Acta Pharmaceutica Turcica
44:195- 203 (2002)

Iridoid, Phenylethanoid and Flavonoid Glycosides from *Phlomis sintenisii*

Phlomis sintenisii'den Elde Edilen İridoit, Feniletanoit ve Flavonoit Glikozitleri

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Abstract

From the overground parts of *Phlomis sintenisii*, three iridoid glucosides, lamiide (**1**), auroside (**2**) and ipolamiide (**3**), four phenylethanoid glycosides, verbascoside (= acteoside) (**4**), martynoside (**5**), isomartynoside (**6**) and forsythoside B (**7**) as well as two flavon diglycosides, stachyspinoside (**8**) and chrysoeriol 7-*O*-β-D-allopyranosyl-(1→2)-β-D-glucopyranoside (**9**) were isolated. The structures of the isolated compounds were elucidated by means of spectroscopic (UV, IR, HR-MALDI MS, 1D- and 2D-NMR) evidence.

Key words: *Phlomis sintenisii*, iridoids, phenylethanoids, flavonoids.

Introduction

Some members of the genus *Phlomis* from Turkish flora are used as tonic and stimulant in Anatolian folk medicine (Baytop, 1999) and reported to possess medicinal properties (Saracoğlu *et al.*, 1995). Turkish *Phlomis* species are known to contain iridoids (Başaran *et al.*, 1991; Çalış *et al.*, 1990b and 1991; Ersöz *et al.*, 2001a-c and 2002a,b; Harput *et al.*, 1998 and 1999; Saracoğlu *et al.*, 1995 and 1997; Takeda *et al.*, 1999 and 2000), phenylethanoids (Çalış *et al.*, 1990a,b and 1991; Ersöz *et al.*, 2001a-c and 2002a,b; Harput *et al.*, 1998 and 1999; Saracoğlu *et al.*, 1995, 1997, 1998 and 2002; Takeda *et al.*, 1999), lignans (Ersöz *et al.*, 2002b), neolignans (Ersöz *et al.*, 2002c; Saracoğlu *et al.*, 2002), monomeric phenylpropanoids (Ersöz *et al.*, 2001a) and monoterpenes (Saracoğlu *et al.*, 1995; Ersöz *et al.*, 2002a). In continuation of our systematic investigation on the chemical constituents of Turkis *Phlomis* species, we now investigated *P. sintenisii* Rech. fil., an endemic herb growing in the steppes and volcanic hills at elevations of 930-1525 m in Eastern Anatolia (Huber-Morath, 1982). The present paper deals with the isolation and structure elucidation of the iridoid glucosides lamiide (**1**), auroside (**2**) and ipolamiide (**3**) as

well as the phenylethanoid glycosides, verbascoside (= acteoside) (4), martynoside (5), isomartynoside (6) and forsythoside B (7) together with the flavon diglycosides, stachyspinoside (8) and chrysoeriol 7-*O*-β-D-allopyranosyl-(1→2)-β-D-glucopyranoside (9) from the aerial parts of the title plant.

Materials and Methods

General Experimental Procedures

The UV (MeOH) spectra were recorded on a Hitachi HP 8452 A spectrophotometer. The FTIR (KBr) spectra were determined on a Perkin-Elmer 2000 FTIR spectrophotometer. NMR mesurements in CD_3OD at room temperature were measured using Bruker AMX 300 spectrometer (^1H: 300.13 and ^{13}C: 75.5 MHz). Positive mode HR-MALDI MS data were taken on a ionspec-Ultima-FTMS instrument with DHB as matrix substance. Polyamide (Polyvinyl-polypyrrolidone, D^R BENDER+D^R HOBEIN AG, No. P-6755) and silica gel 60 (0.063-0.200 mm, Merck) were used for open column chromatography. Middle-pressure liquid chromatography (MPLC) was performed on a Büchi 681 glass column (2.5x46 cm) packed with LiChroprep RP-18 (Merck) using a Lewa M5 peristaltic pump. Vacuum-liquid chromatography (VLC) was realized on a glass column (4.7x47 cm) packed with silica gel 60 (0.063-0.200 mm, Merck). TLC analyses were carried out on pre-coated silica gel 60 F_{254} aluminium sheets (Merck). Compounds were detected by UV fluorescence and spraying 1% vanilin/H_2SO4, followed by heating at 105 °C for 1-2 min.

Plant Material

Phlomis sintenisii Rech. fil. was collected from Elazığ, between Maden and Elazığ, steppe, 1260 m (E. Anatolia, Turkey), in June 2001. Voucher specimens have been deposited in the Herbarium of the Biology Department, Hacettepe University, Ankara, Turkey (HUB 9409).

Extraction and Isolation

The air dried and powdered aerial parts of *P. sintenisii* (250 g) were maserated with MeOH (2500 ml) overnight and extracted with MeOH at 40 °C. After filtration, the plant material was extracted with MeOH (2000 ml) at 40 °C for the second time. The combined methanolic extracts were evaporated under reduced pressure to obtain the crude methanolic extract (38 g). The resultant methanolic extract was dissolved in H_2O (50 ml) and the water soluble portion was succesively extracted with $CHCl_3$ (4x100 ml). The remaining water phase was then lyophilized (23.7 g) and applied to silica gel-VLC (200 g). Elution with $CHCl_3$-MeOH-H_2O mixtures (80:20:1→50:50:5) and MeOH gave 6 main fractions (Frs. A-F). Fr. B (799 mg) which were fractionated by MPLC eluting with MeOH-H_2O mixtures (20-100%) to yield 14 fractions (frs. B_1-B_{14}). Fr. B_{12} (32 mg) was rechromatographed over silica gel CC (12.5 g) with CH_2Cl_2-MeOH-H_2O mixtures (80:20:1→80:20:2) to give compound **5** (10 mg). 1.0 g of fr. C was subjected to MPLC eluting with MeOH-H_2O mixtures (10-100%) to yield compounds **1** (19.6 mg), **2** (12 mg) and **3** (130.5 mg). Fr. D (1.72 g) was subjected to polyamide CC (20 g). Elution with H_2O and MeOH-H_2O mixtures (25-100% MeOH) afforded compounds **4** (82 mg) and **6** (10 mg) as well as a fraction (fr. D_8, 170 mg) rich in compounds **8** and **9**. Fr. D_8 (170 mg) was then applied to silica gel CC (25 g) and eluted with EtOAc-MeOH-H_2O mixture (100:10:5) to collect 34 fractions (Frs. $D_{8\text{-}1}$-$D_{8\text{-}34}$). Compound **8** (9.6 mg) was then chrystallized from frs. $D_{8\text{-}9}$-$D_{8\text{-}14}$ whereas, compound **9** (4 mg) was isolated from frs. $D_{8\text{-}26}$-$D_{8\text{-}34}$ in pure form. An aliquot of Fr. E (4.0 g) was

fractionated by MPLC eluting with H_2O, *i*-PrOH-H_2O mixtures (5-40% *i*-PrOH) and MeOH to afford compound 7 (440 mg).

Results

Lamiide (1): UV, IR, ^1H (300.13 MHz, CD_3OD), and ^{13}C (75.5 MHz, CD_3OD) NMR data were identical to those reported in the literature (Başaran, 1991; Ersöz *et al.*, 2001a, Saracoğlu *et al.*, 1997).
Auroside (2): UV, IR, ^1H (300.13 MHz, CD_3OD), and ^{13}C (75.5 MHz, CD_3OD) NMR data were identical to those reported in the literature (Harput *et al.*, 1999).
Ipolamiide (3): UV, IR, ^1H (300.13 MHz, CD_3OD), and ^{13}C (75.5 MHz, CD_3OD) NMR data were identical to those reported in the literature (Ersöz *et al.*, 2002a).
Verbascoside (4): UV, IR, ^1H (300.13 MHz, CD_3OD), and ^{13}C (75.5 MHz, CD_3OD) NMR data were identical to those reported in the literature (Ersöz *et al.*, 2001a; Harput *et al.*, 1999).
Martynoside (5): UV, IR, ^1H (300.13 MHz, CD_3OD), and ^{13}C (75.5 MHz, CD_3OD) NMR data were identical to those reported in the literature (Çalış *et al.*, 1984).
Isomartynoside (6): UV, IR, ^1H (300.13 MHz, CD_3OD), and ^{13}C (75.5 MHz, CD_3OD) NMR data were identical to those reported in the literature (Çalış *et al.*, 1984).
Forsythoside B (7): UV, IR, ^1H (300.13 MHz, CD_3OD), and ^{13}C (75.5 MHz, CD_3OD) NMR data were identical to those reported in the literature (Ersöz *et al.*, 2001; Harput *et al.*, 1999; Saracoğlu *et al.*, 1997).
Stachyspinoside (8): UV λ_{max} (MeOH) nm: 269, 344; (NaOMe): 259, 406; ($AlCl_3$): 275,367; ($AlCl_3$+HCl): 276, 346, 361; (NaOAc); 267, 345, 412 (sh); (NaOAc+H_3BO_3): 268, 344; IR $\upsilon_{max.}$ (KBr) cm^{-1}: 3384 (OH), 1714 (est. C=O), 1661 (γ-pyrone C=O), 1608, 1508 (arom. ring); ^1H NMR (300.13 MHz, DMSO-d_6) (*see* Table 1); ^{13}C NMR (75.5 MHz, DMSO-d_6) (*see* Table 1); HR-MALDI positive ion mode (DHB matrix): 689 $[M+Na]^+$, 667 $[M+H]^+$.
Chrysoeriol 7-*O*-β-D-allopyranosyl-(1→2)-β-D-glucopyranoside (9): UV λ_{max} (MeOH) nm: 269, 345; (NaOMe): 260, 407; ($AlCl_3$): 275, 298 (sh),389; ($AlCl_3$+HCl): 277,299 (sh), 390; (NaOAc); 268, 345, 412 (sh); (NaOAc+H_3BO_3): 270, 345; IR $\upsilon_{max.}$ (KBr) cm^{-1}: 3452 (OH), 1654 (γ-pyrone C=O), 1604, 1544, 1508 (arom. ring);^1H NMR (300.13 MHz, DMSO-d_6) (*see* Table 1); ^{13}C NMR (75.5 MHz, DMSO-d_6) (*see* Table 1).

Discussion

Water soluble part of the methanolic extract prepared from the aerial parts of *P. sintenisii* on repeated CC (polyamide and silica gel), MPLC and VLC furnished compounds **1-9** (Fig. 1). Compounds **1-7** were identified by direct comparison with the authentic samples on TLC and by comparing their physical and spectroscopic data with those reported in the literature and as lamiide (1) (Başaran, 1991; Ersöz *et al.*, 2001a, Saracoğlu *et al.*, 1997). auroside (2) (Harput *et al.*, 1999), ipolamiide (3) (Ersöz *et al.*, 2002a), verbascoside (= acteoside) (4) (Ersöz *et al.*, 2001a; Harput *et al.*, 1999), martynoside (5) (Çalış *et al.*, 1984), isomartynoside (6) (Çalış *et al.*, 1984) and forsythoside B (7) (Ersöz *et al.*, 2001; Harput *et al.*, 1999; Saracoğlu *et al.*, 1997). The structure elucidation of compounds **8** and **9** were realized based on the following evidence.

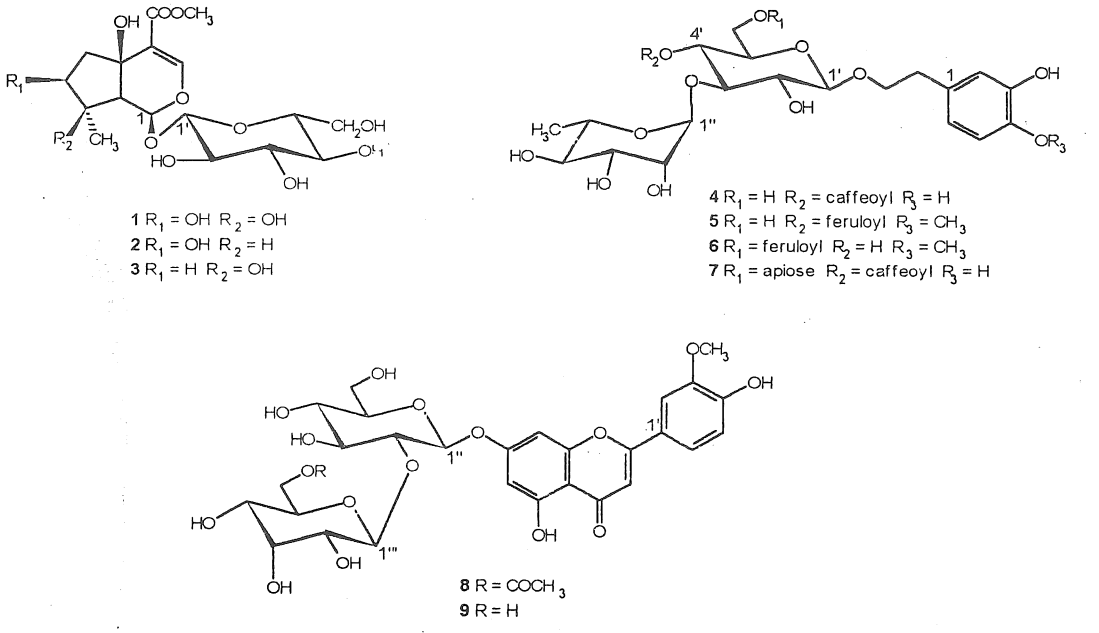
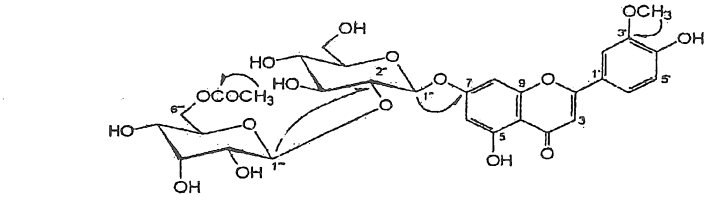


Figure 1. Compounds isolated from *Phlomis sintenisii*

Compound **8** was isolated as an amorphous yellow powder. Its ^{1}H and ^{13}C NMR spectra showed the presence of aromatic systems and sugar moieties. Using common shift reagents (Mabry *et al.*, 1970) UV (λ_{max} 269, 344 nm) spectroscopic data suggested that **8** was a flavone. The IR spectrum was characterized by the absorption bands for hydroxyl (3384 cm^{-1}), ester carbonyl (1714 cm^{-1}), γ-pyrone carbonyl (1661 cm^{-1}) and aromatic rings (1608, 1508 cm^{-1}). The positive ion mode HR-MALDI mass spectrum showed a molecular ion peak at *m/z* 689 $[M+Na]^{+}$, consistent with the molecular formula $C_{30}H_{34}O_{17}$. In the ^{1}H NMR spectrum of compound **8** (Table 1) three aromatic proton resonances at δ_H 7.58 (2H, H-2'/H-6') and 6.94 (d, J = 8.2 Hz, H-5') indicated the 3',4'-disubstitution pattern of ring B. Moreover, two signals in the aromatic region appeared as *meta*-coupled doublets at δ_H 6.44 (J = 2.0 Hz, H-6) and 6.80 (J = 2.0 Hz, H-8) were consistent with a 5,7-dihydroxy substituted A ring of a flavonoid. Singlet signals at δ_H 6.98 (1H) and 3.88 (3H) were readily attributed to H-3 and a methoxyl group, respectively. Additionally, the proton signal appeared at δ_H 1.93 (s, 3H) was assigned to a acetoxymethyl function. Two anomeric proton signals at δ_H 5.21 (d, J = 7.2 Hz) and 4.78 (d, J = 7.9 Hz) indicated the presence of two sugar units which, according to UV and ^{1}H NMR spectroscopic data, were attached to C-7. The complete interpretation of the NMR data was based on the ^{1}H-^{1}H DQF-COSY, ^{1}H-^{13}C HSQC and HMBC (Fig. 2) experiments. Thus, the NMR data of **8** indicated the presence of chrysoeriol as aglycone (Markham and Chari, 1982; Markham and Geiger, 1994). The ^{13}C NMR and DEPT-135 spectra of compound **8** showed 30 carbon resonances (10 C, 16 CH, 2 CH_2, and 2 CH_3), 16 of which could be assigned to chrysoeriol and 2 for an acetyl function (δ_C 170.4 and 20.6). The remaining 12 resonances revealed the presence of two hexose units

in 8. The structure of the disaccharide unit was elucidated using DQF-COSY and HSQC experiments. Thus, on the basis of the chemical shifts, multiplicity of the signals and absolute values of the coupling constants, two sugar residues were identified as β-glucopyranosyl (Agrawal, 1989; Markham and Geiger, 1994) and β-allopyranosyl (Chari *et al.*, 1981). Although, a 9.5 ppm downfield shift of C-2" (δ_C 82.8) resonance of glucose suggested that the allose to be placed at this position, however, the position of each sugar residue was unambiguously determined by the HMBC experiment which showed long-range correlations between the anomeric proton of allose (δ_H 4.78, H-1''') and C-2" of glucose, the anomeric proton of glucose (δ_H 5.21, H-1") and C-7 (δ_C 162.8) of chrysoeriol. Additionally, H_2-6''' [δ_H 4.10 (br d, J = 11.7 Hz and 3.98 (dd, J = 11.7, 5.5 Hz)] and C-6''' (δ_C 64.0) resonances of allose were shifted downfield indicating that the hydroxyl group at C-6'''(OH) of allose was involved in the ester linkage. On the other hand, the methoxyl singlet at δ_H 3.88 was correlated with C-3' carbon resonance at δ_C 148.1 showing the attachment of the methoxyl group at C-3' of ring B.



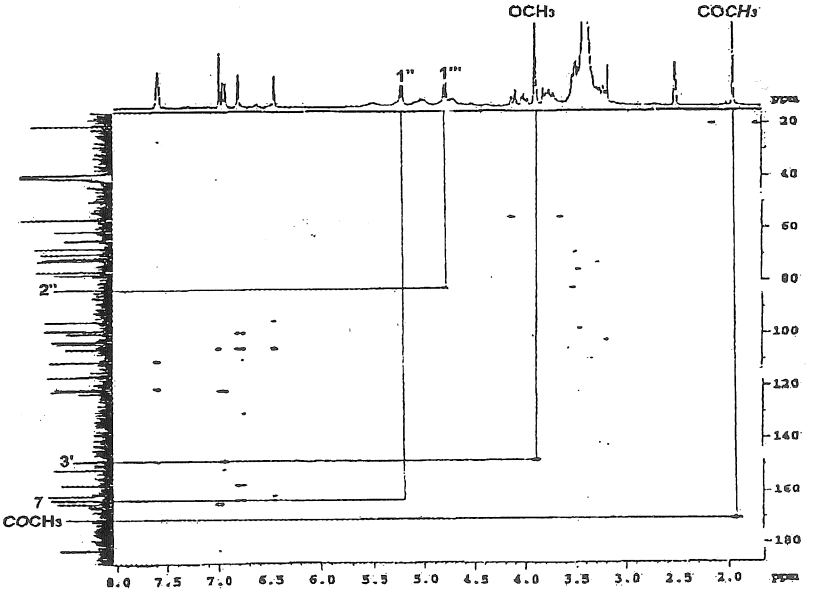


Figure 2. ^1H-^{13}C HMBC spectrum for **8**. Arrows point from H to C

Table 1. ^{13}C and ^{1}H NMR (DMSO-d_6, ^{13}C: 75.5 MHz; ^{1}H: 300.13 MHz) spectroscopic data[a] of stachyspinoside (**8**) and chrysoeriol 7-*O*-β-D-allopyranosyl-(1→2)-β-D-glucopyranoside (**9**) and HMBC correlations of stachyspinoside (**8**)

C/H Atom		**8**			**9**	
		δ_C ppm	δ_H ppm, *J*(Hz)	HMBC (H→C)	δ_C ppm	δ_H ppm, *J* (Hz)
Aglycone						
2	C	164.2			164.2	
3	CH	103.5	6.98 s	C-2, C-10, C-1'	103.5	6.90 s
4	C	182.1			182.1	
5	C	161.2			161.1	
6	CH	99.5	6.44 d (2.0)	C-5, C-7, C-8,C-10	99.8	6.46 d (2.0)
7	C	162.8			162.9	
8	CH	95.0	6.80 d (2.0)	C-6, C-7, C-9,C-10	95.0	6.90 d (2.0)
9	C	156.9			156.9	
10	C	105.4			105.5	
1'	C	122.3			122.4	
2'	CH	110.2	7.58 †	C-3', C-6'	110.0	7.50 d (2.0)
3'	C	148.1			148.1	
4'	C	151.0			151.0	
5'	CH	115.8	6.94 d (8.9)	C-1', C-3'	116.0	6.84 d (8.0)
6'	CH	120.5	7.58 †	C-2'	120.6	7.58 dd (8.0, 2.0)
3'-OCH_3	CH_3	56.0	3.88 s	C-3'	56.0	3.88 s
Glucose						
1''	CH	98.4	5.21 d (7.2)	C-7	98.1	5.15 d (7.2)
2''	CH	82.8	3.43 †		82.8	
3''	CH	75.8	3.48 †		75.8	
4''	CH	69.2	3.22 †		69.2	
5''	CH	77.1	3.48 †		77.1	
6''	CH_2	60.5	3.72 br d (11.5)		61.5	
			3.45 †			
Allose						
1'''	CH	102.6	4.78 d (7.9)	C-2''	102.2	4.78 d (7.9)
2'''	CH	71.7	3.18 dd (7.9, 2.3)		71.9	
3'''	CH	70.9	3.85 †		70.9	
4'''	CH	67.1	3.30 †		67.3	
5'''	CH	71.5	3.75 †		74.6	
6'''	CH_2	64.0	4.10 br d (11.7)		61.5	
			3.98 dd (11.7,5.5)			
$COCH_3$	CH_3	20.6	1.93 s	C=O		
$COCH_3$	C	170.4				

[a]All carbon and proton resonances were assigned on the basis of 2D NMR (DQF-COSY, HSQC ve HMBC) experiments

† Signal pattern unclear due to overlapping

Compound 9 was isolated as an amorphous yellow powder. It showed similar UV spectrum ($\lambda_{max.}$ 269, 345 nm) to that of compound 8, indicating the presence of a flavon structure. However, the characteristic ester carbonyl absorption band shown for 8 was disappeared in the IR spectrum of 9. The ^{1}H and ^{13}C NMR data of compound 9 (Table 1) were essentially identical to that of 8 indicating the similar structural features and glycosidation pattern, except for the absence of the resonances due to an acetoxy function in allose unit. Thus, 9 appeared to be a deacyl derivative of compound 8. This assumption was provided by the chemical shift value of C-6''' (δ_C 61.5) resonance of the allose moiety, exhibiting no unusual shift due to an acylation. Therefore, compound 9 was identified as chrysoeriol 7-*O*-β-D-allopyranosyl-(1→2)-β-D-glucopyranoside. This compound, previously isolated from *Sideritis grandiflora* (Lamiaceae) (Rabanal *et al.*, 1982) however, being reported in a member of the genus *Phlomis* for the first case.

Özet

Phlomis sintenisii'nin toprak üstü kısımlarından üç iridoit glukoziti, lamiit (1), aurozit (2), ipolamiit (3), dört feniletanoit glikoziti, verbaskozit (= akteozit) (4), martinozit (5), izomartinozit (6) ve forsitozit B (7) yanında iki flavon diglikoziti, stakispinozit (8) ve krizoeriyol 7-*O*-β-D-allopiranozil-(1→2)-β-D-glukopiranozit (9) elde edilmiştir. Elde edilen bileşiklerin yapıları spektroskopik (UV, IR, HR-MALDI MS, 1D- ve 2D-NMR) yöntemler kullanılarak aydınlatılmıştır.

Acknowledgments

Financial supports by the Turkish Scientific and Technical Research Council (TÜBİTAK) and Bulgarian Academy of Science (BAS) are gratefully acknowledged. The authors also thank Dr. Oswald Grater and Dr. Walter Amrein (ETHZ) for recording HR-MALDI mass spectra.

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Accepted: 1.11.2002