Turk J Chem
26 (2002) , 947 – 954.
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New Triterpenic Saponins from *Cephalaria transsylvanica*

Süheyla KIRMIZIGÜL*and Hüseyin ANIL
Ege University, Faculty of Science, Department of Chemistry,
35100 Bornova, İzmir-TURKEY
e-mail: kgul@sci.ege.edu.tr

Received 09.05.2002

Three new triterpenic saponins, 3-*O*-[β-D-xylopyranosyl (1→4)-β-D- glucopyranosyl (1→4)-β-D-glucopyranosyl (1→3)-α-L-rhamnopyranosyl (1→4) -β-D-xylopyranosyl] hederagenin 28-*O*-[β-D-glucopyranosyl (1→4)- β-D-glucopyranosyl] ester (**1**), 3-*O*-[β-D-glucopyranosyl (1→4)- β-D-glucopyranosyl (1→3)-α-L-rhamnopyranosyl (1→4)- β-D-xylopyranosyl] hederagenin 28-*O*-[β-D-glucopyranosyl] ester (**2**) and 3-*O*-[β-D-glucopyranosyl (1→3)- α-L-rhamnopyranosyl (1→4)- β-D-xylopyranosyl] hederagenin(**3**) were isolated from *Cephalaria transsylvanica.* After cleavage of the ester-glycosidic linkage of the bisdesmosidic compounds, two new prosapogenins, 3-*O*-[β-D-xylopyranosyl (1→4)- β-D-glucpyranosyl (1→4)- β-D-glucopyranosyl (1→3)- α-L-rhamnopyranosyl (1→4)- β-D-xylopyranosyl] hederagenin (**4**) and 3-*O*-[β-D-glucopyranosyl (1→4)- β-D-glucopyranosyl (1→3)- α-L-rhamnopyranosyl (1→4)- β-D-xylopyranosyl] hederagenin (**5**) were also isolated. The structures of the compounds were established by chemical and spectroscopic means.

Key Words: Cephalaria transsylvanica, dipsacaceae, hederagenin, triterpenic saponins.

Introduction

Cephalaria transsylvanica L. (Dipsacaceae) is an annual flowering plant with lilac flowers. It grows in southern and central Europe, and western, south-western and central Anatolia, Turkey[1]. This species has been used in folk medicine due to its wide range of biological activities[2,3]. In our previous phytochemical investigations on this plant some triterpenic saponins belonging to the oleanane series were obtained[4,5]. Some saponins have shown activity against various bacteria and fungi[6]. This knowledge prompted us to investigate *Cephalaria transsylvanica* once more in detail for their natural occurrence. Here, the isolation and structural determination of three new triterpenic saponins, namely transsylvanosides **L**, **M**, and **N**, are reported.

*Corresponding author

Experimental

General

Optical rotations were measured by a Schmidt-Haensch Polartronic E Polarimeter. IR spectra were recorded as KBr pellets on a Bruker IFS-48 FT-IR spectrometer. ^{1}H-NMR (400 Hz) and ^{13}C-NMR (100 MHz) spectra were run in pyridine-d_5 on a Bruker-Spectrospin Avance DPX 400 instrument with TMS as internal standard. FAB-mass spectra were carried out on a VG 20-250 quadrupole mass spectrometer with Xe bombardment using MeOH as solvent and polyethylene glycol as matrix. For GC (6890) and GC-mass (6890-5973 MSD) analysis a Hewlett-Packard system was used, with HP-5 MS column (30 m x 0.25 mm x 0.25 μm, He, temp. 130-280°C, 30 min^{-1}). Merck 7743 and 7747 silica gels were used for CC and prep. TLC respectively. TLC was performed on precoated silica gel 60 (Merck 5554) plates sprayed with 10% H_2SO_4 solution. Cellulose F (Merck 5574) plates were used for sugar analysis spraying with aniline phthalate reagent for visualization of spots. Sephadex-LH-20-100 (Sigma) was used for the purification of compounds.

$CHCl_3$:MeOH:H_2O solvent systems were used with increasing polarity adding with MeOH as A- 65:35:10, B- 65:35:10 + 10% MeOH, C- 65:35:10 + 15% MeOH, D- 65:35:10 + 20% MeOH, E- EtOAc:pyridine: H_2O / 2:1:2 and F- $CHCl_3$:MeOH / 15:3 solvent systems were also successfully used during chromatographic studies. For solvent systems A-D the lower phases were utilized.

Plant Material

Plant samples were collected in July, 1994, in Bornova, İzmir. A voucher specimen is deposited (No.7435) and identified in the Herbarium Centre of Ege University.

Extraction and isolation

Air-dried and powdered aerial parts of *C. transsylvanica* (900 g) were successively extracted with 80% MeOH (3 x 4 L). Vacuum dried residue was washed with hexane, CH_2Cl_2 and Me_2CO to remove apolar substances separately. The remaining residue was dissolved in H_2O and extracted with n-BuOH. The evaporated BuOH layer (9 g) was subjected to a Si gel column. The column was eluted with solvent systems A, B, C, D in an increasing polarity. During A solvent system elution compound **3** was obtained, and during solvent system D elution compounds **1** and **2** were obtained. Purification of these compounds was done using Sephadex-LH 20 with solvent systems A and D. After purification, compounds **1** (38 mg), **2** (3 mg) and **3** (64 mg) were obtained as amorphous powders.

Transsylvanoside L: 3-*O*-[β-D-xylopyranosyl (1→4)- β-D-glucopyranosyl (1→4)- β-D-glucopyranosyl (1→3)-α-L-rhamnopyranosyl (1→4)- β-D-xylopyranosyl] hederagenin-28-*O*-[β-D-glucopyranosyl (1→4)- β-D-glucopyranosyl] ester (**1**) : 38 mg, amorphous powder, $[\alpha]^{27}$+49.29° (c, 0.63, MeOH). FT-IR (KBr): 3380 (OH), 1740 (C=O), 1620 (C=C), 1071 cm^{-1} (C-O-C). ^{1}H-NMR (pyridine-d_5, 400 MHz), see Table 1; ^{13}C-APT (pyridine-d_5, 100 MHz), see Table 2. Negative-ion FAB-mass m/z: 1529 $[M-H]^-$, 1367 $[M-H-162]^-$, 1205 $[M-H-(2x162)]^-$, 1073 $[M-H-(2x162+132)]^-$, 911 $[M-H-(3x162+132)]^-$, 749 $[M-H-(4x162+132)]^-$, 603 $[M-H-(4x162+132+146)]^-$, 471 $[M-H-(4x162+2x132+146)]^-$. Molecular peak was seen at 1552 $[M+Na]^+$ in the positive-ion FAB-mass spectrum.

Table 1. Partial ^{1}H- nmr data of **1-5** in pyridine-d_5.

Compound	Aglycone protons	Sugar Protons
1	0.78 s (3H), 0.89 s (3 H)	1.55 d (J=5.5 Hz, H-6$''$)
	0.92 s (3H), 0.96 s (3H)	4.60 brs (H-1$''$)
	1.12 s (3H), 1.15 s (3H)	4.66 d (J=8.2 Hz, H-1$'''''$)
	2.95 m (H-3α)	4.84 d (J=7.7 Hz, H-1$''''$)
	5.47 d (J=3.4 Hz, H-12)	5.00 d (J=8.1 Hz, H-1$'''$)
		5.11 d (J=7.8 Hz, H-1$'$)
		5.21 d (J=8.0 Hz, H-1$''''''$)
		5.23 d (J=7.5 Hz, H-1$'''''''$)
2	0.95 s (3H), 0.98 s (3H)	1.53 d (J=5.3 Hz, H-6$''$)
	1.00 s (3H), 1.07 s (3H)	4.41 d (J=8.0 Hz, H-1$'$)
	1.10 s (3H), 1.14 s (3H)	5.00 d (J=7.4 Hz, H-1$'''$)
	3.19 m (H-3α)	5.32 d (J=8.2 Hz, H-1$''''$)
	5.39 brs (H-12)	5.40 brs (H-1$''$)
		6.20 d (J=7.0 Hz, H-1$'''''$)
3	0.89 s (3H), 0.90 s (3H)	1.48 d (J=6.0 Hz, H-6$''$)
	0.93 s (3H), 1.00 s (3H)	5.50 d (J=5.5 Hz, H-1$'''$)
	1.02 s (3H), 1.13 s (3H)	5.81 d (J=5.8 Hz, H-1$'$)
	3.14 m (H-3α)	6.26 brs (H-1$''$)
	5.40 d (J=3.1 Hz, H-12)	
4	0.88 s (3H), 0.90 s (3H)	1.53 d (J=5.4 Hz, H-6$''$)
	0.92 s (3H), 0.98 s (3H)	5.06 d (J=7.7 Hz, H-1$'''$)
	1.10 s (3H), 1.14 s (3H)	5.15 d (J=7.4 Hz, H-1$'$)
	3.13 m (H-3α)	5.17 d (J=8.2 Hz, H-1$'''''$)
	5.42 brs (H-12)	5.22 d (J=7.0 Hz, H-1$''''$)
		5.40 brs (H-1$''$)
5	0.88 s (3H), 0.92 s (3H)	1.51 d (J=5.5 Hz, H-6$''$)
	0.95 s (3H), 1.00 s (3H)	4.80 brs (H-1$''$)
	1.03 s (3H, 1.15 s (3H)	5.00 d (J=7.4 Hz, H-1$''''$)
	3.17 s (H-3α)	5.15 d (J=8.0 Hz, H-1$'''$)
	5.40 brs (H-12)	5.23 d (J=7.1 Hz, H-1$'$)

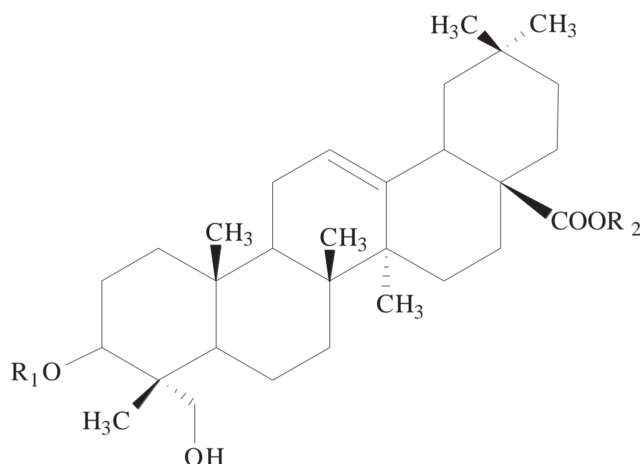
Transsylvanoside M: 3-*O*-[β-D-glucopyranosyl (1→4)-β-D-glucopyranosyl (1→3)- α-L-rhamnopyranosyl (1→4)- β-D-xylopyranosyl] hederagenin 28-*O*-[β-D-glucopyranosyl] ester (**2**): 33 mg, amorphous powder, $[\alpha]^{27}$+21.92° (c, 1.64, MeOH). FT-IR (KBr): 3388 (OH), 1738 (C=O), 1620 (C=C), 1074 cm^{-1} (C-O-C). ^{1}H-NMR (pyridine-d_5, 400 MHz), see Table 1; ^{13}C-APT (pyridine-d_5, 100 MHz), see Table 2. Negative-ion FAB-mass m/z: 1235 [M-H]$^-$, 1073 [M-H-162]$^-$, 911 [M-H-(2x162)]$^-$, 749 [M-H-(3x162)]$^-$, 603 [M-H-(3x162+146)]$^-$, 471 [M-H-(3x162+146+132)]$^-$. Positive-ion FAB-mass spectrum gave a molecular peak signal at 1259 [M+Na]$^+$.

Transsylvanoside N: 3-*O*-[β-D-glucopyranosyl (1→3)-α-L-rhamnopyranosyl (1→4)- β-D-xylopyranosyl] hederagenin (**3**): 64 mg, amorphous powder, $[\alpha]^{27}$+12.09° (c, 0.85, MeOH). FT-IR (KBr): 3390 (OH), 1730 (C=O), 1618 (C=C), 1074 cm^{-1} (C-O-C). ^{1}H-NMR (pyridine-d_5, 400 MHz), see Table 1; ^{13}C-NMR (pyridine-d_5, 100 MHz), see Table 2. The negative-ion FAB-mass m/z: 911 [M-H]$^-$, 749 [M-H-162]$^-$, 603 [M-H-162-146]$^-$, 471 [M-H-162-146-132]$^-$. Molecular peak was seen at 934 [M+Na]$^+$ in positive-ion FAB-mass spectrum.

Table 2. ^{13}C-NMR-APT chemical shifts of **1-5** in pyridine-d_5.

Carbon	Compound				
	1	**2**	**3**	**4**	**5**
Aglycone					
C-3	82.6	82.3	82.4	81.8	82.0
C-12	122.1	122.0	122.0	122.0	122.0
C-13	144.0	144.3	144.2	144.1	144.3
C-23	68.0	68.7	66.5	68.2	68.5
C-28	176.5	176.8	180.0	179.9	180.1
C-3 sugars					
C-1$'$	107.3	105.5	106.4	106.3	105.7
C-2$'$	73.3	72.8	73.0	74.0	72.5
C-3$'$	75.0	75.5	75.5	75.5	75.0
C-4$'$	78.5	78.8	80.0	78.4	78.5
C-5$'$	66.4	66.0	64.0	66.4	65.2
C-1$''$	100.0	101.0	101.0	100.7	101.1
C-2$''$	71.0	72.8	74.0	72.3	72.0
C-3$''$	81.2	81.2	81.4	81.3	82.2
C-4$''$	73.3	72.6	71.3	73.2	72.5
C-5$''$	70.0	69.4	71.0	70.0	70.1
C-6$''$	18.2	18.2	18.4	18.2	18.1
C-1$'''$	104.1	104.3	104.4	104.4	104.1
C-2$'''$	75.0	74.7	74.3	74.8	74.5
C-3$'''$	78.2	78.0	78.2	78.2	77.5
C-4$'''$	78.5	78.7	69.2	78.8	78.8
C-5$'''$	75.3	77.0	78.0	76.0	75.4
C-6$'''$	62.5	62.7	62.2	62.5	62.2
C-1$''''$	105.4	105.1		104.5	105.0
C-2$''''$	75.0	75.0		75.0	74.7
C-3$''''$	78.3	78.7		78.5	78.2
C-4$''''$	78.6	72.1		78.8	71.5
C-5$''''$	75.5	75.5		75.7	75.4
C-6$''''$	62.7	62.2		63.0	62.6
C-1$'''''$	106.0			106.2	
C-2$'''''$	74.3			75.0	
C-3$'''''$	75.0			75.3	
C-4$'''''$	77.5			77.4	
C-5$'''''$	62.0			62.5	
C-28 sugars					
C-1$''''''$	97.1	95.5			
C-2$''''''$	71.4	75.2			
C-3$''''''$	75.5	75.5			
C-4$''''''$	78.7	72.4			
C-5$''''''$	76.5	76.8			
C-6$''''''$	65.0	62.3			
C-1$'''''''$	105.2				
C-2$'''''''$	74.0				
C-3$'''''''$	77.1				
C-4$'''''''$	71.9				
C-5$'''''''$	77.9				
C-6$'''''''$	66.0				

Alkaline hydrolysis of the saponins: Saponins **1-3** (15 mg each) were dissolved in MeOH (5 mL) separately. pH was adjusted to 12-13 with dry methanolic NaOMe, and the mixtures were left overnight at room temperature. After neutralizing with 2M HCl the mixtures were concentrated to dryness under vacuum[4]. The residues were first solved in H_2O then extracted with n-BuOH giving hydrolysed compounds separately. Together with chromatographic and spectroscopic results, the findings suggested that saponins **1** and **2** produced the new prosapogenins **4** and **5** and saponin **3** remained unchanged (see Figure).



	R_1	R_2
1	Xyl (1→4)Glc(1→4)Glc(1→3)Rha(1→4)Xyl-	Glc(1→4)Glc-
2	Glc(1→4)Glc(1→3)Rha(1→4)Xyl-	Glc-
3	Glc(1→3)Rha(1→4)Xyl-	H
4	Xyl (1→4)Glc(1→4)Glc(1→3)Rha(1→4)Xyl-	H
5	Glc(1→4)Glc(1→3)Rha(1→4)Xyl-	H
6	H	H

Glc: β-D-glucopyranosyl
Rha: α-L-rhamnopyranosyl
Xly: β-D-xylopyranosyl

Figure. Structures of compounds **1-6**.

Prosapogenin 4: 10 mg, amorphous powder, $[\alpha]^{27}$: -11.15° (c, 0.82, MeOH). FT-IR (KBr): 3392 (OH), 1730 (C=O), 1620 (C=C) and 1072 cm^{-1} (C-O-C). ^{1}H-NMR (pyridine-d_5, 400 MHz), see Table 1; ^{13}C-NMR (pyridine-d_5, 100 MHz), see Table 2. Negative-ion FAB-mass m/z: 1205 $[M-H]^-$, 1073 $[M-H-132]^-$, 911 $[M-H-132-162]^-$, 749 $[M-H-(132+2x162)]^-$, 603 $[M-H-(132+2x162+146)]^-$, 471 $[M-H-(2x132+2x162+146)]^-$. Molecular peak was seen at 1228 $[M+Na]^+$ in the positive-ion FAB-mass spectrum.

Prosapogenin 5: 9 mg, amorphous powder, $[\alpha]^{27}$: -15.43° (c, 1.11, MeOH). FT-IR (KBr): 3390 (OH), 1730 (C=O), 1618 (C=C) and 1074 cm^{-1} (C-O-C). ^{1}H-NMR (pyridine-d_5, 400 MHz), see Table 1; ^{13}C-NMR (pyridine-d_5, 100 MHz), see Table 2. Negative-ion FAB-mass m/z: 911 $[M-H]^-$, 749 $[M-H-162]^-$, 603 $[M-H-162-146]^-$, 471 $[M-H-162-146-132]^-$.

Acid hydrolysis of saponins: Solutions of saponins (15 mg each) in 80% MeOH-benzene (1:1) (5 mL) were refluxed for 6 h at 95°C with 2M HCl (5 mL) separately. The organic layers were evaporated under

reduced pressure. H_2O was added to each mixture and aglycones were extracted using $CHCl_3$. The TLC analysis of the $CHCl_3$ layers with F solvent system gave the same aglycone for all compounds. Hederagenin (**6**) has been identified by chromatographic and spectroscopic means m.p. 327°C, $[\alpha]^{27}= +77.5°$ (c, 1.04, MeOH)[4,7].

Identification of the sugars of saponins

The aqueous layers of hydrolysed saponins were neutralized with saturated Na_2CO_3 solution and concentrated to dryness. The residues were then compared with standard sugars using solvent system G in TLC. Detection of the spots was done with aniline phthalate solution. In the next step, these layers were silylated for GC analysis using trimethylchlorosilane and hexamethyldisilazane in dry pyridine under a $CaCl_2$ tube for 1 h at 60°C[8]. Analysis of the silylated sugars resulted in a glucose-rhamnose-xylose ratio of 4:1:2 for **1**, 3:1:1 for **2** and 1:1:1 for **3** in GC.

Methylation and identification of methylated sugars

Compounds (10 mg each) were methylated twice with Ag_2O (0.15 g) and CH_3I (0.75 mL) in dry DMF. Permethylated saponins were methanolysed with 5% anhydrous methanolic HCl for 5 h at 80°C[8,9]. The methylated methyl monosaccharides were identified by comparison with authentic samples.

Results and Discussion

The negative-ion FAB-mass spectrum of compound **1** showed a deprotonated molecular ion peak at m/z 1529 and the other fragments suggested the sequential loss of four hexose, two deoxyhexose and one pentose units from the molecular ion. The positive-ion FAB-mass spectrum confirmed a molecular ion peak at m/z 1552 $[M+Na]^+$. The FAB-mass spectra and ^1H and ^{13}C-NMR data together with GC and GC-mass results, therefore indicated the formula $C_{70}H_{115}O_{36}$ for **1** (see Tables 1 and 2). The ^1H-NMR spectrum showed the existence of six methyl groups of aglycone by singlets at δ 0.78, 0.89, 0.92, 0.96, 1.12 and 1.15. The methyl group signal of rhamnose was seen at δ 1.55 as a doublet. The doublet at δ 5.47 belonged to the olefinic proton of aglycone. The double bond signals at δ 122.1 and 144.0 in the ^{13}C-NMR spectrum indicated that aglycone was an oleanane-Δ^{12} type[4]. The anomeric proton signals at δ 4.66, 4.84, 5.00, 5.11, 5.21 and 5.23 as doublets were due to D-glucose and D-xylose. Their coupling constants confirmed β-glycosidic linkages[9]. The broad singlet at δ 4.60 was attributed to the anomeric proton of α-L-rhamnose. The anomeric carbon signals at δ 97.1, 104.1, 105.2, 105.4 were assigned to four glucose units. The signals at δ 106.0 and 107.3 belonged to xylose units and the other peak at δ 100.0 was related to rhamnose. The C-3 signal at δ 82.6 and the C-28 signal at δ 176.5 inferred that compound **1** is bisdesmosidic. The ester group absorption at 1740 cm^{-1} in the IR spectrum in addition to the other IR absorptions confirmed this ester glycosidic linkage[10,11]. The glycosidic linkages of sugars were established by GC-mass analysis of methylated methyl monosaccharides. These results were consistent with the ^{13}C-NMR data of saponin (see Tables 1 and 2)[12–16].

The basic hydrolysis of **1** resulted in prosapogenin (**4**). The anomeric carbon signals at δ 106.3, 100.7, 104.4, 104.5 and 106.2 in the ^{13}C-NMR were indicative of the presence of five sugar units. Compound **4** also produced an apparent molecular ion peak in negative-ion FAB-mass at m/z: 1205 $[M-H]^-$ indicating the molecular formula $C_{58}H_{94}O_{26}$. The ^1H-NMR spectrum of **4** displayed anomeric proton signals at δ 5.06,

5.15, 5.17, 5.22 and 5.40. Comparison of the ^{13}C-NMR spectra of **4** with those of **1** showed the loss of the two anomeric carbon signals at δ 97.1 and 105.2 and 10 resonance signals. Compound **1** is therefore composed of two disaccharide chains, one linked to C-3 by a glycosidic bond and the other linked to C-28 by an esteric linkage. This indicates that saponin is bisdesmosidic.

The IR spectrum of transsylvanoside **M** (**2**) showed characteristic hydroxyl (3388 cm^{-1}) and ester (1838 cm^{-1}) absorptions. Anomeric carbon signals were observed at δ 95.5, 101.0, 104.3, 105.1 and 105.5 in the ^{13}C-NMR spectrum. Five anomeric proton signals at δ 4.41, 5.00, 5.32, 5.40 and 6.20 were in agreement with the ^{13}C-NMR spectrum. The molecular ion peak at m/z: 1235[M-H]$^-$ indicated the molecular formula $C_{59}H_{96}O_{27}$, followed by fragments at m/z: 1073, 911, 749, 603 and 471. The base peak at m/z: 1073 suggested that a glucose was linked to hederagenin by an ester function[13].

Alkaline hydrolysis of **2** resulted in a new prosapogenin **5**. The anomeric proton signals of **5** at δ 4.80, 5.00, 5.15 and 5.23 were in agreement with the ^{13}C-NMR spectrum in which the respective carbons were observed at δ 101.1, 104.1, 105.0 and 105.7. The sequence of sugars was deduced from positive and negative-ion FAB-mass spectra. The corresponding molecular formula is determined to be $C_{59}H_{96}O_{27}$.

The negative-ion FAB-mass spectrum of transsylvanoside **N** (**3**) produced a deprotonated molecular ion peak at m/z: 911 [M-H]$^-$, and fragment ions at m/z: 749, 603 and 471. The molecular ion peak was confirmed by a signal at m/z: 934 [M+Na]$^+$ in the positive-ion FAB-mass spectrum, indicating the molecular formula $C_{47}H_{76}O_{17}$ for **3**. Basic hydrolysis results showed no difference from **3** as determined by chromatographic and spectroscopic means. Some IR absorptions, 3980 cm^{-1} (OH), 1695 cm^{-1} (C=O), C-3 (δ 82.4) and C-28 (δ 180.0), suggested that sugars were linked only at C-3 to the aglycone (see Table 2)[7,8]. This means that the saponin is monodesmosidic.

The results of GC analysis of all silylated monosaccharides and GC-mass analysis of methylated methyl monosaccharides together with the above findings determined the structures of compounds **1-6** in the Figure.

Acknowledgements

The authors wish to thank The Scientific and Technical Research Council of Turkey and METU for the spectroscopic analysis.

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