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Two oleanene glycosides from the aerial parts of *Caltha polypetala*

T. Baykal[a], E. Bedir[b], I. Calis[b,*], R. Aquino[c], S. Piacente[c], C. Pizza[c]

[a]*Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, TR-06100, Ankara, Turkey*
[b]*Department of Pharmacognosy, Faculty of Pharmacy, Hacettepe University, TR-06100, Ankara, Turkey*
[c]*Dipartimento di Scienze Farmaceutiche, Università degli Studi di Salerno, 84084 Penta di Fisciano, Salerno, Italy*

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Abstract

Two new oleanene glycosides (**1**–**2**) possessing hederagenin as the aglycone were isolated from the methanolic extract of the aerial parts of *Caltha polypetala* together with four known glycosides. The saccharide portion linked to C-3 of the aglycone is made up of α-L-arabinopyranose, α-L-rhamnopyranose and galactopyranose in the new compounds; while compound **1** possesses linked to C-28 a trisaccharide moiety made up of two β-D-glucopyranose and one α-L-rhamnopyranose unit, in compound **2** the 28-COOH group is free. The structures were elucidated by 1D and 2D NMR experiments including ^{1}H–^{1}H (DQF-COSY, 1D-TOCSY, 2D-ROESY) and ^{1}H–^{13}C (HSQC, HMBC) spectroscopy. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Caltha polypetala*; Ranunculaceae; Saponins; NMR analysis

1. Introduction

Caltha is a small genus of Ranunculaceae, which is represented by only *Caltha polypetala* Hochst. in the flora of Turkey (Davis, 1982). Preparations made from *Caltha polypetala* are used as sedative in traditional folk medicine (Baytop, 1984). In this paper we describe the isolation and structure elucidation by FABMS and NMR analysis of two new glycosides **1**–**2** together with four known glycosides (**3**–**6**) all showing hederagenin as the aglycone. Three of the isolated glycosides are bidesmosides possessing sugar chains linked at C-3 and C-28; the other three are monodesmosides with a sugar chain linked at C-3. All the saponins can be obtained by eliminating a terminal sugar unit from the most complex compound **1**.

2. Results and discussion

Compound **1** had a molecular formula $C_{65}H_{106}O_{31}$, as determined by ^{13}C, ^{13}C DEPT NMR and negative-ion FABMS. The FABMS spectrum of **1** showed the $[M-H]^-$ ion at *m/z* 1381 and prominent fragments at *m/z* 1203 $[(M-H)-178]^-$, and *m/z* 1219 $[(M-H)-162]^-$ (cleavage of a hexose unit with or without glycosidic oxygen), at *m/z* 1073 due to the subsequent loss of one deoxyhexose unit, at m/z 911 and 749 due to the sequential losses of two hexose units. A peak at *m/z* 471 was attributed to the aglycone moiety. The ^{13}C NMR spectrum showed 65 signals, of which 30 were assigned to a triterpenoid moiety (Mahato & Kundu, 1994) and 35 to a saccharide portion. The ^{1}H NMR spectrum of the aglycone moiety of **1** showed signals for six tertiary methyl groups (δ 0.73, 0.83, 0.94, 0.98, 1.02, 1.21) and typical signals of H-3ax at δ 3.64 (*dd, J* = 11.1 and 4.5 Hz) due to the presence of β-OH group at C-3 position (De Tommasi, Piacente, De Simone & Pizza, 1993). Further features were signals at δ5.35 (1H, *t, J* = 3.4 Hz), δ3.32 (1H, *d, J* = 11.5) and 3.62 (1H, *d,*

* Corresponding author. Tel.: +90-312-3051089; fax: +90-312-3114777.
E-mail address: acalis@dominet.in.com.tr (I. Calis)

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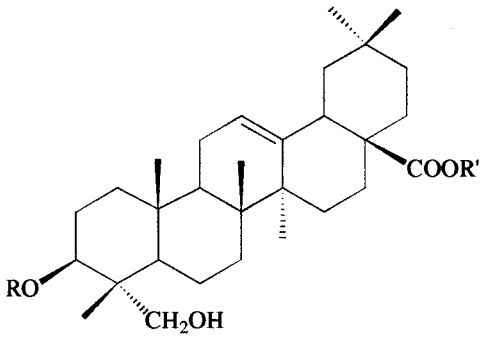

	R	R'
1	β-D-gal 1–>3 α-L-rha 1->2 α-L-ara	α-L-rha 1->4 β-D-glc 1->6 β-D-glc
2	β-D-gal 1->3 α-L-rha 1->2 α-L-ara	H
3	α-L-ara	H
4	α-L-rha 1->2 α-L-ara	H
5	α-L-ara	α-L-rha 1->4 β-D-glc 1->6 β-D-glc
6	α-L-rha 1->2 α-L-ara	α-L-rha 1->4 β-D-glc 1->6 β-D-glc

$J=11.5$) ascribable, respectively, to an olefinic and primary alcoholic function. These data also indicated an oleanolic acid derivative with one of the methyl group substitued by a $-CH_2OH$ function (Mahato & Kundu, 1994).

In the ^{13}C NMR spectrum the signals at δ123.5 and 144.9 ascribable to C-12 and C-13 confirmed the Δ^{12} oleanene skeleton (Mahato & Kundu, 1994). A signal at δ178.3 and the carbon resonances of ring D and E suggested the occurrence of a glycosylated –COOH group at C-28 (De Tommasi et al., 1993). Full assignments of the proton and carbon resonances of the aglycone (see Experimental) were secured by ^1H–^1H DQF–COSY (Bodenhausen, Freeman, Morris, Neidermeyer & Turner, 1977) and HSQC (Bodenhausen & Ruben, 1980) spectra. The alcoholic function was located at C-23 on the basis of the downfield shift (+4.2) exhibited by C-4 (δ43.6) and the highfield shift (−5.0 ppm; −6.4 ppm; −3.5 ppm) exhibited respectively by C-3 (δ83.3), C-5 (48.0) and C-24 (13.0) in comparison with the same carbon resonances in an oleanene skeleton bearing a Me-23 (Mahato & Kundu, 1994). Also the chemical shift of Me-24 in the ^1H NMR spectrum (δ_H 0.73) was diagnostic for a 23-CH_2OH. The HMBC (Martin & Crouch, 1991) (8 Hz) spectrum of **1** confirmed the position of the alcoholic function showing significative cross-peaks, due to $^2J_{C-H}$ and $^1J_{C-H}$ correlations between H-23 (δ3.32) and C-3 (δ83.3), C-4 (δ43.6) and C-24 (δ13.0). On the basis of the foregoing data the aglycone of **1** was identified as 3β,23-dihydroxyolean-12-en-28-oic acid, known as hederagenin (Mahato & Kundu, 1994). Glycosylation of the alcoholic function at C-3 and esterification of the –COOH group were indicated by the downfield shift (+13 ppm) and highfield shift (−3 ppm) observed respectively for these carbon resonances in **1**, relative to the corresponding signals in hederagenin (Mahato & Kundu, 1994).

The sugar portion of **1** contained in the ^1H NMR spectrum (Table 2), six anomeric proton signals (δ4.45, *d*, $J=8.0$ Hz; δ4.51, *d*, $J=8.0$ Hz; δ4.53, *d*, $J=3.0$ Hz; δ4.88, *d*, $J=1.5$ Hz; δ5.20, *d*, $J=1.5$ Hz; δ5.37, *d*, $J=8.0$ Hz) and methyl doublets (δ1.29, *d*, $J=6.5$ Hz; 1.31, *d*, $J=6.5$ Hz) suggesting the occurrence of two deoxyhexose units. The other sugar signals were overlapped in the region between δ3.33 and 4.30. The structures of the oligosaccharide moieties were deduced using 1D-TOCSY and 2D-NMR experiments. Because of the selectivity of the multi-step coherence transfer, the 1D-TOCSY method (Davis & Bax, 1985) allowed the subspectrum of a single monosaccharide unit to be extracted from the crowded overlapped region. The isolated anomeric proton signals resonating in an uncrowded region of the spectrum (between δ4.45 and 5.37) were the starting point for the 1D-TOCSY experiments. Selected 1D-TOCSY obtained irradiating each

anomeric proton signal yielded the subspectrum of each sugar residue. In some cases, because of the small coupling constants, the distribution of magnetization around the spin system was impeded. For this reason, for example, it was possible to identify only three protons (δ3.67, 3.67, 3.79) coupled to the anomeric signal at δ4.53 in the case of arabinose (Table 1). In the case of the 6-deoxyhexoses, easier identification of all of the proton signals was accomplished by also recording 1D-TOCSY experiments irradiating the methyl doublets. Since in the TOCSY method both direct and relayed connectivities occurr, we also recorded a DQF-COSY spectrum. The results of 1D-TOCSY and DQF-COSY experiments allowed the sequential assignments of all of the proton resonances to the individual monosaccharides as reported in Table 1. Thus the shifts of the sugar resonances, summarized in Table 1, were attributable to L-arabinopyranosyl (δH-1_{ara} = 4.53), α-L-rhamnopyranosyl (δH-$1_{rha'}$ = 5.20), α-L-rhamnopyranosyl (δ H-$1_{rha''}$ = 4.88), β-D-galactopyranosyl (δH-1_{gal} = 4.51), β-D-glucopyranosyl (δH-$1_{glu'}$ = 5.37), β-D-glucopyranosyl (δH-$1_{glu''}$ = 4.45) units. In the case of the arabinopyranosyl unit, the J_{H1-H2} coupling constant (3.0), has been reported not to be diagnostic on its own, owing to the high conformational mobility of arabinopyranosides ($^4C1 \leftrightarrow {}^1C4$) (Ishii et al., 1981). As we reported in previous works (Bodenhausen et al., 1977; Piacente, Pizza, De Tommasi & De Simone, 1995) evidence of α-L-arabinopyranoside was obtained from the ROESY (De Tommasi et al., 1993) spectrum which showed NOE from C-1_{ara} to C-2_{ara}, C-3_{ara} and C-5_{ara} as expected for an α-L-arabinopyranoside in rapid $^4C1 \leftrightarrow {}^1C4$ conformational exchange.

Table 1
^{13}C and ^1H NMR assignments of the sugar portion of compound **1**[a]

Sugar	δ_C	δ_H (*J* in Hz)
Ara-1 (at C-3 agl.)	104.7	4.53 *d* (3.0)
Ara-2	76.5	3.67 *dd* (3.0, 8.5)
Ara-3	73.5	3.67 *dd* (3.0, 8.5)
Ara-4	69.4	3.79 *m*
Ara-5	65.3	3.54 *dd* (3.5, 12.0)
		3.87 *dd* (2.0, 12.0)
Glc-1′ (at C-28)	95.7	5.37 *d* (8.0)
Glc-2′	73.5	3.37 *dd* (8.0, 9.0)
Glc-3′	77.8	3.44 *t* (9.0)
Glc-4′	70.5	3.44 *t* (9.0)
Glc-5′	77.8	3.56 *ddd* (2.5, 4.5, 9.0)
Glc-6′	69.1	3.83 *dd* (4.5, 12.0)
		4.12 *dd* (2.5, 12.0)
Glc-1″ (at C-6 Glc′)	104.1	4.45 *d* (8.0)
Glc-2″	74.9	3.27 *dd* (8.0, 9.0)
Glc-3″	76.5	3.50 *t* (9.0)
Glc-4″	79.2	3.57 *t* (9.0)
Glc-5″	76.5	3.33 *ddd* (2.0, 4.5, 9.0)
Glc-6″	61.3	3.69 *dd* (4.5, 9.0)
		3.87 *dd* (2.0, 9.0)
Rha 1″ (at C-4 glc″)	102.8	4.88 *d* (1.5)
Rha 2″	72.0	3.87 *dd* (1.5, 2.5)
Rha 3″	71.8	3.66 *dd* (2.5, 9.0)
Rha 4″	73.4	3.45 *t* (9.0)
Rha 5″	70.1	4.00 *m*
Rha 6″	17.5	1.31 *d* (6.5)
Rha 1′ (at C-2 ara)	101.5	5.20 *d* (1.5)
Rha 2′	70.9	4.30 *dd* (1.5, 2.5)
Rha 3′	82.6	3.91 *dd* (2.5, 9.0)
Rha 4′	72.1	3.59 *t* (9.0)
Rha 5′	69.6	3.95 *m*
Rha 6′	17.5	1.29 *d* (6.5)
Gal-1 (at C-3 rha′)	106.4	4.51 *d* (8.0)
Gal-2	72.7	3.65 *dd* (8.0, 9.3)
Gal-3	74.3	3.53 *dd* (3.5, 9.3)
Gal-4	70.0	3.85 *m*
Gal-5	76.3	3.58 *m*
Gal-6	62.1	3.74 *dd* (4.5, 12.0)
		3.80 *dd* (2.5, 12.0)

[a] Assignments confirmed by DQF-COSY, 1D-TOCSY, 2D-ROESY, HSQC and HMBC.

HSQC experiments, which correlated all the proton resonances with those of each corresponding carbon, allowed the assignments of interglycosidic linkages by comparison of the observed carbon chemical shifts with those of the corresponding methylpyranosides. The absence of any ^{13}C NMR glycosydation shift for one of the α-L-rhamnopyranosyl unit (rha″), and or the β-D-galactopyranosyl unit suggested that these sugars were terminal units. Glycosydation shifts were observed for C-2_{ara} (δ76.5), C-$3_{rha'}$ (δ82.6), C-$6_{glu'}$ (δ69.1) and C-$4_{glu''}$ (δ79.2) (Table 1). Chemical shifts of H-1glu′ (δ5.37) and C-$1_{glu'}$ (δ95.7) indicated that this sugar unit was involved in an ester linkage with the C-28 carboxylic group (Elgamal, Soliman, Karawya, Mikhova & Duddeck, 1995). The positions of the sugar residues were unambigously defined by the HMBC experiment. A cross peak due to long-range correlations between C-3 (δ83.3) of the aglycone and H-1_{ara} (δ4.53) indicated that arabinose was the sugar residue linked to C-3 of the aglycone, a cross-peak between C-2_{ara} (δ76.5) and H-$1_{rha'}$ (δ5.20) indicated that rhamnose was the second unit of the trisaccharide chain at C-3 of the aglycone; finally a cross peak was observed between C-3_{rha} (δ82.6) and H-1 (δ4.51) of the terminal galactose unit. Similarly, the sequence of the trisaccharide chain at C-28 was indicated by the crosspeaks between C-$6_{glu'}$ (δ69.1) and H-$1_{glu''}$ (δ4.45), C-$4_{glu''}$ (δ79.2) and H-1 of the terminal rhamnose (δ4.88). A cross peak between H-1 of glu′ (δ5.37) and the ^{13}C NMR resonance of the aglycone carbonyl group (δ178.3) provided definitive evidence for an ester linkage between the trisaccharide chain and the aglycone. Thus compound **1** was identified as the new 3β-*O*-β-D-galactopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L -arabinopyranosyl-23-hydroxyolean-12-en-28-oic acid–28-*O*-α-L-rhamnopyra-

nosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl ester.

Compound **2** ($C_{47}H_{76}O_{17}$) showed, in the negative ion FABMS spectrum, a quasi molecular anion $[M-H]^-$ at *m/z* 911, and prominent fragments at *m/z* 749 $[(M-H)-162]^-$, and *m/z* 603 $[(M-H)-(162+146)]^-$ due to the subsequent loss of a hexose and a deoxyhexose units. Also in this case the peak ascribable to the aglycone was observed *m/z* 471. Comparison of ^1H and ^{13}C NMR data of compound **2** with those of **1** (Table 1) indicated identical aglycone and saccharide chain at C-3. The only difference between the two compounds was the absence of the sugar chain linked to C-28 in **2**. In good agreement with this evidence was the chemical shift of C-28 (δ181.2) typical of a free carboxylic group (Mahato & Kundu, 1994). On the basis of these evidences compound **2** was identified as the new 3β -*O*-β-D-galactopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl-23-hydroxyolean-12-en-28-oic acid.

On the basis of NMR data compound **3** was identified as koelreuteria saponin A or fatsiaside B1 previously isolated from a lot of sources among which *C. palustris* (Bhandary, Gray & Rastagi, 1987) and *C. polypetala* (Vugalter, Dekanosidze, Dzhikiya & Kemertelidze, 1986); compound **4** as α-hederin previously isolated from *Hedera helix* (Hostettmann, Hostetmann-Koldas & Sticher, 1980), *H. nepalensis* (Kizu, Kitayama, Nakatani, Tomimori & Namba, 1985), and *C. palustris* (Bhandary et al., 1987); compound **5** is reported as a secondary metabolite of *H. nepalensis* (Kizu et al., 1985), *H. helix* (Elias et al., 1991) and *C. polypetala* (Shashka & Kemertelidze, 1988); compound **6** was identified as hederasaponin C previously isolated from *Kalopanax septemlobus* (Shao, Kasai, Xu & Tanaka, 1989), *H. nepalensis* (Kizu et al., 1985) and *Astrantia major* (Hiller et al., 1990).

3. Experimental

3.1. General

A Bruker DRX-600 spectrometer operating at 599.2 MHz for ^1H and 150.86 for ^{13}C using the UXNMR software package was used for NMR measurements in CD_3OD solutions. 2D experiments: ^1H–^1H DQF-COSY (double quantum filtered direct chemical shift correlation spectoscopy) (Bodenhausen et al., 1977), inverse detected ^1H–^{13}C HSQC (heteronuclear single quantum coherence) (Bodenhausen & Ruben, 1980) and HMBC (heteronuclear multiple bond connectivity) (Martin & Crouch, 1991) and ROESY (rotating-frame overhauser enhancement spectroscopy) (Kessler, Gresinger, Kerssebaum, Wagner & Ernst, 1987) were obtained by employing the conventional pulse sequences as described previously. The selective excitation spectra, 1D TOCSY (Davis & Bax, 1985) were acquired using waveform generator-based GAUSS shaped pulses, mixing time ranging from 100 to 120 ms and a MLEV-17 spin-lock field of 10 kHz preceded by a 2.5 ms trim pulse. Optical rotations were measured on a Perkin–Elmer 141 polarimeter using a sodium lamp operating at 589 nm in 1% w/v solutions in MeOH. FABMS were recorded in a glycerol matrix in the negative ion mode on a VG ZAB instrument (Xe atoms of energy of 2–6 KV).

3.2. Plant material

Caltha polypetala (Ranunculaceae) was collected from Ilgaz Mountain, Çankiri, Center Anatolia, in May 1996. Voucher specimens have been deposited at the Herbarium of Gazi University, Ankara, Turkey.

3.3. Extraction and isolation

The air-dried, powdered aerial parts of *C. polypetala* (4.6 kg) were extracted several times with methanol at room temperature. The solvent was removed by rotary evaporation, yielding 540.2 g of extract. An aliquot of the extract (20 g) dissolved in water was subjected to VLC using reversed-phase material (C-18, 150 g), employing H_2O and H_2O–MeOH mixtures with decreasing polarity, yielding eight fractions (fractions 1–8). Fractions 7 and 8 were rich in saponins (7.75 g, 1.30 g, respectively). An aliquot of the fraction 7 (3.0 g) was subjected to column chromatography (silica gel, 150 g) using $CHCl_3$–MeOH (90:10) and $CHCl_3$–MeOH–H_2O (85:15:0.5, 80:20:1, 80:20:2, 70:30:3 and 61:32:7) to give nine main fractions (frs. A–I). Fr. A (80 mg) was applied to silica gel column (30 g) eluting with EtOAc–MeOH–H_2O (100:10:5 and 100:15:10) to give compound **4** (38 mg). Fr. E (131 mg) was chromatographed on a silica gel column (15 g) using $CHCl_3$–MeOH–H_2O (70:30:3) to yield compound **5** (34 mg). Fr. F (434 mg) was subjected to a silica gel column (30 g) using $CHCl_3$–MeOH–H_2O (70:30:3 and 61:32:7) to give compounds **5** (11 mg) and **6** (70 mg). Fr. I (477 mg) was applied to column chromatography (silica gel, 25 g); eluting with $CHCl_3$–MeOH–H_2O (70:30:3 and 61:32:7) to give compound **1** (440 mg). An aliquot of the fraction 8 (300 mg) was chromatographed on a silica gel column (30 g) using $CHCl_3$-MeOH (90:10 and 85:15) and $CHCl_3$-MeOH–H_2O (80:20:1, 80:20:2 and 70:30:3) to give five fractions (frs. 8a–8e). Fr. 8a was compound **3** (16 mg). Fr. 8e (25 mg) was applied to gel chromatography (Sephadex LH-20, 16 g) eluting with MeOH to yield compound **2** (13.2 mg).

3.5. Compound 1

$[\alpha]D^{25} = -18.60^{\circ}$ (*c*0.1, MeOH); ^{1}H NMR data of the aglycone (CD_3OD, 600 MHz): δ5.35 (1H, *t*, $J = 3.4$ Hz, H-12), 3.64 (1H, *dd*, $J = 4.5$ and 11.1 Hz, H-3), 2.90 (1H, *dd*, $J = 3.0$ and 11.0 Hz, H-18), 1.21 (3H, *s*, H_3-27), 1.02 (3H, *s*, H_3-25), 0.98 (3H, *s*, H_3-30), 0.94 (3H, *s*, H_3-29), 0.83 (3H, *s*, H_3-26), 0.73 (3H, *s*, H_3-24); ^{13}C NMR data of the aglycone (150 MHz, CD_3OD): 178.3 (C-28), 144.9 (C-13), 123.5 (C-12), 83.3 (C-3), 64.8 (C-23), 48.1 (C-9), 48.0 (C-5), 47.1 (C-19), 47.0 (C-17), 43.6 (C-4), 42.5 (C-18), 42.7 (C-14), 40.5 (C-8), 39.3 (C-1), 37.3 (C-10), 34.8 (C-21), 33.2 (C-29), 33.0 (C-7, C-22), 31.2 (C-20), 28.6 (C-15), 26.0 (C-2, C-27), 24.3 (C-11), 23.6 (C-16, C-30), 19.0 (C-6), 17.3 (C-26), 16.1 (C-25), 13.0 (C-24); ^{1}H and ^{13}C NMR of the sugar moieties: see Table 1; FABMS *m*/*z* 1381 $[M-H]^-$, 1203 $[(M-H)-178]^-$, 1219 $[(M-H)-(162)]^-$, 1073 $[(M-H)-(162+146)]^-$, 911 $[(M-H)-(162+162+146)]^-$, 749 $[(M-H)-(162+162+162+146)]^-$.

3.5. Compound 2

$[\alpha]D^{25} = +36.2^{\circ}$ (*c*0.1, MeOH); ^{1}H NMR data of the aglycone (CD_3OD, 600 MHz): superimposable on those reported for compound **1**; ^{13}C NMR data of the aglycone (CD_3OD, 150 MHz): superimposable on those reported for compound **1** except the signal ascribable to C-28 (δ181.2); ^{1}H and ^{13}C NMR of the sugar moieties: superimposable to those reported for the corresponding sugars in **1**; FABMS *m*/*z* 911 $[M-H]^-$, 749 $[(M-H)-162]^-$, 603 $[(M-H)-(162+146)]^-$.

Compounds **3** (Bhandary et al., 1987; Vugalter et al., 1986), **4** (Hostettmann et al., 1980; Kizu et al., 1985; Bhandary et al., 1987), **5** (Kizu et al., 1985; Elias et al., 1991; Shaska & Kemertelidze, 1988) and **6** (Shao et al., 1989; Kizu et al., 1985; Hiller et al., 1990)) were identified on the basis of their FABMS and NMR values in comparison with literature data.

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