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C21 steroidal glycosides with cytotoxic activities from *Cynanchum otophyllum*

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ABSTRACT

Eight new C21 steroidal glycosides, namely cynanotins A–H (**1**–**8**), together with fifteen known analogues, were isolated from the roots of *Cynanchum otophyllum*. Their structures were elucidated by spectroscopic analysis and chemical methods. In this study, all of isolates were tested for their vitro inhibitory activities against five human tumor cell lines (HL-60, SMMC-7721, A-549, MCF-7 and SW480). Compounds **3**–**15** showed moderate cytotoxic activities against HL-60 cell lines with IC_{50} values ranging from 11.4 to 37.9 μM. Compounds **5**, **9**, and **10** showed marked or moderate cytotoxic activities against five human tumor cell lines with IC_{50} values ranging from 11.4 to 36.7 μM. Compound **11** displayed moderate cytotoxic activities against HL-60, SMMC-7721, MCF-7 and SW480 cell lines with IC_{50} values of 12.2–30.8 μM. Compared to the positive control (IC_{50}: 35.0 μM), compounds **5**, **9**–**11** exhibited more potential inhibitory activity against MCF-7 cells (IC_{50}: 16.1–25.6 μM).

Cynanchumot ophyllum (Asclepiadaceae) is mainly distributed in the southwest of China,[1] whose dried root and/or rhizome parts have long been used as folk medicine to treat rheumatalgia, phlegm, geriatric diseases, immune deficiency, and other illnesses.[2] Research found that C21 steroids were the main bioactive constituents and have exhibited a wide spectrum of pharmacological activities, such as antitumor, antiepileptic, anti-depressant, antifungal, anti-aging, anti-viral, and appetite suppressing effects.[3–11] Previous phytochemical investigation resulted in the isolation of several C21 steroidal glycosides with cytotoxic activities.[4] Thus, to further search for the bioactive C21 steroidal sapogenins, the root of *C. otophyllum* was investigated and eight new pregnane glycosides, namely cynanotins A–H (**1**–**8**) and fifteen known analogues (**9**–**23**) (Fig. 1) were isolated. Herein, we reported the isolation and structural elucidation of these compounds, as well as their cytotoxicity for five human tumor cell lines (HL-60, SMMC-7721, A-549, MCF-7 and SW480).

Compound **1** was obtained as white amorphous powders, had a molecular formula $C_{35}H_{50}O_{11}$ as determined by HRESIMS *m/z* 669.3247 ([M+Na]$^+$, calcd. 669.3245). IR spectrum showed the absorption bands for hydroxyl (3438 cm^{-1}), carbonyl (1707 cm^{-1}) and olefinic (1609 cm^{-1}) groups. The ^{1}H NMR spectrum of **1** revealed the presence of two singlet methyl protons (δ_H1.64, s; δ_H1.15, s), two doublet methyl protons (δ_H 1.03, d, *J* = 6.3 Hz; δ_H 1.22, d, *J* = 6.2 Hz), one olefinic proton [δ_H 5.35 d, *J* = 4.8 Hz, H-6)] and four aromatic protons of a parasubstituted benzene ring [δ_H 6.80 (2H, dd, *J* = 8.9 and 3.0 Hz, H-4′, 6′) and 7.79 (2H, d, *J* = 8.8 Hz, H-3′, 7′)]. The ^{13}C NMR spectrum of **1** displayed 35 carbon resonances, belonging to four methyls, eight methylenes, thirteen methines (including five olefinic/aromatic, seven oxygenated), and nine quaternary carbons (including three olefinic/aromatic, one ester carbonyl, three oxygenated). Aforementioned data indicated that **1** was a typical C21 steroidal glycoside with a *p*-hydroxybenzoyl and a sugar moiety.

1D NMR data of **1** showed that it had the same aglycone fraction as caudatin-3-*O*-*β*-D-cymaropyranosyl-(1→4)-*β*-D-oleandropyranosyl-(1→4)-*β*-D-cymaropyranoside,[12] while their only difference was the oxygenated methine at C-20 in **1** instead of carbonyl group in the later. A long-range HMBC correlations (Fig. 2) of H-3 (δ_H 3.57, m) with C-1, C-2, and C-4; of H-6 (δ_H 5.35, d, *J* = 4.8 Hz) with C-5 (δ_C 140.1), C-7 (δ_C 35.3), and C-8 (δ_C 75.0); of H-9 (δ_H 1.58) with C-8, C-12 (δ_C 75.3), and C-14 (δ_C 89.2); of H_3-18 (δ_H 1.64) with C-12, C-14, and C-17 (δ_C 89.4); of H_3-21 (δ_H 1.24, d, *J* = 6.3 Hz) with C-17 and C-20 (δ_H 71.4); of H-12 with C-1′ (δ_C 167.9), of H-3′, H-4′, H-6′, and H-7′ with C-2′, C-5′; of H-3′ and H-7′ with C-1′, further confirmed above deduction.

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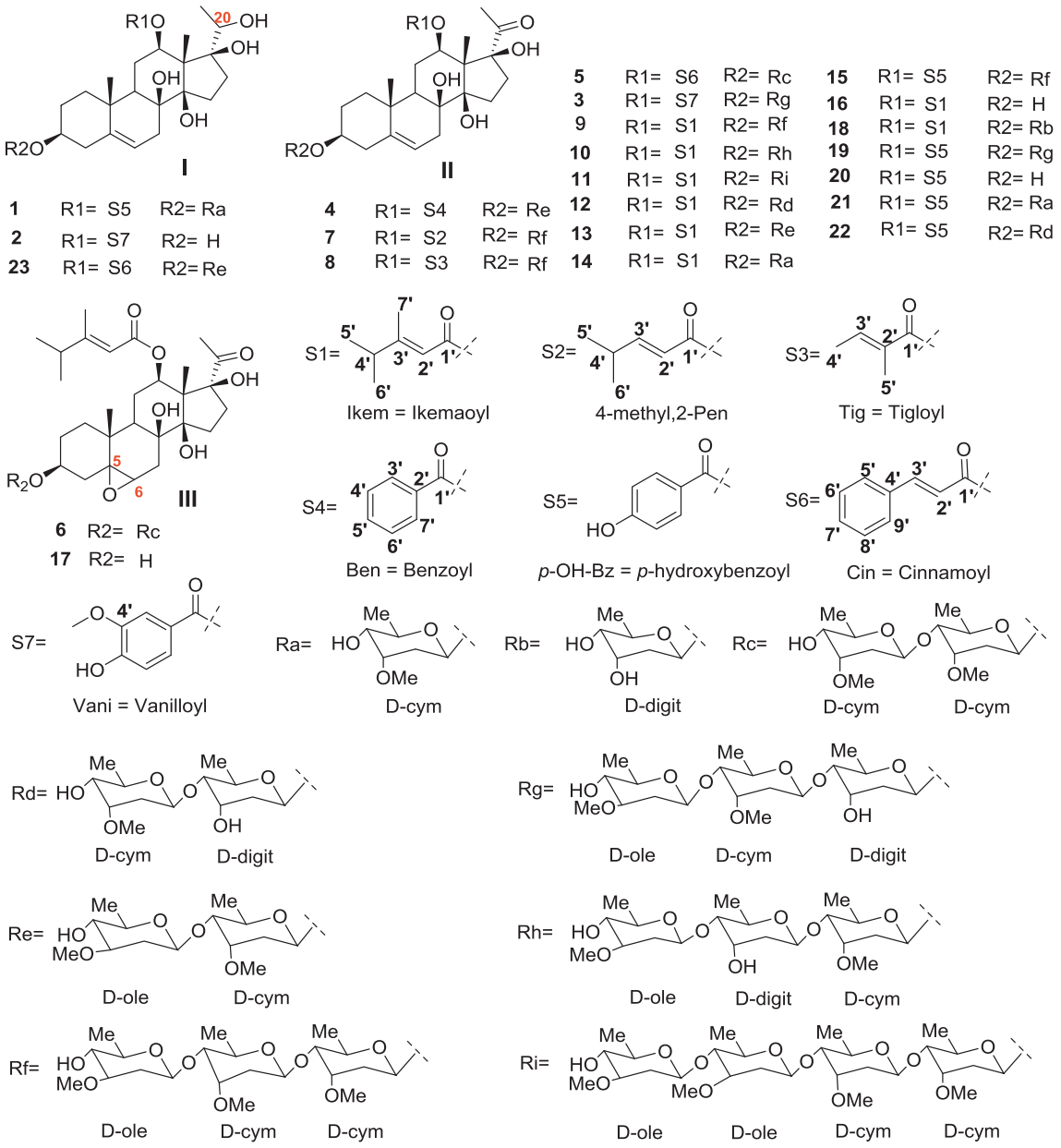

Fig. 1. Chemical structure of compounds **1**–**23** isolated from *Cynanchumot ophyllum*.

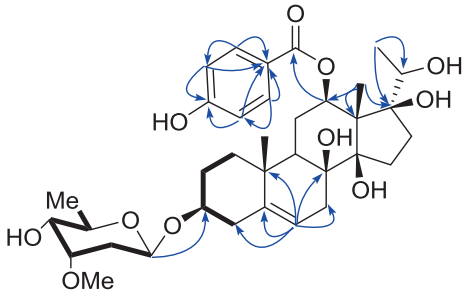

Fig. 2. The selected HMBC (H→C) and ^{1}H–^{1}H COSY (H–H) correlations of compound **1**.

For the sugar moiety, the characteristic anomeric proton and carbon signals at δ_H 4.85 (m) and δ_C 97.2 and a series of ^{1}H–^{1}H COSY correlations of H-1″/H-2″/H-3″/H-4″/H-5″/H$_3$-6″, together with the HMBC correlations of the methoxyl with C-3″ and of H-1″ with C-3, indicated that the sugar moiety could be a cymaropyranose and it was located at C-3. Furthermore, The sugar was identified as *β*-D-cymaropyranose by comprising R_f and optical rotation data of monosaccharides in the hydrolysates with authentic compounds and published spectroscopic data,[13,14] respectively.

Hence, **1** was determined to be 12-*O*-*p*-hydroxybenzoylsarcostin3-*O*-*β*-D-cymaropyranoide and named cynanotin A (**1**).

Compound **2**, as white amorphous powders, had molecular formula of $C_{29}H_{40}O_9$, which was determined by HRESIMS *m*/*z* 555.2564 $[M+Na]^+$ (calcd. 555.2565). The NMR spectra of **2** bore a resemblance to those of **1**, with the notable differences being the absence of a cymarose and sp^2 methine and the presence of an additional methoxyl and a sp^2 quaternary carbon in **2**, which implied that **2** was a C_{21} steroidal aglycone with a vanilloyl at C-12. In the HMBC spectrum of **2**, the observed correlations of OMe with C-4′ (δ_C 148.7); of H-3′ (δ_H 7.73, d, J = 1.9 Hz) and H-7′ (δ_H 7.63, dd, J = 8.3 and 1.9 Hz) with C-2′ (δ_C 125.3), C-4′, C-5′ (δ_C

153.1), C-6′ (δ_C 115.9), and C-1′ (δ_C 167.9); of H-12 (δ_H 4.84, dd, J = 11.5 and 4.2 Hz) with C-1′ confirmed above deduction. Hence, compound **2** was defined as 12-*O*-vanilloyl-sarcostin and named cynanotin B (**2**).

The molecular formula $C_{49}H_{72}O_{18}$ of **3** was established by the HRESIMS *m/z* 987.4355 $[M+K]^+$ (calcd. 987.4350). IR spectrum showed the absorption bands for hydroxyl (3440 cm^{-1}), carbonyl (1711 cm^{-1}) and olefinic (1632 cm^{-1}) groups. Comparison 1D NMR spectroscopic data (Tables S1 and S2) of **3** and **2** showed that they had the same aglycone, with the significant difference in the replacement of the oxymethine by a ketone carbonyl, respectively, as well as the presence of an additional three sugars moiety. The HMBC correlations of H_3-21 (δ_H 2.11, s) and H_2-16 (δ_H 1.84, m; δ_H 2.17, m) with C-20 (δ_C 212.1), and C-17 (δ_C 93.1) confirmed that C-20 was a ketone carbonyl. Additionally, combinned the characteristic 1D NMR data and coupling constants of three sugars and hydrolysis experiment, as well as TLC analysis, three sugars were assigned unambiguously to be β-digitoxopyranosyl, β-oleandropyranosyl and β-cymaropyranosyl units. Furthermore, the absolute configuration of the deoxysugars was D-series by comparing with the OR reported in the literature.[13–15] The sequence of the three sugar units located at C-3 of the aglycone was elucidated by HMBC spectrum, in which distinct correlations from δ_H 4.97 (β-D-digitoxopyranosyl H-1″) to δ_C 79.3 (C-3); from δ_H 4.79 (β-D-cymaropyranosyl H-1‴) to δ_C 83.8 (β-D-digitoxopyranosyl C-4″); from δ_H 4.62 (β-D-oleandropyranosyl H-1⁗) to δ_C 83.6 (β-D-cymaropyranosyl C-4‴) were observed. Thus, compound **3** was established as 12-*O*-vanilloyl-deacylmetaplexigenin 3-*O*-β-D-oleandropyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-digitoxo-pyranoside, and named cynanotin C (**3**).

The molecular formula of **4** was determined to be $C_{42}H_{60}O_{13}$ on the basis of the HRESIMS *m/z* 795.3947 $[M+Na]^+$ (calcd. 795.3926). IR spectrum showed the absorption bands for hydroxyl (3448 cm^{-1}), carbonyl (1709 cm^{-1}), and ester carbonyl (1637 cm^{-1}) groups. 1D NMR spectroscopic data (Tables S1 and S2) showed that **4** was also a C_{21} steroidal saponin with a two sugar moeity, and the aglycone fraction was similar with **1**. However, careful comparison of the 1D NMR spectra of **4** and **1** exhibited that a one-substituted phenyl was present in **4** and the oxygenated methine was replaced by a ketone carbonyl in **1**. The further confirmation was established from the HMBC correlations of H-3′ (δ_H 7.94 m), H-4′ (δ_H 7.47, t, J = 7.7 Hz), H-5′ (δ_H 7.60 m), H-6′ (δ_H 7.47, t, J = 7.7 Hz), and H-7′ (δ_H 7.94 m) with C-2′ (δ_C 131.5); of H-3′ and H-7′ with C-1′ (δ_C 166.7); of H-12 (δ_H 4.30, dd, J = 9.8 and 7.3 Hz) with C-1′; of H_3-21 (δ_H 2.04 s) and H_2-16 (δ_H 1.72 m;2.85 m) with C-20 (δ_C 212.3).

Furthermore, two anomeric carbon signals at δ_C 97.2 and 102.8, correlating with anomeric protons at δ_H 4.89 (m), 4.59 (dd, J = 9.9 and 2.0 Hz), respectively, were observed in the 1D NMR spectra of **4**. Similarly, on the basis of the 2D NMR correlations, and by comparison R_f and OR with the literature,[16] two sugar were assigned to one β-D-cymaropyranose and one β-D-oleandropyranose. Moreover, the sugar sequence and position of **4** was determined by the HMBC correlations of δ_H 4.89 (H-1′ of β-cymaropyranosyl) with δ_C 79.3 (C-3), and δ_H 4.59 (H-1″of β-oleandropyranose) with δ_C 83.8 (C-4′of β-cymaropyranosyl). Therefore, **4** was deduced to be 12-*O*-benzoyl-deacylmetaplexigenin3-*O*-β-D-oleandropyranosyl-(1→4)-β-D-cymaropyranoside and named cynanotin D(**4**).

The molecular formula of **5** was determined to be $C_{44}H_{62}O_{13}$ by analyzing the HRESIMS *m/z* 837.3830 $[M+K]^+$ (calcd. 837.3822) and ^{13}C NMR spectrum. The NMR spectra of **6** were similar to those of **5**. However, a cinnamyl unit [δ_C 165.8 (C-1′), 119.2 (C-2′), 144.8 (C-3′), 134.9 (C-4′), 128.5 (C-5′/C9′), 129.2 (C-6′/8′)and 130.5 (C-7′)] in **5** replaced the benzoyl group at C-12 in **4**, which was confirmed by the HMBC correlation of H-12 (δ_H 5.17, m) with C-1′ (δ_C 165.8). The detailed analysis of the NMR and MS data, as well as comparison with references indicated that its aglycone was kidjoranin.[17] In addition, two deoxysuger units in **6** were characterized by NMR signals at δ_H 5.27 (m), and δ_H 5.07 (m); δ_C 96.2 and δ_C 100.4, indicating that **6** possessed a β-cymaropyranosyl-(1→4)-β-cymaropyranosyl sugar sequence, in accordance with the results of acid hydrolysis of **5**. The sugar moiety was linked to C-3 by HMBC correlation from H-1″ to C-3. Meanwhile, the D configurations of the monosaccharide moiety were identified according to their OR values. Thus, **5** was identified as kidjoranin 3-*O*-β-D-cymaropyranosyl-(1→4)-β-D-cymaropyranoside and named cynanotin E (**5**).

On the basis of HRESIMS *m/z* 833.4088 $[M+K]^+$ (calcd. 833.4084), the molecular formula of **6** was assigned as $C_{42}H_{66}O_{14}$. The observed four singlet methyl protons [δ_H 1.05, 1.81, 2.25, 2.04 (each 3H, s, H_3-19, 18, 7, 21)], four doublet methyl protons [δ_H 0.93 (6H, dd, J = 8.7, 6.8 Hz, H_3-5′, 6′)], one olefinic proton [δ_H 5.83 (s, H-2′)], two anomeric protons (δ_H 5.18 dd, J = 9.7 and 2.0 Hz; δ_H 5.08 m) and a series of oxygenated methine protons in the ^1H NMR spectrum of **6**, coupled with 42 carbon resonances in its ^{13}C NMR spectrum indicated that **6** was a C21 steroidal diglycoside with two sugars. The further analysis of 1D NMR spectra showed that its aglycone was the same as compound **17**[18] possesing a ikemoyl at C-12 and a 5α,6α-epoxyl group. This was supported by the HMBC correlations (Fig. 3) of H_3-5′ (δ_H 0.93, dd, J = 8.7 and 6.8 Hz), H_3-6′ (δ_H 0.93, dd, J = 8.7 and 6.8 Hz), and H_3-7′ (δ_H2.25, s) with C-4′ (δ_C 38.0) and C-3′ (δ_C 165.6); of H_3-2′ with C-1′ (δ_C 165.8), C-3′, and C-4′; of H-12 (δ_H 72.1) with C-1′; of H-6 (δ_H 3.36, d, J = 2.7 Hz) with C-4 (δ_C 35.8), C-5 (δ_C 64.2), C-7 (δ_C 65.4), and C-8 (δ_C 75.8). As for sugar moiety, the coupling constants of anomeric proton and its 2D NMR correlations indicated that **6** have two β-cymaropyranose connecting to C-3. By comparing the TLC and OR data of monosaccharides in the hydrolysates with authentic compounds and published spectroscopic data,[13,14] the two sugars were assigned as D-configuration, Finally, **6** was determined to be 5α,6α-epoxy-caudatin-3-*O*-β-D-cymaropyranosyl-(1→4)-β-D-cymaropyranoside and named cynanotin F (**6**).

Compound **7** had a molecular formula of $C_{48}H_{76}O_{16}$ based on HRESIMS *m/z* 931.5026 $[M+Na]^+$ (calcd. 931.5026). IR spectrum showed absorption bands for hydroxyl (3438 cm^{-1}) and carbonyl (1714 cm^{-1}) groups as well as a C=C band (1633 cm^{-1}). Comparison of the 1D NMR data between **7** and **6** showed the absence of a singlet methyl and a sp^2 quaternary carbon, nevertheless the presence of a sp^2 methine and an additional oleandrose in **7**. In the HMBC spectrum, two doublet methyls, H_3-5′ (δ_H 1.07, d, J = 6.8 Hz) and H_3-6′ (δ_H 1.07, d, J = 6.8 Hz) showed the correlations with C-4′ (δ_C 25.8), and C-3′ (δ_C 157.1), while H-3′ (δ_H 6.85, dd, J = 15.7 and 6.9 Hz) and H-2′ correlated with C-1′ (δ_C 167.2) and C-4′. Meanwhile, the correlations of H_3-5′/H-4′/H-3′/H-2′ were also observed in the ^1H–^1H COSY spectrum of **7**. Above information indicated that a substitute of 4-methyl-2-pentenoyl present in **7**. Furthermore, the key HMBC correlation of H-12 (δ_H 4.51, dd, J = 11.8 and 4.1 Hz) with C-1′ (δ_C 167.2) illustrated that the substitute was located at C-12.

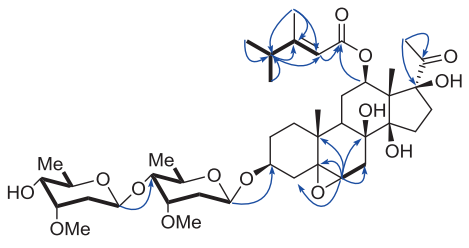

Fig. 3. The selected HMBC (H→C) and ^1H–^1H COSY (H–H) correlations of compound **6**.

Table 1
The cytotoxicity data of compounds **3–15**. (IC_{50}: μM).

Compounds	HL-60	A-549	SMMC-7721	MCF-7	SW480
3	37.9	>40	>40	>40	>40
4	15.6	>40	>40	>40	>40
5	20.6	35.5	33.1	25.6	36.7
6	15.8	>40	>40	>40	>40
7	25.8	>40	>40	>40	>40
8	15.6	>40	>40	>40	>40
9	11.4	27.7	27.9	16.1	30.3
10	12.9	30.4	27.4	17.2	24.8
11	12.2	>40	30.8	18.0	28.8
12	15.7	>40	>40	>40	>40
13	15.4	>40	>40	>40	>40
14	25.6	>40	>40	>40	>40
15	29.1	>40	>40	>40	>40
DDP	3.9	32.9	13.8	35.0	26.9

DDP (*cis*-Dichlorodiamineplatinum (II)) as positive control.

In the ^{13}C NMR spectrum of compound **7**, three anomeric carbon resonances at δ_C 97.2, δ_C 101.2, and δ_C 102.8 revealed the presence of three sugar residues, and they were assigned to be two cymarose and one oleanose by comparing the 1D NMR spectroscopic data with those of otophylloside B.[19] Furthermore, the HMBC correlations of H-1″ with C-3; of H-1‴ with C-4″; of H-1⁗ with C-4‴, along with their positive specific rotation values[13–15] confirmed the sugar chain fragment was 3-*O*-*β*-D-oleandropyranosyl-(1→4)-*β*-D-cymaropyranosyl-(1→4)-*β*-D-cymaropyranoside. Finally, the structure of **7** was determined and named cynanotin G (**7**).

Compound **8** was obtained as white amorphous powders, had a molecular formula $C_{47}H_{74}O_{16}$ as determined by *m*/*z* 933.4617 $[M+K]^+$ (calcd. 933.4608). The 1D NMRspectra of **8** reseabled those of **7,** except for a tigloyl group in **8** instead of the 4-methyl-2-pentenoyl at C-12 in **7**, which was confirmed by the HMBC correlations of H_3-4′ (δ_H 1.80, d, *J* = 6.8 Hz) and H_3-5′ (δ_H 1.78, s) with C-2′ (δ_C 129.9), C-3′ (δ_C 138.6), and C-1′ (δ_C 168.1); of H-12 (δ_H 4.49, d, *J* = 12.1 Hz) with C-1′. Similarly, compaired with 1D NMR spectroscopic data of **7**, they had the same sugar chian fragment. On the basis of the coupling constants of the anomeric protons [δ_H 4.85, d, *J* = 9.5 Hz, H-1″; δ_H 4.78, d, *J* = 9.9 Hz, H-1‴; δ_H 4.58, d, *J* = 9.8 Hz, H-1⁗], the relative configuration of H-1″, H-1‴, and H-1⁗ were α-oriented. Moreover, the absolute configurations of the oleandrose and cymarose were determined as D by comparing the optical rotation with the known compounds in literature.[13–15] Thus, compound **8** was determined as in cisagenin A 3-*O*-*β*-D-oleandropyranosyl-(1→4)-*β*-D-cymaropyranosyl-(1→4)-*β*-D-cymaropyranoside and named cynanotin H (**8**).

The sixteen known C21 steroidal glycosides were identified by comparison of experimental and literature spectroscopic data as otophylloside B (**9**),[20] caudatin-3-*O*-*β*-D-oleandro-pyranosyl-(1→4)-*β*-D-digitoxopyranosyl-(1→4)-*β*-D-cymaro-pyranoside (**10**),[21] caudatin-3-*O*-*β*-D-oleandropyranosyl-(1→4)-*β*-D-olean-dropyranosyl-(1→4)-*β*-D-cymaropyranosyl-(1→4)-*β*-D-cymar-opyranoside (**11**),[10] caudatin-3-*O*-*β*-D-cymaropyranosyl-(1→4)-*β*-D-digitoxopyranoside (**12**),[16] caudatin-3-*O*-*β*-D-oleandropyran-osyl-(1→4)-*β*-D cymaropyrano-side (**13**),[16] caudatin 3-*O*-*β*-cymaropyranoside (**14**),[22] otophylloside A (**15**),[11] caudatin (**16**),[23] 5α,6α-epoxycaudatin (**17**),[16] caudatin 3-*O*-*β*-D-digitoxopyran-oside (**18**),[24] qinyangshengenin-3-*O*-*β*-D-oleandropyranosyl-(1→4)-*β*-D-cymaropyranosyl-(1→4)-*β*-D-digitoxo-pyranoside (**19**),[25] qingyangshengenin (**20**),[26] cynotophylloside C (**21**),[11] qingyangshengenin 3-*O*-*β*-D-cymaropyranosyl-(1→4)-*β*-D-digit-oxopyranoside (**22**),[11] 3-*O*-*β*-D-oleandropyranosyl-(1→4)-*β*-D-cymaropyranosylpenupgenin (**23**).[27]

Cytotoxic effects of compounds **3–15** were tested against five human tumor cell lines (HL-60, SMMC-7721, A-549, MCF-7, and SW480) by MTS method. As results in Table 1, compounds **3–15** showed moderate cytotoxic activities against HL-60 cell line with IC_{50} values ranging from 11.4 to 37.9 μM. Compounds **5**, **9**, and **10** showed marked or moderate cytotoxic activities against five human tumor cell lines with IC_{50} values ranging from 20.6 to 36.7, from 11.4 to 30.3, from 12.9 to 30.4 μM, respectively. Compound **11** displayed moderate cytotoxic activities against HL-60, SMMC-7721, MCF-7 and SW480 cell lines with IC_{50} values of 12.2, 30.8, 18.0, and 28.8 μM, respectively. Compared to the positive control (IC_{50}: 35.0 μM), compounds **5**, **9**–**11** exhibited more potential inhibitory activity against MCF-7 cells with IC_{50} values of 25.6, 16.1, 17.2, and 18.0 μM, respectively.

Twenty-three C21 steroidal glycosides, including eight new compounds, namely cynanotins A–H (**1**–**8**) and fifteen known ones were isolated from the roots of *C. otophyllum*. Interestingly, compounds possessing the substitutes of tigloyl, 4-methyl-2-pentenoyl, and vanilloyl at C-12 were first identified from this species. Meanwhile, cytotoxicity assay showed that these compounds containing above substitutes showed weak cytotoxicities against HL-60, while compounds **9** and **10** possessing ikemaoyl group at C-12 and three sugars at C-3 displayed moderate activities against five human tumor cell lines (HL-60, SMMC-7721, A-549, MCF-7 and SW480), suggesting that the ikemaoyl group and three sugars could be the key active groups.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmcl.2018.03.078.

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