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Indole alkaloid glycosides from *Isatis tinctoria* roots

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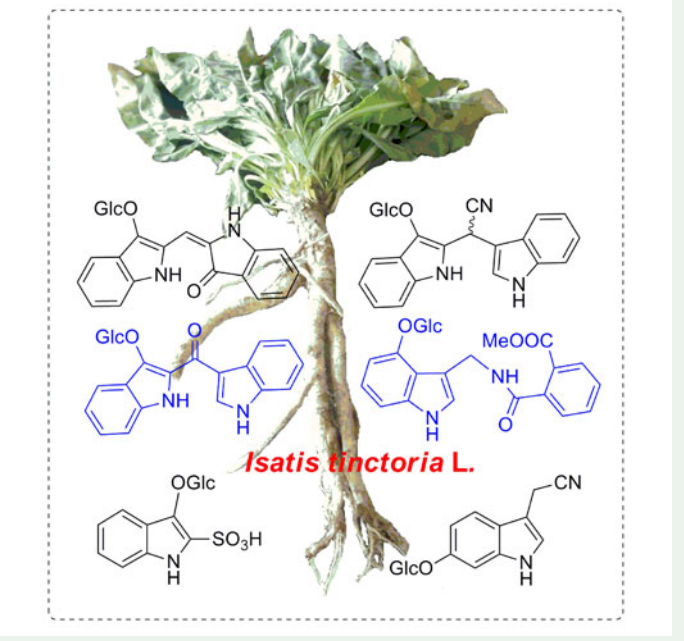
ABSTRACT

Isatindigoside A and B (**1** – **2**), two new indole alkaloid glycosides along with five known ones (**3** – **7**) were obtained from the roots of *I. tinctoria*. Their structures were determined as isatindigoside A (**1**), isatindigoside B (**2**), isatindosulfonicacid A 3-*O*-*β*-D-glucopyranoside (**3**), indole-3-acetonitrile 6-*O*-*β*-D-glucopyranoside (**4**), isatindigobisindoloside A (**5**), isatindigobisindoloside B (**6**) isatindigobisindoloside F (**7**), by physicochemical properties and spectroscopic methods including 1 D, 2 D NMR, IR, HR-ESI-MS data. Nitric oxide (NO) inhibitory activities of all of the isolated compounds (**1** – **7**) were also evaluated. Compounds **2** and **7** showed inhibitory effects against LPS-stimulated RAW 264.7 cells with IC_{50} values of 27.6 μM and 18.8 μM, respectively.



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1. Introduction

Isatis tinctoria L. (Chinese pharmacopeia named *Isatis indigotica* Fort., Cruciferae), a biennial herbaceous plant, is widely distributed and cultivated in China (Guo et al. 2018). Its roots, named Ban Lan Gen, are usually used as traditional Chinese medicines (TCMs) for the treatment of different kinds of diseases, especially for the treatments of influenza, cold, fever and infections (Xi et al. 2018; Xie et al. 2011; Yang et al. 2014). Various kinds of compounds, including alkaloids (Chen et al. 2012), lignans (Meng et al. 2017b), organic acids, flavonoids (Wu et al. 2011) and nucleotides (Liu et al. 2018) have been isolated from the extracts. Among them, indole alkaloids are considered as the main active constituents which process anti-inflammatory, antiviral, antibacterial and antitumor activities (Chen et al. 2015). As part of our research project to explore more bioactive lead compounds from TCMs (Cui et al. 2015; Zhang et al. 2014), the chemical constituents and pharmacological investigation of *I. tinctoria* were studied and seven indole alkaloid glycosides were obtained. Isatindigoside A and isatindigoside B (**1**and **2**), were deduced as two undescribed ones, whose structures were determined by extensive spectroscopic data analysis, including 1 D, 2 D NMR, IR and HR-ESI-MS data analysis. The known glycosides (**3** − **7**) were identified by comparison of spectroscopic and optical rotation data with those reported in the literatures as isatindosulfonicacid A 3-*O*-β-D-glucopyranoside (**3**) (Meng et al. 2017a), indole-3-acetonitrile 6-*O*-β-D-glucopyranoside (**4**) (Li et al. 2003), isatindigobisindoloside A (**5**) (Liu et al. 2015), isatindigobisindoloside B (**6**) (Liu et al. 2015) and isatindigobisindoloside F (7) (Liu et al. 2015). The nitric oxide (NO) inhibitory activities of all the isolated compounds (**1** − **7**) were also evaluated. Reported herein are the isolation, structure elucidation and the NO inhibitory activities of these compounds.

2. Results and discussion

Isatindigoside A (**1**) was obtained as a white amorphous powder with $[\alpha]_D^{20}-11.4^\circ$ (*c* 0.21, MeOH). Its molecular formula was assigned as $C_{24}H_{26}N_2O_9$, implying 13 indices of hydrogen deficiency (IHD), by the 1 D NMR data and the HR-ESI-MS positive molecular ion peak observed at *m/z* 487.1714 $[M+H]^+$, (calcd for 487.1711 $[M+H]^+$). The ^1H NMR spectrum of **1** showed signals of a 1, 2, 3-trisubstitute benzene ring (Chen et al. 2015) at δ_H 6.69 (1H, d, $J=7.7$ Hz, H-5′), 6.96 (1H, dd, $J=7.7$, 7.3 Hz, H-6′), 7.07 (1H, d, $J=7.3$ Hz, H-7′); an ortho-disubstituted benzene ring (Liu et al. 2016) at δ_H 7.89 (1H, d, $J=8.0$ Hz, H-4″), 7.09 (1H, dd, $J=8.0$, 8.5 Hz, H-5″), 7.51 (1H, dd, $J=8.5$, 8.5 Hz, H-6″), 8.56 (1H, d, $J=8.5$ Hz, H-7″); a trisubstituted double bond at δ_H 7.24 (1H, s, H-2′); a disubstituted methylene proton at δ_H 4.01 (1H, d, $J=16.5$ Hz, H-1a) and 4.08 (1H, d, $J=16.5$ Hz, H-1b) and also showed signals of an anomeric proton 5.01 (1H, d, $J=7.8$ Hz, Glc-H1) and a methoxy proton at δ_H 3.57 (3H, s, 3″-OMe). The ^{13}C NMR spectrum displayed 24 carbon signals, based on the DEPT 135° and 2 D NMR experiments (Figure S17, Supplementary material), a *O*-glucopyranosyl unit (Liu et al. 2015) and a 1*H*-indol-3-methane moiety (Liu et al. 2015) as well as a methyl 2-carbamoylbenzoate moiety (Trachsel et al. 2009) were observed. The 1*H*-indol-3-methane moiety was connected with the methyl 2-carbamoylbenzoate moiety via a C-1 − N-1″ (C-N) bond which was supported by the HMBC correlations of H1/C-2″ and the downfield of

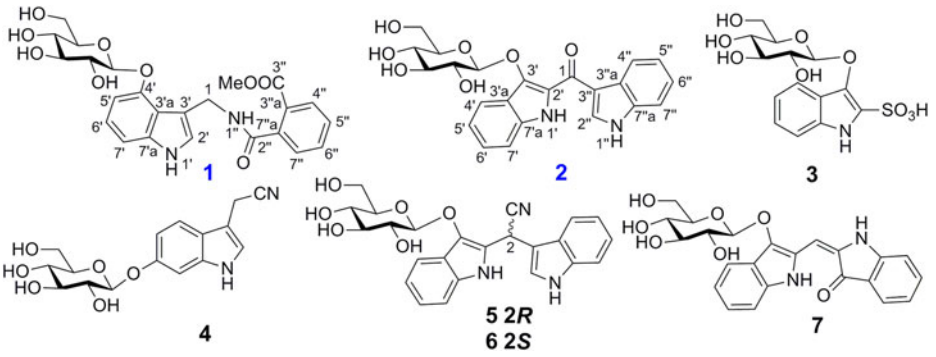

Figure 1. Structures of compounds 1–7.

C-1 at δ_C (37.9) compared with a C-C disubstituted bond methane at δ_C(20.2) (Liu et al. 2015). The 4′-*O*-glucopyranosyl unit was deduced by the HMBC correlations of Glc-H1/C-4′ and the downfield of C-4′ at δ_C (153.1) (Chen et al. 2012; Liu et al. 2016). Acid hydrolysis of **1** resulted in the product of D-glucose which was confirmed by GC analysis derivatives of the hydrolysate of **1** and the authentic sugars (t_R D-glucose 41.3 min, t_R L-glucose 40.9 min). The large coupling constant of Glc-H1 ($J = 7.8$ Hz) revealed the β-glucopyranosyl linkage in **1** (Song et al. 2015b; Zhang et al. 2016). The structure of isatindigoside A (**1**) was thus deduced as depicted (Figure 1).

Isatindigoside B (**2**) was isolated as a yellow amorphous power, $[\alpha]_D^{20} -5.4°$ (*c* 0.13, MeOH), with a molecular formula as $C_{23}H_{22}N_2O_7$, (14 IHD), which was deduced from the 1 D NMR data and the HR-ESI-MS positive molecular ion peak observed at *m/z* 439.1507 $[M+H]^+$, (calcd for 439.1500 $[M+H]^+$). The ^{13}C NMR spectrum displayed 23 carbon signals, based on the DEPT 135° and HSQC experiments, a *O*-glucopyranosyl unit (107.0, 74.3, 76.8, 70.1, 77.6, 61.4) was observed by comparing its NMR data with the literatures (Liu et al. 2016; Liu et al. 2015), the remaining 17 carbons (13 IHD), compared with the reported literatures (Chen et al. 2012; Liu et al. 2015), represent a bisindole aglycone of **2**. This was deduced by ^1H-^1H COSY and HMBC data analysis (Figure S17, Supplementary material). ^1H-^1H COSY correlations of H-4′/H-5′/H-6′/H-7′ along with the HMBC correlations of NH-1′/C-2′, C-3′, C-3′a and C-7′a deduced a 1*H*-indol-2, 3-diyl moiety in **2**; ^1H-^1H COSY correlations of H-4″/H-5″/H-6″/H-7″ along with the HMBC correlations of H-2″/C-1, C-3″ and C-3″a and NH-1″/C-2″, C-3″ and C-7″a deduced a 1*H*-indol-3-one moiety in **2**. HMBC correlations of N-1′/C-1, C-2′ and C-3′; H-2″/C-1, C-3″ and N-1″/C-2″ and C-3″ indicated the the two indolyl moieties were conjugated as bis(indol-2′/3″-yl)methanone. HMBC correlation of Glc-H1/C-3′ indicated the *O*-glucopyranosyl unit linked at C-3′ of the aglycone. The D-absolute configuration of the glucose moiety in **2** was deduced as the same method as **1**. The large coupling constant of Glc-H1 ($J = 7.8$ Hz) supported the β-glucopyranosyl linkage in **2** (Song et al. 2015a). Accordingly, the structure of isatindigoside B (**2**) was elucidated as depicted (Figure 1).

Indole alkaloids are one of the main types of alkaloids in *I. tinctoria*, which have been reported to process potential anti-inflammatory effects (Yang et al. 2014). This pharmacologic action, together with the traditional use for the treatment of epidemic hepatitis promoted us to test inhibitory effects on NO production, a main

indicator to assess the inflammatory activities (Hu et al. 2018). Herein, all the glycosides (**1** − **7**) were assessed for their abilities to inhibit NO production in LPS-stimulated RAW 264.7 cells. The IC_{50} values (Table S2) showed that only compounds **2** and **7** exhibited inhibitory activities (27.6 μM and 18.8 μM, respectively) against NO production.

3. Experimental

The **General experimental procedures** and **Extraction and isolation** sections see Supplementary material.

3.1. Plant material

The *I. tinctoria* roots (Ban Lan Gen) were collected on July, 2017 from the Daqing city, HeiLongJiang Province of China, and it was authenticated by one of our Co-authors Rui Wang professor (School of Pharmacy, Shanghai University of Traditional Chinese Medicine). A voucher specimen (herbarium No. 20170716SL) has been deposited in the Medicinal Plants Herbarium (MPH), School of Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

3.2. Isatindigoside A (**1**), white amorphous power; $[\alpha]_D^{20}-11.4^\circ$ (*c* 0.21, MeOH); IR (KBr) ν_{max}: 3363, 2924, 1703, 1667, 1611, 1514, 1443, 1310, 1260, 1073, 1026, 957, 762 cm^{-1}; HRESIMS: *m/z* 487.1714 $[M+H]^+$, (calcd for 487.1711 $[M+H]^+$); EIMS: 487 $[M+H]^+$, 485 $[M-H]^-$, 453 $[M-OCH_3]^-$, 323 $[M-glc]^-$; ^1H NMR (Methanol-d_4, 600 MHz, δ in ppm): 4.01 (1H, d, $J=16.5$ Hz, H-1a), 4.08 (1H, d, $J=16.5$ Hz, H-1b), 7.24 (1H, s, H-2′), 6.69 (1H, d, $J=7.7$ Hz, H-5′), 6.96 (1H, dd, $J=7.7$, 7.3 Hz, H-6′), 7.07 (1H, d, $J=7.3$ Hz, H-7′), 7.89 (1H, d, $J=8.0$ Hz, H-4″), 7.09 (1H, dd, $J=8.0$, 8.5 Hz, H-5″), 7.51 (1H, dd, $J=8.5$, 8.5 Hz, H-6″), 8.56 (1H, d, $J=8.5$ Hz, H-7″), 3.57 (3H, s, OMe), 5.01 (1H, d, $J=7.8$Hz, Glc-H1), 3.54 (1H, m, Glc-H2), 3.39 (1H, m, Glc-H3), 3.30 (1H, overlap, Glc-H4), 3.44 (1H, m, Glc-H5), 3.53 (1H, dd, $J=10.5$, 5.9 Hz, Glc-H6a), 3.77 (1H, dd, $J=10.5$, 2.3 Hz, Glc-H6b); ^{13}C NMR (Methanol-d_4, 150 MHz, δ in ppm): 37.9 (C-1, t), 125.7 (C-2′, d), 108.1 (C-3′, s), 119.2 (C-3′a, s), 153.1 (C-4′, s), 104.4 (C-5′, d), 123.7 (C-6′, d), 107.3 (C-7′, d), 140.6 (C-7′a, s), 175.7 (C-2″, s), 168.9 (C-3″, s), 118.2 (C-3″a, s), 131.9 (C-4″, d), 124.2 (C-5″, d), 134.9 (C-6″, d), 122.0 (C-7″, d), 141.4 (C-7″a, s), 52.6 (OMe, q), 101.9 (Glc-C1, d), 75.1 (Glc-C2, d), 78.2 (Glc-C3, d), 71.7 (Glc-C4, d), 78.0 (Glc-C5, d), 62.8 (Glc-C6, t), or see Table S1 (Supplementary material).

3.3 Isatindigoside B (**2**), yellow amorphous power; $[\alpha]_D^{20}-5.4^\circ$ (*c* 0.13, MeOH); IR (KBr) ν_{max}: 3420, 2925, 1728, 1647, 1617, 1518, 1464, 1396, 1250, 1071, 1030, 888, 759 cm^{-1}; HRESIMS: *m/z* 439.1507 $[M+H]^+$, (calcd for 439.1500 $[M+H]^+$), EIMS: 439 $[M+H]^+$, 437 $[M-H]^-$, 275 $[M-glc]^-$; ^1H NMR (DMSO-d_6, 600 MHz, δ in ppm): 12.55 (1H, brs, H-1′), 7.94 (1H, d, $J=8.1$ Hz, H-4′), 7.05 (1H, td, $J=8.1$, 7.3 Hz, H-5′), 7.22 (1H, td, $J=7.7$, 7.3 Hz, H-6′), 6.91 (1H, d, $J=7.7$ Hz, H-7′), 11.01 (1H, brs, H-1″), 8.12 (1H, s, H-2″), 7.71 (1H, d, $J=7.4$ Hz, H-4″), 7.03 (1H, td, $J=7.7$, 7.4 Hz, H-5″), 7.28 (1H, td, $J=8.3$, 7.7 Hz, H-6″), 7.51 (1H, d, $J=8.3$ Hz, H-7″), 4.64 (1H, d, $J=7.8$ Hz, Glc-H1), 3.46 (1H, overlap, Glc-H2), 3.27 (1H, overlap, Glc-H3), 3.28 (1H, overlap, Glc-H4), 3.21 (1H, m, Glc-H5), 3.53 (1H, dd, $J=11.8$, 5.7 Hz, Glc-H6a), 3.77 (1H, dd, $J=11.8$, 2.4 Hz, Glc-H6b);

^{13}C NMR (DMSO-d_6, 150 MHz, δ in ppm): 169.6 (C-1, s), 121.0 (C-2′, s), 143.2 (C-3′, s), 125.3 (C-3′a, s), 120.7 (C-4′, d), 120.3 (C-5′, d), 128.5 (C-6′, d), 110.2 (C-7′, d), 135.2 (C-7′a, s), 122.2 (C-2″, d), 106.9 (C-3″, s), 120.1 (C-3″a, s), 119.9 (C-4″, d), 121.9 (C-5″, d), 126.4 (C-6″, d), 112.8 (C-7″, d), 140.3 (C-7″a, s), 107.0 (Glc-C1, d), 74.3 (Glc-C2, d), 76.8 (Glc-C3, d), 70.1 (Glc-C4, d), 77.6 (Glc-C5, d), 61.4 (Glc-C6, t), or see Table S1 (Supplementary material).

3.4. Absolute configuration determination of sugar

Solutions of **1** and **2** (1.8 mg each) in 2 M hydrochloric acid (4 mL) was hydrolyzed at 80 °C for 2 h. After cooling, each solution was concentrated under vacuum, dissolved with water, and extracted twice with dichloromethane (CH_2Cl_2). The aqueous parts were treated via a similar method described previously (Cui et al. 2015). The D configurations of the glucose moiety in **1** and **2** were confirmed through comparison their retention times (t_R) with those of authentic sugar samples (t_R D-glucose 41.3 min, t_R L-glucose 40.9 min).

3.5. Inhibitory assay of NO production

Cytotoxicity was examined using the Cell Counting Kit-8 (CCK-8). The absorbance at 450 nm was measured using a microplate reader (Thermo Fisher Scientific). Viability was defined as the ratio (expressed as a percentage) of absorbance values of treated cells to untreated cells.

Compounds **1**–**7** were dissolved in dimethyl sulfoxidediluted (DMSO) with complete medium to 6 degrees of concentration (0.1 μmol • L^{-1}, 1 μmol • L^{-1}, 10 μmol • L^{-1}, 25 μmol • L^{-1}, 50 μmol • L^{-1}, 100 μmol • L^{-1}) for inhibition rate determination. RAW 264.7 cells were maintained in Dulbecco's modified Eagle's medium (high-glucose condition) supplemented with 10% fetal calf serum, 100 U/ml penicillin, and 100 μg/mL streptomycin at 37 °C in 5% CO_2. RAW 264.7 cells were pre-treated with each tested compound for 30 min, and then stimulated with lipopolysaccharide (LPS) (100 ng/mL) for 24 h. Aminoguanidine hydrochloride (100 μM) was used as a positive control. The NO production was measured using the Griess reagent. Briefly, cell culture supernatant was reacted with equal volumes of Griess reagent in a 96-well plate for 10 min, and then the absorbance at 540 nm was measured by a plate reader. All experiments were performed in triplicate. All of the tested compounds were prepared as stock solutions with a concentration of 10 mM in DMSO. The IC_{50} values of compounds **1** – **7** were calculated (see Table S2, Supplementary material).

4. Conclusions

Seven indole alkaloid glycosides were obtained from the roots of *I. tinctoria*, among them, compounds **2** and **7** exhibited inhibitory activities against NO production with IC_{50} values of 27.6 μM and 18.8 μM. This study enriched the chemical and pharmacological diversity of *I. tinctoria*.

Disclosure statement

The authors declare no competing financial interest.

Acknowledgement

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