Turk J Chem
33 (2009) , 667 – 675.

doi:10.3906/kim-0812-60

Secondary metabolites from *Nepeta heliotropifolia*

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Received 23.12.2008

Two iridoid glycosides, ixoroside (**1**) and nepetanudoside B (**2**); 1 phenylpropanoid glycoside, coniferine (**3**); 2 flavone glycosides, apigenin 7-*O*-glucuronide (**4**) and apigenin 7-*O*-glucopyranoside (**5**); 2 triterpenes, oleanolic acid **(6)** and ursolic acid **(7)**; and 1 sterol, β-sitosterol **(8)**, were isolated from the aerial parts of *Nepeta heliotropifolia* Lam. (Lamiaceae). Their structures were identified by means of spectroscopic methods (1D- and 2D-NMR, UV, and EIMS).

Key Words: Lamiaceae, *Nepeta heliotropifolia,* iridoid glycosides, flavone glycosides, triterpenoids.

Introduction

The genus *Nepeta* (Lamiaceae) is represented by 33 species in the *Flora of Turkey*,[1] 17 of which are endemic. *Nepeta* species are commonly used in Turkish folk medicine as stomachics and stimulants.[2] Iridoids,[3–7] phenylethanoid[8] and phenylpropanoid[4,9] glycosides, terpenoids,[6,7,10–15] steroids,[6,7,13] lactones,[6,7,16,17] nepetalactams,[18] nepetalactols,[19] flavonoids,[20,21] phenolic acids,[4,7] and essential oils[14] were previously reported from *Nepeta* species. In the present study, we report the isolation and structure elucidation of 2 iridoid glycosides, ixoroside (**1**) and nepetanudoside B (**2**); 1 phenylpropanoid glycoside, coniferine (**3**); 2 flavone glycosides, apigenin 7-*O*-glucuronide (**4**) and apigenin 7-*O*-glucopyranoside (**5**); 2 triterpenes, oleanolic acid **(6)** and urso-

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lic acid **(7)**; and 1 sterol, β-sitosterol (**8**), isolated from the aerial parts of *Nepeta heliotropifolia*. The structures of the compounds were elucidated by spectroscopic methods (1D- and 2D-NMR, UV, and EIMS).

Experimental

General experimental procedures: The UV (MeOH) spectra were recorded on an Agilent 8453 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Mercury plus 400 MHz for proton and 100 MHz for carbon by using TMS as internal standard. The solvents were $CDCl_3$, CD_3OD, and DMSO-d_6. EIMS was performed on a Finnigan MAT 95 spectrometer. Silica gel 60 (0.063-0.200 mm, Merck) and Sephadex LH-20 (Fluka) were used for open column chromatographic separations. Lichroprep RP-18 (25-40 μm, Merck) reversed phase material was used for vacuum liquid chromatography (VLC). TLC analyses were carried out on pre-coated Kieselgel 60 F_{254} aluminum sheets (Merck). Compounds were detected by UV fluorescence and spraying 1% vanillin-H_2SO_4 reagent, followed by heating at 105 °C for 1-2 min.

Plant material: *Nepeta heliotropifolia* (Lamiaceae) was collected from the wetlands along the road from Ankara to Afyonkarahisar in May 2005. A voucher specimen has been deposited in the Herbarium of the Pharmacognosy Department, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey (HUEF 05007).

Extraction and pre-purification: Open air-dried and powdered aerial parts of the plant (465 g) were extracted 3 times with MeOH at 40 °C (3 × 2.5 L). After filtration, the combined extracts were evaporated under vacuum to dryness (58 g). The residue was suspended in H_2O (150 mL) and the water soluble portion was partitioned between *n*-hexane (8 × 0.5 L), $CHCl_3$ (4 × 0.2 L), EtOAc (5 × 0.2 L), and *n*-BuOH (5 × 0.4 L). Organic phases were condensed to dryness in vacuo. The residues obtained were 14 g, 11 g, 3 g, and 11 g, respectively.

Isolation of the compounds: *n*-Butanol extract (11 g) was chromatographed on a silica gel column eluting with $CHCl_3$-MeOH mixtures (90:10 → 20:80) to yield 2 main fractions (Frs. A-B, Fr. A: 1 g, Fr. B: 5 g). Fr. A was subjected to VLC using reversed-phase material, and MeOH-H_2O mixtures (0%-50%) as solvent to give Fr. A_1 and Fr. A_2. Fr. A_1 was subjected to a silica gel column eluting with EtOAc-MeOH-H_2O mixtures (100:17:13) to yield Fr. $A_{1.1}$ (29 mg) and Fr. $A_{1.2}$ (34 mg). Fr. $A_{1.1}$ gave pure compound **1** (29 mg). Purification of Fr. $A_{1.2}$ by Sephadex LH-20 CC using MeOH yielded compound **3** (18 mg). Fr. A_2 was found to be compound **2** (109 mg) in pure form. Fr. B was subjected to VLC using reversed-phase material and MeOH-H_2O mixtures (0%-75%) as solvent to give Fr. B_1 and Fr. B_2. Purification of Fr. B_1 by Sephadex LH-20 CC using MeOH gave compound **4** (10 mg). The EtOAc extract (3 g) was subjected to VLC on reversed-phase material using MeOH-H_2O mixtures (0%-75%) to give Fr. C and Fr. D. Fr. C was eluted with MeOH from the Sephadex LH-20 column to give compound **5** (10 mg). The $CHCl_3$ extract (11 g) was fractioned over a silica gel column with *n*-hexane-EtOAc (90:10 → 40:60) mixtures to afford Fr. E and Fr. F. The former was subjected to a silica gel column eluting with *n*-hexane-EtOAc (70:30 → 50:50) mixtures to yield Fr. E_1 (167 mg) and Fr. E_2. Purification of Fr. E_1 by Sephadex LH-20 CC using $CHCl_3$-MeOH (1:1) gave a mixture of compounds **6** and **7** (60 mg). The *n*-hexane extract (14 g) was applied to repeated silica gel columns with *n*-hexane-EtOAc (90:10 → 50:50) mixtures to give compound **8**.

Results

Ixoroside (1): UV $\lambda_{max.}$(MeOH) nm: 249; IR $\upsilon_{max.}$ (KBr) cm^{-1}: 3400, 1730, 1640; EIMS m/z 197 [M-Glu]$^+$ (calc. for $C_{16}H_{24}O_9$). ^{13}C-NMR (100 MHz, DMSO-d_6) and ^{1}H-NMR (400 MHz, DMSO-d_6) data are given in Table 1.

Table 1. Spectroscopic data of compound **1** [^{13}C-NMR (DMSO-d_6, 100 MHz) and ^{1}H-NMR (DMSO-d_6, 400 MHz)] and **2** [^{13}C-NMR (CD_3OD, 100 MHz) and ^{1}H-NMR (CD_3OD, 400 MHz)].

	1				**2**			
C/H	DEPT	δ_C	δ_H	J(Hz)	DEPT	δ_C	δ_H	J(Hz)
Aglycone								
1	CH	99.6	5.38 d	2.9	CH	100.8	5.13 d	5.8
3	CH	162.6	7.40 s		CH	152.3	7.50 d	0.8
4	C	124.4			C	111.8		
5	CH	28.9	2.88 m		CH	34.5	3.03 dd	14.0/7.0
6	CH_2	28.8	1.31 m 2.08 m		CH_2	38.6	2.08 m 2.72 m	
7	CH_2	40.9	1.43 m m 1.57 m		CH	126.8	5.48 bs	
8	C	78.3			C	139.0		
9	CH	51.1	2.22 m		CH	49.3	2.72 m	
10	CH_3	25.0	1.15 s		CH_3	15.1	1.84 s	
11	C	191.5	9.16 s		C	170.0		
Glucose								
1'	CH	103.2	4.45 d	8.1	CH	103.3	4.59d	7.8
2'	CH	74.3	2.90-3.35 m+		CH	74.1	3.24-3.40 m+	
3'	CH	77.3	2.90-3.35 m+		CH	77.2	3.24-3.40 m+	
4'	CH	70.3	2.90-3.35 m+		CH	70.0	3.24-3.40 m+	
5'	CH	78.0	2.90-3.35 m+		CH	77.0	3.24-3.40 m+	
6'	CH_2	61.6	3.43 dd 3.63 dd	11.7/5.5 11.0/1.5	CH_2	61.3	3.69 dd 3.84 dd	12.1/4.8 12.1/2.0

+: overlapped signals

Nepetanudoside B (2): UV $\lambda_{max.}$(MeOH) nm: 236; IR $\upsilon_{max.}$ (KBr) cm^{-1}: 3320, 1680, 1634; EIMS m/z 195 [M-Glu]$^+$ (calc. for $C_{16}H_{22}O_9$). ^{13}C-NMR (100 MHz, CD_3OD) and ^{1}H-NMR (400 MHz, CD_3OD) data are given in Table 1.

Coniferine (3): UV $\lambda_{max.}$(MeOH) nm: 257; EIMS m/z 179 [M-Glu]$^+$ (calc. for $C_{16}H_{22}O_8$). ^{13}C-NMR (100 MHz, CD_3OD) and ^{1}H-NMR (400 MHz, CD_3OD) data are given in Table 2.

Apigenin 7-*O*-glucuronide (4): EIMS m/z 269 [M-Glu]$^+$ (calc. for $C_{21}H_{18}O_{11}$). ^{13}C-NMR (100 MHz, DMSO-d_6) and ^{1}H-NMR (400 MHz, DMSO-d_6) data are given in Table 3.

Apigenin 7-*O*-glucopyranoside (5): EIMS m/z 269 $[M\text{-}Glu]^+$ (calc. for $C_{21}H_{20}O_{10}$). ^{13}C-NMR (100 MHz, DMSO-d_6) and ^{1}H-NMR (400 MHz, DMSO-d_6) data are given in Table 3.

Table 2. ^{13}C-NMR (CD_3OD, 100 MHz) and ^{1}H-NMR (CD_3OD, 400 MHz) spectroscopic data of compound **3**.

	3			
C/H Aglycone	DEPT	δ_C	δ_H	J(Hz)
1	C	132.5		
2	CH	110.2	7.06 d	1.8
3	C	149.6		
4	C	146.4		
5	CH	116.7	7.10 d	8.4
6	CH	119.5	6.94 dd	8.4/1.8
7	CH	130.1	6.54 d	16.1
8	CH	127.7	6.27 dt	15.8/5.6
9	CH_2	62.5	4.20 dd	5.6/1.3
3-OMe	CH_3	55.5	3.86 s	
Glucose				
1'	CH	101.5	4.89 d	7.8
2'	CH	73.7	3.46 m	
3'	CH	77.0	3.37 m	
4'	CH	70.1	3.37 m	
5'	CH	76.6	3.46 m	
6'	CH_2	61.3	3.86 m 3.69 dd	12.0/4.8

Oleanolic acid (6): EIMS m/z 456 $[M]^+$ (calc. for $C_{30}H_{48}O_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 5.24 (1H, t, J=3.6 Hz, H-12), 3.21 (1H, *dd*, J=10.2/4.4 Hz, H-3), 2.82 (1H, *dd*, J=12.7/4.3 Hz, H-18), 0.96 (3H, s, Me-23), 0.78 (3H, s, Me-24), 0.84 (3H, s, Me-25), 0.76 (3H, s, Me-26), 1.25 (3H, s, Me-27), 0.87 (3H, s, Me-29), 0.93 (3H, s, Me-30). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 38.6 (C-1), 26.7 (C-2), 78.5 (C-3), 39.2 (C-4), 55.5 (C-5), 18.3 (C-6), 32.6 (C-7), 39.6 (C-8), 48.1 (C-9), 37.0 (C-10), 22.7 (C-11), 122.4 (C-12), 144.1 (C-13), 42.0 (C-14), 27.7 (C-15), 22.8 (C-16), 46.7 (C-17), 41.5 (C-18), 46.1 (C-19), 30.4 (C-20), 33.7 (C-21), 32.3 (C-22), 28.8 (C-23), 14.7 (C-24), 15.1 (C-25), 16.5 (C-26), 25.2 (C-27), 180.4 (C-28), 32.8 (C-29), 23.3 (C-30).

Ursolic acid (7): EIMS m/z 456 $[M]^+$ (calc. for $C_{30}H_{48}O_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 5.28 (1H, t, J=3.6 Hz, H-12), 3.21 (1H, *dd*, J=10.2/4.4 Hz, H-3), 2.18 (1H, d, J=11.7 Hz, H-18), 1.19 (1H, m, H_a-22), 2.00 (1H, *dd*, J=13.0/4.0 Hz, H_b-22), 1.25 (3H, s, Me-23), 0.98 (3H, s, Me-24), 0.77 (3H, s, Me-25), 1.08 (3H, s, Me-26), 1.14 (3H, s, Me-27), 0.93 (3H, d, J=6.5 Hz, Me-29), 0.91 (3H, d, J=5.9 Hz, Me-30). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 39.2 (C-1), 27.5 (C-2), 78.5 (C-3), 38.7 (C-4), 55.5 (C-5), 18.3 (C-6), 33.1 (C-7), 39.6 (C-8), 47.8 (C-9), 36.9 (C-10), 16.6 (C-11), 125.7 (C-12), 138.4 (C-13), 41.7 (C-14), 29.5 (C-15), 24.1 (C-16), 47.7 (C-17), 53.1 (C-18), 39.2 (C-19), 39.2 (C-20), 30.5 (C-21), 36.9 (C-22), 28.0 (C-23), 15.2 (C-24), 14.8 (C-25), 16.4 (C-26), 23.1 (C-27), 180.4 (C-28), 22.9 (C-29), 22.8 (C-30).

Table 3. ^{13}C-NMR (DMSO-d$_6$, 100 MHz) and ^{1}H-NMR (DMSO-d$_6$, 400 MHz) spectroscopic data of compounds **4** and **5**.

	4				**5**			
C/H Aglycone	DEPT	δ_C	δ_H	J(Hz)	DEPT	δ_C	δ_H	J(Hz)
2	C	164.9			C	165.0		
3	CH	103.5	6.80 s		CH	103.6	6.84 s	
4	C	182.6			C	182.6		
5	C	162.4			C	162.5		
6	CH	100.2	6.42 d	1.8	CH	100.1	6.42 d	2.2
7	C	163.7			C	163.6		
8	CH	95.3	6.77 d	1.8	CH	95.5	6.81 d	2.2
9	C	157.6			C	157.6		
10	C	105.9			C	106.0		
1'	C	121.3			C	121.3		
2'	CH	129.4	7.87 d	8.8	CH	129.3	7.93 d	9.1
3'	CH	116.7	6.88 d	8.8	CH	116.7	6.90 d	8.8
4'	C	161.7			C	161.7		
5'	CH	116.7	6.88 d	8.8	CH	116.7	6.90 d	8.8
6'	CH	129.4	7.87 d	8.8	CH	129.3	7.93 d	9.1
Glucuronic acid					Glucose			
1"	CH	100.3	5.05 d	7.3	CH	100.5	5.05 d	7.3
2"	CH	73.6	3.13-3.40 m+		CH	73.7	3.14-3.39 m+	
3"	CH	77.2	3.13-3.40 m+		CH	77.8	3.14-3.39 m+	
4"	CH	72.6	3.13-3.40 m+		CH	70.2	3.14-3.39 m+	
5"	CH	74.4	3.61 d	10.3	CH	77.1	3.14-3.39 m+	
6"	C	172.6			CH_2	61.2	3.55 dd 3.73 dd	11.9/6.2 11.6/1.8

+: overlapped signals

β-sitosterol (8): EIMS m/z 414 $[M]^+$ (calc. for $C_{29}H_{50}O$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.52 (1H, m, H-3), 2.25 (2H, m, H-4), 5.35 (1H, m, H-6), 0.69 (3H, s, Me-18), 1.01 (3H, s, Me-19), 0.92 (3H, d, J=6.4 Hz, Me-21), 0.83 (3H, d, J=6.8 Hz, Me-26), 0.81 (3H, d, J=6.9 Hz, Me-27), 0.85 (3H, t, J=7.8 Hz, Me-29). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 37.4 (C-1), 31.8 (C-2), 72.0 (C-3), 42.5 (C-4), 140.9 (C-5), 121.9 (C-6), 32.1 (C-7), 32.1 (C-8), 50.3 (C-9), 36.7 (C-10), 21.3 (C-11), 39.9 (C-12), 42.5 (C-13), 56.9 (C-14), 24.5 (C-15), 28.4 (C-16), 56.2 (C-17), 12.0 (C-18), 19.6 (C-19), 36.3 (C-20), 19.0 (C-21), 34.1 (C-22), 26.2 (C-23), 46.0 (C-24), 29.3 (C-25), 20.0 (C-26), 19.2 (C-27), 23.2 (C-28), 12.2 (C-29).

Discussion

The methanol extract of the aerial parts of *Nepeta heliotropifolia* was suspended in water and extracted with n-hexane, $CHCl_3$, EtOAc, and n-BuOH, consecutively. From these extracts 8 known compounds were

isolated by various chromatographic techniques: 2 iridoid glycosides, ixoroside (**1**) and nepetanudoside B (**2**); 1 phenylpropanoid glycoside, coniferine (**3**); 2 flavone glycosides, apigenin 7-*O*-glucuronide (**4**) and apigenin 7-*O*-glucopyranoside (**5**); 2 triterpenes, oleanolic acid **(6)** and ursolic acid **(7)**; and 1 sterol, β-sitosterol **(8)** (Figures 1 and 2). The structures of the isolated compounds were elucidated by 1D- and 2D-NMR (HMBC, HMQC and NOESY), UV, and EIMS.

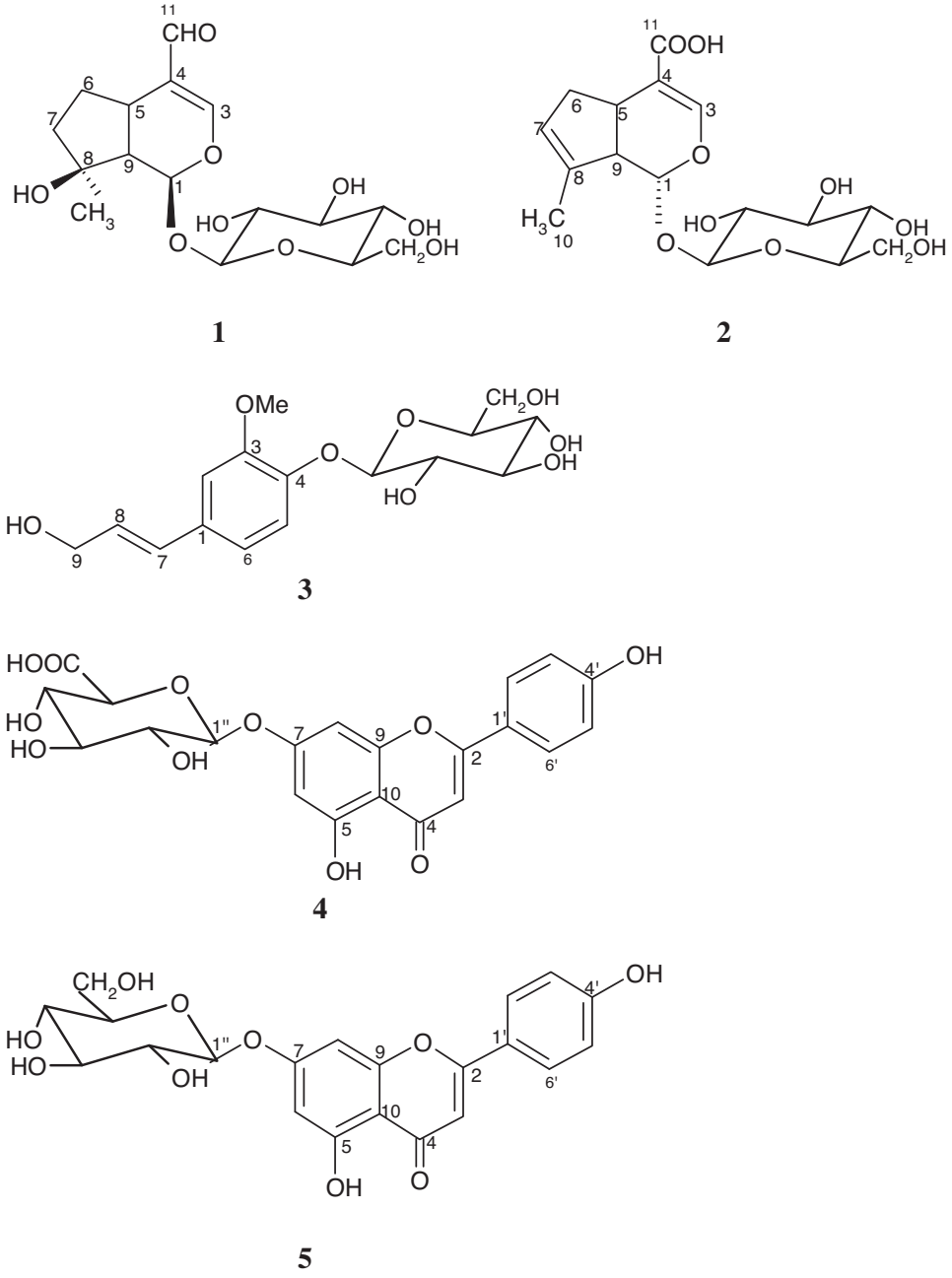

Figure 1. Isolated compounds (**1-5**) from *Nepeta heliotropifolia*.

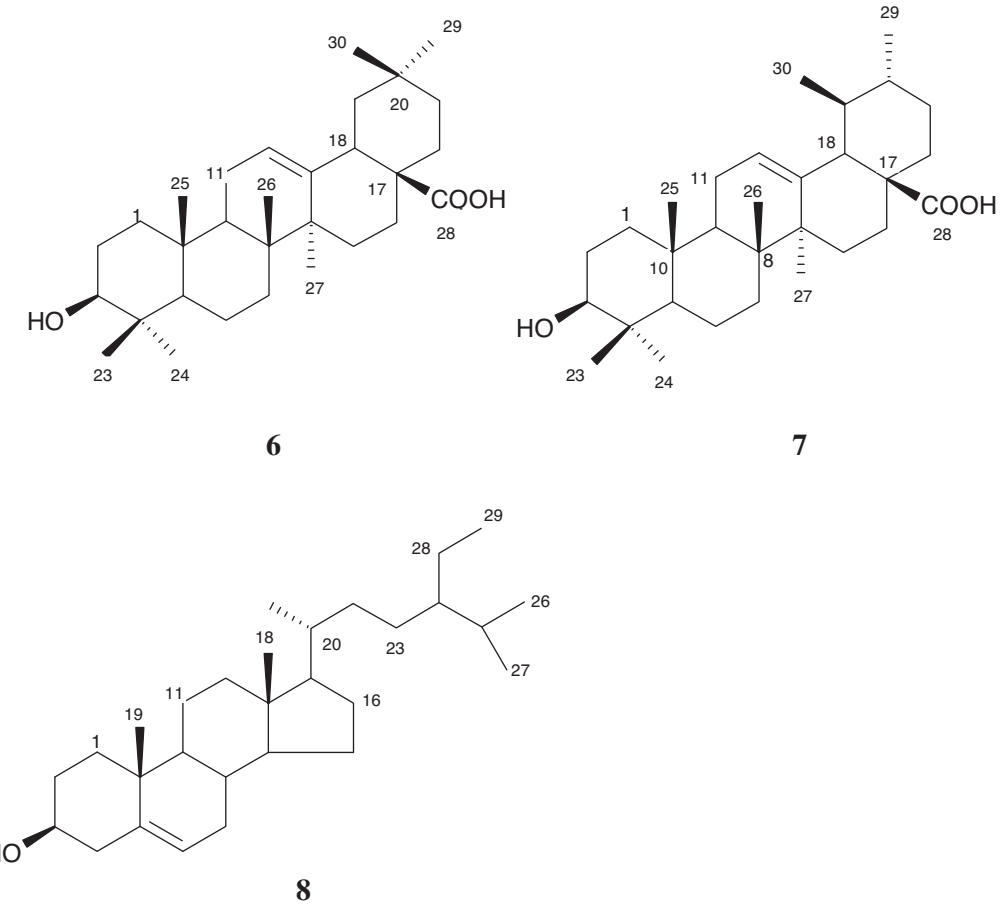

Figure 2. Isolated compounds (**6-8**) from *Nepeta heliotropifolia.*

The UV and IR spectra of compounds **1** and **2** showed the presence of a conjugated enol-ether system. The ^{1}H-NMR spectrum of compound **1** contained signals due to an acetal proton (δ_H 5.38), an olefinic proton (δ_H 7.40), an α,β-unsaturated aldehyde proton (δ_H 9.16), 2 methines (δ_H 2.22, 2.88), 2 methylenes (δ_H 1.31 and 2.08; δ_H 1.43 and 1.57), and a tertiary methyl proton (δ_H 1.15). Additional signals in the region of δ_H 2.90 and 3.63 (6H) accompanied by an anomeric proton resonance at δ_H 4.45 (d, J=8.1 Hz) showed that compound **1** contained a β-glucopyranosyl unit. The ^{13}C-NMR spectrum of compound **1** displayed 16 signals, 6 of which could be attributed to a β-glucopyranosyl unit and 10 of which were ascribed to a cyclopentanpyran ring system. The connectivities of the molecular fragments were established by a hetero-nuclear multiple-bond correlation experiment (HMBC). On the other hand, the chemical shift values of C-8 and H_3-10 indicated the presence of a tertiary hydroxyl group at the C-8 position. Based on the spectral data, compound **1** was established as ixoroside.[22]

The ^{1}H-NMR spectrum of compound **2** showed signals due to an acetal proton (δ_H 5.13), 2 olefinic protons (δ_H 7.50, 5.48), 2 methines (δ_H 2.72, 3.03), 1 methylene proton (δ_H 2.08 and 2.72), and 1 methyl proton (δ_H 1.84). In addition, the presence of signals at δ_H 3.24, 3.84 (6H) and δ_H 4.59 (d, J=7.8 Hz) were consistent with a β-glucopyranosyl unit. The ^{13}C-NMR spectrum of compound **2** was almost identical to that of **1** and exhibited characteristic signals for an iridoid structure with a 10-carbon skeleton and a β-glucopyranosyl

unit. According to its NMR data and a comparison with those given in the literature, the structure of **2** was established as nepetanudoside B.[5]

Compound **3** was obtained as an amorphous powder. The ^{1}H-NMR spectrum of compound **3** showed signals due to 3 aromatic protons (δ_H 6.94, 7.06, and 7.10), 2 olefinic protons (δ_H 6.27, 6.54), 1 methylene proton (δ_H 4.20), and 1 methoxyl proton (δ_H 3.86). In addition, the presence of signals at δ_H 3.37, 3.69 (6H) and δ_H 4.89 (d, J= 7.8 Hz) were consistent with a β-glucopyranosyl unit. The ^{13}C-NMR spectrum of compound **3** displayed 16 signals, 6 of which could be attributed to a β-glucopyranosyl unit and 1 to a methoxyl unit, while 9 were ascribed to a phenylpropanoid system. The connectivities of the molecular fragments were established by a hetero-nuclear multiple-bond correlation experiment (HMBC). According to its NMR data and a comparison with those given in the literature, the structure of **3** was established as coniferine.[23,24]

Compounds **4** and **5** were obtained as a yellowish powder. Their structures were identified as apigenin 7-O-glucuronide[25,26] and apigenin 7-O-glucopyranoside,[27] respectively, by comparing their ^{1}H- and ^{13}C-NMR data with previously published data and by direct comparison with the authentic samples on a TLC plate.

Compounds **6, 7**, and **8** were obtained as a white powder. Their structures were identified as oleanolic acid[28], ursolic acid,[29] and β-sitosterol,[30] respectively, by comparing their ^{1}H- and ^{13}C-NMR data with previously published data.

To our knowledge, nepetanudoside B,[5] apigenin 7-O-glucuronide,[21] apigenin 7-O-glucopyranoside,[21] oleanolic acid,[6,7,11,15] ursolic acid,[6,7,11,15] and β-sitosterol[6,7,11] have been reported from different *Nepeta* species. This study is the first report on the isolation and structure elucidation of coniferin from *Nepeta* species and ixoroside from the family Lamiaceae.

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