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Two new meroterpenoids from the gum resin of *Ferula ammoniacum* (D.Don) Spalik, M.Panahi, Piwczyński & Puchałka

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ABSTRACT

The gum of *Ferula ammoniacum* (D.Don) Spalik, M.Panahi, Piwczyński & Puchałka is an herbal remedy used in traditional medicines for its effectiveness against various ailments. The phytochemical analysis of the ethyl acetate extract of the gum ammoniacum led to the discovery of two novel meroterpene derivatives, **1** and **2**. The structural elucidation of these isolated compounds was accomplished though 1D and 2D NMR spectroscopy, and HRESIMS, alongside comparison with existing literature data. Compound **1** represents a previously unreported meroterpenoid with a unique natural skeleton. A plausible biosynthetic pathway for this compound has also been proposed.

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1. Introduction

Ferula ammoniacum (D.Don) Spalik, M.Panahi, Piwczyński & Puchałka (Apiaceae family), also known as *Dorema ammoniacum* (D. Don) (Nazir et al., 2021), is distributed in central Iran as well as in several Asian countries, including Afghanistan, India, Turkmenistan, and Pakistan (Mozaffarian, 1996). *F. ammoniacum* locally referred to as "Kandal", "Vasha", and "Koma-Kandal", typically reaches a height of 1-2 m during the spring and early summer (Mobeen et al., 2018). It is regarded as an important medicinal plant in the arid and semi-arid regions of Iran, particularly in the provinces of Yazd, Isfahan, and Semnan (Mozaffarian, 1996; Yousefzadi et al., 2011). This plant exudes a medicinal gum resin (Fig. 1), known as gum ammoniacum from the pores of its stems, leaves, and petioles during the flowering and fruiting stages (Pandpazir et al., 2018). Gum ammoniacum rapidly hardens into rounded tears, known as "Tear Ammoniacum" in commerce. Tear ammoniacum comprises small, rounded or irregular masses ranging from about 0.5 to 3 cm. It is hard and brittle but becomes soft when heated. Its dull surface is pale yellow and darkens with age, while the fractured surface appears milky white to pale brownish-yellow and is opaque with a waxy luster. The alternative form, "lump ammoniacum," consists of clusters of tears that often include fragments of the plant and other debris. It has a balsamic resinous odor and a bitter, unpleasant, somewhat acrid taste (Chisholm, 1911; Mobeen et al., 2018). In the Unani medical tradition, gum ammoniacum is valued for its antispasmodic properties and is utilized in the treatment of liver enlargement, chronic bronchitis, persistent coughing and asthma as mentioned by Avicenna and Razi (Mobeen et al., 2018; Mazaheritehrani et al., 2020). It serves as an anthelmintic for gastrointestinal disorders in Iranian

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traditional medicine (ITM) (Adhami et al., 2013). Gum ammoniacum continues to be used in both Indian and Western Medicine and is recognized in the British pharmacopoeia for its antispasmodic and expectorant effects (Norton et al., 2004). Additionally, this resin has demonstrated antibacterial and vasodilatory properties (Rajani et al., 2002; Irvani et al., 2010).

Up to now, the phytochemistry of *F. ammoniacum* has been poorly investigated. In previous studies, three sesquiterpene chromandiones (ammodoremin, doremon A, and an analogue of doremon A), two sesquiterpene coumarin derivatives (ammoresinol and 7-hydroxyferprenin), and four sesquiterpene derivatives (dshamirone and kopetdaghin C-E) were identified in the gum of this plant (Appendino et al., 1991; Adhami et al., 2013; Mazaheritehrani et al., 2020). Two phloroacetophenone glycosides together with three phenolic acid derivatives were isolated from the roots of the plant (Etemadi-Tajbakhsh et al., 2020). The essential oil of different parts of the plant, including leaves, stems, fruits, and seeds, have also been analyzed several times and different compounds reported from each organ (Yousefzadi et al., 2011; Hosseini et al., 2014; Zandpour et al., 2016; Masoudi and Kakavand, 2017).

In this study, we report the isolation and structural characterization of two novel meroterpene derivatives from gum ammoniacum.

2. Experimental

2.1. Apparatus

Optical rotation was recorded using a JASCO P-2000 polarimeter (Easton, MD, USA). A Bruker Avance II 600 NMR spectrometer operated at 600.19 MHz for ^{1}H and 150.91 MHz for ^{13}C was used to measure the one- and two-dimensional NMR experiments. The spectra were acquired at 300 K in chloroform-*d* with chemical shifts δ in ppm and coupling constant *J* in Hz). HRMS data were determined on a microOTOF-QII (Bruker) mass spectrometer in the positive electrospray ionization (ESI) mode. ESIMS parameters included a 1:5 HPLC split, a dry temperature of 220 °C, a dry gas (N2) flow of 6.00 L/min, a nebulizer pressure of 23.2 psi, and full-scan mode covering *m/z* 100-1500. Analytical and semi-preparative HPLC separations were conducted using an Agilent 1100 series (MA, USA), using a Eurospher II 100-5 C18 with precolumn (5 µm, 4.6 × 250 mm) column (KNAUER, USA), and a Sunfire™ Prep C18 OBD™ (5 µm, 19 × 50 mm) column (Waters, USA), respectively. Column chromatography utilized silica gel (Merck, Darmstadt, Germany), Sephadex LH-20 gel (GE Healthcare, Sweden), and reverse-phase C-18 (Merck, Germany). TLC was performed on silica gel 60 F254 precoated plates (Merck, Darmstadt, Germany). Double-distilled solvents were employed for extraction and open column separations.

2.2. Plant material

Gum ammoniacum was purchased from an herbal medicine shop in Shahroud in September 2017 (Batch number: 523111-1). The gum had been collected from Torud, Shahroud, Semnan Province, Iran (geographical coordinates: 35° 25′ 32.01′′ N, 55° 00′ 32.46′′ E) at about 800 m a.s.l., during July 2017. The plant and gum were collected from the growing area and authenticated by the expert botanist Dr. A. Sonboli. A voucher specimen (MPH-2945) was deposited at the Herbarium of the Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Tehran, Iran. Morphological description and characteristics, and Identification was also performed according to the tests specified in the British Herbal Pharmacopoeia (British Herbal Pharmacopoeia, 1993), and The Unani Pharmacopeia of India (The Unani Pharmacopeia of India, 2008).

Fig. 1. Photograph representing the arial parts of *F. ammoniacum* resin (gum ammoniacum).

2.3. Extraction and isolation

A total of 2.0 kg of gum ammoniacum was powdered and extracted with EtOAc (3 × 10 L) each for 48 hours at ambient temperature. The EtOAc extract was concentrated under reduced pressure, to afford 890 g of a brown gummy extract. Subsequently, 800 g of the EtOAc extract was subjected to silica gel column chromatography (Diameter 10.0 cm, 70-230 mesh, 2 kg) with an *n*-hexane/EtOAc gradient (95:5, 9:1, 85:15, 8:2, 75:25, 7:3, 65:35, 6:4, 55:45, 5:5, 4:6, 3:7, 2:8, 1:9, and 0:1; *v/v%*; elution volume: 6 L of each), followed by increasing concentrations of MeOH in EtOAc (95:5, 85:15, and 6:4; *v/v%*; elution volume: 3 L of each). A total of 400 fractions were collected, and fractions with similar R_f values, as observed on TLC (detection at 254 nm and after spraying with anisaldehyde), were combined into eighteen major fractions F1-F18 (Table 1). Fraction F10 (34 g, eluted with *n*-hexane/EtOAc [30:70]) was further fractionated using silica gel column chromatography (4.5 × 66 cm, 70-230 mesh, 600 g) and eluted with an *n*-hexane/EtOAc gradient (9:1, 8:2, 7:3, 6:4; *v/v%*; elution volume: 2.5 L of each) to give five subfractions ($F10_1$-$F10_5$). Subfraction $F10_3$ (1.0 g, eluted with *n*-hexane/EtOAc [80:20]) was subjected to Sephadex LH-20 column chromatography (2 × 60 cm,

35 g) using a MeOH/$CHCl_3$ isocratic elution (7:3; *v/v%*; elution volume: 1.5 L) to obtain three subfractions ($F10_{3.1}$-$F10_{3.3}$). Subfraction $F10_{3.3}$ (400 mg) was further separated using silica gel column chromatography (1 × 60 cm, 70-230 mesh, 25 g) and eluted with an *n*-hexane/EtOAc gradient (7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, and 0:1; *v/v%*; elution volume: 100 mL of each), followed an increase in Me_2CO in EtOAc (95:5, 85:15, 7:3, 5:5 and 4:6; *v/v%*; elution volume: 50 mL of each), resulting nine subfractions ($F10_{3.3.1}$-$F10_{3.3.9}$). Subfraction $F10_{3.3.5}$ (25 mg) was then purified by semi-preparative HPLC (MeOH/H_2O, isocratic 70:30; *v/v%*) to isolated compound **1** (0.7 mg, t_R 5.3 min). Additionally, part of the residue from fraction F11 (30 g, eluted with *n*-hexane/EtOAc [30:70]) was separated on a silica gel column chromatography (4.5 × 80 cm, 70-230 mesh, 500 g), using an *n*-hexane/Me_2CO isocratic elution (9:1; *v/v%*; elution volume: 20 L), resulting in eight subfractions ($F11_1$-$F11_8$). Subfraction $F11_6$ (1.78 g) was further purified using reverse-phase C-18 open column chromatography (2.5 × 20 cm, 45 g) with a MeOH/H_2O gradient (9:1, 95:5, and 1:0; *v/v%*; elution volume: 500 mL of each), leading to collection of nine subfractions ($F11_{6.1}$-$F11_{6.9}$). Subfraction $F11_{6.8}$ (263 mg, eluted with 100% MeOH) was further separated using silica gel column chromatography (1.5 × 52 cm, 70-230 mesh, 20 g), with an *n*-hexane/EtOAc gradient (8:2, 7:3, 6:4, 5:5; *v/v%*; elution volume: 300 mL of each), yielding to ten subfractions ($F11_{6.8.1}$-$F11_{6.8.10}$). Compound **2** (4.5 mg) was eventually isolated from subfraction $F11_{6.8.2}$.

Compound **1**: A colorless gum, $[\alpha]^{20}_D$ +6 (c 0.1, $CHCl_3$), ^{1}H and ^{13}C NMR data see Table 2, HRESIMS *m/z* 249.1119 $[M + H]^+$ (calcd for $C_{14}H_{17}O_4^+$, 249.1122).

Compound **2**: A yellowish gum, $[\alpha]^{20}_D$ +2 (c 0.1, $CHCl_3$), ^{1}H and ^{13}C NMR data, see Table 2, HRESIMS *m/z* 385.2752 $[M + H]^+$ (calcd for $C_{25}H_{37}O_3^+$, 385.2738).

2.3. Extraction and isolation

A total of 2.0 kg of gum ammoniacum was powdered and extracted with EtOAc (3 × 10 L) each for 48 hours at ambient temperature. The EtOAc extract was concentrated under reduced pressure, to afford 890 g of a brown gummy extract. Subsequently, 800 g of the EtOAc extract was subjected to silica gel column chromatography (Diameter 10.0 cm, 70-230 mesh, 2 kg) with an *n*-hexane/EtOAc gradient (95:5, 9:1, 85:15, 8:2, 75:25, 7:3, 65:35, 6:4, 55:45, 5:5, 4:6, 3:7, 2:8, 1:9, and 0:1; *v/v%*; elution volume: 6 L of each), followed by increasing concentrations of MeOH in EtOAc (95:5, 85:15, and 6:4; *v/v%*; elution volume: 3 L of each). A total of 400 fractions were collected, and fractions with similar R_f values, as observed on TLC (detection at 254 nm and after spraying with anisaldehyde), were combined into eighteen major fractions F1-F18 (Table 1). Fraction F10 (34 g, eluted with *n*-hexane/EtOAc [30:70]) was further fractionated using silica gel column chromatography (4.5 × 66 cm, 70-230 mesh, 600 g) and eluted with an *n*-hexane/EtOAc gradient (9:1, 8:2, 7:3, 6:4; *v/v%*; elution volume: 2.5 L of each) to give five subfractions ($F10_1$-$F10_5$). Subfraction $F10_3$ (1.0 g, eluted with *n*-hexane/EtOAc [80:20]) was subjected to Sephadex LH-20 column chromatography (2 × 60 cm, 35 g) using a MeOH/$CHCl_3$ isocratic elution (7:3; *v/v%*; elution volume: 1.5 L) to obtain three subfractions ($F10_{3.1}$-$F10_{3.3}$). Subfraction $F10_{3.3}$ (400 mg) was further separated using silica gel column chromatography (1 × 60 cm, 70-230 mesh, 25 g) and eluted with an *n*-hexane/EtOAc gradient (7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, and 0:1; *v/v%*; elution volume: 100 mL of each), followed an increase in Me_2CO in EtOAc (95:5, 85:15, 7:3, 5:5 and 4:6; *v/v%*; elution volume: 50 mL of each), resulting nine subfractions ($F10_{3.3.1}$-$F10_{3.3.9}$). Subfraction $F10_{3.3.5}$ (25 mg) was then purified by semi-preparative HPLC (MeOH/H_2O, isocratic 70:30; *v/v%*) to isolated compound **1** (0.7 mg, t_R 5.3 min). Additionally, part of the residue from fraction F11 (30 g, eluted with *n*-hexane/EtOAc [30:70]) was separated on a silica gel column chromatography (4.5 × 80 cm, 70-230 mesh, 500 g), using an *n*-hexane/Me_2CO isocratic elution (9:1; *v/v%*; elution volume: 20 L), resulting in eight subfractions ($F11_1$-$F11_8$). Subfraction $F11_6$ (1.78 g) was further purified using reverse-phase C-18 open column chromatography (2.5 × 20 cm, 45 g) with a MeOH/H_2O gradient (9:1, 95:5, and 1:0; *v/v%*; elution volume: 500 mL of each), leading to collection of nine subfractions ($F11_{6.1}$-$F11_{6.9}$). Subfraction $F11_{6.8}$ (263 mg, eluted with 100% MeOH) was further separated using silica gel column chromatography (1.5 × 52 cm, 70-230 mesh, 20 g), with an *n*-hexane/EtOAc gradient (8:2, 7:3, 6:4, 5:5; *v/v%*; elution volume: 300 mL of each), yielding to ten subfractions ($F11_{6.8.1}$-$F11_{6.8.10}$). Compound **2** (4.5 mg) was eventually isolated from subfraction $F11_{6.8.2}$.

Compound **1**: A colorless gum, $[\alpha]^{20}_D$ +6 (c 0.1, $CHCl_3$), ^{1}H and ^{13}C NMR data see Table 2, HRESIMS *m/z* 249.1119 $[M + H]^+$ (calcd for $C_{14}H_{17}O_4^+$, 249.1122).

Compound **2**: A yellowish gum, $[\alpha]^{20}_D$ +2 (c 0.1, $CHCl_3$), ^{1}H and ^{13}C NMR data, see Table 2, HRESIMS *m/z* 385.2752 $[M + H]^+$ (calcd for $C_{25}H_{37}O_3^+$, 385.2738).

3. Results and Discussion

The EtOAc extract of gum ammoniacum was subjected to multiple chromatographic techniques, including repeated column chromatography (CC), Sephadex LH-20, reverse-phase C-18 open column chromatography, and semi-preparative HPLC, resulting in isolation of two novel compounds, designated as compounds **1** and **2** (Fig. 2). These compounds were structurally characterized through comprehensive spectroscopic analysis, including ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{1}H COSY, HSQC-DEPT, HMBC, and NOESY techniques, HRESIMS, and by comparing their data with those reported in the literature.

3.1. Structural identification

Compound **1** was isolated as a colorless gum. HRESIMS analysis confirmed its molecular formula $C_{14}H_{16}O_4$, with a molecular ion peak at *m/z* 249.1119 (calcd for $[M + H]^+$ 249.1122). The ^{1}H-NMR spectrum suggested the presence of a 1,2,4-trisubstituted benzene ring,

Table 1
Experimental yield of all fractions.

Name of fractions	Amount (g)	Name of subfractions	Amount (g)	Name of subfractions	Amount (mg)	Name of subfractions	Amount (mg)	Name of subfractions	Amount (g)	Name of subfractions	Amount (mg)	Name of subfractions	Amount (mg)
F1	11.5	F101	6.3	F103.1	350.8	F103.3.1	32.1	F111	4.2	F116.1	125.3	F116.8.1	12.1
F2	27.4	F102	6.8	F103.2	200.3	F103.3.2	44.2	F112	3.8	F116.2	90.4	F116.8.2	6.1
F3	51.2	F103	4.2	F103.3	400.2	F103.3.3	36.5	F113	4.3	F116.3	101.3	F116.8.3	38.3
F4	52.8	F104	10.2			F103.3.4	33.6	F114	3.1	F116.4	180.6	F116.8.4	25.2
F5	25.1	F105	14.8			F103.3.5	25.4	F115	2.8	F116.5	185.2	F116.8.5	36.3
F6	76.5					F103.3.6	43.1	F116	3.4	F116.6	170.5	F116.8.6	23.4
F7	54.9					F103.3.7	29.2	F117	2.4	F116.7	285.3	F116.8.7	16.2
F8	34.2					F103.3.8	37.3	F118	3.8	F116.8	263.1	F116.8.8	35.1
F9	14.1					F103.3.9	63.1			F116.9	326.1	F116.8.9	20.2
F10	54.2											F116.8.10	15.6
F11	44.3												
F12	31.7												
F13	23.1												
F14	10.9												
F15	25.6												
F16	28.8												
F17	32.8												
F18	24.9												

Table 2
^{1}H and ^{13}C NMR spectroscopic data for compounds **1** and **2** ($CDCl_3$) (600 MHz for ^{1}H and 150 MHz for ^{13}C NMR; δ in ppm).

	1		2	
	δH (*J* in Hz)	**δC**	**δH (*J* in Hz)**	**δC**
1	5.07 d (10.8), 5.27 d (17.3)	112.2	3.33, qt (14.1, 7.0)	46.3
2	5.88, dd (17.3, 10.8)	143.3	2.14-2.20, m, 2.32-2.38, m	30.9
3	-	85.0	5.01-5.03, m	121.5
4	1.79-1.83, m, 1.92-1.98, m	36.6	-	137.5
5	1.43, s	26.6	1.87-1.92, m	39.9
6	-	-	1.89-1.93, m, 1.99-2.03, m	26.8
7	-	-	4.99-5.01, m	123.9
8	-	-	-	134.8
9	-	-	1.87-1.92, m	39.7
10	-	-	1.89-1.93, m, 1.99-2.03, m	26.8
11	-	-	5.05-5.07, m	124.4
12	-	-	-	131.3
13	-	-	1.65, s	25.9
14	-	-	1.52, s	16.2
15	-	-	1.52, s	15.9
16	-	-	1.57, s	17.8
17	-	-	1.62, d (8.8)	23.5
1′	-	111.8	-	114.2
2′	-	165.5	-	165.7
3′	6.38, brs	103.7	6.36, brs	103.4
4′	-	162.4	-	162.3
5′	6.36, brd (8.3)	107.9	6.34, brd (8.6)	107.6
6′	7.75, d (8.3)	132.2	7.65, d (8.6)	132.8
7′	-	201.9	-	208.5
8′	5.26, t (8.0)	78.9	3.84, s	55.6
9′	2.20-2.25, m, 2.27-2.31, m	29.4	-	-

a vinyl group, an oxygenated methine, two sp^3 methylenes, and one methyl group (Table 2). The ^{13}C NMR spectrum revealed 14 carbon signals, including a monosubstituted double bond, a carbonyl carbon, and four aromatic and aliphatic oxygen-bearing carbons. The 2D NMR spectra suggested the presence of a 3-methyl-3-vinyltetrahydrofuran moiety (C-1-C-5 and C-8′-C-9′), which was further supported by an HMBC correlation between H_2-1/H-2 with C-3; H_2-4 with C-2 and C-5; and H_3-5 with C-2, C-3, and C-4 (Fig. 3). HMBC cross-peaks of H_2-9′ and H-6′ with C-7′ confirmed the connection between C-8′ and the benzene ring (C-1′) via the carbonyl carbon (C-7′). NOESY correlations between H-2 and H-4α suggested that these protons are on the same side (Fig. 4). The *syn* conformation of the H-8′ and H_3-5 was indicated by a NOESY correlation between H_3-5 with H-8′. Therefore, the structure of compound **1** was established as shown in Fig. 2.

Compound **2** was obtained as a yellowish gum. HRESIMS analysis established its molecular formula as $C_{25}H_{36}O_3$, with a molecular ion peak at *m/z* 385.2752 (calcd for $[M + H]^+$ 385.2738) by HRESIMS. The NMR data of compound **2** closely resembled those of compound **3**, previously isolated from *Ferula mongolica* (Choudhary et al., 2001), except for an additional methyl group (δ_H/δ_C 1.26/23.5) at C-1. The location of this methyl group was confirmed by comparing the ^{1}H and ^{13}C NMR resonance at C-1 (**2**: CH, δ_H/δ_C 1.62/46.3; **3**: CH_2, δ_H/δ_C 2.97/40.7) and C-7′ (**2**: C, δ_C 208.5; **3**: C, δ_C 206.4), along with HMBC correlation from the methyl group to C-3 and C-4; H-1 to C-2, C-3, and C-7′; and H-3 to C-1, C-2, and C-5 in compound **2**. The relative configuration at C-1 was determined to be R, supported by NOE correlations were observed between H-1 and H-3. Hence, compound **2** was determined as 1,4′-*O*-dimethyldshamirone (Fig. 2).

We proposed a plausible biosynthetic pathway for compound **1** (Fig. 5). The process beings with the condensation of benzoyl CoA derivative (A) and

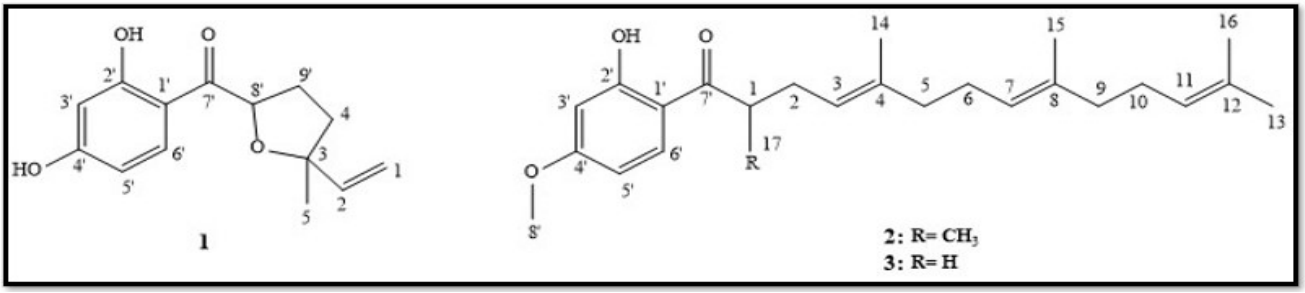

Fig. 2. Chemical structure of compounds **1** and **2**.

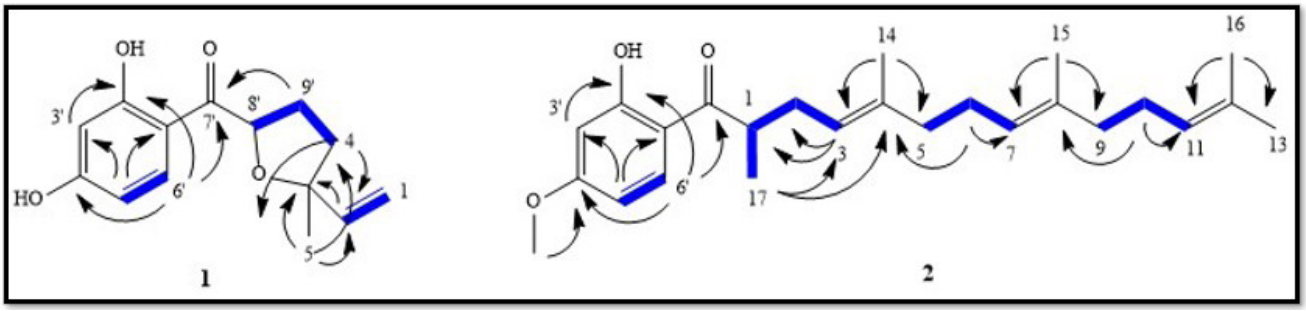

Fig. 3. Key COSY (blue bonds) and HMBC (black arrows) correlations for compounds **1** and **2**.

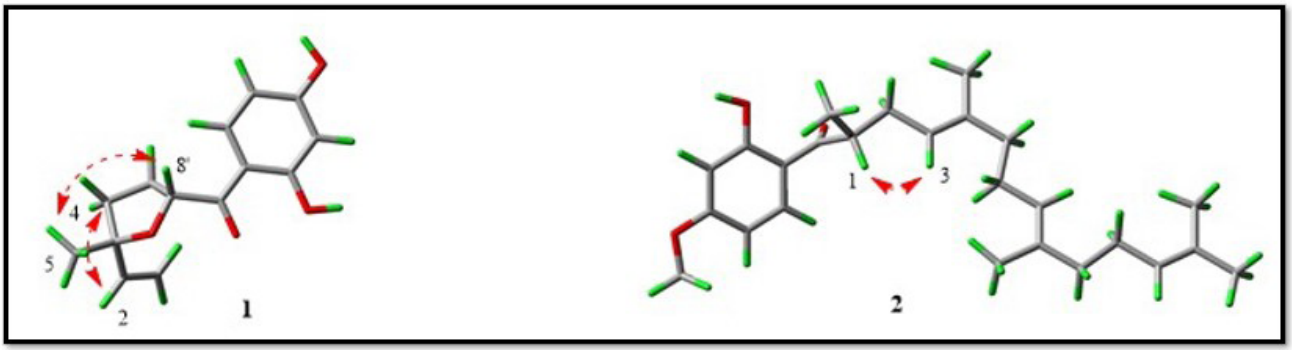

Fig. 4. Key NOESY correlations for compounds **1** and **2**.

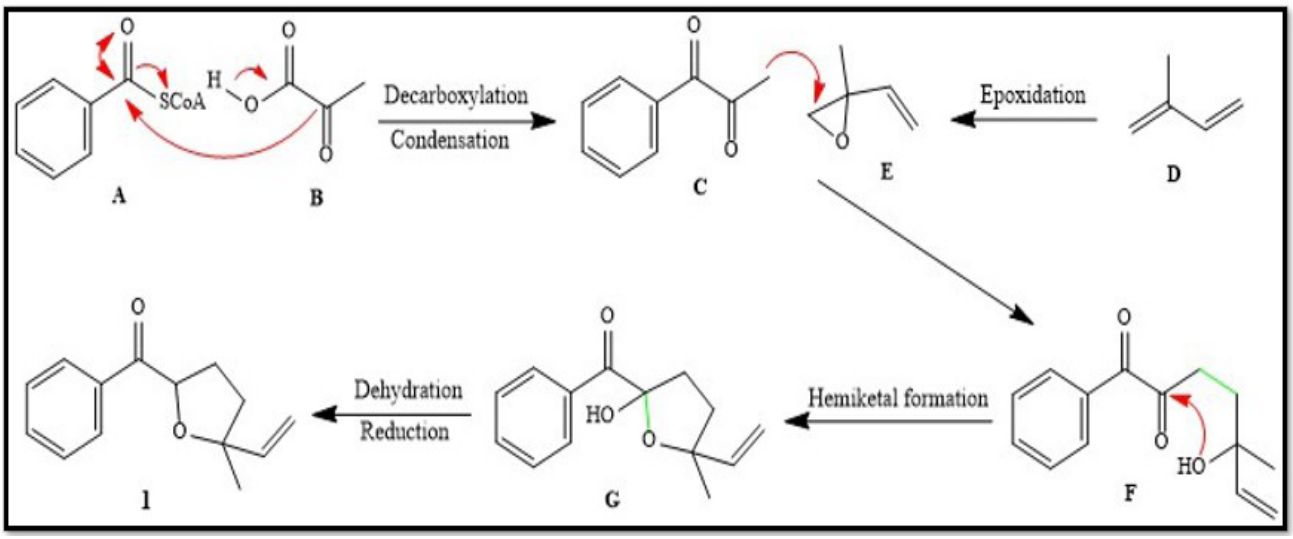

Fig. 5. Proposed biosynthesis pathway of compound **1**.

pyruvic acid (B), resulting in the formation of diketone (C). This diketone, then undergoes condensation with 2-methyl-2-vinyloxirane (E), which is produced via the epoxidation of isoprene unit (D), leading to the creation of intermediate (F). The pathway concludes with the formation of a hemiketal (G), followed by dehydration, and subsequent reduction, ultimately yielding compound **1** (Tanaka et al., 2016).

Compound **1** is a new meroterpenoid with an unprecedented skeleton, synthesized through the involvement of the acetate and mevalonate pathways, in addition to pyruvic acid. Meanwhile, compound **2** is a sesquiterpene derivative, with similar compounds previously reported in the Apiaceae family. Its structure closely resembles dshamirone, which was originally isolated from gum ammoniacum (Adhami et al., 2013). Dshamirone has also been identified in the roots of *Ferula dshaudshamyr* Korovin. (Kamilov and Nikonov, 1976), *Ferula ferulioides* (Steud.) Korov. (Kojima et al., 1998), and *Ferula heuffelii* Griseb. ex Heuff. (Pavlovic et al., 2015).

4. Concluding remarks

In conclusion, this study reports the discovery of two previously undescribed compounds from the EtOAc extract of gum ammoniacum, each comprising an aromatic moiety and a terpenoid segment (C-5 in **1** and C-15 in **2**). The structural elucidation was accomplished through comprehensive spectroscopic analyses, including 1D and 2D NMR, HRESIMS, with comparisons made to existing. Notably, compound **1** features an isoprenoid with a novel skeleton, and a plausible biosynthetic pathway for its formation has been proposed.

Acknowledgments

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Author contribution statement

Maryam Kharatha was responsible for conceptualization, conducting the literature search, and implementing experimental procedures. She also prepared the initial draft of the manuscript. Mahdi Moridi Farimani took charge of designing and coordinating the project. Mostafa Alilou measured the NMR spectra. All authors reviewed and approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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