(I)). The final R1 value was 0.0331 (all data). The final wR2 value was 0.0792 (all data). The goodness of fit on F² was 1.070. Flack parameter was −0.06 (9).

Crystallographic data for piasezkiiosine A (deposition numbers: CCDC 2131492) has been deposited in the Cambridge Crystallographic Data Centre.

3.5. Acid hydrolysis of 3–4
Each compound (5.0 mg) was individually refluxed in 6% HCl (5.0 ml) at 80°C for 2 h. Each reaction mixture was extracted with CHCl₃ (3 × 6 ml), and the H₂O phase was dried using a N₂ stream. The residues were separately subjected to column chromatography over silica gel with EtOAc-EtOH-H₂O (7:4:1) as eluent to yield glucose (0.97 mg) from 3, [α]D²⁰ +49.5 (c 0.10, H₂O); and glucose (1.53 mg) from 4, [α]D²⁰ +49.0 (c 0.15, H₂O), respectively. The sugars were confirmed as D-glucose by comparison with an authentic sample on TLC (EtOAc-EtOH-H₂O, 7:2:1, Rf 0.09) and by measuring its optical rotation as shown above.

3.6. Cytotoxicity assay
Compounds 1–4 were tested for cytotoxicity against five human tumor cell lines, HCT-116 (human colon cancer cell line), U251 (human brain tumor stem cell line), HGC27 (human gastric cancer cell line), HepG2 (human hepatoma cell line) and MCF7 (human breast cancer cell line) by means of an MTT method described in the literature. Taxol was used as the positive control [9].
3.7. Inhibitory effects on NO production in LPS-activated microglia

Compounds 1–4 were tested for the ability to inhibit LPS-activated NO production in the BV2 cell line based on the reported method. Curcumin was used as positive control [10].

Disclosure statement

No potential conflict of interest was reported by the author(s).

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