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Abstract

Eight previously undescribed triterpenoid saponins, scabiostellatosides A-H (**1**-**8**), and three known compounds were isolated from the whole plant *Scabiosa stellata* Cav. The structures of these compounds were identified on the basis of extensive NMR and HRESIMS data analysis. Scabiostellatoside F (3-*O*-[*β*-D-glucopyranosyl-(1→4)-*β*-D-glucopyranosyl-(1→4)-*β*-D-glucopyranosyl-(1→4)-*α*-L-rhamnopyranosyl-(1→3)-*β*-D-xylopyranosyl-(1→3)-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-xylopyranosyl]-oleanolic acid) exhibited good cytotoxic activity against fibrosarcoma cell line (HT1080) with IC_{50} value of 12.0 ± 0.2 μM.

Keywords: *Scabiosa stellate* Cav., Caprifoliaceae, triterpenoid saponins, cytotoxic activity.

1. Introduction

Scabiosa stellata Cav., known by the common name starflower pincushions, belong to the Caprifoliaceae family. It is an endemic North African herbaceous, bristly-hairy annual plant (Pottier-Alapetite, 1981). In folk medicine, leaves and flowers of *Scabiosa stellata* was used in Morocco against heel cracks (Bammi and Douira, 2002). The majority of *Scabiosa*, comprising about 100 species, occurs in the Mediterranean region (Carlson et al., 2012) and among them, approximately 12 species can be found in Algeria (Quezel and Santa, 1963). Up to date, chemical investigations of *Scabiosa* species have mainly revealed the presence of saponins (Alimbaeva et al., 1977, Baykal et al., 1998, Zheng et al., 2004), flavonoids, coumarins (Garaev et al., 2008), and iridoid glucosides (Papalexandrou et al., 2003, Polat et al., 2010). The aglycone of *Scabiosa* saponins were identified as oleanolic acid, hederagenin, and ursolic acid with glucose, rhamnose, xylose, and arabinose as sugar (Akimaliev et al., 1976, Yusifova and Movsumov 2015, Zheng et al., 2004), or pomolic acid with glycoside containing an allose in *Scabiosa rotata* saponins (Baykal et al., 1997, Baykal et al., 1998). A recent study about the *n*-hexane extract of *S. stellata* showed the presence of fatty acids and derivatives, *β*-sitosterol, stigmasterol, oleanolic and ursolic acids (Rahmouni et al., 2017). In a continuing of our search for bioactive constituents from Algerian flora, the whole plant *S. stellata* was investigated and seven previously undescribed oleanane-type and one ursane-type triterpenoid saponins, named scabiostellatosides A-H (**1**-**8**) were isolated (Figure 1), together with three known compounds (**9**-**11**) from the hydro alcoholic extract. The cytotoxic activity of triterpenoid saponins was evaluated *in vitro* against fibrosarcoma (HT1080) cell line. Herein, the isolation, structural elucidation and cytotoxic activity of these compounds were described.

2. Results and discussion

The dried whole plant *Scabiosa stellata* Cav. was extracted with 70% EtOH, and the concentrated extract was subjected to Diaion HP-20 resin chromatography to obtain fractions I-V. The saponins-rich fraction (IV) was separated by flash chromatography and semi-preparative RP_{18}-HPLC. A total of eleven compounds were obtained, comprising eight previously undescribed triterpenoid saponins (**1**-**8**, scabiostellatosides A-H) and 3 known compounds (Figure 1). Structural elucidation was performed by spectral methods including 1D-, 2D-NMR and HRESIMS techniques. Acid hydrolysis of an aliquot of the saponin-rich fraction (IV) allowed the identification of five monosaccharides as D-glucose, D-xylose, D-glucuronic acid, L-arabinose and L-rhamnose by comparison with authentic samples (see experimental section). The known compounds were elucidated as 3-*O*-[*β*-D-glucopyranosyl-(1→2)-*β*-D-glucuronopyranosyl]-28-*O*-[*β*-D-glucopyranosyl]-hederagenin (palustroside III) (Udayama et al., 1998) (**9**), ursolic acid (**10**) (Mahato and Kundu, 1994) and 3-*O*-[3-*O*-acetyl-6-*O*-(*p*-coumaroyl)-*β*-D-glucopyranosyl]-kaempferol (**11**) (Christopoulou et al., 2008). Their spectroscopic data were in perfect agreement with those reported in the literature.

Scabiostellatoside A (**1**) was obtained as amorphous, white powder and possessed a molecular formula of $C_{64}H_{104}O_{29}$, deduced from the positive HRESIMS analysis (*m/z* 1359.6552, $[M+Na]^+$). The ^1H NMR spectrum showed characteristic signals of an olean-12-ene skeleton with seven methyl singlet signals at δ_H 0.83, 0.88, 0.93, 0.97, 0.99, 1.05 and 1.18, an oxymethine δ_H 3.15 (1H, dd, J = 11.6, 4.2 Hz), together with one olefinic proton resonance at δ_H 5.27 (1H, t, J = 3.4 Hz). The ^{13}C NMR spectrum showed resonance for one carboxyl or ester group (δ_C 176.7), two olefinic carbons (δ_C 122.4, 143.5), one oxygenated methane (δ_C 89.2), and seven methyls (δ_C 14.8, 15.8, 16.6, 22.6, 24.9, 27.2, 32.1). Taken together, these data were indicative of a typical oleanolic acid (Alabdul Magid et al., 2015). This assumption was confirmed by analysis of the COSY, TOCSY, ROESY, HSQC and HMBC spectra which

allowed the full assignment of the proton and carbon resonances of the aglycone (Table 1). The deshielding effect observed at H-18 signal (δ_H 2.86, dd, J = 13.9, 3.8 Hz), due to magnetic anisotropy effect of carbonyl at C-28, is in agreement with a *cis* fusion between D and E rings. In the ROESY spectrum, correlations observed between H-3/H-5 and H-5/H-9 indicated their α-axial orientation and thus the β-orientation of the oxygen at C-3. The ROESY correlations between H_3-23/H-5 and H-9 and H-9/ H_3-27 indicated the α-orientation of CH_3-23 and CH_3-27. In the same manner, the ROESY correlations between H_3-25/ H_3-24, H_3-25/H_3-26, H_3-26/H-18, H-18/CH_3-30 indicated their β-axial orientation. The chemical shifts of C-3 (δ_C 89.2) and C-28 (δ_C 176.7) revealed that **1** is a bisdesmosidic glycoside. The sugar part of **1** consists of six residues as evidenced by ^{1}H and ^{13}C NMR spectra which displayed six anomeric protons at δ_H 4.36 (d, J = 7.8 Hz), 4.49 (d, J = 7.6 Hz), 4.51 (d, J = 5.3 Hz), 5.19 (d, J = 1.5 Hz), 5.20 (d, J = 1.7 Hz) and 5.37 (d, J = 8.1 Hz), which correlated in the HSQC spectrum to carbons at δ_C 103.3, 105.1, 103.9, 101.1, 100.1 and 94.4, respectively (Table 2). All the protons within each monosaccharide spin system were delineated, starting from the anomeric protons, using COSY, TOCSY and ROESY spectra. After assignments of the protons, the ^{13}C-NMR resonances of each sugar unit were identified by HSQC and further confirmed by HMBC. All the monosaccharides were determined to be in pyranose form by their ^{13}C-NMR data and confirmed by ROESY spectrum. In this way, two α-L-rhamnopyranose units (rha and rha′) were easily identified both by equatorial anomeric protons (δ_H 5.20, d, J = 1.5 Hz, rha; 5.19, d, J = 1.4 Hz, rha′) and 6.2 Hz methyl doublets (δ_H 1.24, rha; 1.27, rha′). The presence of these rha and rha′ was confirmed from their typical pattern in the ^{1}H-NMR spectrum; the small coupling constant between H-2 and H-3 ($J_{H\text{-}2eq,H\text{-}3ax}$ = 3.5 Hz) and the large coupling constants between H-3 and H-4 $J_{H\text{-}3ax,H\text{-}4ax}$ ($\geq$ 9.5 Hz) as summarized in Table 2. The α-configuration of rha and rha′ also was confirmed by the chemical shift of their C-5 (δ_C 68.6) (Chang et al., 2007). The rha unit ($\delta_{H\text{-}1}$ 5.20) was

revealed to be C-3 mono-substituted ($\delta_{C\text{-}3}$ 80.6) whereas the rha′ unit ($\delta_{H\text{-}1}$ 5.19) was found to be in terminal position (Table 2). Starting from the anomeric proton signals at δ_H 5.37 and 4.36, the NMR signals belonging to each system were assigned to two β-D-glucopyranose units (glc, $\delta_{H\text{-}1}$ 5.37; glc′, $\delta_{H\text{-}1}$ 4.36) because H-2, H-3 and H-4 exhibit large, *anti*-vicinal couplings (≥ 7.8 Hz) indicating that all are axials (Table 2). The relatively large $^3J_{H\text{-}1,H\text{-}2}$ values of the glc and glc′ (7.8-8.1), indicated a β anomeric orientation for the both glucopyranose units. The considerably downfield shift of C-6 of the glc unit ($\delta_{C\text{-}6}$ 68.1) suggested that glc was 6-monosubstituted. This was confirmed by the existence of an HMBC cross-peak between glc′-H-1 and glc-C-6. The fifth sugar unit was identified as α-L-arabinopyranose (ara, δ_{H1} 4.51, d, J = 5.3 Hz). The relatively large $^3J_{H\text{-}1\text{-}H\text{-}2}$ and $^3J_{H\text{-}2\text{-}H\text{-}3}$ (7.1 Hz) of H-2 require that it must be axial and has two axial neighbors. The small couplings $^3J_{H\text{-}3\text{-}H\text{-}4}$ (3.4 Hz) indicated that the H-4 is equatorial (Table 2). The α-arabinopyranose unit was determined to be in an α-configuration based on the ROESY correlations observed between the α-axial protons H-1/H-3, H-3/H-5ax and H-1/H-5ax. The downfield shift of C-2 of the ara unit ($\delta_{C\text{-}2}$ 75.0) suggested that it was 2-monosubstituted. The NMR signals belonging to the ara unit assigned by interpretation of 2D-NMR spectra and confirmed by comparing the ^{13}C NMR chemical shifts with those of related systems reported in the literature (Alabdul Magid et al., 2015, Zheng et al., 2004). The last monosaccharide unit was identified as β-D-xylopyranose (xyl, δ_{H1} 4.49, d, J = 7.6 Hz) by interpretation of 2D-NMR spectra. The H-1, H-2, H-3 and H-4 of xyl exhibited large vicinal couplings (≥ 7.6 Hz) indicating that all are axial (Table 2). The β-configuration of xyl unit was confirmed by the observation of ROESY correlations between the α-axial protons H-1/H-3, H-3/H-5ax and H-1/H-5ax. The downfield shift of C-3 of the xyl unit ($\delta_{C\text{-}3}$ 82.1) suggested that it was 3-monosubstituted. The ^{1}H- and ^{13}C-NMR spectra of **1** displayed many similarities with those of scabiosaponin A (3-*O*-[β-D-

glucopyranosyl-(1→4)-*β*-D-xylopyranosyl-(1→3)-*α*-L-rhamnopyranosyl-(1→2)-*α*-L-arabinopyranonosyl]-28-*O*-[*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl]-oleanolic acid) (Zheng et al., 2004), the difference was the nature and the position of attachement of last sugar residue attached to the xylose, *α*-L-rhamnopyranose in **1** and *β*-D-glucopyranose in scabiosaponin A. The final step in the structural elucidation of **1** consisted of determination of the linkage sites both between the monosaccharide units and to the aglycone moiety. The cross-peak observed in the HMBC spectrum between glc′-H-1/glc-C-6 and glc-H-1/aglycone-C-28 established the point of attachment of the di-saccharide [glc′-(1→6)-glc] to the C-28 of the aglycone. In a similar fashion, the HMBC correlation between rha′-H-1/ xyl-C-3, xyl-H-1/rha-C-3, rha-H-1/ara-C-2 and ara-H-1/aglycone-C-3 indicated that the tetra-saccharide [rha′-(1→3)-xyl-(1→3)-rha-(1→2)-ara] was linked to the C-3 of the aglycone (Figure 2). In addition, ROESY correlations confirming the interglycosidic linkage and the point of attachment of the tetra-saccharide at the H-3 of the aglycone were observed between glc′-H-1/glc-H_2-6, rha′-H-1/xyl-H-3, xyl-H-1/rha-H-3, rha-H-1/ara-H-2 and ara-H-1/aglycone-H-3. Based on all the foregoing evidence, scabiostellatoside A (**1**) was elucidated as 3-*O*-[*α*-L-rhamnopyranosyl-(1→3)-*β*-D-xylopyranosyl-(1→3)-*α*-L-rhamnopyranosyl-(1→2)-*α*-L-arabinopyranonosyl]-28-*O*-[*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl]-oleanolic acid.

The HRESIMS in the positive ion mode indicated that scabiostellatoside B (**2**) and (**1**) possessed the same molecular formula $C_{64}H_{104}O_{29}$, as deduced from the $[M + Na]^+$ ion at *m/z* 1359.6548 (calcd for $C_{64}H_{104}O_{29}Na$, 1359.6561). The detailed analysis of 1D- and 2D-NMR spectra of **2** and comparison of its spectral data with those of **1** indicated the presence of the oleanolic acid as aglycone in 2, a 6-monosubstituted *β*-D-glucopyranose (glc, $\delta_{H\text{-}1}$ 5.37, d, J = 8.0 Hz; $\delta_{C\text{-}6}$ 68.1), a terminal *β*-D-glucopyranose (glc′, $\delta_{H\text{-}1}$ 4.36, d, J = 7.8 Hz), a terminal *α*-rhamnopyranose (rha′, δ_{H1} 5.20, d, J = 1.7 Hz), a 3-monosubstituted *α*-rhamnopyranose (rha,

δ_{H1} 5.39, d, J = 1.7 Hz; $\delta_{C\text{-}3}$ 80.8), and a 3-monosubstituted β-xylopyranose (xyl′, δ_{H1} 4.48, d, J = 7.7 Hz; $\delta_{C\text{-}3}$ 82.1) (Table 4). The ^{1}H and ^{13}C NMR values of **2** were almost superimposable on those of **1** (Tables 2 and 4) excepting those corresponding to the sugar identified in **1** as 2-monosubstituted α-L-arabinopyranose. Instead, a second β-xylopyranose unit (xyl) was identified starting from the anomeric proton δ_H 4.39 (d, J = 7.1 Hz), characterized by the large coupling constants $J_{H\text{-}1,H\text{-}2}$, $J_{H\text{-}2,H\text{-}3}$ and $J_{H\text{-}3,H\text{-}4}$ (≥ 7.1 Hz) as summarized in Table 4 (Zheng et al., 2004). The long-rang correlations observed in the HMBC spectrum between glc′-H-1/glc-C-6, glc-H-1/aglycone-C-28, rha′-H-1/xyl′-C-3, xyl′-H-1/rha-C-3, rha-H-1/xyl-C-2 and xyl-H-1/aglycone-C-3 indicated that the tetrasaccharide [rha′-(1→3)-xyl′-(1→3)-rha-(1→2)-xyl] was linked to the C-3 of the aglycone whereas a disaccharide [glc′-(1→6)-glc] was linked to C-28 of the aglycone. In addition, as in **(1)**, complementary pairs of ROESY correlations were found between anomeric and carbinol protons on opposite sides of the interglycosidic linkage and H-3 of the aglycone. The structure of scabiostellatoside B (**2**) was therefore identified as 3-*O*-[α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-β-D-xylopyranosyl]-28-*O*-[β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl]-oleanolic acid.

The molecular formula of scabiostellatoside C (**3**) was established as $C_{70}H_{114}O_{34}$ from the $[M+Na]^+$ peak at 1521.7097 in HR-ESI-MS spectrum (calcd for $C_{70}H_{114}O_{34}Na$, 1521.7089). The structure of aglycone of **3** was recognized by ^{1}H-and ^{13}C-NMR analysis (Table 1) using the correlations observed in 2D-NMR spectra to be, as in **1** and **2**, oleanolic acid. The NMR spectroscopic data of **3** were almost identical with those of **1** except for an additional hexose unit (Table 2). Extensive 2D-NMR analysis (COSY, ROESY, HSQC, HMBC, TOCSY and HSQC-TOCSY) enabled the full assignments of the resonances of six sugar units identified as 2-monosubstituted α-L-arabinopyranonosyl (ara) ($\delta_{H\text{-}1}$ 4.51, d, J = 5.3 Hz; $\delta_{C\text{-}2}$ 74.9), 3-monosubstituted α-L-rhamnopyranosyl (rha) ($\delta_{H\text{-}1}$ 5.21, brs; $\delta_{C\text{-}3}$ 80.6), 3-monosubstituted β-

D-xylopyranosyl (xyl) ($\delta_{H\text{-}1}$ 4.49, d, J = 7.6 Hz; $\delta_{C\text{-}3}$ 81.7), 4-monosubstituted α-L-rhamnopyranosyl (rha′) (δ_{H1} 5.19, brs; $\delta_{C\text{-}4}$ 82.3), 6-monosubstituted β-D-glucopyranosyl (glc) ($\delta_{H\text{-}1}$ 5.37, d, J = 8.2 Hz; δ_{C6} 68.1) and terminal β-D-glucopyranosyl (glc′) ($\delta_{H\text{-}1}$ 4.36, d, J = 7.8 Hz). The supplementary hexose unit was identified as a second terminal β-D-glucopyranose unit (glc′′) (δ_{H1} 4.61, d, J = 7.6 Hz; $\delta_{C\text{-}1}$ 104.3). The deshielded signals of rha′-C-4 ($\delta_{C\text{-}4}$ 82.3) indicated that the additional glucopyranose moiety was attached to C-4 of the rha′ unit. As in **1**, the cross-peaks observed in the HMBC spectrum between glc′-H-1/glc-C-6 and glc-H-1/aglycone-C-28 established the point of attachment of the di-saccharide [glc′-(1→6)-glc] to the C-28 of the aglycone whereas, the HMBC correlation between glc′′-H-1/rha′-C-4, rha′-H-1/xyl-C-3, xyl-H-1/rha-C-3, rha-H-1/ara-C-2 and ara-H-1/aglycone-C-3 indicated that the penta-saccharide [glc′′-(1→4)-rha′-(1→3)-xyl-(1→3)-rha-(1→2)-ara] was linked to the C-3 of the aglycone. Based on all the evidences, the structure of scabiostellatoside C (**3**) was elucidated as 3-*O*-[β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-*O*-[β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl]-oleanolic acid.

Scabiostellatoside D (**4**) had the same molecular formula of **3** ($C_{70}H_{114}O_{34}$), deduced from the peak at *m/z* 1521.7096 $[M+Na]^+$ in the HRESIMS spectrum (calcd for 1521.7089, $C_{70}H_{114}O_{34}Na$). The ^{1}H- and ^{13}C-NMR spectra of **4** displayed many similarities with those of **3**, especially for the resonances assigned to oleanolic acid, three β-D-glucopyranose units (glc, glc′ and glc′′), two α-L-rhamnopyranose units (rha and rha′) and one β-D-xylopyranose unit (xyl′) (Tables 2 and 4). The identities of the monosaccharides were determined by a combination of ^{1}H-^{1}H-COSY, TOCSY, HSQC, HSQC-TOCSY, HMBC and ROESY NMR experiments. As in **2**, starting from the anomeric proton at $\delta_{H\text{-}1}$ 4.39 (d, J = 7.1 Hz), 2D-NMR spectra analysis led to the assignment of the set of protons and carbon signals of a 2-

monosubstituted β-D-xylopyranose unit (xyl) (δ_{C-2} 76.7). Furthermore, all sites of glycosidations were also established by a HMBC experiment showing long-range correlations between glc′-H-1/glc-C-6, glc-H-1/aglycone-C-28, glc′′-H-1/rha′-C-4, rha′-H-1/xyl′-C-3, xyl′-H-1/rha-C-3, rha-H-1/xyl-C-2, and xyl-H-1/aglycone-C-3. Consequently, the structure of scabiostellatoside D (**4**) was established as 3-*O*-[β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-β-D-xylopyranonosyl]-28-*O*-[β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl]-oleanolic acid.

The positive HRESIMS of scabiostellatoside E (**5**) displayed an $[M+Na]^+$ ion peak at *m/z* 1521.7075, corresponding to the molecular formula $C_{70}H_{114}O_{34}$ (calcd for $C_{70}H_{114}O_{34}$ Na, 1521.7089), suggesting an additional hexose unit compared to **1**, as in **3**. Comparison of ^{1}H and ^{13}C NMR values and the analysis of the 2D-NMR spectra showed that **3** and **5** contained the same aglycone (oleanolic acid) (Table 1). The ^{1}H and ^{13}C NMR spectra of **5** indicated the presence of seven sugar units which displayed seven anomeric protons and carbons, as in **3** (Table 2). The detailed analysis of the 2D-NMR spectra led to the identification, as in **3**, of one α-L-arabinopyranonosyl unit (ara) (δ_{H-1} 4.55, d, J = 6.9 Hz), two α-L-rhamnopyranosyl units: rha (δ_{H-1} 5.26, d, J = 1.8 Hz) and rha′ (δ_{H-1} 5.19, d, J = 1.6 Hz), one β-D-xylopyranosyl (xyl) (δ_{H-1} 4.49, d, J = 7.7 Hz) and three β-D-glucopyranosyl units: glc (δ_{H-1} 5.37, d, J = 8.1 Hz), glc′ (δ_{H-1} 4.36, d, J = 7.8 Hz) and glc′′ (δ_{H-1} 4.47, d, J = 7.6 Hz) (Table 2). The deshielded signal of the C-4 carbon (δ_{C-4} 78.1) (Δ +10.4 ppm) of the α-L-arabinopyranonosyl residue in **5**, when compared to this in **3,** suggested that the glc′′ unit was attached to ara-C-4. An HMBC experiment made clear all interglycosidic connectivities showing correlations between glc′-H-1/glc-C-6 (δ_{C-6} 68.1), glc-H-1/aglycone-C-28 (δ_{C-28} 176.6), glc′′-H-1/ara-C-4 (δ_{C-4} 78.1), rha′-H-1/ xyl-C-3 (δ_{C-3} 82.0), xyl-H-1/rha-C-3 (δ_{C-3} 80.5), rha-H-1/ara-C-2 (δ_{C-2} 75.2) and ara-H-1/aglycone-C-3 (δ_{C-3} 89.1). Consequently, the structure of scabiostellatoside

E (**5**) was concluded to be 3-*O*-[α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-{β-D-glucopyranosyl-(1→4)-}α-L-arabinopyranonosyl]-28-*O*-[β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl]-oleanolic acid.

The HRESIMS in the positive ion mode indicated that scabiostellatoside F (**6**) and compound **5** possessed the same molecular formula $C_{70}H_{114}O_{34}$, as deduced from the $[M + Na]^+$ ion at *m/z* 1521.7080 (calcd for $C_{70}H_{114}O_{34}Na$, 1521.7089). Comparison of ^1H and ^{13}C NMR values of **6** with those of **2** and **4** and the analysis of the 2D-NMR spectra showed that **6** was a 3-monodesmoside of oleanolic acid ($\delta_{C\text{-}3}$ 88.9 and δ_{C28} 179.8) (Table 3). The NMR data (Table 4) indicated the presence of seven sugar moieties which were identified by detailed analysis of the 2D-NMR spectra and by comparison of **6** spectral data with those of **2** and **4** as two β-D-xylopyranosyl units: xyl ($\delta_{H\text{-}1}$ 4.40, d, J = 7.2 Hz) and xyl′ ($\delta_{H\text{-}1}$ 4.47, d, J = 7.7 Hz), two α-L-rhamnopyranosyl units: rha ($\delta_{H\text{-}1}$ 5.38, d, J = 1.7 Hz) and rha′ ($\delta_{H\text{-}1}$ 5.21, brs) and three β-D-glucopyranosyl units: glc (δ_{H1} 4.48, d , J = 8.0 Hz), glc′ (δ_{H1} 4.42, d , J = 7.9 Hz) and glc′′ ($\delta_{H\text{-}1}$ 4.64, d, J = 7.9 Hz). The deshielded signals of glc-C-4 ($\delta_{C\text{-}4}$ 76.8) and glc′′-C-4 ($\delta_{C\text{-}4}$ 79.1) suggested that there were 4-monosubstituted. This is confirmed by the HMBC correlations between the signals glc-H-1/glc′-C-4 ($\delta_{C\text{-}4}$ 78.8), and glc-H-1/glc′′-C-4 ($\delta_{C\text{-}4}$ 79.1). In addition, the HMBC correlations glc′′-H-1/rha′-C-4 ($\delta_{C\text{-}4}$ 82.6) rha′-H-1/ xyl′-C-3 ($\delta_{C\text{-}3}$ 81.7), xyl′-H-1/rha-C-3 ($\delta_{C\text{-}3}$ 80.7), rha-H-1/xyl-C-2 ($\delta_{C\text{-}2}$ 76.8) and xyl-H-1/aglycone-C-3 ($\delta_{C\text{-}3}$ 88.9), defined the locations of the sugars in the molecule. Therefore, compound **6** (scabiostellatoside F) was assigned as 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-β-D-xylopyranosyl]-oleanolic acid.

Scabiostellatoside G (**7**) exhibited in the HRESIMS analysis (positive ion mode) a pseudo-molecular ion peak at *m/z* 1157.5363 $[M + Na]^+$, consistent with the molecular formula of

$C_{54}H_{86}O_{25}$ (calcd for $C_{54}H_{86}O_{25}Na$, 1157.5356). The ^{13}C-NMR spectrum (Table 5) showed 54 carbon signals, of which 24 were assigned to four sugar moieties and 30 to the aglycone including six tertiary methyl groups at δ_C 12.0 (C-24), 15.2 (C-25), 16.5 (C-26), 25.0 (C-27), 32.1 (C-29) and 22.6 (C-30), a hydroxymethyl carbon at δ_C 63.4 (C-23), an oxygen-bearing methane carbon at δ_C 82.3 (C-3) and an ester carbonyl group at δ_C 175.7 (C-28). Furthermore, olefinic carbon signals appeared at δ_C 122.4 (C-12) and 143.5 (C-13) which was also confirmed by the signal at δ_H 5.27 (t, J = 3.4 Hz) due to H-12 in the ^{1}H-NMR spectrum. All these data are characteristic of hederagenin (3β,23-dihydroxy-12-oleanen-28-oic acid) as in palustroside III (**9**) (Udayama et al., 1998). Complete assignment of each proton and carbon signals of the hederagenin was achieved by extensive 2D-NMR analysis and in good agreement with data given in the literature (Table 5) (Alabdul Magid et al., 2006; Udayama et al., 1998). The δ_C values of C-3 and C-28 suggested that compound **7** was a bidesmosidic hederagenin glycoside with saccharide units attached to these positions, as in **9**. A quick inspection of the ^{1}H and ^{13}C NMR spectra of **7** indicated the presence of four monosaccharide units through the easily identifiable signals for their anomeric protons (δ_H 4.36, 4.56, 4.71 and 5.37) and carbons (δ_C 94.4, 102.8, 103.2 and 103.2). The analysis of COSY, TOCSY, ROESY, HSQC and HMBC experiments led to the identification of a β-D-glucuronic acid unit starting from the anomeric proton at δ_H 4.56 (d, J = 7.5 Hz), characterized by a five spin system possessing large coupling constants ($J_{H\text{-}1,H\text{-}2}$, $J_{H\text{-}2,H\text{-}3}$, $J_{H\text{-}3,H\text{-}4}$, and $J_{H\text{-}4,H\text{-}5} \geq$ 7.5 Hz), a doublet axial proton H-5 ($J_{H\text{-}4,H\text{-}5}$ = 9.0 Hz) (Table 6) and a carbonyl C-6 at δ_C 176.2 coupled with H-5 of the same sugar in the HMBC spectrum. The NMR data showed a lowfield position of C-2 of the β-D-glucuronic acid unit (δ_C 80.2) indicating it to be substituted at this position. The sugar units with anomeric protons at δ_H 5.37 (d, J = 8.1 Hz), 4.36 (d, J = 7.8 Hz) and 4.71 (d, J = 7.7 Hz) corresponded to three β-D-glucopyranose units (glc, glc′ and glc″, respectively), characterized by the large coupling constants ($J_{H\text{-}1,H\text{-}2}$, $J_{H\text{-}2,H\text{-}3}$, $J_{H\text{-}3,H\text{-}4}$, and $J_{H\text{-}}$

$_{4,H-5}$ ≥ 7.7 Hz) as summarized in Table 6. The rOe interactions observed in the ROESY spectrum between H-1, H-3 and H-5 of D-glucuronic acid and D-glucose units confirmed the *α*-axial orientation of these protons and the *β*-anomeric configuration. The ^{1}H- and ^{13}C-NMR spectra of **7** displayed many similarities with those of giganteoside M (3-*O*-[*β*-D-galactopyranosyl-(1→2)-*β*-D-glucuronopyranosyl]-28-*O*-[*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl]-hederagenin) (Tabatadze et al., 2007), especially for the resonances assigned to hederagenin, *β*-D-glucuronopyranosyl (glcA) and two *β*-D-glucopyranose units (glc and glc′). The difference was the nature of sugar residue attached to the C-2 of glcA; *β*-D-glucopyranose in **7** and *β*-D-galactopyranose in giganteoside M. In the HMBC spectrum of **7**, cross-peaks were observed between glc′′-H-1/glcA-C-2 (δ_{C-2} 80.2), glcA-H-1/aglycone-C-3 (δ_{C-3} 82.3), glc′-H-1/glc-C-6 (δ_{C-6} 68.1) and glc-H-1/aglycone-C-28 (δ_{C-28} 175.7). These evidences led to the assignment of **7** as 3-*O*-[*β*-D-glucopyranosyl-(1→2)-*β*-D-glucuronopyranosyl]-28-*O*-[*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl]-hederagenin.

The HRESIMS spectrum of scabiostellatoside H (**8**) exhibited an ion at *m/z* 995.4836 $[M+Na]^{+}$, which was in accordance with the molecular formula of $C_{48}H_{76}O_{20}$ (calcd 955.4828, $C_{48}H_{76}O_{20}Na$). The ^{1}H- and/or ^{13}C-NMR spectra of **8** exhibited signals for a double bond [δ_H/δ_C 5.27 (t, *J* = 3.4 Hz)/125.7 (C-12); 137.1 (C-13)], four tertiary methyls [δ_H/δ_C 0.78 (s)/13.6 (CH_3-24); 1.07 (s)/16.5 (CH_3-25); 0.87 (s)/16.4(CH_3-26); 1.15 (s)/22.6 (CH_3-27)], two secondary methyls [δ_H/δ_C 0.92 (d, *J* = 6.3 Hz)/16.2 (CH_3-29); 0.99 (d, *J* = 6.3 Hz)/20.1 (CH_3-30)], two oxymethines [δ_H/δ_C 3.54 (d, *J* = 9.5 Hz)/86.1 (CH-3); 3.82 (m)/66.4 (CH-2)], a hydroxymethylene [δ_H/δ_C 3.30 (d, *J* = 11.8 Hz), 3.70 (d, *J* = 11.8 Hz)/62.5 (CH_2-23)], a methine [δ_H/δ_C 2.26 (d, *J* = 11.4 Hz)/52.8 (CH- 18)] and an ester carbonyl [δ_C 176.7 (C-28)], characteristic of an urs-12-en-28-oic-acid derivative (Table 5), which was trihydroxylated in positions C-2*α*, C-3*β* and C-23, as in asiatic acid (Acebey-Castellon et al., 2011). The large coupling constant between the vicinal diol H-2 and H-3 ($J_{H-2,H-3}$ = 9.5 Hz) indicated that the

two protons adopted a quasi *trans*-diaxial relationship. The location of the primary hydroxyl group (δ_H 3.30 and 3.70, each d, J = 11.8 Hz) at C-23 was deduced from the chemical shift of C-24 at δ_C 13.6 characteristic of an axial position, and by comparison of the ^{13}C NMR spectrum with that of asiatic acid. The α-equatorial orientation of H_3-23 was confirmed by the correlations observed in the ROESY spectrum between H_3-23 and H-3 and H-5 and between H-3/H-5 and H-5/H-9 α-axial oriented. In the same manner, the ROESY correlations observed between H-2/H_3-24, H_3-25 and between H_3-25/H-26, confirmed the β-axial orientation of these CH_3 and H-2. The assignments of other proton and carbon signals of the aglycone were accomplished by analysis of the usual 2D COSY, ROESY, HSQC and HMBC experiments (Table 5). The ^1H and ^{13}C NMR values were in full agreement with those reported in the literature for asiatic acid (Acebey-Castellon et al., 2011). Further analysis of the ^1H and ^{13}C NMR spectra of **8** revealed the presence of three anomeric protons at δ_H 4.55, 5.34 and 5.37 correlated in the HSQC spectrum with three anomeric carbons at δ 102.4, 101.0 and 94.3, respectively (Table 6). Complete assignment of each glycoside proton system was achieved by analysis of 2D-NMR experiments. A β-D-glucopyranose unit (glc) was identified starting from the anomeric proton at δ_H 5.37 (d, J = 8.1 Hz). The second monosaccharide whose anomeric proton resonates at δ 4.55 (d, J = 7.5 Hz) was identified as a β-D-glucuronic acid (glcA), as in compound **7**, characterized by its H-5 (δ_H 3.64, d J = 9.4 Hz) and the carbonyl C-6 at δ_C 176.5 (Table 6). The third sugar unit was identified as terminal α-L-rhamnopyranose (rha), as in compounds **1** and **2** (Tables 2 and 6). In the HMBC experiment, the cross-peaks observed between rha-H-1/glcA-C-2 ($\delta_{C\text{-}2}$ 78.0), glcA-H-1/aglycone-C-3 ($\delta_{C\text{-}3}$ 86.1) and glc-H-1/aglycone-C-28 ($\delta_{C\text{-}28}$ 176.7) led to the assignment of compound **8** as 3-*O*-[α-L-rhamnopyranosyl-(1→2)-β-D-glucuronopyranosyl]-28-*O*-[β-D-glucopyranosyl]-asiatic acid.

Compounds **1-8** were evaluated for their cytotoxicity against fibrosarcoma cell line (HT1080) by using the metabolic WST1 cell viability assay (Lehbili et al., 2017). Among the tested compounds, the monodesmoside **6** exhibited an interesting antiproliferative effect at lower concentration (IC_{50} 12.0 ± 0.2 µM). The bidesmosides **2**, **4** and **5** were less active (IC_{50} 49.0 ± 0.7, 40.0 ± 0.7 and 38.0 ± 0.8 µM, respectively). The asiatic acid derivative (**8**) exhibited also moderate cytotoxicity (IC_{50} 40 ± 0.8 µM). Compounds **1**, **3** and **7** were not active at the concentration of 50 µM. Comparison of results of active compounds **2** and **4** with this of **1** and **3** suggested that the cytotoxic activity may be related to the nature of the sugar residue attached at C-3 of the aglycone; xylose in **2** and **4** and arabinose in **1** and **3**. Comparison of values of compounds **3** and **5** with arabinose attached to C-3 of aglycone suggested that the presence of a ramified sugar chain in **5** (IC_{50} 38.0 ± 0.8 µM) is more favorable to cytotoxic activity than a linear chain in **3**.

In summary, eleven structurally diverse compounds were isolated and identified from 70% EtOH crude extract of *Scabiosa stellata*, among them eight triterpenoid saponins were previously undescribed and their cytotoxic activity against fibrosarcoma cell line (HT1080) were evaluated. Compounds **1-6** are glycosides of oleanolic acid, compounds **7** and **9** are bidesmosides of hederagenin with glucuronic acid linked to C-3 of aglycone, and **8** is a bidesmoside of ursolic acid. Comparison of compounds **1-9** with saponins previously identified in *Scabiosa* species indicated that oleanolic saponins (**1-5**) were similar to Scabiosaponins A-K and hookeroside A isolated from *S. tshiliensis* (Zheng et al, 2004) with a gentiobiose attached to the aglycone in C-28. The presence of a glucuronic acid linked to C-3 of aglycone (compounds **7-9**) was observed for the first time in *Scabiosa* saponins in witch xylose or arabinose unit was generally linked to C-3 as in compounds **1-6** and in scabrioside A-D (Baykal 1999, Baykal et al., 1997, Baykal et al., 1998), songoroside A (Akimaliev et al.,

1988), songoroside C, G, I, M and O (Akimaliev et al., 1976). The monodesmoside **6** exhibited an interesting antiproliferative effect at lower concentration.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on a Perkin Elmer model 341 polarimeter (589 nm, 20 °C). ^{1}H-, ^{13}C-NMR and 2D-NMR measurements were recorded in CD_3OD on a Bruker Avance III 500 spectrometer (^{1}H at 500 MHz and ^{13}C at 125 MHz) or on a Bruker Avance AVIII-600 spectrometer (^{1}H at 600 MHz and ^{13}C at 150 MHz) equipped with a 5 mm TCI cryoprobe. 2D-NMR experiments were performed using standard Bruker microprograms (TopSpin 3.2 software). Exact masses were measured on a Micromass Q-TOF (Manchester, UK) high-resolution mass spectrometer. Mass spectra were recorded in the positive-ion mode in the range *m*/*z* 100−2000, with a mass resolution of 20 000 and an acceleration voltage of 0.7 kV. CC was carried out on HP-20 resin (Sigma Aldrich). Flash chromatography was carried out on a Grace Reveleris system equipped with dual UV and ELSD detection using Grace® cartridges (Silica gel or RP-C_{18}). HPLC separations were performed on a Dionex apparatus equipped with an ASI-100 autosampler, an Ultimate 3000 pump, a STH 585 column oven, a diode array detector UVD 340S and a Chromeleon software. A prepacked RP-C_{18} column (Phenomenex 250 x 15 mm, Luna 5 µ) was used for semi-preparative HPLC. The eluting mobile phase consisted of H_2O with TFA (0.0025%) and CH_3CN with a flow rate of 5 mL/min and the chromatogram was monitored at 205 and 210 nm. Thin-layer chromatographies (TLC) were carried out using silica gel 60 F_{254} pre-coated aluminium plates (0.2 mm, Merck). After developing with solvent systems, TLC were sprayed with 50% H_2SO_4 followed by heating.

3.2. Plant material

The whole plant *Scabiosa stellata* Cav. was collected in June 2015 from Constantine (North eastern of Algeria). The plant was identified by Kamel Kabouche and a voucher specimen (LOST.Cs.06.15) has been deposited at the University of Constantine, Algeria.

3.3. Extraction and isolation

The dried and powdred *S. stellata* whole plant (653 g) was macerated in 70% EtOH (3 × 3 L, 24h) at room temperature. After filtration and concentration under low pressure, the 70% EtOH extract (118 g) was separated on a Diaion HP-20 resin column (4.3 x 40 cm), eluted with H_2O-MeOH (0, 25, 50, 75 and 100%, each 2 L), to give fractions A-E, respectively. Fraction D (8.3 g) was fractionated by flash chromatography over silica gel, eluted by a gradient system of $CHCl_3$-MeOH-H_2O (10:0:0 to 4:6:0.5), in 35 min to afford 40 sub-fractions (f_1-f_{40}). Fraction f_{31} (300 mg) was submitted to a flash chromatography over RP-C_{18}, eluted by a gradient system of 18-60% CH_3CN, in 32 min to afford compound **1 (**4.5mg). Fraction f_{33} (105 mg) was purified by semi-prep. HPLC using a gradient from 25% to 35% CH_3CN in 10 min, then isocratic elution at 35% CH_3CN for 20 min to yield 7 mg of compound **2** (t_R 21.9). Fraction f_{34} (154 mg) was purified by flash chromatography over RP-C_{18}, eluted with MeOH: H_2O (30% to 100%, in 30 min) to yield 4 mg of compound **8**. The purification by semi-prep. HPLC of subfractions 36-38 obtained from f_{34} led to compounds **3** (t_R 11.5, 7 mg) and **4** (t_R 12.6, 8 mg) (isocratic elution with 35% CH_3CN). Fraction f_{35} (150 mg) was subjected to flash chromatography over RP-C_{18}, eluted with MeOH: H_2O (10% to 60%, in 30 min) to yield compounds **5** (5 mg), **6** (3 mg) and **9** (3 mg). Fraction f_{36} (500 mg) was purified by flash chromatography over RP-C_{18}, eluted with MeOH: H_2O (10% to 60%, in 30 min) to give compound **7** (4 mg). Fraction E was submitted to flash chromatography over silica gel, eluted by a gradient system of $CHCl_3$-MeOH (10:0 to 4:6), in 32 min to afford **10** (15 mg) and **11** (18 mg).

3.4. Acid hydrolysis

Acid hydrolysis was carried out to obtain the sugar residues of compounds **1-8**. An aliquot of the saponin mixture (100 mg of fraction D of the Diaion HP-20 resin chromatography) was treated with 2 N TFA (trifluoroacetic acid, aqueous solution, 15 mL) at 90 °C for 6 h. After extraction with CH_2Cl_2 (10 mL x 3), the water-soluble layer was evaporated to dryness. The sample (55 mg) was purified by preparative Si gel TLC (MeCOEt:iso-PrOH:Me_2CO:H_2O, 20:10:7:6)) to afford rhamnose [2.5 mg, R_f = 0.73, $[\alpha]^{20}_D$ +11 (*c* 0.21, H_2O)]; arabinose [2 mg, R_f = 0.59, $[\alpha]^{20}_D$ +43 (*c* 0.17, H_2O)]; xylose [1.9 mg, R_f = 0.52, $[\alpha]^{20}_D$ +18 (*c* 0.2, H_2O)]; glucose [4 mg, R_f = 0.48, $[\alpha]^{20}_D$ +30 (*c* 0.33, H_2O)] and glucuronic acid [0.9 mg, R_f = 0.1, $[\alpha]^{20}_D$ +29.2 (*c* 0.08, H_2O)].

3.5. Cell proliferation assay

The fibrosarcoma cells (HT1080) were cultured in Minimum Essential Media (MEM) supplemented with 10% fetal bovine serum (FBS) and 1% Penicillin Streptomycin (PS) at 37 °C with 5% CO_2 and harvested every three days for maintenance. Compounds **1-8** were dissolved in DMSO. For treatment, cells were plated at a density of 10^4 cells/mL in 24-well plates at 37 °C. After 24h, the culture medium was discarded and cells were treated with the compounds in a fresh culture medium at various concentrations for 72h, while the same dilution volume of DMSO was added in negative control wells. The concentration of DMSO did not exceed 0.1% to avoid significant toxicity on the tested cells. Therefore, the cells were washed once with 1 mL of D-PBS and then detached with 0.2% Trypsin/EDTA. Cell counting was carried out on a KOVA® slide and with a phase contrast microscope as indicated by the manufacturer. Cell growth was calculated in percentage as the fraction of cell number in treated and control cells. IC_{50} was determined as the concentration of each compound which induced 50% inhibition of cell growth. The values represent averages of three independent experiments. Doxorubicin was used as a positive control agent.

***3.6. Scabiostellatoside A (1)*:** amorphous, white powder; $[\alpha]^{20}_{D}$ –20.8 (*c* 0.35, MeOH); ^{1}H (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data, see tables 1 and 2; HRESIMS *m/z* 1359.6552 (calcd for $C_{64}H_{104}O_{29}Na$, 1359.6561).

***3.8. Scabiostellatoside B (2)*:** amorphous, white powder; $[\alpha]^{20}_{D}$ –25 (*c* 0.20, MeOH); ^{1}H (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data, see tables 3 and 4; HRESIMS *m/z* 1359.6548 (calcd for $C_{64}H_{104}O_{29}Na$, 1359.6561).

***3.9. Scabiostellatoside C (3)*:** amorphous, white powder; $[\alpha]^{20}_{D}$ –27.8 (*c* 0.18, MeOH); ^{1}H (600 MHz, CD_3OD) and ^{13}C NMR (150 MHz, CD_3OD) data, see tables 1 and 2; HRESIMS *m/z* 1521.7097 (calcd for $C_{70}H_{114}O_{34}Na$, 1521.7089).

***3.10. Scabiostellatoside D (4)*:** amorphous, white powder; $[\alpha]^{20}_{D}$ –24.3 (*c* 0.28, MeOH); ^{1}H (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data, see tables 3 and 4; HRESIMS *m/z* 1521.7096 (calcd for $C_{70}H_{114}O_{34}Na$, 1521.7089).

***3.11. Scabiostellatoside E (5)*:** amorphous, white powder; $[\alpha]^{20}_{D}$ –26 (*c* 0.26, MeOH); ^{1}H (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data, see tables 1 and 2; HRESIMS *m/z* 1521.7075 (calcd for $C_{70}H_{114}O_{34}Na$, 1521.7089).

***3.12. Scabiostellatoside F (6)*:** amorphous, white powder; $[\alpha]^{20}_{D}$ –10 (*c* 0.1, MeOH); ^{1}H (600 MHz, CD_3OD) and ^{13}C NMR (150 MHz, CD_3OD) data, see tables 3 and 4; HRESIMS *m/z* 1521.7080 (calcd for $C_{70}H_{114}O_{34}Na$, 1521.7089).

***3.13. Scabiostellatoside G (7)*:** amorphous, white powder; $[\alpha]^{20}_{D}$ –11.8° (*c* 0.28, MeOH); ^{1}H (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data, see tables 5 and 6; HRESIMS *m/z* 1157.5363 (calcd for $C_{54}H_{86}O_{25}Na$, 1157.5356).

***3.14. Scabiostellatoside H (8)*:** amorphous, white powder; $[\alpha]^{20}_{D}$ –20° (*c* 0.21, MeOH); ^{1}H (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data, see tables 5 and 6; HRESIMS *m/z* 995.4836 (calcd 955.4828, $C_{48}H_{76}O_{20}Na$).

Supporting Information

HRESIMS and 1D- and 2D-NMR spectra of compounds **1**-**8**.

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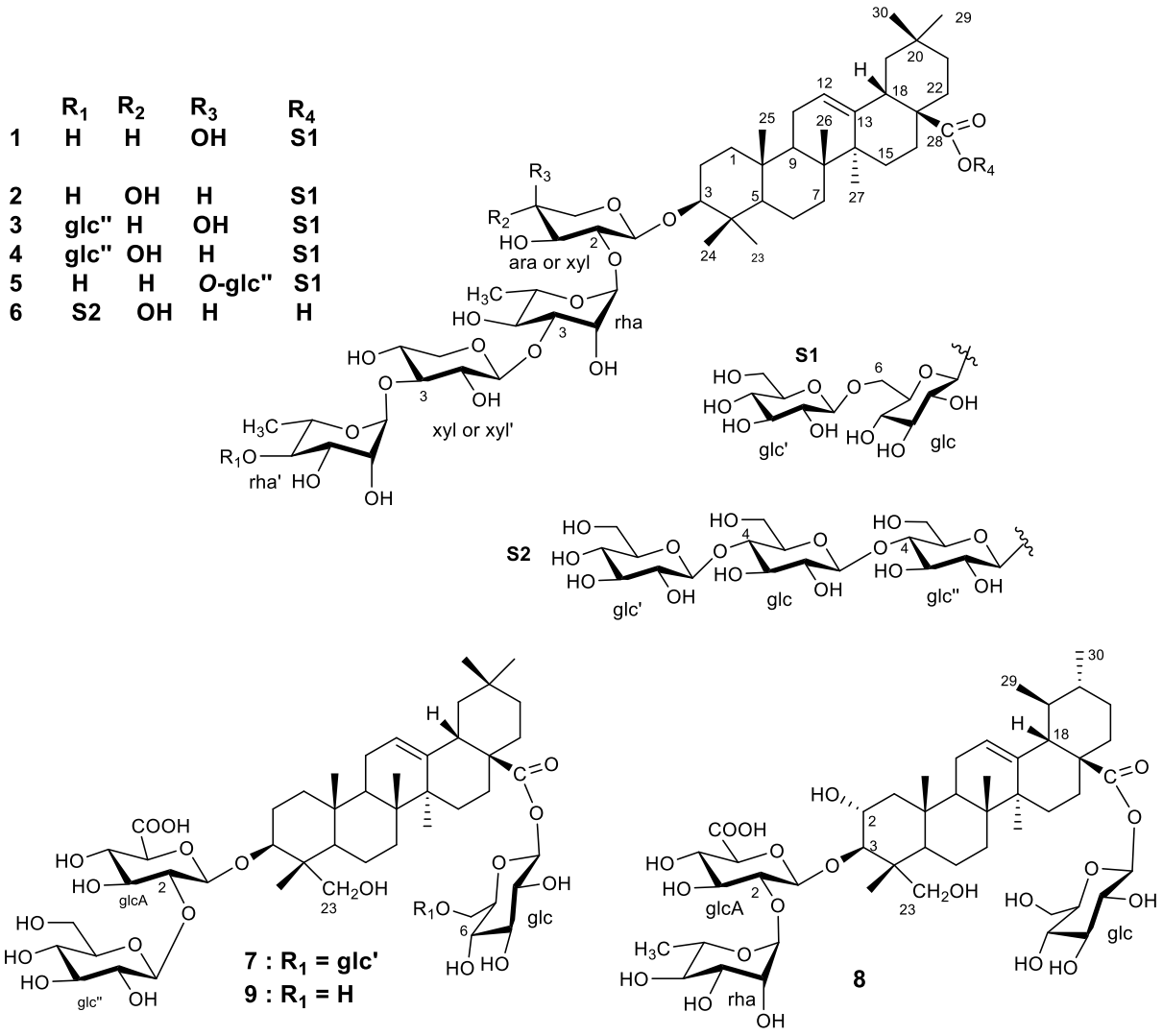


Figure 1. The structures of compounds **1**-**9** isolated from the whole plant *Scabiosa stellata*.

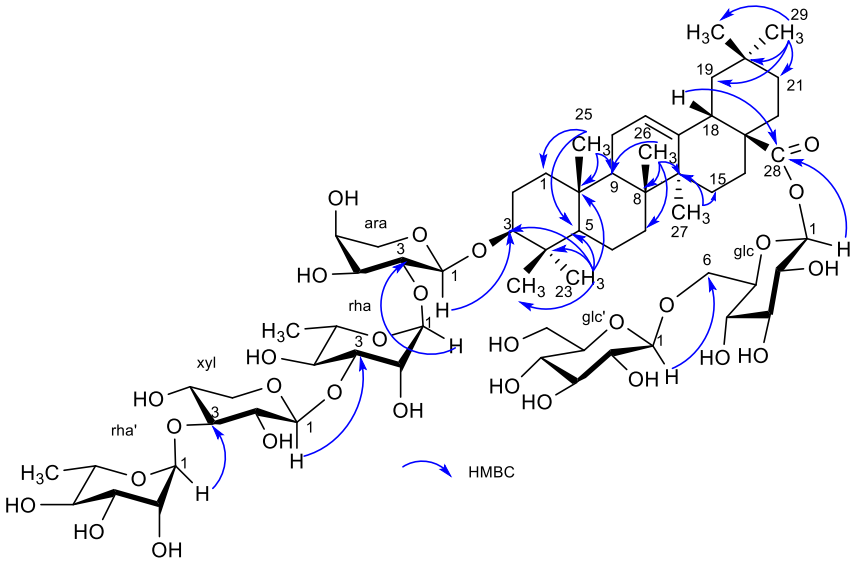


Figure 2. Key HMBC correlations for compound **1**.

Table 1. NMR spectroscopic data for the aglycone moieties for compounds **1**, **5** (500 MHz, CD_3OD) and **3** (600 MHz, CD_3OD).

position	**1**		**3**		**5**	
	δ_H m (*J* in Hz)	δ_C	δ_H m (*J* in Hz)	δ_C	δ_H m (*J* in Hz)	δ_C
1	1.01 m	38.6	1.01 m	38.6	1.00 m	38.5
	1.65 m		1.65 dt (13.6, 3.5)		1.64 dt (12.7, 2.5)	
2	1.73 m	25.7	1.74 m	25.7	1.73 m	25.6
	1.86 m		1.86 m		1.82 m	
3	3.15 dd (11.6, 4.2)	89.2	3.14 dd (11.6, 4.3)	89.2	3.14 dd (11.7, 4.4)	89.1
4	-	38.9	-	38.9	-	38.8
5	0.81 m	55.7	0.80 m	55.7	0.80 m	55.7
6	1.42 td (13.7,3.5)	18.0	1.44 m	18.0	1.45 td (13.9, 3.8)	17.9
	1.57 m		1.57 m		1.57 m	
7	1.33 m	32.5	1.34 m	32.5	1.33 m	31.7
	1.51 td (13.1, 3.5)		1.52 td (12.7, 3.3)		1.49 m	
8	-	39.3	-	39.3	-	39.2
9	1.60 m	47.7	1.60 m	48.2	1.59 m	47.6
10	-	36.5	-	36.5	-	36.4
11	1.92 m	23.2	1.92 m	23.4	1.90 m	23.1
12	5.27 t (3.4)	122.4	5.27 t (3.4)	122.3	5.27 t (3.5)	122.3
13	-	143.5	-	143.5	-	143.4
14	-	41.5	-	41.5	-	41.4
15	1.10 dt (14.3, 2.5)	27.5	1.10 dt (13.5, 2.9)	27.5	1.10 dt (13.9, 2.7)	27.4
	1.81 td (14.3, 4.4)		1.81 td (14.0, 3.7)		1.81 td (13.9, 3.9)	
16	1.73 m	22.6	1.73 m	22.6	1.73 m	22.5
	2.08 td (13.7, 3.8)		2.07 td (13.7, 3.7)		2.07 td (13.6, 4.0)	
17	-	46.7	-	46.7	-	46.6
18	2.86 dd (13.9, 3.8)	41.2	2.88 dd (13.5, 4.0)	41.2	2.88 dd (13.7, 4.4)	41.1
19	1.17 m	45.9	1.18 m	45.8	1.16 m	45.8
	1.74 m		1.74 m		1.73 m	
20	-	30.1	-	30.1	-	30.0
21	1.25 m	33.5	1.24 m	33.5	1.24 m	33.4
	1.41 td (14.1, 4.1)		1.43 td (13.8, 3.7)		1.41 td (13.9, 3.8)	
22	1.62 m	31.8	1.62 m	32.8	1.62 m	32.1
	1.73 m		1.74 td (13.0, 3.7)		1.73 td (13.0, 3.7)	
23	1.05 s	27.2	1.04 s	27.2	1.07 s	27.1
24	0.88 s	15.8	0.88 s	15.8	0.87 s	15.7
25	0.99 s	14.8	0.98 s	14.8	0.99 s	14.7
26	0.83 s	16.6	0.83 s	16.4	0.82 s	16.3
27	1.18 s	24.9	1.18 s	24.9	1.18 s	24.8
28	-	176.7	-	176.7	-	176.6
29	0.93 s	32.1	0.93 s	32.1	0.93 s	32.0
30	0.97 s	22.6	0.96 s	22.6	0.96 s	22.6

Table 2. NMR spectroscopic data for the aglycone moieties for compounds **1**, **5** (500 MHz, CD_3OD) and **3** (600 MHz, CD_3OD).

position	1		3		5	
	δ_H m (*J* in Hz)	δ_C	δ_H m (*J* in Hz)	δ_C	δ_H m (*J* in Hz)	δ_C
ara (at C-3)						
1	4.51 d (5.3)	103.9	4.51 d (5.3)	103.9	4.45 d (6.9)	104.1
2	3.78 dd (7.1, 5.3)	**75.0**	3.78 dd (7.1, 5.3)	**74.9**	3.75 dd (7.8, 6.9)	**75.2**
3	3.73 dd (7.1, 3.4)	72.3	3.73 dd (7.1, 3.4)	72.3	3.81 dd (7.8, 3.1)	72.5
4	3.79 m	67.7	3.79 m	67.7	3.92 m	**78.1**
5	3.52 dd (11.9, 2.3)	63.3	3.52 brd (12.4)	63.3	3.57 m	63.5
	3.86 m		3.86 m		4.16 dd (12.2, 3.1)	
rha						
1	5.20 d (1.5)	100.1	5.21 brs	100.1	5.26 d (1.8)	99.9
2	4.08 dd (3.5, 1.7)	70.4	4.08 dd (3.0, 1.7)	70.2	4.11 dd (3.5, 1.8)	70.2
3	3.85 dd (9.5, 3.5)	**80.6**	3.85 dd (9.5, 3.0)	**80.6**	3.88 dd (9.6, 3.5)	**80.5**
4	3.58 t (9.5)	71.4	3.58 t (9.5)	71.4	3.58 t (9.6)	71.3
5	3.91 m	68.6	3.91 m	68.6	3.94 m	68.5
6	1.24 d (6.2)	16.4	1.25 d (6.2)	16.6	1.25 d (6.2)	16.5
Xyl						
1	4.49 d (7.6)	105.1	4.49 d (7.6)	105.1	4.49 d (7.7)	105.0
2	3.40 dd (8.1, 7.6)	74.4	3.40 dd (8.8, 7.6)	74.5	3.41 dd (8.9, 7.7)	74.3
3	3.48 t (8.1)	**82.1**	3.48 t (8.8)	**81.7**	3.48 t (8.9)	**82.0**
4	3.55 m	68.4	3.55 m	68.3	3.55 m	68.2
5	3.24 t (11.4)	65.7	3.24 dd (11.0, 9.2)	65.7	3.24 t (11.4)	65.6
	3.89 m		3.88 dd (11.0, 5.3)		3.90 dd (12.1, 5.1)	
rha′						
1	5.19 d (1.4)	101.1	5.19 brs	100.8	5.19 d (1.6)	101.0
2	3.95 dd (3.5, 1.5)	70.9	3.98 dd (3.3, 1.5)	70.9	3.96 dd (3.3, 1.6)	70.8
3	3.72 dd (9.7, 3.5)	70.8	3.97 dd (9.2, 3.3)	70.8	3.73 dd (9.3, 3.3)	70.7
4	3.41 t (9.7)	72.6	3.64 t (9.2)	**82.3**	3.42 t (9.3)	72.5
5	4.02 m	68.6	4.13 m	67.2	4.04 m	68.5
6	1.27 d (6.2)	16.5	1.35 d (6.2)	16.6	1.27 d (6.3)	16.4
glc″						
1			4.61 d (7.6)	104.3	4.47 d (7.6)	104.6
2			3.22 dd (8.9, 7.6)	74.7	3.30 m	73.8
3			3.38 t (8.9)	76.7	3.38 t (8.9)	76.6
4			3.31 t (8.9)	70.1	3.29 t (8.9)	69.9
5			3.27 m	76.6	3.33 m	76.5
6			3.71 dd (12.0, 5.2)	61.3	3.68 dd (12.0, 5.4)	61.2
			3.86 dd (12.0, 2.3)		3.86 dd (12.0, 2.3)	
glc (at C-28)						
1	5.37 d (8.1)	94.4	5.37 d (8.2)	94.4	5.37 d (8.1)	94.3
2	3.34 t (8.1)	72.5	3.35 t (8.2)	72.4	3.36 t (8.1)	72.5
3	3.42 dd (9.6,8.1)	76.8	3.44 t(8.2)	76.7	3.44 m	76.8
4	3.44 t (9.6)	69.5	3.45 t (8.2)	69.5	3.46 t (9.6)	69.5
5	3.52 m	76.4	3.52 m	76.4	3.53 m	76.4
6	3.78 dd (11.4,4.3)	**68.1**	3.79 dd (11.4, 4.7)	**68.1**	3.79 dd (11.8, 4.1)	**68.1**
	4.13 dd (11.4,1.8)		4.14 dd (11.4, 1.7)		4.13 dd (11.8, 2.1)	
glc′						
1	4.36 d (7.8)	103.3	4.36 d (7.8)	103.2	4.36 d (7.8)	103.1
2	3.22 t (7.8)	73.6	3.22 t (7.8)	73.7	3.23 dd (8.5, 7.8)	73.6
3	3.37 dd (8.9,7.8)	76.7	3.37 dd (8.3, 7.8)	76.8	3.37 m	76.3
4	3.30 t (8.9)	70.1	3.31 t (8.3)	70.1	3.32 t (8.5)	70.0
5	3.24 m	76.3	3.29 m	76.6	3.27 m	76.5
6	3.69 dd (11.8,5.4)	61.2	3.67 dd (11.9, 5.5)	61.3	3.68 dd (12.0, 5.4)	61.2
	3.86 dd (11.8,2.5)		3.86 m		3.86 dd (12.0, 2.3)	

Table 3. N NMR spectroscopic data for the aglycone moieties for compounds **2**, **4** (500 MHz, CD_3OD) and **6** (600 MHz, CD_3OD).

Position	**2**		**4**		**6**	
	δ_H m (*J* in Hz)	δ_C	δ_H m (*J* in Hz)	δ_C	δ_H m (*J* in Hz)	δ_C
1	0.98 m	38.7	1.00 m	38.6	0.98 m	38.7
	1.62 m		1.62 m		1.62 m	
2	1.69 m	25.9	1.72 m	25.8	1.69 m	25.9
	1.82 dt (13.5, 3.2)		1.82 dt (13.1, 3.5)		1.82 dt (13.5, 3.2)	
3	3.14 dd (11.5, 4.0)	88.9	3.15 dd (11.8, 3.5)	88.8	3.14 dd (11.5, 4.0)	88.9
4	-	38.9	-	38.8	-	38.6
5	0.78 *br*d (12.2)	55.9	0.80 *br*d (12.3)	55.8	0.78 *br*d (12.2)	55.9
6	1.42 td (13.9, 3.8)	18.0	1.42 td (13.9, 3.8)	17.9	1.42 td (13.9, 3.8)	18.0
	1.56 m		1.55 m		1.56 m	
7	1.33 m	32.5	1.34 m	31.7	1.33 m	32.5
	1.51 m		1.51 m		1.51 m	
8	-	39.3	-	39.2	-	39.3
9	1.59 m	47.9	1.59 m	47.6	1.59 m	48.4
10	-	36.5	-	36.4	-	36.5
11	1.91 m	23.2	1.91 m	23.1	1.91 m	23.1
12	5.27 t (3.5)	122.4	5.27 t (3.8)	122.3	5.27 t (3.5)	121.8
13	-	143.5	-	143.4	-	143.5
14	-	41.4	-	41.4	-	41.6
15	1.10 m	27.5	1.10 dt (13.1, 3.5)	27.4	1.06 m	27.6
	1.80 m		1.81 td (13.1, 3.5)		1.82 m	
16	1.73 m	22.6	1.73 m	22.6	1.62 m	22.8
	2.07 td (13.7, 3.0)		2.07 td (13.8, 3.7)		1.98 td (13.7, 3.0)	
17	-	46.7	-	46.6	-	46.7
18	2.88 dd (13.8, 3.9)	41.2	2.88 dd (13.7, 4.9)	41.1	2.88 dd (13.8, 3.9)	41.6
19	1.17 m	45.9	1.17 m	45.8	1.13 m	45.9
	1.72 m		1.74 m		1.70 m	
20	-	30.1	-	30.1	-	30.1
21	1.23 m	33.5	1.24 m	33.4	1.20 m	33.7
	1.40 m		1.41 m		1.40 m	
22	1.61 m	31.8	1.61 m	32.5	1.56 m	31.8
	1.73 m		1.73 td (12.5, 3.5)		1.76 m	
23	1.07 s	27.5	1.07 s	27.0	1.07 s	27.5
24	0.88 s	15.8	0.88 s	15.8	0.88 s	15.8
25	0.98 s	14.8	0.98 s	14.7	0.98 s	14.6
26	0.82 s	16.4	0.82 s	16.6	0.86 s	16.5
27	1.18 s	24.9	1.18 s	24.8	1.18 s	24.9
28	-	176.7	-	176.6	-	179.8
29	0.93 s	32.1	0.93 s	32.0	0.93 s	32.3
30	0.96 s	22.6	0.96 s	22.6	0.96 s	22.7

Table 4. NMR spectroscopic data of the sugar moieties for compounds **2**, **4** (500 MHz, CD_3OD) and **6** (600 MHz, CD_3OD).

position	2		4		6	
	δ_H m (*J* in Hz)	δ_C	δ_H m (*J* in Hz)		δ_H m (*J* in Hz)	δ_C
xyl at C-3						
1	4.39 d (7.1)	105.0	4.39 d (7.1)	104.9	4.40 d (7.2)	105.0
2	3.40 m	**76.8**	3.34 dd (8.1, 7.0)	**76.7**	3.40 dd (8.2, 7.2)	**76.8**
3	3.44 t (8.2)	77.4	3.45 t (8.0)	77.4	3.45 t (8.2)	77.4
4	3.47 *br*t (8.2)	70.2	3.47 m	70.2	3.48 m	70.2
5	3.19 dd (11.4, 9.0)	65.2	3.21 dd (10.5, 9.1)	65.1	3.19 dd (10.5, 9.1)	65.1
	3.86 dd (11.4, 5.1)		3.85 dd (10.5, 5.2)		3.86 dd (10.5, 5.2)	
rha						
1	5.39 d (1.7)	99.9	5.38 d (1.7)	99.9	5.38 d (1.7)	99.9
2	4.13 dd (2.9, 1.7)	70.2	4.13 dd (3.1, 1.7)	70.1	4.13 dd (3.0, 1.7)	70.1
3	3.90 dd (9.5, 2.9)	**80.8**	3.90 dd (9.5, 3.1)	**80.7**	3.90 dd (9.5, 3.0)	**80.7**
4	3.58 t (9.5)	71.4	3.58 t (9.5)	71.3	3.53 t (9.5)	71.4
5	4.00 dq (8.4, 6.9)	68.4	4.01 m	68.5	3.99 m	68.5
6	1.25 d (6.9)	16.6	1.25 d (6.2)	16.6	1.25 d (6.2)	16.6
xyl′						
1	4.48 d (7.7)	105.1	4.47 d (7.7)	105.0	4.47 d (7.7)	105.0
2	3.40 dd (8.9, 7.7)	74.4	3.40 dd (8.8, 7.7)	74.4	3.40 dd (8.8, 7.7)	74.5
3	3.48 t (8.9)	**82.1**	3.49 t (8.8)	**81.6**	3.49 t (8.8)	**81.7**
4	3.54 *br*t (8.9)	68.6	3.53 m	68.3	3.53 m	68.3
5	3.22 dd (10.9, 8.0)	65.7	3.24 dd (11.4, 10.1)	65.6	3.24 dd (11.3, 10.0)	65.7
	3.90 m		3.88 dd (11.4, 2.3)		3.88 dd (11.3, 2.3)	
rha′						
1	5.20 d (1.7)	101.1	5.21 d (1.6)	100.7	5.21 *br*s	100.7
2	3.96 dd (3.3, 1.7)	70.9	3.97 dd (3.3, 1.6)	70.8	3.98 dd (3.3, 1.2)	70.8
3	3.72 dd (9.5, 3.3)	70.8	3.96 dd (9.2, 3.3)	70.7	3.97 dd (9.2, 3.3)	70.9
4	3.41 t (9.5)	72.6	3.64 t (9.2)	**82.2**	3.63 t (9.2)	**82.6**
5	4.03 dq (9.5, 6.5)	68.4	4.12 m	67.1	4.13 m	67.1
6	1.28 d (6.5)	16.5	1.34 d (6.2)	16.3	1.34 d (6.2)	16.6
glc″					**glc″at rha′-C-4**	
1			4.61 d (7.9)	104.6	4.64 d (7.9)	104.2
2			3.22 t (8.4)	74.6	3.29 t (8.5)	74.4
3			3.39 t (8.4)	76.6	3.55 t (8.4)	75.2
4			3.33 m	71.3	3.61 t (8.4)	**79.1**
5			3.30 m	76.5	3.42 m	75.2
6			3.68 dd (11.9, 5.5)	61.2	3.90 m	60.4
			3.86 dd (11.9, 2.2)		3.90 m	
glc (at C-28)	**glc at C-28**		**glc at C-28**		**glc at glc″-C-4**	
1	5.37 d (8.0)	94.4	5.37 d (8.1)	94.3	4.48 d (8.0)	103.0
2	3.34 m	72.5	3.35 m	72.4	3.31 dd (8.5, 8.0)	73.3
3	3.43 t (8.5)	76.8	3.44 t (8.8)	76.6	3.55 t (8.5)	74.8
4	3.44 t (8.5)	69.5	3.42 t (8.8)	69.4	3.61 t (8.5)	**78.8**
5	3.52 m	76.4	3.51 m	76.3	3.49 m	75.2
6	3.78 dd (11.7,5.0)	**68.1**	3.79 dd (11.7, 5.0)	**68.0**	3.83 m	60.1
	4.14 dd (11.7,2.0)		4.14 dd (11.7, 1.6)		3.93 m	
glc′	**glc′→glc-C-6**		**glc′→glc-C-6**		**glc′at glc-C-4**	
1	4.36 d (7.8)	103.2	4.36 d (7.8)	103.2	4.42 d (7.9)	103.2
2	3.21 dd (8.6,7.8)	73.7	3.22 dd (8.4, 7.8)	73.6	3.24 dd (8.6, 7.9)	73.5
3	3.37 t (8.6)	76.6	3.38 t (8.4)	76.8	3.38 t (8.6)	76.4
4	3.31 t (8.6)	70.2	3.31 t (8.5)	70.1	3.33 m	69.9
5	3.27 m	76.6	3.27 m	76.5	3.36 m	76.6
6	3.68 dd (12.0,5.5)	61.3	3.68 dd (11.9, 5.5)	61.2	3.68 dd (11.8, 5.5)	61.0
	3.86 dd (12.0,2.0)		3.86 dd (11.9, 2.2)		3.90 dd (11.8, 2.2)	

Table 5. NMR spectroscopic data of the aglycone moieties for compounds **7** and **8** (500 MHz, CD_3OD).

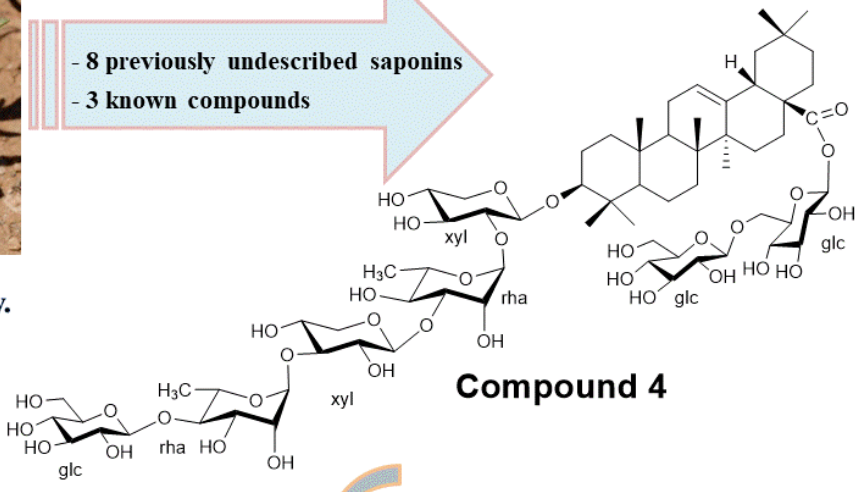
position	**7**		**8**	
	δ_H m (*J* in Hz)	δ_C	δ_H m (*J* in Hz)	δ_C
1	0.98 m	38.3	0.92 m	46.8
	1.62 m		2.05 dd (11.1, 4.2)	
2	1.78 m	25.1	3.82 m	66.4
	1.97 m			
3	3.66 dd (11.5, 3.7)	82.3	3.54 d (9.5)	86.1
4	-	42.7	-	44.1
5	1.25 m	46.9	1.35 m	46.3
6	1.39 m	17.5	1.36 m	17.4
	1.49 m		1.49 m	
7	1.29 m	32.0	1.31 m	32.2
	1.60 m		1.70 td (13.5, 3.5)	
8	-	39.3	-	39.4
9	1.64 m	47.9	1.63 m	47.9
10	-	36.2	-	37.2
11	1.92 m	23.2	1.99 m	23.1
12	5.27 t (3.4)	122.4	5.27 t (3.4)	125.7
13	-	143.5	-	137.1
14	-	41.6	-	42.1
15	1.11 m	27.5	1.11 m	27.8
	1.80 m		1.98 td (13.3, 4.2)	
16	1.73 m	22.6	1.78 dt (13.0, 4.2)	23.8
	2.07 m		2.10 td (13.0, 4.2)	
17	-	46.7	-	47.5
18	2.87 dd (14.1, 4.3)	41.2	2.26 d (11.4)	52.8
19	1.28 m	45.8	1.41 m	39.0
	1.73 m			
20		30.1	0.98 m	39.0 38.9
21	1.23 m	33.5	1.37 m	30.3
	1.40 m		1.52 td (13.1, 4.1)	
22	1.62 m	31.8	1.66 m	36.1
	1.73 m		1.78 dt (13.0, 4.2)	
23	3.27 d (11.2)	63.4	3.30 d (11.8)	62.7
	3.75 d (11.2)		3.70 d (11.8)	
24	0.72 s	12.0	0.78 s	13.6
25	1.00 s	15.2	1.07 s	16.5
26	0.82 s	16.5	0.87 s	16.4
27	1.19 s	25.0	1.15 s	22.6
28	-	175.7	-	176.7
29	0.92 s	32.1	0.92 d (6.3)	16.2
30	0.95 s	22.6	0.99 d (6.3)	20.1

Table 6. NMR spectroscopic data of the sugar moieties for compounds **7** and **8** (500 MHz, CD_3OD).

position	**7**		**8**	
	δ_H m (*J* in Hz)	δ_C	δ_H m (*J* in Hz)	δ_C
glcA at C-3				
1	4.56 d (7.5)	102.8	4.55 d (7.5)	102.4
2	3.57 dd (9.0, 7.5)	80.2	3.49 dd (9.4, 7.5)	78.0
3	3.63t (9.0)	76.9	3.56 t (9.4)	77.4
4	3.47 t (9.0)	72.1	3.47 t (9.4)	72.6
5	3.58 d (9.0)	74.9	3.64 d (9.4)	75.0
6		176.2		176.5
glc/rha	**glc at glcA-C-2**		**rha at glcA-C-2**	
1	4.71 d (7.7)	103.2	5.34 d (1.6)	101.0
2	3.24 t (8.3)	74.8	4.06 dd (3.1, 1.6)	70.3
3	3.36 m	76.4	3.81 dd (9.2, 3.1)	70.6
4	3.26 t (8.5)	70.3	3.40 t (9.2)	72.5
5	3.25 m	76.9	3.91 dq (9.5, 6.3)	69.0
6	3.65 m	61.5	1.25 d (6.3)	16.7
	3.82 dd (12.0, 2.1)			
glc at C-28				
1	5.37 d (8.1)	94.4	5.37 d (8.1)	94.3
2	3.34 m	72.5	3.34 m	72.5
3	3.42 t (8.4)	76.4	3.42 t (8.7)	76.9
4	3.44 t (8.4)	69.5	3.38 t (8.7)	69.8
5	3.52 m	76.9	3.34 m	77.2
6	3.77 m	68.1	3.71 dd (12.0, 1.2)	61.1
	4.14 dd (12.2, 1.6)		3.82 dd (12.0, 3.8)	
glc′ at glc-C-6				
1	4.36 d (7.8)	103.2		
2	3.23 t (7.8)	72.5		
3	3.37 m	76.4		
4	3.31 t (8.6)	70.3		
5	3.32 m	76.9		
6	3.69 m	61.3		
	3.86 dd (12.2, 1.2)			

***Scabiosa stellata* Cav.**
(Caprifoliaceae)

- 8 previously undescribed saponins
- 3 known compounds



Compound 4

Cytotoxic activity against fibrosarcoma cell line (HT1080)

Good cytotoxic activity (IC_{50} 12.0 ± 0.2 µM)