Two new polyhydroxylated triterpenoids from *Salvia urmiensis* and their cytotoxic activity

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**ABSTRACT**

Two new polyhydroxylated triterpenoids were isolated from the acetone extract of the aerial parts of *Salvia urmiensis* Bunge. Their structures were elucidated by 1D and 2D NMR and HR-ESI-MS analyses as olean-12-ene-1β,3β,11α,22α-tetraol (1) and urs-12-ene-1β,3β,11β,22α-tetraol (2). The effect of these compounds on cell viability of MCF-7 cells was investigated by the MTT assay. Compounds 1 and 2 showed weak cytotoxicity with IC$_{50}$ values of 110.23 ± 0.12 and 88.35 ± 0.09 μM, respectively.

**ARTICLE HISTORY**

Received 20 October 2015
Accepted 17 December 2015

**KEYWORDS**

*Salvia urmiensis*; triterpenoid; polyhydroxylation; cytotoxic activity

1. Introduction

The genus *Salvia* is one of the largest members of the family Lamiaceae, comprising more than 900 species, large widespread all over the world. *Salvia* species have been used in traditional medicine all around the world since the ancient times. Their essential oils and extracts have shown antimicrobial, antioxidant, antidiabetic, antitumour, antiplasmodial and anti-inflammatory activities (Sivropoulo et al. 1997; Dorman & Deans 2000; Ulubelen 2003; Tepe et al. 2004; Kamatou et al. 2008; Şenol et al. 2010; Chan et al. 2011; Loizzo et al. 2014; Bahadori et al. 2015). Many *Salvia* species are used as herbal tea and in food, cosmetics,
perfumery and the pharmaceutical industry, and some species are grown in gardens as ornamental plants (Kahraman et al. 2010). A diverse spectrum of secondary metabolites has been identified in *Salvia* species (Wu et al. 2012). In Iran, there is a high diversity of *Salvia* species and accessions which includes 61 species, 17 of them are endemic (Jamzad 2012). Some Iranian *Salvia* species have been investigated from a phytochemical viewpoint, and their biological activities (Moridi Farimani et al. 2008, 2012; Gandomkar et al. 2011; Rafatian et al. 2012; Farjam et al. 2013; Habibi et al. 2013; Ebrahimi et al. 2014; Esmaeili & Moridi Farimani 2014; Moridi Farimani & Mazarei 2014; Moridi Farimani & Miran 2014; Akaberi et al. 2015; Salimikia et al. 2016). *Salvia urmiensis* Bunge is an aromatic perennial herb that is found in the West Azerbaijan province of northwestern Iran. We recently identified several triterpenoids with rare carbon skeletons from the *n*-hexane and acetone extracts of this species (Moridi Farimani et al. 2013; Moridi Farimani, Bahadori, et al. 2015; Moridi Farimani, Mohammadi, et al. 2015). Further examination of the acetone extract of *S. urmiensis* led to the isolation of two new triterpenoids, with polyhydroxylated oleanane and ursane skeletons (1, 2) on the basis of extensive spectroscopic data (Figure 1). Also, cytotoxic activity of the purified compounds was determined on MCF-7 cells.

2. Results and discussion

Compound 1 was obtained as a white, amorphous powder. Its molecular formula, $C_{30}H_{50}O_{4'}$, was determined on the basis of its HR-ESI-MS spectrum ($m/z$ 497.3593 [M + Na]$^+$, Calcd 497.3601) with 6° of unsaturation. The $^{13}$C NMR spectrum revealed 30 carbon resonances which were resolved into eight methyl, seven methylene, eight methine and seven quaternary carbons as categorised by HSQC and APT experiments. $^{13}$C NMR data showed one tri-substituted C=C group ($\delta_C$ 124.5, 147.0) and four oxygen-bearing sp$^3$ carbons at $\delta_C$ 66.0, 75.0, 75.6, and 76.7. According to the degree of unsaturation, the structure of 1 must be pentacyclic due to the absence of any other sp or sp$^2$ carbon signals. The $^1$H NMR spectrum in conjunction with the HSQC spectrum showed resonances for an olefinic proton at $\delta_H$ 5.15 (1H, d, $J = 3.8$ Hz), four protons at $\delta_H$ 3.10 (1H, dd, $J = 11.5$ and 4.5 Hz), $\delta_H$ 3.39 (1H, dd, $J = 11.5$ and 5.0 Hz), $\delta_H$ 3.43 (1H, dd, $J = 11.5$ and 4.5 Hz) and $\delta_H$ 4.15 (1H, dd, $J = 8.5$ and

![Figure 1. Chemical structures of the isolated compounds.](image-url)
indicative of oxygenated methines, and eight methyl singlets at $\delta_H 0.69, 0.84, 0.86, 0.89, 0.90, 0.94, 0.97$ and $1.18$. Therefore, the structural features were reminiscent of a poly-hydroxylated oleane type triterpenoid. Analysis of HMBC correlations confirmed the location of substituents. The signals of H$_3$-23 ($\delta_H 0.89$) and H$_3$-24 ($\delta_H 0.69$) were correlated with the resonances of an oxygen-bearing carbon (C-3, $\delta_C 75.6$), an aliphatic methine (C-5, $\delta_C 52.1$) and a quaternary carbon (C-4, $\delta_C 38.7$), suggesting that one hydroxyl group was located at C-3. A second hydroxyl group was assigned to be at C-1 according to the HMBC cross peaks of H-1 ($\delta_H 3.39$) with C-2 ($\delta_C 34.7$), C-3 and C-25 ($\delta_C 12.2$), and also of H-3 ($\delta_H 3.10$) with C-1 ($\delta_C 76.7$). $^1$H–$^1$H COSY correlations of methylene protons at C-2 ($\delta_H 1.65$ and $1.72$) with both H-1 and H-3 supported the A-ring 1,3-dihydroxy moiety. Strong HMBC correlations between H-11 ($\delta_H 4.15$) and C-9 ($\delta_C 55.5$), C-12 ($\delta_C 124.5$) and C-13 ($\delta_C 147.0$) were used to assign a third hydroxy group to C-11. This confirmed by $^1$H–$^1$H COSY correlations between H-11 and two other methinic protons at $\delta_H 1.63$ (H-9) and $\delta_C 5.15$ (H-12). HMBC correlations of H$_3$-29 ($\delta_H 0.84$) and H$_3$-30 ($\delta_H 0.86$) with C-19 ($\delta_C 45.3$), C-20 ($\delta_C 31.0$), and C-21 ($\delta_C 42.2$), H-21 ($\delta_H 1.30$) with C-22 ($\delta_C 75.0$), and H$_3$-28 ($\delta_H 0.9$) with C-17 ($\delta_C 38.1$), C-18 ($\delta_C 46.7$), and C-22 ($\delta_C 75.0$) confirmed the nature of ring E with a hydroxyl group at C-22. The downfield shifts of C-17 ($\delta_C 38.1$) and C-21 ($\delta_C 42.2$), and $^1$H–$^1$H COSY correlations between H-21 ($\delta_H 1.30$) and H-22 ($\delta_H 3.43$) supported this assignment. The relative configuration of 1 was corroborated by a NOESY spectrum and coupling constants ($^3J_{H-H}$). Diagnostic cross-peaks between H$_3$-23, H-3 and H-5, between H-5 and H-1, and between H-3 and H-1 clarified the $\beta$-orientations of OH-3 and OH-1. The coupling constants of H-1 (dd, 11.5, 5.0 Hz), H-3 (dd, 11.5, 4.5 Hz) and H-5 (dd, 11.5, 2.0 Hz) confirmed their axial orientations. Likewise, NOESY correlations between H-11, H$_3$-25 and H$_3$-26 confirmed their occupation of the same face of the molecule. The coupling constants of H-11 (dd, 8.5, 3.8 Hz) confirmed that the hydroxyl group was in an equatorial orientation. Equally, diagnostic cross peaks between H-22, H-18 and H$_3$-28 were observed and confirmed their cofacial orientation. Furthermore, the coupling constants of H-22 (dd, 11.5, 4.5 Hz) corroborated the equatorial orientation of the hydroxyl group. Therefore, the structure of 1 was determined as olean-12-ene-1$\beta$,3$\beta$,11$\alpha$,22$\alpha$-tetraol.

Compound 2 was isolated as an amorphous powder. It had the same molecular formula C$_{30}$H$_{50}$O$_4$ (m/z 497.3605 [M + Na]$^+$, Calcd 497.3601), as 1. The NMR spectroscopic data of 2 showed strong similarities to those of 1. In particular, rings A, B, C and D appeared to be identical. However, in the $^1$H and $^{13}$C NMR spectrum of 2, the signals of two methyl singlets at $\delta_H/\delta_C 0.84/33.0$ and $0.86/23.9$ in 1 were replaced by two methyl doublets ($\delta_H/\delta_C 0.85/17.2$ and $0.86/20.9$). Also, the resonances of a methylene ($\delta_H 1.01$ and $1.65$; $\delta_C 45.3$) and a quaternary carbon ($\delta_C 45.3$) in 1 were replaced by those of two methine at $\delta_H/\delta_C 1.32/38.8$ and $1.35/31.6$. Careful inspection of the resonances in the E-ring region revealed the ursane skeleton of 2 with the hydroxyl group at C-22, as in 1. Analysis of the NOESY spectrum confirmed the relative configuration of all stereochemically centres as obtained for 1. Thus, the structure of 2 was elucidated to be urs-12-ene-1$\beta$,3$\beta$,11$\alpha$,22$\alpha$-tetraol (Figure 1).

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to measure the viability of MCF-7 tumour cell line after exposure to compounds 1 and 2, compared with paclitaxel as positive control (0.032 ± 0.005 μM). Both compounds reduced weakly the cell viability of MCF-7 cell line in a dose-dependent manner. The IC$_{50}$ values of compounds 1 and 2 were determined as 110.23 ± 0.12 and 88.35 ± 0.09 μM, respectively.
3. Experimental section

3.1. General experimental procedures

HR-ESI-MS was carried out on a Bruker 147 microTOF-ESI-MS system. NMR spectra were recorded on Bruker AVANCE III-500 spectrometer operating at 500.13 MHz for $^1$H NMR and 125.77 MHz for $^{13}$C NMR with TMS as an internal standard. IR spectra were recorded using a Bruker Tensor 27 spectrometer. Optical rotations were measured using a Perkin Elmer-341 automatic digital polarimeter. Silica gel (70–230 mesh) was used for column chromatography (CC), and precoated silica gel F$_{254}$ (20 cm × 20 cm) plates for TLC, both supplied by the Merck.

3.2. Plant material

The aerial parts of *S. urmiensis* were collected at full flowering stage in May 2012 in Takab, West Azarbaijan province in Iran. A voucher specimen (MPH-1220) has been deposited in the herbarium of Medicinal Plants and Drugs Research Institute of Shahid Beheshti University, Tehran, Iran.

3.3. Extraction and isolation

Aerial parts of *S. urmiensis* Bunge Sw. (5.0 kg) were crushed and extracted with n-hexane (2 L × 30 L) to remove the less polar components. Then, the residue was extracted with acetone (4 L × 30 L) at room temperature for 7 days. The solution was concentrated under reduced pressure. The crude acetone extract (160 g) was mixed with H$_2$O (1.0 L) to form a suspension and partitioned successively with n-hexane and EtOAc to yield n-hexane (80 g), EtOAc (60 g) and H$_2$O (20 g) soluble fractions. The EtOAc-soluble fraction was subjected to a silica gel CC with a gradient of the n-hexane–EtOAc and then EtOAc–MeOH as eluent. A total of 15 fractions (F1–F15) were combined with the aid of TLC analysis. Fraction 12 [0.7 g, eluted with EtOAc–MeOH (98:2)] was applied on silica gel CC and eluted with CH$_2$Cl$_2$–MeOH (10:1) to afford five subfractions (frs. 12a–12e). Subfraction 12a was recrystallised in methanol to give compound 1 (6 mg). Fraction 13 [2.6 g, eluted with EtOAc–MeOH (95:5)] was subjected to another silica gel CC, eluted with chloroform–acetone (80:20 to 65:35) to afford nine subfractions (frs. 13a–13i). Subfraction 13d was further separated on silica gel CC, eluted with CH$_2$Cl$_2$-acetone (1:1) to give compound 2 (15 mg).

3.3.1. Olean-12-ene-1β,3β,11α,22α-tetraol (1)

White amorphous powder; $[\alpha]_{D}^{25} +37$ (c 0.1, DMSO); IR (KBr): v $\max$ 3420, 2927, 1642, 1461, 1386, 1010 cm$^{-1}$; $^1$H NMR (CDCl$_3$ + CD$_3$OD, 500 MHz): δ 0.58 (1H, dd, $J = 2.0$, 11.5 Hz, H-5), 0.69 (3H, s, H-24), 0.84 (3H, s, H-29), 0.86 (3H, s, H-30), 0.89 (3H, s, H-28), 0.90 (3H, s, H-27), 0.94 (3H, s, H-25), 0.97 (3H, s, H-26), 0.98 (1H, m, H-15α), 1.01 (1H, m, H-19α), 1.18 (3H, s, H-27), 1.28 (1H, m, H-16β), 1.30 (2H, m, H-21), 1.24 (1H, m, H-7β), 1.44 (1H, m, H-7α), 1.45 (1H, m, H-6α), 1.55 (1H, m, H-15β), 1.57 (1H, m, H-6β), 1.63 (1H, d, $J = 8.5$ Hz, H-9), 1.65 (1H, m, H-2α), 1.65 (1H, m, H-16α), 1.65 (1H, m, H-19β), 1.72 (1H, m, H-2β), 1.95 (1H, dd, $J = 3.5$, 10.0 Hz, H-18), 3.10 (1H, dd, $J = 4.5$, 11.5 Hz, H-3), 3.39 (1H, dd, $J = 5.0$, 11.5 Hz, H-1), 3.43 (1H, dd, $J = 4.5$, 11.5 Hz, H-22), 4.15 (1H, dd, $J = 3.8$, 8.5 Hz, H-11), 5.15 (1H, d, $J = 3.8$ Hz, H-12), $^{13}$C NMR (125 MHz, CDCl$_3$+CD$_3$OD): δ 12.2 (C-25), 15.1 (C-24), 17.6 (C-26), 18.0 (C-6), 18.8 (C-16), 23.9 (C-30), 24.1 (C-28), 25.0 (C-27), 25.7 (C-15), 27.7 (C-23), 31.0 (C-20), 33.0 (C-29), 33.1 (C-7), 34.7 (C-2), 38.1 (C-17), 38.7 (C-4),
3.3.2. Urs-12-ene-1β,3β,11α,22α-tetraol (2)

White amorphous powder; \([\alpha]_D^{25} +30\) (c 0.1, DMSO); IR (KBr): \(v_{\text{max}} \) 3432, 2931, 2868, 1632, 1459, 1378, 1006 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\) + CD\(_3\)OD, 500 MHz): \(\delta\) 0.55 (1H, d, \(J = 9.9\) Hz, H-5), 0.70 (3H, s, H-24), 0.81 (3H, s, H-28), 0.85 (3H, d, \(J = 5.8\) Hz, H-29), 0.86 (1H, m, H-16α), 0.86 (3H, d, \(J = 5.9\) Hz, H-30), 0.90 (3H, s, H-23), 0.95 (1H, m, H-15α), 0.98 (3H, s, H-25), 0.98 (3H, s, H-26), 1.11 (3H, s, H-27), 1.23 (1H, m, H-7α), 1.32 (1H, m, H-19), 1.35 (1H, m, H-20), 1.45 (1H, m, H-7β), 1.49 (1H, m, H-6α), 1.53 (2H, m, H-21), 1.57 (1H, d, \(J = 8.4\) Hz, H-6β), 1.59 (1H, d, \(J = 8.4\) Hz, H-9), 1.63 (1H, m, H-2β), 1.64 (1H, m, H-18), 1.68 (1H, m, H-15β), 1.72 (1H, m, H-2α), 1.84 (1H, dt, \(J = 4.5, 13.2\) Hz, H-16β), 3.14 (1H, dd, \(J = 4.4, 11.6\) Hz, H-3), 3.27 (1H, brt, \(J = 2.9\) Hz, H-22), 3.39 (1H, dd, \(J = 4.4, 11.5\) Hz, H-1), 4.15 (1H, d, \(J = 3.5, 8.4\) Hz, H-11), 5.18 (1H, d, \(J = 3.5\) Hz, H-12), \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 12.9 (C-25), 15.0 (C-24), 17.6 (C-26), 18.0 (C-6), 27.6 (C-16), 20.9 (C-30), 21.8 (C-28), 23.1 (C-27), 26.3 (C-15), 27.7 (C-23), 31.6 (C-20), 17.2 (C-29), 33.2 (C-7), 34.9 (C-2), 37.5 (C-17), 38.9 (C-4), 37.7 (C-21), 43.0 (C-8), 43.0 (C-14), 43.7 (C-10), 38.8 (C-19), 53.0 (C-18), 52.4 (C-5), 56.0 (C-9), 66.1 (C-11), 75.1 (C-22), 75.4 (C-3), 77.0 (C-1), 127.4 (C-12), 142.0 (C-13); HR-ESI-MS 497.3605 [M + Na]\(^+\) (Calcd 497.3601 for C\(_{30}\)H\(_{50}\)NaO\(_4\)).

3.4. Cytotoxicity assay

3.4.1. Cell culture and treatment

The human breast adenocarcinoma (MCF-7) cell line was purchased from National Cell Bank of Iran, Pasteur Institute (Tehran, Iran), and maintained in DMEM medium supplemented with 10% fetal bovine serum and 100 U/mL penicillin and 100 μg/mL streptomycin. This cell was kept at 37 °C in a humidified atmosphere containing 5% CO\(_2\). Compounds 1 and 2 were dissolved in DMSO to make a stock of 1 mM and further diluted to final concentrations of 10–1000 μM with the serum free culture medium.

3.4.2. Cell viability assay

Cell viability was determined using the MTT assay. Briefly, 2.5 × 10\(^4\) cells were seeded in 96-well plates at 37 °C with 5% CO\(_2\) for overnight incubation and treated with appropriate concentrations of compounds of 1 and 2 for 24 h. The cells were then incubated with a serum-free medium containing MTT at a final concentration of 0.5 mg/mL for 4 h. The dark formazan crystals formed were dissolved in DMSO and the absorbance was measured at 570 nm.

4. Conclusion

Two new polyhydroxylated triterpenoids were isolated from the acetone extract of aerial parts of S. urmiensis Bunge. All previously reported triterpenoids of this plant were rare in nature having a ε-lactone E-ring or a C\(_{17}\)–C\(_{22}\) E-seco-ursane skeletons (Moridi Farimani et al. 2013, Farimani, Bahadori, et al. 2015, Farimani, Mohammadi, et al. 2015). While compounds 1 and 2 have usual skeletons as pentacyclic triterpenoids with four hydroxyl group at C-1, C-3, C-11 and C-22. Several polyhydroxylated ursane and oleanane type triterpenoids were previously found in different Salvia species (e.g. Salvia kronenburgii, Salvia argentea L. and...
Salvia argentea var. aurasica (Pomel) Batt. & Trab.) (Bruno et al. 1987; Topçu et al. 2004; Lakhal et al. 2014). All of these compounds possess some hydroxyl or acetoxy group at different situations. However, the most distinguished feature of the isolated compounds from S. urmiensis is their hydroxylation at C-22.

Supplementary material

1D and 2D NMR spectra of compounds 1 and 2 can be found as Supporting Information.

Acknowledgements

Financial support by the Shahid Beheshti University Research Council is gratefully acknowledged. All spectra were performed at the Department of Pharmaceutical Sciences, Division of Pharmaceutical Biology, University of Basel. The kind assistance of Prof M. Hamburger, Dr S.N. Ebrahimi, and all other staff is gratefully appreciated.

Disclosure statement

No potential conflict of interest was reported by the authors.

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