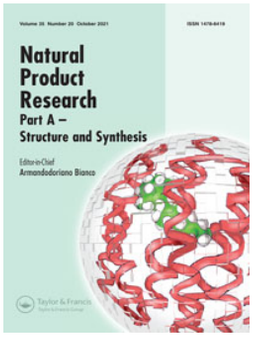

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Phenoxychromone and 4-hydroxyisoflavans from the roots of *Glycyrrhiza uralensis*

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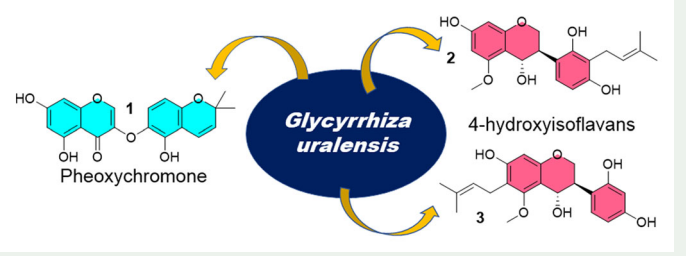
ABSTRACT

In an attempt to find species specific markers, a phenoxychromone (**1**) and eight isoflavonoids including six isoflavans (**2-7**) and two isoflavanones (**8** and **9**) were isolated from the root of *Glycyrrhiza uralensis*. Among the isolated phenolic compounds, glycyurelone (**1**), glycyurelvanins A and B (**2** and **3**) were found to be undescribed while others, (−)-vestitol (**4**), conferol A (**5**), glyasperin C (**6**), glyasperin D (**7**), (−)-licoisoflavanone (**8**), and (−)-3′-(γ,γ-dimethylallyl)kievitone (**9**) were previously reported. All compounds except **4** and **5** were prenylated and majority of these possess isoflavan scaffold with highly conserved stereo specificity at C-3 center. Structure elucidation was mainly based on extensive NMR, ECD and mass spectral data analysis.



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1. Introduction

For centuries, licorice (*Glycyrrhiza* spp. root) has been integral part of various formularies due to its unique medicinal features. The sweet taste of the root inspired the Greek to name it *Glykos rhiza,* which means sweet root. However, the English name originated from *liquiritia,* which is the Latin word for licorice (Karaaslan and Dalgıç

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2014). Licorice is well known in the Fabaceae family for being the most commonly prescribed herbal medicine in traditional medicines (Kao et al. 2014). Licorice has been used for the treatment of several illnesses, such as gastric ulcer, asthma, sore throat, fever, and liver diseases (Ji et al. 2016). However, the most common uses are connected with relieving coughs, soothing sore throats, and relieving asthma, aside from its use as a flavoring agent (Zhang et al. 2012). The biological studies of extracts and isolated compounds of *G. uralensis* have been reported in numerous reports (Lee et al. 2009; Gou et al. 2016; Bao et al. 2019; Gou et al. 2020; Wang et al. 2020). To date, more than 400 chemical constituents have been discovered among *Glycyrrhiza* species, including triterpenoid saponins, flavonoids, and other phenolic constituents. Glycyrrhizin, a triterpenoid saponin in licorice, is widely used as a natural sweetener.

Three *Glycyrrhiza* species (*G. glabra* L., *G. uralensis* Fisch, and *G. inflata* Bat) have been mentioned in the Chinese pharmacopeia as the source of licorice. However, recognizing the exact species is challenging due to the morphological similarity (Kondo et al. 2007). Phytochemical profiling might be a proper approach to distinguish *Glycyrrhiza* spp. Targeted isolation was performed on *G. uralensis* roots as part of a program to isolate the specialized metabolites which could be used as species specific markers. As a result, nine phenolic metabolites including three previously undescribed were isolated from the root of *G. uralensis*. The undescribed compounds were characterized as prenylated phenoxychromone (glycyurelone, **1**) and isoflavans (glycyurelvanins A and B, **2** and **3**) based on NMR and mass spectral data analysis.

2. Results and discussion

The compounds (Figure 1) were isolated from a methanol extract of the roots of *G. uralensis* by column chromatography (CC) using different adsorbents such as normal and reversed-phase silica gel and Sephadex LH-20. Compound **1** was obtained as the yellow-brown amorphous solid. Its molecular formula, $C_{20}H_{16}O_7$, was established based on an $[M\text{-}H]^-$ ion peak at *m/z* 367.0830 (calcd for $C_{20}H_{15}O_7$, 367.0818) in the HRESIMS. The ^{1}H- and ^{13}C-NMR data showed resonances consistent with a 3,5,7-trioxygenated chromen-4-one moiety [δ_H/δ_C 8.51 (1H, s)/149.2 (CH-2), 6.34 (1H, d, $J = 2.2$ Hz)/99.1 (CH-6), 6.49 (1H, d, $J = 2.2$ Hz)/94.2 (CH-8), δ_C 141.0 (C-3), 177.7 (C-4), 162.0 (C-5), 164.8 (C-7), 158.2 (C-9), and 105.0 (C-10)]. In addition, the resonances, credential to dioxygenatedphenyl containing 2,2-dimethylchromene unit were also observed [δ_H/δ_C 6.23 (1H, d, $J = 8.7$ Hz)/107.1 (CH-5′), 6.99 (1H, d, $J = 8.7$ Hz)/119.1 (CH-6′), 6.72 (1H, d, $J = 10.0$ Hz)/116.7 (CH-1′′), 5.72 (1H, d, $J = 10.0$ Hz)/129.5 (CH-2′′), 1.39 (6H, s)/27.0 (CH_3-4′′, 5′′), δ_C 139.2 (C-1′), 144.4 (C-2′), 110.8 (C-3′), 150.4 (C-4′), and 75.5 (C-3′′)]. The cross-peaks in the HMBC spectrum, shown in Figure S1 (Supplementary material), confirmed the locations of substitution in 3,5,7-trioxygenated chromen-4-one and 2,2-dimethylchromene skeletons. Based on comparative ^{13}C-NMR chemical shifts of C-3 and C-1′ with known glycybridin I (Li et al. 2017), the chromenone and chromene units in **1** were tethered via an ether bridge. Ultimately, the structure of **1**, named glycyurelone, was elucidated as shown in Figure 1.

Compound **2**, the brown amorphous solid, exhibited an $[M\text{-}H_2O\text{-}H]^-$ ion peak at *m/z* 353.1394 (calcd for $C_{21}H_{21}O_5$, 353.1389) in the HRESIMS that lead to the molecular

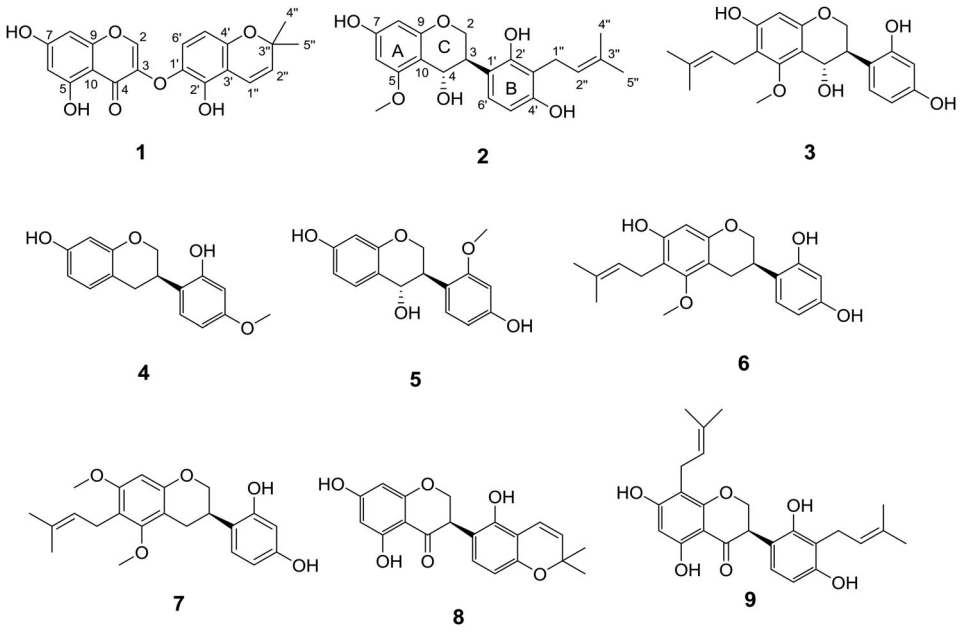

Figure 1. Structures of compounds **1–9**.

formula, $C_{21}H_{24}O_6$. The resonances in the ^{1}H-NMR spectrum for a spin system consisting of two oxymethines and an oxymethylene [δ_H 4.18 (1H, dd, $J = 10.8$, 5.8 Hz, H-2α), 3.53 (1H, t, $J = 10.8$ Hz, H-2β), 3.38 (1H, ddd, $J = 10.8$, 6.6, 5.0 Hz, H-3), and 5.53 (1H, d, $J = 6.6$ Hz, H-4)], a set of *meta*-coupled protons [δ_H 6.18 (1H, d, $J = 2.2$ Hz, H-6) and 6.02 (1H, d, $J = 2.2$ Hz, H-8)], and *ortho*-coupled protons [δ_H 6.38 (1H, d, $J = 7.9$ Hz, H-5′) and 6.95 (1H, d, $J = 7.9$ Hz, H-6′)] were characteristic of 4-hydroxyisoflavan derivative (Zhang et al. 2010). A spin system in ring C was supported by the ^{1}H-^{1}H COSY couplings of H-3 (δ_H 3.38) with H_2-2 (δ_H 4.18/3.53) and H-4 (δ_H 5.53). The ^{1}H- and ^{13}C-NMR data also showed resonances for an isoprenyl [δ_H/δ_C 3.30 (1H, dd, $J = 13.8$, 7.4 Hz) and 3.23 (1H, dd, $J = 13.8$, 7.4 Hz)/22.7 (CH_2-1′′), 5.33 (1H, t, $J = 7.4$ Hz)/122.7 (CH-2′′), 1.77 (3H, s)/16.9 (CH_3-4′′), and 1.64 (3H, s)/25.1 (CH_3-5′′) and δ_C 130.4 (C-3′′)] and a methoxy group [δ_H/δ_C 3.86 (3H, s)/55.1]. The cross-peaks of H_2-1′′ (δ_H 3.30/3.23) with C-2′ (δ_C 159.0) and C-4′ (δ_C 155.9) and H-2′′ (δ_H 5.33) with C-3′ (δ_C 111.0) and those of methoxy protons and H-6 (δ_H 6.18) with C-5 (δ_C 161.4) confirmed the locations of an isoprenyl at C-3′ and methoxyl at C-5, respectively. The NMR data assignment (Tables S1 and S2, Supplementary material) was based on HSQC, HMBC, and ^{1}H-^{1}H COSY spectral data. Furthermore, the absolute configurations of C-3 and C-4 of **2** were established from the electronic circular dichroism (ECD) spectrum. It was reported that (3*R*,4*S*)-4-hydroxyisoflavan exhibits a positive Cotton effect at 220-250 nm and a negative Cotton effect at 250-300 nm, while (3*S*,4*R*)-4-hydroxyisoflavan shows reverse Cotton effects at these wavelengths (Kim et al. 2009, 2010). The ECD spectrum of **2** showed a positive Cotton effect at 238 nm and a negative Cotton effect at 256 nm, this suggested the absolute configurations of C-3 and C-4 as 3*R* and 4*S*, respectively. Hence, **2** (named glycyurelvanin A) was characterized as shown in Figure 1.

Compound **3** was obtained as a brown amorphous solid and its molecular formula, $C_{21}H_{24}O_6$, was established based on an $[M\text{-}H_2O\text{-}H]^-$ ion peak at *m/z* 353.1393 (calcd for $C_{21}H_{21}O_5$, 353.1389) in the HRESIMS. Analysis of the NMR data revealed that **3**, similar to **2**, was a prenylated 4-hydroxyisoflavan derivative. The NMR data of **3** resembled those of **2**, except for the resonances of *ortho*-coupled methines in ring B of **2** were replaced with an ABX system [δ_H/δ_C 6.33 (1H, d, $J = 2.2$ Hz)/97.7 (CH-3′), 6.38 (1H, dd, $J = 8.0$, 2.2 Hz)/107.3 (CH-5′), and 7.14 (1H, d, $J = 8.0$ Hz)/124.9 (CH-6′)] in **3** and of one of the *meta*-coupled methines in ring A of **2** was replaced with a non-protonated carbon (δ_C 115.5) in **3**. These changes indicated that the isoprenyl unit moved to ring A in **3**. The isoprenyl unit was located at C-6 by the cross-peaks (Figure S1, Supplementary material) of H_2-1′′ (δ_H 3.36/3.29) with C-5 (δ_C 160.9) and C-7 (δ_C 157.6) and H-2′′ (δ_H 5.28) with C-6 (δ_C 115.5) in the HMBC spectrum. The 3*R* and 4*S* configurations in **3** were assigned based on the facts of positive and negative Cotton effects in its ECD spectrum as explained for compound **2**. The assignment of NMR data (Tables S1 and S2, Supplementary material) was done by HSQC, HMBC, and ^1H-^1H COSY spectral data analysis. Ultimately, glycyurelvanin B (**3**) was characterized as shown in Figure 1.

Previously described compounds were identified as, (−)-vestitol (**4**) (Piccinelli et al. 2005), conferol A (**5**) (Khan et al. 2009), glyasperin C (**6**) (Zeng et al. 1992), glyasperin D (**7**) (Zeng et al. 1992), (−)-licoisoflavanone (**8**) (Fukai and Nomura 1995; McKee et al. 1997), (−)-3-(γ,γ-dimethylallyl)kievitone (**9**) (O'Neill et al. 1986) by analyses of their NMR and mass spectral data which also corroborated with those of reported data in the literature.

3. Experimental section

3.1. General experimental procedures

The specific rotations were measured on an AUTOPOL IV Automatic Polarimeter (Rudolph, Hackettstown, NJ, USA). IR spectra were acquired on an Agilent Technologies Carry 630 FTIR. Electronic circular dichroism data were recorded on Olis DSM 20 ECD digital subtractive method circular dichrometer with a DeSa subtractive double grating monochromator. NMR spectra were measured on Bruker AU III 500 MHz NMR spectrometer and chemical shifts were referenced to the residual solvent signals. MS data were recorded on an Agilent Technologies 6200 series mass spectrometer. UV-visible spectra were recorded on Varian Cary 50 Bio UV-visible spectrophotometer. Flash silica gel (32-63μ, Dynamic Adsorbents Inc), reversed-phase C_{18} silica (Polar bond, J. T. Baker), and Sephadex LH-20 (Sigma) were used as adsorbents in column chromatography (CC). TLC was performed on Silica gel F_{254} aluminum sheet (20 × 20 cm, Sorbent Tech.) or Silica 60 RP-18 F_{254} S aluminum sheet (20 × 20 cm, Merck). Preparative TLC was performed on silica gel GF plate with UV_{254} (500 μm, 20 × 20 cm, Supelco). The detection was performed at UV-254 nm. Spots were visualized by spraying with 0.5% vanillin (Sigma) solution in conc. H_2SO_4–EtOH (5:95) followed by heating. Analytical grade solvents (Fisher Chemicals) were used for extraction and purification.

3.2. Plant material

G. uralensis roots were purchased from a commercial source. The authenticity of plant material was verified by co-TLC of its methanolic extract with that of a repository botanical reference plant material available at the National Center for Natural Products Research (NCNPR), University of Mississippi (voucher # 14929). The purchased material was also identified by a botanist and deposited at the NCNPR's repository (sample # 13455) .

3.3. Extraction and isolation

The powder of *G. uralensis* roots (3.5 kg) was extracted with methanol (8 L × 3 × 20 h) at room temperature. A crude extract (465 g) was obtained after evaporating the solvent under reduced pressure at 45 °C. A part (100 g) was resolved by CC over silica gel (24″ × 3″) using chloroform-methanol (1:0 to 0:1) gradients. The resulting fractions were combined into seven fractions (A-G) on the basis of the similarity in TLC profiles. Fraction A (3.5 g) was divided into three subfractions (A1-A3) by CC on Sephadex LH-20 (36″ × 1″) using methanol as the solvent. Subfraction A3 (1.5 g) was subjected to silica gel (40″ × 2″) CC using chloroform-methanol mixtures [1:0 (2 L), 99:1 (4 L), 98:2 (4 L), and 98:3 (2 L)] to give six fractions (A3a-A3f). Compounds **1** (9.5 mg) and **5** (10.0 mg) were obtained from fraction A3a by CC [RP-C_{18} silica gel (6″ × 1″), water/methanol [1:1 (300 mL), 2:3 (500 mL), 3:7 (300 mL), 1:4 (300 mL), and 0:1 (500 mL)] followed by preparative thin layer chromatography (PTLC) [silica gel, hexanes/ethyl acetate (7:3)]. Compounds **8** (35.6 mg) and **9** (27.6 mg) were obtained from fraction A3b by CC [RP-C_{18} silica gel (6″ × 1″), water/methanol [2:3 (200 mL), 7:13 (200 mL), 3:7 (200 mL), 1:3 (200 mL) followed by PTLC [silica gel, ethyl acetate/chloroform/hexanes/(2:3:5)]. Compounds **2** (35.6 mg) and **3** (27.6 mg) were obtained from fractions A3c and A3d respectively by CC [silica gel (15″ × 0.4″), hexanes/ethyl acetate (7:3)] followed by PTLC [silica gel, hexanes/acetone/(3:2)]. Compound **4** (12.6 mg) were obtained from fraction B (1.1 g) by repeated CC [Sephadex LH-20 (36″ × 1″), methanol] and [silica gel (40″ × 0.7″), hexanes/ethyl acetate (4:1 (700 mL), 7:3 (600 mL), 3:2 (2 L))]. Fraction C (0.6 g) was applied to CC over Sephadex LH-20 (36″ × 1″) using methanol to purify compound **7** (215.5 mg). Compound **6** (129.2 mg) was purified from fraction F (250 mg) by CC [silica gel (36″ × 0.7″), hexanes/ethyl acetate (3:2, 2 L and 1:1, 2 L].

3.3.1. Glycyurelone (1)

Yellow-brown amorphous solid. UV (MeOH) λ_{max} 283 nm; IR ν_{max} 3425, 2900, 1690 (sh), 1610, 1490, 1480, 1370, 1200, 1150, 1140 cm^{-1}; HRESIMS *m/z* 367.0830 $[M\text{-}H]^-$ (calcd. for $C_{20}H_{15}O_7$, 367.0818); ^{1}H-NMR data (acetone-d_6, 500 MHz) δ_H 8.51 (1H, s, H-2), 6.34 (1H, d, $J = 2.2$ Hz, H-6), 6.49 (1H, d, $J = 2.2$ Hz, H-8), 6.23 (1H, d, $J = 8.7$ Hz, H-5′), 6.99 (1H, d, $J = 8.7$ Hz, H-6′), 6.72 (1H, d, $J = 10.0$ Hz, H-1″), 5.72 (1H, d, $J = 10.0$ Hz, H-2″), 1.39 (6H, s, H_3-4″, 5″), (Table S1, Supplementary material); ^{13}C-NMR data (acetone-d_6, 125 MHz) δ_C 149.2 (C-2), 141.0 (C-3), 177.7 (C-4), 162.0 (C-5), 99.1 (C-6), 164.8 (C-7), 94.2 (C-8), 158.2 (C-9), 105.0 (C-10), 139.2 (C-1′), 144.4 (C-2′), 110.8 (C-3′), 150.4 (C-4′), 107.1 (C-5′), 119.1 (C-6′), 116.7 (C-1″), 129.5 (C-2″), 75.5 (C-3″), 27.0 (C-4″), 27.0 (C-5″), (Table S2, Supplementary material).

3.3.2. Glycyurelvanin A (2)

Brown amorphous solid. $[\alpha]^{24}_{D}$ −20.0 (*c* 0.1, MeOH); UV (MeOH) λ_{max} 292 nm; IR ν_{max} 3410, 2900, 1620, 1600, 1460, 1450, 1390, 1250, 1150, 1140, 1040 cm^{-1}; HRESIMS *m/z* 353.1394 $[M\text{-}H_2O\text{-}H]^-$ (calcd. for $C_{21}H_{21}O_5$, 353.1389); ^{1}H-NMR data (acetone-d_6, 500 MHz) δ_H 4.18 (1H, dd, *J* = 10.8, 5.0 Hz, H-2α), 3.53 (1H, t, *J* = 10.8 Hz, H-2β), 3.38 (1H, ddd, *J* = 10.8, 6.6, 5.0 Hz, H-3), 5.53 (1H, d, *J* = 6.6 Hz, H-4), 6.18 (1H, d, *J* = 2.2 Hz, H-6), 6.02 (1H, d, *J* = 2.2 Hz, H-8), 6.38 (1H, d, *J* = 7.9 Hz, H-5′), 6.95 (1H, d, *J* = 7.9 Hz, H-6′), 3.30 (1H, dd, *J* = 13.8, 7.4 Hz, H-1′′a), 3.23 (1H, dd, *J* = 13.8, 7.4 Hz, H-1′′b), 5.33 (1H, t, *J* = 7.4 Hz, H-2′′), 1.77 (1H, s, H_3-4′′), 1.64 (1H, s, H_3-5′′), 3.86 (3H, s, OMe), (Table S1, Supplementary material); ^{13}C-NMR data (acetone-d_6, 125 MHz) δ_C 66.1 (C-2), 39.2 (C-3), 74.8 (C-4), 161.4 (C-5), 92.5 (C-6), 159.5 (C-7), 95.5 (C-8), 157.4 (C-9), 101.4 (C-10), 118.0 (C-1′), 159.0 (C-2′), 111.0 (C-3′), 155.9 (C-4′), 106.9 (C-5′), 121.6 (C-6′), 22.7 (C-1′′), 122.7 (C-2′′), 130.4 (C-3′′), 16.9 (C-4′′), 25.1 (C-5′′), 55.1 (OMe), (Table S2, Supplementary material).

3.3.3. Glycyurelvanin B (3)

Brown amorphous solid. $[\alpha]^{22}_{D}$ −65 (*c* 0.1, MeOH); UV (MeOH) λ_{max} 289 nm; IR ν_{max} 3450, 1600, 1500, 1490, 1120, 1050 cm^{-1}; HRESIMS *m/z* 353.1393 $[M\text{-}H_2O\text{-}H]^-$ (calcd. for $C_{21}H_{21}O_5$, 353.1389); ^{1}H-NMR data (acetone-d_6, 500 MHz) δ_H 4.18 (1H, dd, *J* = 10.8, 4.9 Hz, H-2α), 3.54 (1H, t, *J* = 10.8 Hz, H-2β), 3.41 (1H, ddd, *J* = 10.8, 6.7, 4.9 Hz, H-3), 5.61 (1H, d, *J* = 6.7 Hz, H-4), 6.27 (1H, s, H-8), 6.33 (1H, d, *J* = 2.2 Hz, H-3′), 6.38 (1H, dd, *J* = 8.0, 2.2 Hz, H-5′), 7.14 (1H, d, *J* = 8.0 Hz, H-6′), 3.36 (1H, dd, *J* = 14.0, 6.8 Hz, H-1′′a), 3.29 (1H, dd, *J* = 14.0, 6.8 Hz, H-1′′b), 5.28 (1H, t, *J* = 6.8 Hz, H-2′′), 1.78 (1H, s, H_3-4′′), 1.67 (1H, s, H_3-5′′), 3.93 (3H, s, OMe), (Table S1, Supplementary material); ^{13}C-NMR data (acetone-d_6, 125 MHz) δ_C 66.1 (C-2), 39.0 (C-3), 75.7 (C-4), 160.9 (C-5), 115.5 (C-6), 157.6 (C-7), 99.1 (C-8), 155.1 (C-9), 106.2 (C-10), 118.3 (C-1′), 160.1 (C-2′), 97.7 (C-3′), 158.7 (C-4′), 107.3 (C-5′), 124.9 (C-6′), 22.5 (C-1′′), 123.8 (C-2′′), 130.0 (C-3′′), 17.1 (C-4′′), 25.0 (C-5′′), 62.2 (OMe), (Table S2, Supplementary material).

4. Conclusions

In an attempt to find the species specific quality markers of *G. uralensis*, phenoxychromone and isoflavonoids including isoflavans, and isoflavanones were isolated and fully characterized. Consequently, nine phenolic compounds, including phenoxychromone, isoflavans, and isoflavanones were isolated. A phenoxychromone derivative (glycyurelone, **1**), and two 4-hydroxyisoflavans (glycyurelvanins A and B, **2** and **3**) were found to be previously undescribed in nature. Nevertheless, targeted isolation together with ECD experiments resulted in identification of several isoflavanones and isoflavans with highly conserved stereo-specificity at the C-3 position. It appears that unique biogenesis in *Glycyrrhiza* is responsible for the installation of chirality at C-3, followed by reduction and deoxygenation to yield several specific isoflavans identified in licorice.

Disclaimer

The findings and conclusions in this article have not been formally disseminated by the US Food and Drug Administration and should not be construed to represent any

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Disclosure statement

No potential conflict of interest was reported by the authors.

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