New Guaianolide-Type Sesquiterpene Lactones from *Inula verbascifolia*

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The aerial parts of *Inula verbascifolia* afforded two new guaianolide-type sesquiterpene lactones. Their structures were determined by spectroscopic methods (IR, MS, ¹H NMR, ¹³C NMR, DEPT, ¹H-¹H COSY, HMQC, and HMBC).

Key words: Asteraceae, *Inula*, Sesquiterpene Lactones

Introduction

The genus *Inula* (family Asteraceae, tribe Inuleae) with about 80–100 species represents a poorly delineated complex (Merxmüller *et al.*, 1977). Chemical investigations of some members of the genus showed that there are two main groups, one containing simple sesquiterpene lactones, especially eudesmanolides, and the second containing simple thymol derivatives (Bohlmann and Zdero, 1977). Plants of the genus *Inula* have been shown to contain high levels of sesquiterpene lactones and have recently received considerable attention due to their antineoplastic and anti-inflammatory effects (Cheng *et al.*, 2011; Harvala *et al.*, 2002; Hua *et al.*, 2012; Kang *et al.*, 2004; Konishi *et al.*, 2002; Li *et al.*, 2012; Qin *et al.*, 2012; Won *et al.*, 2004; Chia and Hsin, 2007). In continuation of our investigation of the medicinal plants of the Asteraceae family (Ahmed *et al.*, 2003), we investigated the chemical constituents of *I. verbascifolia* (Willd.) Hausskn. subsp. *methanea* (Hausskn.) Tutin, which is endemic in Central and South Greece (Ball and Tutin, 1976).

Results and Discussion

The methylene chloride extract of the air-dried aerial parts of *Inula verbascifolia* was chromatographed on silica gel and Sephadex LH-20

columns to give two new sesquiterpenes, **1** and **2**. Compound **1** was obtained as a yellowish oil, $[\alpha]_D^{25} = -20.88^\circ$ (*c* 0.015, MeOH), and its IR spectrum showed absorption bands at 3471 cm⁻¹ (OH) and 1763 cm⁻¹ (C=O). Complete structural information was obtained from ¹H NMR, ¹³C NMR, DEPT, ¹H-¹H COSY, HMQC, HMBC, NOESY, and mass spectra. The ESITOF mass spectrum of **1** exhibited a molecular ion peak [M+Na]⁺ at *m/z* 271 and the exact mass was determined at *m/z* 271.1310, establishing the elemental composition C₁₅H₂₀O₃Na, confirming that the molecular formula of **1** is C₁₅H₂₀O₃. Two fragments were apparent at *m/z* 230 and 215 resulting from loss of a water molecule and a methyl group, respectively, while the two fragments at *m/z* 202 and 201 were attributed to the loss of CO and CHO groups, respectively. The ¹H and ¹³C NMR spectroscopic data of **1** established the presence of a guaianolide-type sesquiterpene. The ¹H NMR spectrum indicated the presence of an olefinic proton at δ_H 5.85 ppm (d, *J* = 7.6 Hz, H-9) and an olefinic methyl group at δ_H 1.74 ppm (s, H-14). A secondary methyl carbon atom appeared at δ_H 1.12 ppm (d, *J* = 6.9 Hz), and correlated with a methyl carbon signal at δ_C 12.20 ppm in HMQC, C-13, and with a multiplet signal at δ_H 2.24 ppm (1H, m) in ¹H-¹H COSY, H-11, suggesting an α -methyl- γ -lactone. Moreover, the examination of

the connectivities in the ^1H - ^1H COSY spectrum of compound **1** indicated strong correlations between the signal at δ_{H} 4.58 ppm (1H, t, $J = 10.2$ Hz, H-6) with the signals at δ_{H} 2.42 ppm (1H, dd, $J = 10.2, 7.9$ Hz, H-5) and 1.87 ppm (1H, t, $J = 11.5$ Hz, H-7), suggesting the presence of a C5H-C6H(O)-C7H moiety. Additionally, the signal at δ_{H} 4.24 ppm (1H, d, $J = 7.6$ Hz, H-8) correlated with two signals at δ_{H} 1.87 ppm (1H, t, $J = 11.5$ Hz, H-7) and 5.85 ppm (1H, d, $J = 7.6$ Hz, H-9), indicating the presence of a C7(H)-C8H(O)-C9H moiety. Accordingly, compound **1** contained a C5H-C6H(O)-C7H-C8H(O)-C9H moiety. The ^{13}C NMR spectroscopic data revealed 15 carbon atoms while their multiplicities (by DEPT analysis) confirmed the number of hydrogen atoms of the formula given above. The carbon atoms were assigned as two methyl, three methylene, seven methine, and three quaternary carbon atoms. The other proton and carbon signals are listed in the Table I. Moreover, all proton and carbon signals were determined by ^1H - ^1H COSY, HMQC, and HMBC. The connectivities of the moieties, the position of the hydroxy group, and the lactonization were established by the HMBC spectrum, the most important correlations were found be-

tween: H-1 (δ_{H} 2.90 ppm) with C-2 (δ_{C} 28.99 ppm), C-5 (δ_{C} 50.91 ppm), C-6 (δ_{C} 81.74 ppm), C-9 (δ_{C} 126.92 ppm), C-10 (δ_{C} 144.87 ppm), and H-6 (δ_{H} 4.58 ppm) with C-4 (δ_{C} 149.81 ppm), C-8 (δ_{C} 63.43 ppm), C-11 (δ_{C} 37.62 ppm), and H-7 (δ_{H} 1.87 ppm) with C-5 (δ_{C} 50.91 ppm), C-11 (δ_{C} 37.62 ppm), C-13 (δ_{C} 12.20 ppm), and H-14 (δ_{H} 1.74 ppm) with C-1 (δ_{C} 44.61 ppm), C-9 (δ_{C} 126.92 ppm), C-10 (δ_{C} 144.87 ppm), and H-15 (δ_{H} 5.05, 5.43 ppm) with C-3 (δ_{C} 32.98 ppm), C-5 (δ_{C} 50.91 ppm). The relative stereochemistry of **1** was established from the coupling constants and NOESY experiments. The relative configuration and stereochemistry at C-5, C-6, and C-7 were derived from the coupling constants ($J_{5,6} = 10.2$ Hz and $J_{6,7} = 11.5$ Hz), which were in agreement with the *trans*-diaxial disposition of the protons at C-5 (α), C-6 (β), and C-7 (α). The NOESY experiments supported the proposed relative configuration by the following correlations: H-8 showed a cross-peak with H-11, whereas H-6 showed cross-peaks with H-1 and H-11, indicating the β -orientation of these protons. Furthermore, strong NOEs were observed between H-5, H-7, and H-2 (δ_{H} 1.68 ppm), suggesting the α -orientation of these protons (Papano *et al.*, 1980; Romo *et al.*, 1968).

Table I. ^1H NMR (600 MHz, CDCl_3) and ^{13}C NMR (125 MHz, CDCl_3) spectroscopic data of compounds **1** and **2**^a.

H	δ_{H} 1	HMBC correlations	δ_{H} 2	HMBC correlations	C	δ_{C} 1	δ_{C} 2
H-1 β	2.90 m	C-5, C-6, C-9, C-10	2.46 m	C-2, C-5, C-6, C-9, C-10	C-1	44.61	44.87
H-2 α	1.68 m	C-1, C-4, C-5	1.65 m	C-1, C-3, C-4, C-5, C-10	C-2	28.99	29.00
H-2 β	1.94 m	C-1, C-4, C-5	1.89 m	C-1, C-4, C-3, C-5, C-10	C-3	32.98	35.02
H-3 α	2.45 m	C-1, C-4, C-5	2.40 dd (14.6, 6.0)	C-1, C-4, C-5	C-4	149.81	152.12
H-3 β	2.32 m	C-4	2.27 m	C-1, C-4, C-5			
H-5 α	2.42 dd (10.2, 7.9)	C-4, C-6	2.02 t (10.0)	C-4, C-6, C-15	C-5	50.91	52.59
H-6 β	4.58 t (10.2)	C-4, C-5, C-8, C-11	3.57 t (10.0)	C-1, C-4, C-5, C-8, C-11	C-6	81.74	77.91
H-7 α	1.87 t (11.5)	C-11, C-13	1.82 dd (10.4, 10.0)	C-5, C-11, C-13	C-7	54.80	54.97
H-8 β	4.24 d (7.6)	C-6, C-7, C-9, C-10, C-11	4.81 d (8.6)	C-6, C-7, C-9, C-10	C-8	63.43	77.31
H-9	5.85 d (7.6)	C-1, C-7, C-8, C-14	5.74 brs	C-1, C-14	C-9	126.92	125.43
					C-10	144.87	139.92
H-11 β	2.24 m	C-8, C-13	2.57 m	C-6, C-7, C-13	C-11	37.62	42.00
					C-12	178.54	177.40
H-13 α	1.12 d (6.9)	C-7, C-11, C-12	1.42 d (7.0)	C-7, C-11, C-13	C-13	12.20	15.71
H-14	1.74 s	C-9, C-10	1.76 s	C-1, C-9, C-10	C-14	23.10	20.00
H-15a	5.05 s	C-4, C-5	5.02 s	C-3, C-5	C-15	110.75	109.81
H-15b	5.43 s	C-4	5.04 s	C-3, C-5			

^a TMS as internal standard. J in Hz.

Thus, compound **1** was identified as 8 α -hydroxy-5 α ,7 α H-guai-4(15),9(10)-dien-12,6 α -olide (Fig. 1), a new natural product.

Compound **2** was obtained as yellowish material. Its EI mass spectrum exhibited a significant molecular ion peak $[M]^+$ at m/z 248, consistent with the molecular formula $C_{15}H_{20}O_3$. The fragment ion at m/z 230 was due to the elimination of a water molecule, suggesting that compound **2** contains one hydroxy group. Its IR spectrum showed absorption bands indicative of a γ -lactone group (1754 cm^{-1}) and an aliphatic hydroxy group (3475 cm^{-1}). Careful inspection of the ^1H NMR spectrum revealed that compound **2** is a sesquiterpene with a guaiane skeleton. The ^1H NMR and ^{13}C NMR spectroscopic data of **2** were very similar to those of **1**, except that the signal of H-5 of **2** appeared at higher field, δ_{H} 2.02 ppm (1H, t,

$J = 10.0\text{ Hz}$, δ_{C} 52.59 ppm), than the H-5 signal of **1** (δ_{H} 2.42 ppm, δ_{C} 50.91 ppm), and H-6 of **2** appeared more up-field at δ_{H} 3.57 ppm (1H, t, $J = 10.0\text{ Hz}$, δ_{C} 77.91 ppm) than that of H-6 in **1** (δ_{H} 4.58 ppm, δ_{C} 81.74 ppm), suggesting that the free hydroxy group is located at C-6. Also, the presence of H-8 in compound **2** at δ_{H} 4.81 ppm (1H, d, $J = 8.6\text{ Hz}$, δ_{C} 77.31 ppm), down-field from the H-8 signal of **1** (δ_{H} 4.24 ppm, δ_{C} 63.43 ppm), indicated a C-7/C-8 *trans*-fused lactone ring. The other proton and carbon signals are listed in Table I. Moreover, all proton and carbon signals were determined by ^1H - ^1H COSY, HMQC, and HMBC. Again, the connectivities of the moieties, the position of the hydroxy group, and the lactonization were established by the HMBC spectrum of **2**, the most important correlations were found between: H-1 (δ_{H} 2.46 ppm) with C-2 (δ_{C} 29.00 ppm),

Compound **1** Compound **2**

Fig. 1. Chemical structures and 3D diagrams of compounds **1** and **2**.

C-5 (δ_C 52.59 ppm), C-6 (δ_C 77.91 ppm), C-9 (δ_C 125.43 ppm), C-10 (δ_C 139.92 ppm), and H-6 (δ_H 3.57 ppm) with C-4 (δ_C 152.12 ppm), C-8 (δ_C 77.31 ppm), C-11 (δ_C 42.00 ppm), and H-7 (δ_H 1.82 ppm) with C-5 (δ_C 52.59 ppm), C-11 (δ_C 42.00 ppm), C-13 (δ_C 15.71 ppm), and H-14 (δ_H 1.76 ppm) with C-1 (δ_C 44.87 ppm), C-9 (δ_C 125.43 ppm), C-10 (δ_C 139.92 ppm), and H-15 (δ_H 5.02, 5.04 ppm) with C-3 (δ_C 35.02 ppm), C-5 (δ_C 52.59 ppm). The relative stereochemistry of **2** was established from the coupling constants and NOESY experiments. The relative configuration and stereochemistry at C-5, C-6, and C-7 were derived from the coupling constants ($J_{5,6} = 10.0$ Hz and $J_{6,7} = 10.0$ Hz), indicating that the orientation of the protons is C-5 (α), C-6 (β), and C-7 (α). The NOESY experiments supported the proposed relative configuration; H-6 showed cross-peaks with H-1, H-8, and H-11, indicating the β -orientation of these protons. Moreover, strong NOEs were observed between H-5, H-7, and H-2 (δ_H 1.65 ppm), suggesting the α -orientation of these protons (Cheng *et al.*, 2012). Therefore, compound **2** was identified as 6 α -hydroxy-5 α ,7 α H-guai-4(15),9(10)-dien-12,8 α -olide (Fig. 1), a new natural product.

The genus *Inula* has been reported as a rich source of sesquiterpenoids, including germacrane, eudesmanes, guaianes, pseudoguaianes, and xanthanes. Our previous work on *I. verbascifolia* afforded the isolation of two new xanthanes and a new germacrane (Ahmed *et al.*, 2003), while in the present work two new guaianes were isolated, complementing the set of the previously reported compounds. Thus, the phytochemistry of *I. verbascifolia* is in agreement with that of the other species of the genus *Inula*. *I. salsoloides* afforded germacranolides (Jeske *et al.*, 1996; Zhou *et al.*, 1994); *I. aschersoniana* gave xanthanolides (Bloszyk *et al.*, 1990), while *I. hupehensis* afforded pseudoguaianolides and guaianolides (Qin *et al.*, 2011).

It is assumed that both the guaiane- and eudesmane-type lactones originate from a common germacrane precursor that is formed via the acetate-mevalonate-FPP (farnesyl pyrophosphate) pathway by a germacrene synthase, an enzyme belonging to the group of sesquiterpene cyclases (Herz, 1977; Bohlmann and Zdero, 1978; Fischer, 1990). Whether this common germacrane precursor is transformed into a guaiane skeleton or a eudesmane skeleton would depend on the position of enzyme-mediated epoxidations. A germacrene C-4–C-5 epoxide would lead to a guaiane,

whereas a germacrene C-1–C-10 epoxide would lead to a eudesmane (Brown *et al.*, 1975; Piet *et al.*, 1995). The previously reported germacrene from *I. verbascifolia* was a germacrene C-4–C-5 epoxide (Ahmed *et al.*, 2003), thus agreeing well with the two new guaianolides reported here.

Experimental

General

Optical rotations were measured on a Perkin-Elmer (Hiroshima, Japan) model 341 polarimeter with a 10-cm cell. IR spectra were recorded on a JASCO (Hiroshima, Japan) FT/IR-5300 spectrometer. ^1H NMR (600 MHz, CDCl_3), ^{13}C NMR (125 MHz, CDCl_3), and the 2D NMR spectra were recorded on a JEOL (Hiroshima, Japan) 500 MHz Lambda spectrometer, with tetramethylsilane (TMS) as an internal standard. EI mass spectra were recorded on a JEOL SX102A mass spectrometer. Column chromatography (CC) was carried out on silica gel 60 (230–400 mesh; Merck, Darmstadt, Germany) and Sephadex LH-20 (Pharmacia Co., Tokyo, Japan). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (0.25 mm; Merck), and spots were detected under UV light and coloured by spraying with 10% H_2SO_4 solution followed by heating.

Plant material

The aerial parts of *I. verbascifolia* were collected from Mt. Parnitha (Attiki), Greece and identified by Dr. Th. Constantinidis, Institute of Systematic Botany, Department of Biotechnology, Agricultural University of Athens, Athens, Greece. A voucher specimen of the collected material (No. I-1) has been deposited in the herbarium of the University of Patras, Patras, Greece.

Extraction and isolation

The air-dried aerial parts (500 g) of *I. verbascifolia* were powdered and extracted with 8 l pure CH_2Cl_2 at room temperature. The extract was concentrated *in vacuo* to obtain a residue of 11 g. The residue was fractionated by flash column chromatography (5 cm x 55 cm) over silica gel (1 kg) eluting with *n*-hexane (100%) with an increasing content of CH_2Cl_2 up to 100% CH_2Cl_2 . The 100% *n*-hexane fraction contained hydrocarbons and waxes. The second fraction (*n*-hexane/ CH_2Cl_2 , 1:1, 2 l) gave a crude material, which was further

purified on Sephadex LH-20 (3 cm x 35 cm; *n*-hexane/CH₂Cl₂/methanol, 7:4:0.5; 500 ml) to give compound **1** (9 mg). The third fraction (CH₂Cl₂, 100%) was further purified on Sephadex LH-20 (3 cm x 35 cm; *n*-hexane/CH₂Cl₂/methanol, 7:4:1; 500 ml) to afford compound **2** (3 mg). The structures of **1** and **2** were determined by spectroscopic methods (IR, MS, ¹H NMR, ¹³C NMR, DEPT, ¹H-¹H COSY, HMQC, and HMBC).

8α-Hydroxy-5α,7αH-guai-4(15),9(10)-dien-12,6αolide (1): C₁₅H₂₀O₃. – Yellowish oil. – [α]_D²⁵ = –20.88° (*c* 0.015, MeOH). – IR (KBr): ν = 3471 (OH), 1763 cm^{–1} (C=O). – ¹H NMR: The ¹H assignment were achieved by ¹H-¹H correlation spectroscopy (COSY), see Table I. – ¹³C NMR: The ¹³C assignments were achieved by HMQC and HMBC, see Table I. – MS (EI, 70 eV): *m/z*

(%) = 248 (11) [M⁺], 230 (83) [M⁺ – H₂O], 215 (13) [M⁺ – H₂O – CH₃], 202 (18), 201 (18), 105 (75); calcd. for C₁₅H₂₀O₃Na 271.1310, found 271.1311.

6α-Hydroxy-5α,7αH-guai-4(15),9(10)-dien-12,8αolide (2): C₁₅H₂₀O₃. – Yellowish material. – IR (KBr): ν = 3475 (OH), 1754 cm^{–1} (C=O). – ¹H NMR: The ¹H assignments were achieved by ¹H-¹H correlation spectroscopy (COSY), see Table I. – ¹³C NMR: The ¹³C assignments were achieved by HMQC and HMBC, see Table I. – MS (EI, 70 eV): *m/z* (%) = 248 (10) [M⁺], 230 (80) [M⁺ – H₂O], 215 (9) [M⁺ – H₂O – CH₃], 105 (71).

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