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Original Article

Badrakemonin, a New Eremophilane-Type Sesquiterpene from the Roots of *Ferula badrakema* Kos.-Pol.

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Abstract

Phytochemical investigation of the dichloromethane extract of the dried roots of *Ferula badrakema* resulted in the identification of one new and six known compounds. Known compounds were sesquiterpene coumarins: mogoltacin, feselol, badrakemin acetate, ferocaulidin, conferone and conferol acetate. The new compound was a sesquiterpene, named badrakemonin. The structures of these compounds were elucidated by extensive NMR spectroscopic methods including 1D-(^{1}H and ^{13}C) and 2D-NMR (HSQC, HMBC, and ROESY) as well as MS experiments.

Keywords: *Ferula badrakema*; Apiaceae; Sesquiterpene; Badrakemonin; Roots.

Introduction

Genus of *Ferula* which belongs to tribe Peucedaneae, subfamily of Apioideae, family of Umbelliferae with 133 species distributed throughout Mediteranean area and central Asia, especially in the former USSR and neighboring countries such as Iran (1-3). More than 70 species of *Ferula* have already been investigated chemically (4-6). Several species of this genus have been used in folk medicine for their antispasmodic, carminative, digestive, expectorant, sedative, antihysteric, laxative, aphrodisiac, antiseptic, and analgesic activities (*7*). The Iranian flora comprises 30 species of *Ferula*, of which some are endemic (2, 8). The popular Persian name of the most of these species is "Koma" (8).

Chemistry of this genus has been studied by many investigators (9) and is well documented as a good source of biologically active compounds such as sesquiterpene derivatives (10-16) and sulfur containing compounds (17-22). A few sesquiterpene coumarin glycosides have also been reported from *Ferula* species (6, 23). Sesquiterpene derivatives, especially sesquiterpene coumarins, were stored in the roots of the plants; therefore the roots are better source for isolating these compounds than the aerial parts. However, to the best of our knowledge, there is no report about eremophilane-type sesquiterpenes from this genus.

Ferula badrakema Kos.-Pol. (Syn = *Ferula afghanistanica*) is a resinous plant with a strong odor which is endemic to Iran (24). The roots of this plant have been used in folk medicine as antiepileptic and antispasmodic drug (7).

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Similar to other species of the genus *Ferula*, *F. badrakema* is a rich source of sesquiterpene coumarins (25). Previously, some sesquiterpene coumarins have been isolated from the roots of the plant (25, 26). In the present study, we have reported the phytochemical study of the plant *F. badrakema.*

Experimental

Plant material

The roots of *F. badrakema* were collected from the Tandoureh park, Khorasan Razavi, Iran, in July 2006. The plant was identified by the department of pharmacognosy, School of pharmacy, Mashhad University of Medical Science. A voucher specimen (No. 1002) has been deposited at the Herbarium of the School of Pharmacy (Mashhad).

General experimental procedures

Melting points were determined on a Electrothermal 9100 apparatus and are uncorrected. The optical rotation was measured on a Polax-2L ATAGO Polarimeter. UV spectra were obtained using a Shimadzu PC-1650 spectrophotometer. ESIMS analyses were performed using a ThermoFinnigan LCQ Deca XP Max ion-trap mass spectrometer equipped with Xcalibur software.

NMR spectra were measured on a Bruker DRX 500 (Bruker Biospin, Rheinstetten, Germany). ^{1}H NMR, ^{13}C NMR, DEPT, ^{1}H-^{1}H COSY, HMBC, HSQC, and ROESY spectra were measured using an inverse-detection probe (5 mm). The operating frequencies were 500.13 MHz for acquiring ^{1}H NMR and 125.75 MHz for ^{13}C NMR spectra. Samples were measured at 300 K in $CDCl_3$ with TMS as the internal standard. Column chromatography was conducted with silica gel 230-400 mesh (Merck). Preparative TLC was performed on GF_{254s} plates (20 × 20 cm, Merck) and observation of plates was carried out under UV CAMAG spectrometer (254 nm).

Extraction and isolation

Dried, powdered roots of *F. badrakema* (383.54 g) were extracted with dichloromethane by maceration. The combined dichloromethane extracts were concentrated *in vacuo* to give a red extract (21.17 g). Part of the extract (13.37 g) was subjected to column chromatography on silica gel (5 cm×50 cm) using gradient compositions of ethyl acetate (EtOAc)-Petroleum ether as eluent [EtOAc-Petroleum ether (1:10, 2200 mL), (1:9, 2000 mL), (1:8, 1800 mL), (1:7, 2400 mL), (1:6, 2100 mL), (1:5, 1200 mL), (1:4, 2000 mL), (1:3, 800 mL), (1:2, 900 mL), (1:1, 2000 mL) and EtOAc (3000 mL)]. The fractions were compared by TLC (on silica gel using EtOAc-petroleum ether as eluent), and those giving similar spots were combined. Twenty-three fractions were finally obtained. Fraction 1 was subjected to silica gel PTLC (EtOAc-petroleum ether, 1:10) to give badrakemonin (4.4 mg). Fraction 10 was also developed on silica gel PTLC (acetone-petroleum ether, 1:4.5) to yield conferol acetate (1.7 mg). Fractions 11 and 12 were subjected to silica gel PTLC (EtOAc-petroleum ether, 2:3) to give badrakemin acetate (14.3 mg). Fractions 13, 14 and 15 also needed more purification with silica gel PTLC (EtOAc-petroleum ether, 2:3) to afford conferone (13.5 mg), mogoltacin (38.8 mg) and feselol (49.2 mg), respectively. Fraction 17 was further purified by silica gel PTLC (EtOAc- petroleum ether, 3:4) to yield mogoltacin (71.2 mg). Fractions 18 and 19 were also further purified by silica gel PTLC (EtOAc-petroleum ether, 3:2) to give ferocaulidin (64.9 mg).

Results and Discussion

Normal-phase column chromatography of the dichloromethane extract of roots, followed by preparative TLC, afforded a new sesquiterpene, badrakemonin, and six known sesquiterpene coumarins, namely mogoltacin, feselol, badrakemin acetate, ferocaulidin, conferone and conferol acetate (Figure 1). The structures of the mentioned known compounds were confirmed according to the melting points, NMR experiments and literature (6, 9, 27).

The ^{1}H and ^{13}C NMR resonances (Table 1) of badrakemonin were assigned by different 2D NMR experiments. The ^{1}H NMR spectrum showed resonances characteristic for three methyl singlets at δ_H 1.50 (H-10), 1.83 (H-8) and 1.86 (H-9), and two methine resonances at δ_H 1.84 (H-15', 1H, septet, J = 6.6 Hz) and 5.76

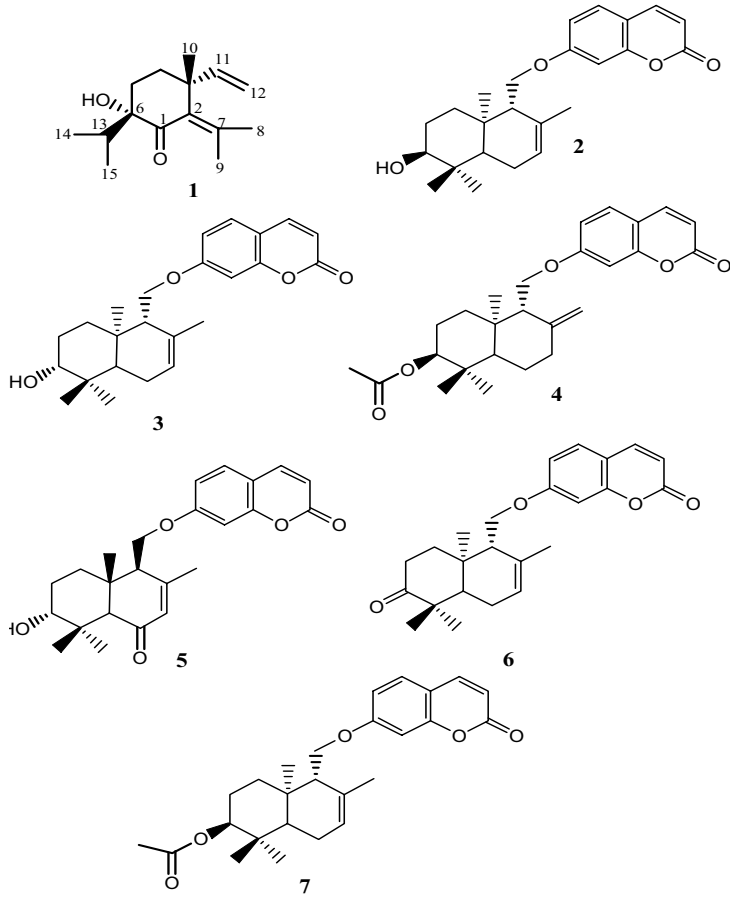

Figure 1. Chemical structures of badrakemonin (**1**), mogoltacin (**2**), feselol (**3**), badrakemin acetate (**4**), ferocaulidin (**5**), conferone (**6**) and conferol acetate (**7**).

(H-11, 1H, dd, *J* = 10.8 and 17.4 Hz).

The ^{13}C NMR resonances showed 15 carbon signals, which could be resolved by DEPT and HSQC experiments into five methyls at δ_C 16.8 (C-14), 17.1 (C-15), 23.8 (C-8), 23.9 (C-10) and 24.9 (C-9), one tertiary alcoholic carbon at δ_C 80.0 characteristic for C-6, three methylenes at δ_C 31.4 (C-5), 37.0 (C-4) and 111.2 (C-12), two methines at δ_C 36.0 (C-13) and 146.0 (C-11), and five quaternary carbons at δ_C 44.9 (C-3), 80.0 (C-6), 137.3 (C-2), 145.6 (C-7) and one carbonyl function which was indicated by the downfield signal at δ_C 211.9 (C-1). In the HMBC spectrum, the correlations of H-4 (δ_H 1.34 and 1.53) with C-3 (δ_C 44.9); H-5 (δ_H 1.75 and 2.14) with C-6 (δ_C 80.0); H-8 (δ_H 1.83) with C-2 (δ_C 137.3) and C-7 (δ_C 145.6); H-9 (δ_H 1.86) with C-2 (δ_C 137.3) and C-7 (δ_C 145.6); H-10 (δ_H 1.50) with C-3 (δ_C 44.9); H-11 (δ_H 5.76) with C-3 (δ_C 44.9) and C-12 (δ_C 111.2); H-12 (δ_H 4.96 and 4.98) with C-11 (δ_C 146.0); H-13 (δ_H 1.84) with C-6 (δ_C 80.0); H-14 (δ_H 0.98) with C-6 (δ_C 80.0) and C-13 (δ_C 36.0); and H-15 (δ_H 0.80) with C-6 (δ_C 80.0) and C-13 (δ_C 36.0) were observed. The proposed structure was further supported by ^{1}H-^{1}H COSY data.

The stereochemistry of the chemical groups at C-3 and C-6 in **1** was determined on the basis of the ROESY experiment, in which cross-peaks were observed from H-10/H-4β pairs and H-10/H-5β pairs (Figure 2).

Badrakemonin: yellow oil; $[\alpha]^{24}_D$: - 52.4 (c 0.07, $CHCl_3$); UV ($CHCl_3$) λ_{max} nm (log ε): 260 (2.97), 280 (2.91) nm; MS: *m/z* (%) = 237 [M + H]$^+$, 222(100 %), 221, 207, 205.

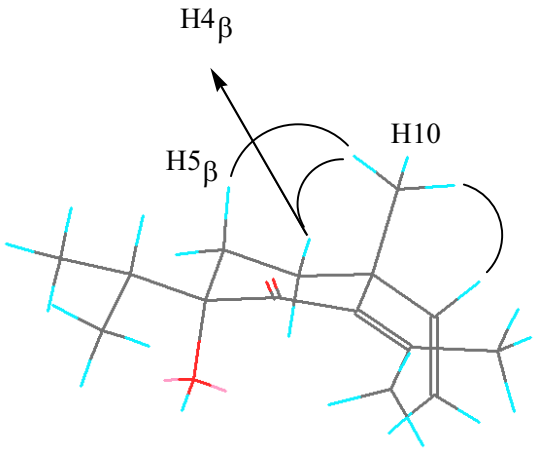

Figure 2. A low-energy conformation of badrakemonin (**1**) using the MM_2 force field and important ROESY correlations for it, observed in 2D ROESY spectrum.

Table 1. ^{1}H NMR and ^{13}C NMR data for badrakemonin ($CDCl_3$, 500 MHz)[a]

Position	^{1}H	^{13}C
1	-	211.9
2	-	137.3
3	-	44.9
4	1.34 ddd (13.8, 5.4, 3) α 1.53 ddd (13.8, 13.8, 3) β	37.0
5	1.75 ddd (14.4, 5.4, 3) α 2.14 ddd (14.4, 13.8, 3) β	31.4
6	-	80.0
7	-	145.6
8	1.83 s	23.8
9	1.86 s	24.9
10	1.50 s	23.9
11	5.76 dd (17.4, 10.8)	146.0
12	4.96 d (10.8) 4.98 d (17.4)	111.2
13	1.84 septet (6.6)	36.0
14	0.98 d (6.6)	16.8
15	0.80 d (6.6)	17.1

[a] J values are in parentheses and reported in Hz; chemical shifts are given in ppm; assignments were confirmed by ^{1}H-^{1}H COSY, HSQC, HMBC and ROESY experiments.

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