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RESEARCH ARTICLE

Sesquiterpene coumarins from the fruits of *Ferula badrakema*

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Abstract
From the fruits of *Ferula badrakema* (Kos.-Pol.) (Umbelliferae), five known sesquiterpene coumarins (conferone, mogoltacin, feselol, ferocaulidin and ligupersin A) were isolated for the first time, using silica gel column chromatography and preparative thin-layer chromatography. The structures were characterized by 1D and 2D NMR experiments.

Keywords: *Ferula badrakema; sesquiterpene coumarins; NMR; chromatography; fruits*

Introduction

The exclusively old world genus *Ferula* (Umbelliferae), with about 130 species, is distributed throughout the Mediterranean area and central Asia, especially in the former USSR and neighboring countries such as Iran. This genus is well documented as a good source of biologically active compounds such as sesquiterpene derivatives (Ahmed et al., 2001; Ahmed, 1999; Valle et al., 1987). *Ferula badrakema* (Kos.-Pol.) (Rechinger et al., 1994), similar to other species of the genus *Ferula*, is a rich source of sesquiterpene coumarins (Bukreeva & Pimenov, 1991). *Ferula badrakema* (Syn. = *F. gumosa*) is a resinous plant and has a strong odor. To our knowledge, no study has been done on the chemistry of the fruits of this species. Previously, some sesquiterpene coumarins have been isolated from the roots of the plant (Kir'yalov, 1967; Bukreeva & Pimenov, 1991). In the present study, we report the isolation and the structure elucidation of five sesquiterpene coumarins from *Ferula badrakema* fruits for the first time (**1**-**5**).

Materials and methods

Plant material

Fruits of *Ferula badrakema* were collected in Hezarmasjed Mountains, north east of Iran, in August 2005, and identified by Mohammadreza Joharchi, Ferdowsi University of Mashhad Herbarium (FUMH). A voucher specimen (1002) is deposited at the Herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Mashhad University of Medical Sciences.

General experimental procedures

The ^{1}H, gCOSY, ROESY, gHSQC, gHMBC NMR experiments were run under standard conditions on a Bruker DRX-600 spectrometer at 300 K. NMR samples were prepared by dissolving each sample in $CDCl_3$ (99.8% D) (Carlo Erba). The spectra were calibrated using the solvent signal as internal standard (^{1}H, δ: 7.27 ppm; ^{13}C, δ 77.0 ppm). The ROESY spectra were executed with a mixing time of 400 ms. The NMR data were processed

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on a Silicon Graphic Indigo2 Workstation using UXNMR software. Column chromatography was conducted with silica gel 230–400 mesh (Merck). Preparative TLC was performed on Silica gel 60 GF_{254} plates (Merck) and observation of plates was carried out under UV CAMAG spectrometer (254 nm).

Extraction and isolation

The air-dried fruits (500 g) were ground into powder, defatted by petroleum ether and extracted exhaustively by maceration with dichloromethane at room temperature. After filtration, the extract was concentrated under vacuum to yield 20 g of a brown residue.

Part of the extract (15 g) was subjected to column chromatography on silica gel (5 × 50 cm) using petroleum ether with increasing volumes of acetone (petrol-Me_2CO (20:1), (15:1), (10:1), (9:1), (8:1), (7:1), (6:1), (5:1), (4:1), (3:1), (2:1), (1:1) and (0:1)). The fractions were compared by TLC (Silica gel using petrol-Me_2CO as solvent), and those giving similar spots were combined. Five fractions were finally obtained. Fractions 1-3 afforded compounds **1** (15 mg), **2** (770 mg) and **3** (48.5 mg) as white crystals, respectively. Fractions 4 and 5 were subjected to silica gel PTLC (petrol-Me_2CO, 2:1) to give compounds **4** (11.2 mg) and **5** (54.5 mg), respectively.

Results and discussion

Normal-phase column chromatography of the dichloromethane extract of fruits of *F. badrakema*, followed by preparative TLC, afforded five sesquiterpene coumarins including conferone (**1**), mogoltacin (**2**), feselol (**3**), ferocaulidin (**4**), and ligupersin A (**5**). The isolated coumarins (Figure 1) were identified by comparison of their NMR with those previously described in the literature (Vandyshev et al., 1972; Nabiev et al., 1978; Kuliev et al., 1980; Murray et al., 1982; Lee & Mabry, 1985;

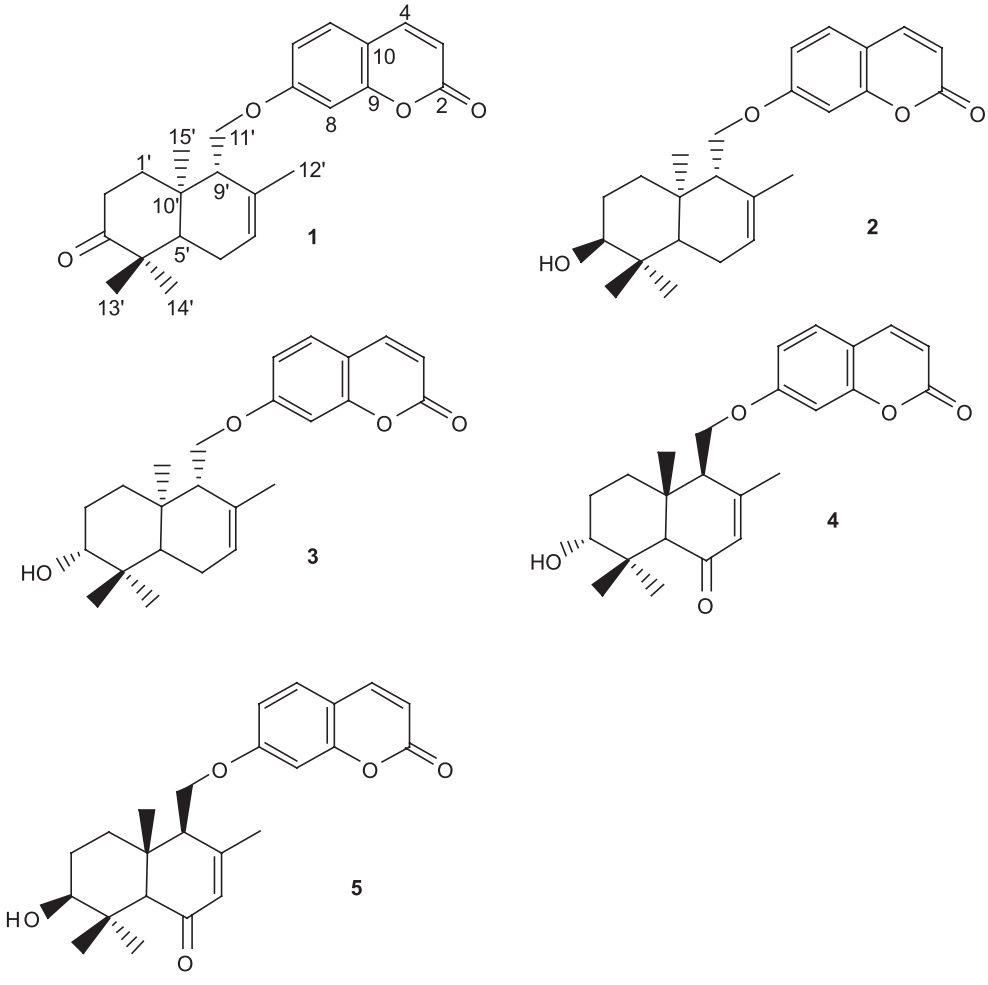

Figure 1. Chemical structures of sesquiterpene coumarins isolated from *Ferula badrakema* fruits.

Abd El-Razek et al., 2003). This is the first report of sesquiterpene coumarins from *F. badrakema* fruits.

The structure of compound **1** was established from analysis of the ^{1}H and ^{13}C NMR spectra (Tables 1 and 2). Compound **1** displayed 24 carbon signals, 9 being typical of an umbelliferone skeleton and the other 15 signals were ascribable to a sesquiterpene moiety. The downfield signal at δ_C 161.5 was assigned to the carbonyl carbon of the coumarin moiety, whereas the downfield signal at δ_C 216.4 was indicative of a ketone group belonging to the sesquiterpene unit. HSQC spectrum classified the carbon signals to four aliphatic methylenes at δ_C 38.8 (C-1′), 34.8 (C-2′), 24.3 (C-6′), and a primary alcoholic carbon at δ_C 67.0 characteristic for C-11′, to nine methines, five of them for umbelliferone moiety at δ_C 113.4 (C-3), 143.7 (C-4), 129.2 (C-5), 113.6 (C-6) and 101.7 (C-8) and to four methyls at δ_C 25.6 (C-12′), 22.7 (C-13′), 25.6 (C-14′), and 14.9 (C-15′). The ^{1}H NMR spectrum of compound **1** showed resonances characteristic for four methyl singlets at δH 1.75 (H-12′),1.17 (H-13′),1.13 (H-14′) and 1.18 (H-15′), and three olefinic resonances at δH 6.28 (H-3), 7.66 (H-4) and 5.62 (H-7′). Three aromatic protons at δH 7.39 (H-5), 6.86 (H-6) and 6.85 (H-8) suggested the presence of a 7, 9, 10-trisubstituted benzene ring, which was supported by the ^{13}C NMR spectrum.

The NMR spectral data of compound **2** were similar to those of compound **1**, except a slight difference in the signals assigned to the sesquiterpene unit which was due to the replacement of the ketone group at C-3′ with an oxymethine. Regarding this portion and with respect to conferone, HMBC spectrum showed the correlations of the secondary alcoholic H-3′ (δ_H 3.52) to δ_C 25.2 (C-2′), δ_C 37.6 (C-4′), and to δ_C 43.8 (C-5′). Other NMR spectral data of compound **2** were closely comparable to those of compound **1**. Hence, the structure of compound **2** was determined as mogoltacin (or conferol).

The NMR spectral data of compound **3** were very similar to those of compound **2**, except for the stereochemistry of C-3′. Thus, the differences between the ^{1}H NMR of compounds **2** and **3** appeared in the signals due to protons on C-2′, C-3′ and methyl groups of 13′ and 14′. In compound **3**, the signals for the H-2′ and H-3′ appeared at δ_H 1.67 and δ_H 3.31, respectively, and those for the methyl groups of 13′ and 14′ at δ_H 1.05 and 0.93, respectively. In compound **2**, the corresponding signals appeared at δ_H 1.69 (H-2′), 3.52 (H-3′), 1.02 (H-13′) and 0.97 (H-14′). ROESY experiments confirmed the stereochemistry of 3′-OH as

Table 1. ^{1}H-NMR data obtained with compounds **1**-**5** (600 MHz, δ ppm).

Position of proton	**1** (*J*)	**2** (*J*)	**3** (*J*)	**4** (*J*)	**5** (*J*)
2	-	-	-	-	-
3	6.28 d (9.6)	6.27 d (9.5)	6.27 d (9.5)	6.30 d (9.5)	6.25 d (9.5)
4	7.66 d (9.6)	7.66 d (9.5)	7.66 d (9.5)	7.67 d (9.5)	7.65 d (9.5)
5	7.39 d (8.4)	7.38 d (8.4)	7.39 d (8.4)	7.39 d (8.4)	7.39 d (8.4)
6	6.86 dd (8.4, 2.3)	6.86 dd (8.4, 2.3)	6.88 dd (8.4, 2.3)	6.87 dd (8.4, 1.8)	6.83 d (8.4)
7	-	-	-	-	-
8	6.85 d (2.3)	6.85 d (2.3)	6.85 d (2.3)	6.86 d (1.8)	6.82 brs
9	-	-	-	-	-
10	-	-	-	-	-
1′	1.66 dd* β 2.30 m α	1.75 m* β 2.01 m* α	1.37 dd (13.2, 4.2) β 2.05 m* α	1.68 m β 2.01 m α	1.55 ddd (15.0, 6.0, 6.0) β 1.97 dt (15.0, 4.2) α
2′	2.31 m β 2.75 ddd (15.3, 6.6) α	1.69 m	1.67 m	1.70 m β 2.00 m α	1.69 m
3′	-	3.52 brs	3.31 brd (10.8)	3.41 brs	3.23 dd (10.8, 4.2)
4′	-	-	-	-	-
5′	1.68 dd*	1.73 dd*	1.30 dd (11.4, 6.0)	2.67 s	2.16 s
6′	2.00 like brd β 2.18 like brt α	2.0 m*	2.01 m*	-	-
7′	5.62 brs	5.59 brs	5.60 brs	5.93 brs	5.89 s
8′	-	-	-	-	-
9′	2.28*	2.37 brs	2.26 brs	2.81 brs	2.66 brs
10′	-	-	-	-	-
11′	a 4.10 dd (9.80, 5.20) b 4.21 dd (9.80, 4.80)	a 4.04 dd (9.60, 6.00) b 4.20 dd (9.60, 3.30)	a 4.03 dd (9.60, 5.40) b 4.19 dd (9.60, 3.00)	a 4.18 dd (10.20, 5.40) b 4.29 dd (10.20, 3.00)	a 4.14 dd (9.60, 5.40) b 4.25 dd (9.60, 3.00)
12′	1.75 s	1.73 s	1.73 s	1.99 s	1.95 s
13′	1.17 s	1.02 s	1.05 s	1.23 s	1.17 s
14′	1.13 s	0.97 s	0.93 s	1.26 s	1.27 s
15′	1.18 s	0.96 s	0.95 s	1.07 s	1.02 s

*Overlapped with other signals.

Table 2. ^{13}C-NMR data obtained with compounds **1**-**5** (125.7 MHz, δ ppm).

Position of carbon	**1**	**2**	**3**	**4**	**5**
2	161.5	161.6	161.6	160.6	160.9
3	113.4	113.4	113.4	112.9	113.3
4	143.7	143.8	143.8	142.9	143.3
5	129.2	129.1	129.1	128.9	128.8
6	113.6	113.5	113.5	112.8	112.6
7	162.2	162.5	162.4	161.1	161.2
8	101.7	101.7	101.7	101.5	101.1
9	156.3	156.3	156.3	155.3	155.6
10	113.0	112.8	112.9	112.7	112.7
1′	38.8	32.2	38.2	31.1	37.3
2′	34.8	25.2	27.7	24.4	26.0
3′	216.4	76.2	79.2	76.1	78.5
4′	47.9	37.6	39.1	36.3	37.6
5′	51.5	43.8	49.7	57.1	62.0
6′	24.3	23.6	23.7	199.8	198.4
7′	124.0	124.2	124.1	129.6	129.5
8′	132.7	132.9	132.7	155.3	155.5
9′	53.4	53.9	54.2	54.8	54.7
10′	36.2	36.0	36.2	41.6	41.9
11′	67.0	67.5	67.4	65.9	65.3
12′	25.6	22.1	22.0	21.6	21.3
13′	22.7	28.5	28.4	21.4	14.8
14′	25.6	22.7	15.3	28.1	28.2
15′	14.9	15.2	15.2	16.1	15.5

β and α conformers for compounds **2** and **3**, respectively. Therefore, compound **3** was determined as feselol.

^{13}C NMR spectrum of compound **4** showed the presence of a ketone group at δ_C 199.8. In the HMBC spectrum, correlations between H-5′ and H-7′ with C-6′, confirmed the location of carbonyl group at C-6′. On the other hand, no resonances were observed for the protons of C-6′ in the ^{1}H NMR spectrum of compound **4**. ^{1}H and ^{13}C NMR spectral data of compound **4** were similar to those of compound **3**, except for the C-6′ and chemical shifts of protons and carbons adjacent to C-6′ (Tables 1 and 2). Compound **4** was assigned to be ferocaulidin according to the mentioned references.

The only difference between structures of compounds **4** and **5** was in the stereochemistry of 3′-OH. In compound **5**, the stereochemistry of 3′-OH was determined by ROESY experiment. In ROESY spectrum of compound **5**, a cross-peak between H-3′ and H-5′, indicated the conformation of 3′-OH as β, while in compound **4**, a cross-peak between H-3′ and Me-15′ was observed, indicating α conformer of H-3′. Compound **5** was determined as the known compound, ligupersin A.

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***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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