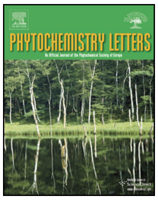
Phytochemistry Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol



Four new C_{21} steroidal glycosides from *Cynanchum otophyllum* Schneid

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ARTICLE INFO

Article history:
Received 27 January 2014
Received in revised form 18 April 2014
Accepted 25 April 2014
Available online xxx

Keywords:
Cynanchum otophyllum
Asclepiadaceae
C_{21} steroidal glycosides
Otophylloside
Qingyangshengenin
Caudatin

ABSTRACT

Four new C_{21} steroidal glycosides, named otophylloside T (**2**), U (**3**), V (**4**) and W (**10**), together with six known compounds including beishouwubenzophenone (**1**), the enzymatic hydrolysate of wallicoside (**5**), Otophylloside M (**6**), Cynanauriculoside E (**7**), Wallicoside (**8**) and Cynauricuoside C (**9**), were isolated from the roots of *Cynanchum otophyllum* Schneid. The structures of the four new C_{21} steroidal glycosides were elucidated as qingyangshengenin-3-O-β-D-thevetopyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-digitoxopyranoside (**2**), qingyangshengenin-3-O-β-D-thevetopyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-cymaropyranoside (**3**), caudatin-3-O-β-D-glucopyranosyl-(1→4)-β-D-oleandropyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-digitoxopyranoside (**4**) and caudatin-3-O-β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→4)-β-D-oleandropyranosyl-(1→4)-β-D-oleandropyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-cymaropyranoside (**10**) by extensive spectroscopic evidence.

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1. Introduction

Cynanchum otophyllum Schneid (Chinese name Qingyangshen), a plant of the genus *Cynanchum* L. (Family: Asclepiadaceae), is mostly distributed in the southwest of China (Ma et al., 2011a; Shi et al., 2013). As a traditional medicinal plant, the dried root of *C. otophyllum* has been used clinically to treat rheumatism, lumbar muscle strain and epilepsy. According to the current knowledge, *C. otophyllum* contains a variety of bioactive constituents; and pregnane glycosides are the main components of this plant (Ma et al., 2011a, 2011b; Shi et al., 2013; Zhao et al., 2013). Due to the broad range of bioactivities such as neuroprotective, antiepileptic, immunoregulatory and antifungal properties, pregnane glycosides have attracted considerable attention in recent years (Ma et al., 2011b; Mu et al., 1986; Li et al., 2006; Zhao et al., 2007). Qingyangshen tablet, a product containing the total glycosides of *C. otophyllum*, has been marketed by Yunnan Baiyao Group Co., Ltd. in 1984 and showed notable protective effects against epilepsy and chronic hepatitis (Kuang et al., 1985; Mu et al., 1986; Pei et al., 1987). In our preliminary study, using entylenetetrazole-induced epileptic zebrafish as model, the activity of different fractions of *C. otophyllum* has been compared and the chloroform part showed the strongest antiepileptic activity. Therefore, in the present study, we only focused on the chloroform fraction. Four new C_{21} steroidal glycosides (**2**–**4**, **10**) (Fig. 1) along with beishouwubenzophenone (**1**) (Zhao et al., 2007), the enzymatic hydrolysate of wallicoside (**5**) (Zhang and Zhou, 1983), Otophylloside M (**6**) (Ma et al., 2007), Cynanauriculoside E (**7**) (Yang et al., 2011), Wallicoside (**8**) (Zhang and Zhou, 1983) and Cynauricuoside C (**9**) (Yang et al., 2011) were discovered in the chloroform fraction. Among them, compound **7** was isolated from *C. otophyllum* for the first time. Compounds **2** and **3** were reported with a sugar chain containing D-thevetose unit, which was rarely discovered in the compounds of *C. otophyllum* except Otophylloside K (Ma et al., 2007). We herein describe the isolation, structure elucidation of these compounds.

2. Results and discussion

Compound **2** was obtained as a white amorphous powder. Its molecular formula $C_{48}H_{70}O_{18}$ was determined by its HR-ESI-MS at m/z 933.4454 $[M-H]^-$ (calcd. for 933.4484) and ^{13}C NMR data (Tables 1 and 2). IR spectrum exhibited the absorption bands for hydroxyl (3462 cm^{-1}), ketone (1709 cm^{-1}), and benzene (1610 and 1512 cm^{-1}) functionalities. The ^1H and ^{13}C NMR spectra

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http://dx.doi.org/10.1016/j.phytol.2014.04.017
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Please cite this article in press as: Shen, D.-Y., et al., Four new C_{21} steroidal glycosides from *Cynanchum otophyllum* Schneid. Phytochem. Lett. (2014), http://dx.doi.org/10.1016/j.phytol.2014.04.017

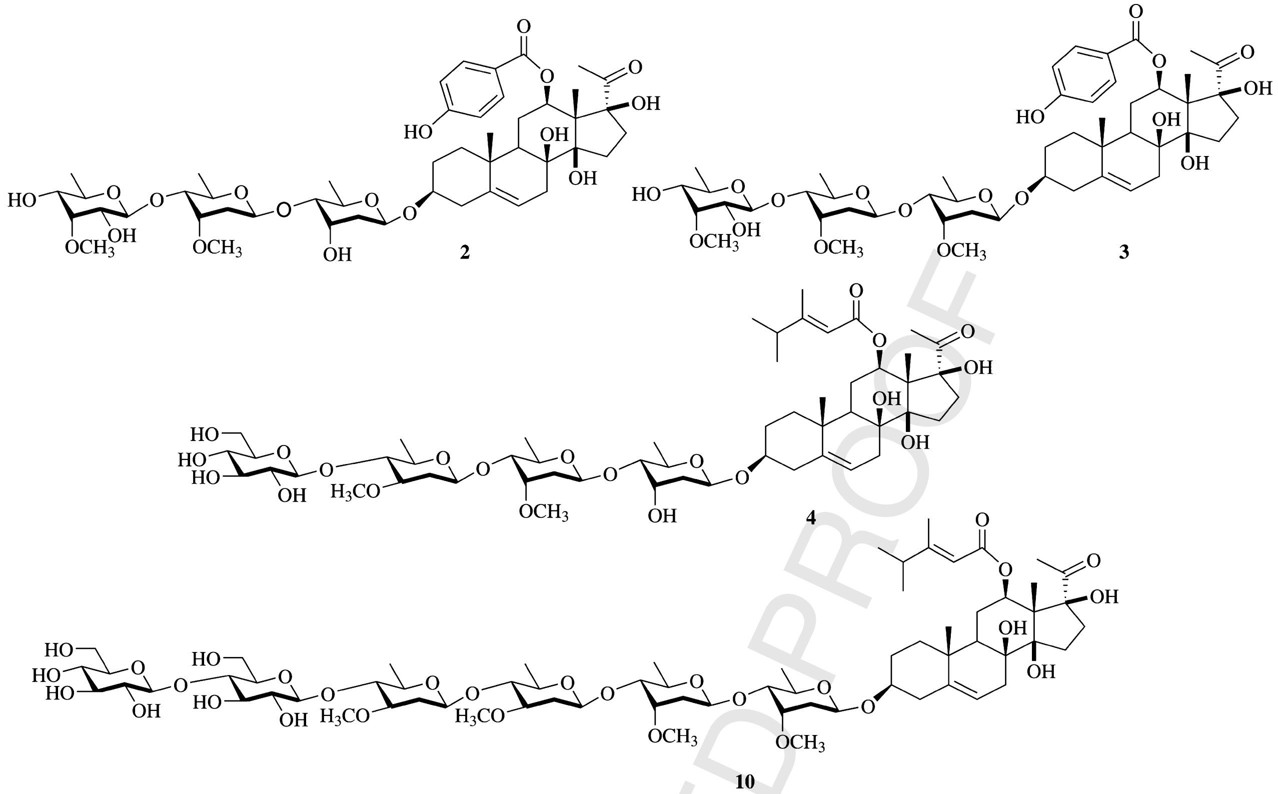

Fig. 1. Chemical structures of compounds **2**, **4**, **10** isolated from *C. otophyllum*.

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(Tables 1–3) extensively analyzed with the aid of $^1H–^1H$ COSY and HSQC experiments. The ^1H NMR spectrum of **2** showed three singlet methyl proton signals of a steroidal skeleton at δ_H 1.31 (3H, s, Me-19), 2.09 (3H, s, Me-18), and 2.42 (3H, s, Me-21), an olefinic proton at δ_H 5.28 (1H, m, H-6), as well as four aromatic protons on a *para*-substituted benzene ring at δ_H 7.24 (2H, d, J = 8.0 Hz, H-4′,6′) and δ_H 8.30 (2H, d, J = 8.0 Hz, H-3′,7′). Further, the NMR spectroscopic data attributed to the aglycone of **2** were in good agreement with those of otophylloside N (**2**) (Ma et al., 2011a,b). Hence, the aglycone of **2** was identified as qingyangshengenin, as confirmed by the $^1H–^1H$ COSY, HMBC and ROESY correlations. The ^1H NMR spectrum of sugar moiety of compound **2** exhibited the following proton signals: three secondary methyl groups signals at δ_H 1.44 (3H, d, J = 8.0 Hz), 1.57 (3H, d, J = 4.0 Hz), and 1.55 (3H, d, J = 8.0 Hz) and two methoxyl groups signals at δ_H 3.57, 3.90 as well as three anomeric proton signals at δ_H 4.76 (d, J = 8.0 Hz), 5.17 (brd, J = 10.0 Hz) and 5.47 (brd, J = 10.0 Hz). The multiples suggested the presence of three 2,6-dideoxy-sugar in a sugar chain and the β-configuration of the three hexose units. Spin-spin couplings and chemical shifts were evaluated with the aid of $^1H–^1H$ COSY, HSQC and HMBC experiments, and the results in Tables 2 and 3 revealed the presence of one D-digitoxose, one D-cymarose, and one D-thevetose (Ma et al., 2011a, 2011b; Li et al., 2006; Srivastava et al., 1991; Ye et al., 2004; Yang et al., 2004). The HMBC correlation between δ_H 5.47 (H-1″) and δ_C 77.6 (C-3) revealed that the β-D-digitoxopyranosyl unit was located at C-3 of the aglycone. Furthermore, the long-distance correlations of C-4 of D-cymarose (δ_C 83.1)/H-1 of D-thevetose (δ_H 4.76) and C-4 of D-digitoxose (δ_C 83.4)/H-1 of D-cymarose (δ_H 5.17) indicated the sequence of oligosaccharide chain. From the above evidence, the structure of **2** was qingyangshengenin-3-O-β-D-thevetopyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-digitoxopyranoside, and named as Otophylloside T.

Compound **3** was isolated as a white amorphous powder, and its molecular formula deduced to be $C_{49}H_{72}O_{18}$ on the basis of the negative ion HR-ESI-MS at m/z 947.4619 $[M-H]^-$ (calcd. for 947.4640) and ^{13}C NMR data (Tables 1 and 2). The NMR spectroscopic data of compound **3** were similar to those of

Table 1
^{13}CNMR (150 MHz) data for the aglycone moieties of compounds **2**–**4** and **10** (δ in ppm, in C5D5N).

Position	**2**[a]	**3**	**4**	**10**
1	38.8	38.9	39.2	39.2
2	29.8	29.8	29.8	29.9
3	77.6	77.6	77.7	77.7
4	39.1	39.2	39.0	39.0
5	139.3	139.3	139.3	139.3
6	119.1	119.1	119.1	119.2
7	34.7	34.7	34.7	34.8
8	74.3	74.3	74.3	74.2
9	44.4	44.4	44.5	44.5
10	37.3	37.4	37.4	37.4
11	25.1	25.1	25.0	25.0
12	73.3	73.3	72.6	72.6
13	58.3	58.4	58.0	58.0
14	89.5	89.5	89.4	89.4
15	33.8	33.8	33.8	33.8
16	33.1	33.1	32.9	33.0
17	92.5	92.5	92.4	92.4
18	10.8	10.8	10.7	10.7
19	18.1	18.1	18.1	18.1
20	209.9	209.8	209.4	209.4
21	27.8	27.8	27.5	27.5
1′	165.3	165.3	166.0	165.9
2′	121.9	121.9	114.1	114.1
3′	132.4	132.4	165.4	165.4
4′	116.2	116.2	38.1	38.1
5′	163.6	163.6	20.8	20.8
6′	116.2	116.2	20.9	20.9
7′	132.4	132.4	16.4	16.4

[a] Measured in C_5D_5N at 100 M.

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