

Coumarins from the Dichloromethane Root Extract of *Heptaptera triquetra* and Their Cytotoxic Activities

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Abstract: A known dihydrofuranocoumarin ester; deltoin (1), together with five known sesquiterpene coumarin ethers; umbelliprenin (2), farnesyl scopoletin (3), karatavicinol (4), colladonin (5), colladin (6), and a novel sesquiterpene coumarin ether; 14'-hydroxybadrakemin (7) were isolated from the cytotoxic dichloromethane extract of the roots of *Heptaptera triquetra*. The cytotoxic activity of the isolated coumarins were evaluated against COLO205 (colon), KM12 (colon), A498 (renal) and UO31 (renal) cancer cell lines.

Keywords: *Heptaptera triquetra*; Apiaceae; coumarins; cytotoxic activity. © 2023 ACG Publications. All rights reserved.

1. Introduction

Cancer still remains one of the leading causes of death worldwide [1]. The discovery of new compounds from natural sources to fight cancer has become a matter of great interest among researchers [2,3]. As part of our continuing studies on potential anticancer phytochemicals from Apiaceae family, we report here the cytotoxic compounds of *Heptaptera triquetra* (Vent.) Tutin which found in the European section of Turkey [4].

The genus *Heptaptera* Marg. & Reuter (Apiaceae) is represented by 11 species worldwide. Four of them, *H. cilicica* (Boiss. & Balansa) Tutin, *H. anisoptera* (DC.) Tutin, *H. anatolica* (Boiss.) Tutin and *H. triquetra* (Vent.) Tutin are growing in Turkey [4,5]. *Heptaptera* species are known to contain sesquiterpene coumarin derivatives [6-13]; these compounds have various biological activities such as cytotoxicity, P-glycoprotein inhibitory, carbonic anhydrase I and II isoenzymes inhibitory, cancer chemopreventive, anti-inflammatory, antibacterial, antileishmanial, antiviral, antidiabetic, and anticholinesterase activity. [8-20].

The sesquiterpene coumarin ethers with an umbelliferone nucleus are commonly found in the genera *Ferula* and *Heptaptera* of the Apiaceae family. Dioscorides and Avicenna described the use of sesquiterpene coumarin-containing *Ferula* gum-resins to treat tumors [21,22].

Initial screening of the root extract of *H. triquetra* confirmed the presence of cytotoxic compounds in the dichloromethane (DCM) extract, and isolation carried out on the DCM extract led to structure elucidation and identification of seven sesquiterpene coumarin ethers with potent and selective cytotoxic activities.

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2. Materials and Methods

2.1. General Experimental Procedures

Optical rotations were measured using an Autopol V Plus polarimeter (Rudolph Research Analytical, Hackettstown, NJ, USA). UV spectra were recorded on the Shimadzu UV-Vis Spectrophotometer, UV-1700 (Kyoto, Japan). Infrared spectra were acquired using an Alpha FT-IR Spectrometer (Bruker, MA, USA). NMR spectra were acquired on a Bruker BioSpin spectrometer (Rheinstetten, Germany) operating at 500 MHz for ^1H and 125 MHz for ^{13}C -NMR and on a Varian (Agilent) Mercury Spectrometer (Palo Alto, CA, USA) operating at 400 MHz for ^1H and 100 MHz for ^{13}C -NMR and equipped with a 5 mm probe in CDCl_3 . ^1H and ^{13}C spectra were referenced to the residual deuterated solvent peaks. HRESIMS data were acquired on an Agilent 6530 Accurate Mass Q-TOF instrument (Santa Clara, CA, USA) and a Triple TOF 5600 mass spectrometer (AB SCIEX, Framingham, MA, USA). The dichloromethane extract was initially purified on a Sephadex LH-20 (GE Healthcare, Chicago, IL, USA) column. Further purification of column fractions was performed using preparative silica gel F254 PLC plates (1 mm thickness) (Merck KGaA, Darmstadt, Germany).

2.2. Plant Material

The roots of *H. triquetra* were collected in the vicinity of Tekirdağ in July 2013 and identified by Prof. Ahmet Duran. A voucher specimen [A. Duran 9704, (KNYA)] was deposited in the Herbarium of Selçuk University. The root material was cut into narrow slices and dried in a well-ventilated area protected from sun light.

2.3. Extraction and Isolation

Air-dried and pulverized root (50 g) of *H. triquetra* was extracted by maceration sequentially with dichloromethane (1.5 L) and methanol (2 L) and concentrated *in vacuo*, to yield crude extracts. Dichloromethane and methanol extracts of the roots were 2.15 g and 4.77 g, respectively. The methanol extract was dissolved in a mixture of methanol/water (10:90) and then partitioned with ethyl acetate (EtOAc); the resulting extracts were separately concentrated *in vacuo* to dryness. Ethyl acetate and aqueous-methanol extracts of the roots were 0.58 g and 4.05 g, respectively.

The dichloromethane extract (2g) was chromatographed on Sephadex LH-20 column (4.5x100 cm), eluted with a hexane/dichloromethane/methanol (14:9:1) mixture to afford 78 fractions, monitored by TLC. The fractions which had the same spots on TLC plates were combined. Compound **2** (132 mg) was precipitated from the combined fractions 9-14. The combined fractions 15-17 were subjected to prep. TLC (1 mm thickness, silica gel F254 developed with cyclohexane/ethyl acetate, 7:3) and compound **3** (1 mg) was obtained. Compound **6** (160 mg) was crystallized from the combined fractions 22-38. The fractions 48-52 were combined and subjected to prep. TLC with cyclohexane/ethyl acetate (1:1) solvent system to yield compound **1** (3 mg). Compound **5** (240 mg) was crystallized from the combined fractions 65-68. The fractions 71-74 were combined and subjected to prep. TLC with cyclohexane/ethyl acetate (1:1) solvent system to yield compounds **4** (2.5 mg) and **7** (2.5 mg).

Hydrolysis of 14'-acetoxybadrakemin (**8**): 20 mg of 14'-acetoxybadrakemin (**8**) (isolated from *Heptaptera anatolica* [8]) was dissolved in 5% NaOH/EtOH solution (3 mL) and left for 6 h at room temperature; the usual work-up gave 12 mg of 14'-hydroxybadrakemin (**7**).

14'-Hydroxybadrakemin (**7**): white amorphous powder, $[\alpha]_{\text{D}}^{25}$ -19.2 (c 0.6, CH_2Cl_2); IR (NaCl) ν_{max} 3401, 3079, 2939, 1727, 1709, 1613, 1555, 1508, 1473, 1403, 1352, 1282, 1231, 1128, 1023, 892, 835 cm^{-1} ; UV (MeOH) λ_{max} (log ϵ): 324 (4.23), 298 (sh) (4.03), 218 (sh) (4.32); ^1H and ^{13}C -NMR (see Table 1); +HRESIMS m/z 399.2168 $[\text{M}+\text{H}]^+$ ($\text{C}_{24}\text{H}_{31}\text{O}_5$, calcd. for 399.2172; err. 1.0 ppm).

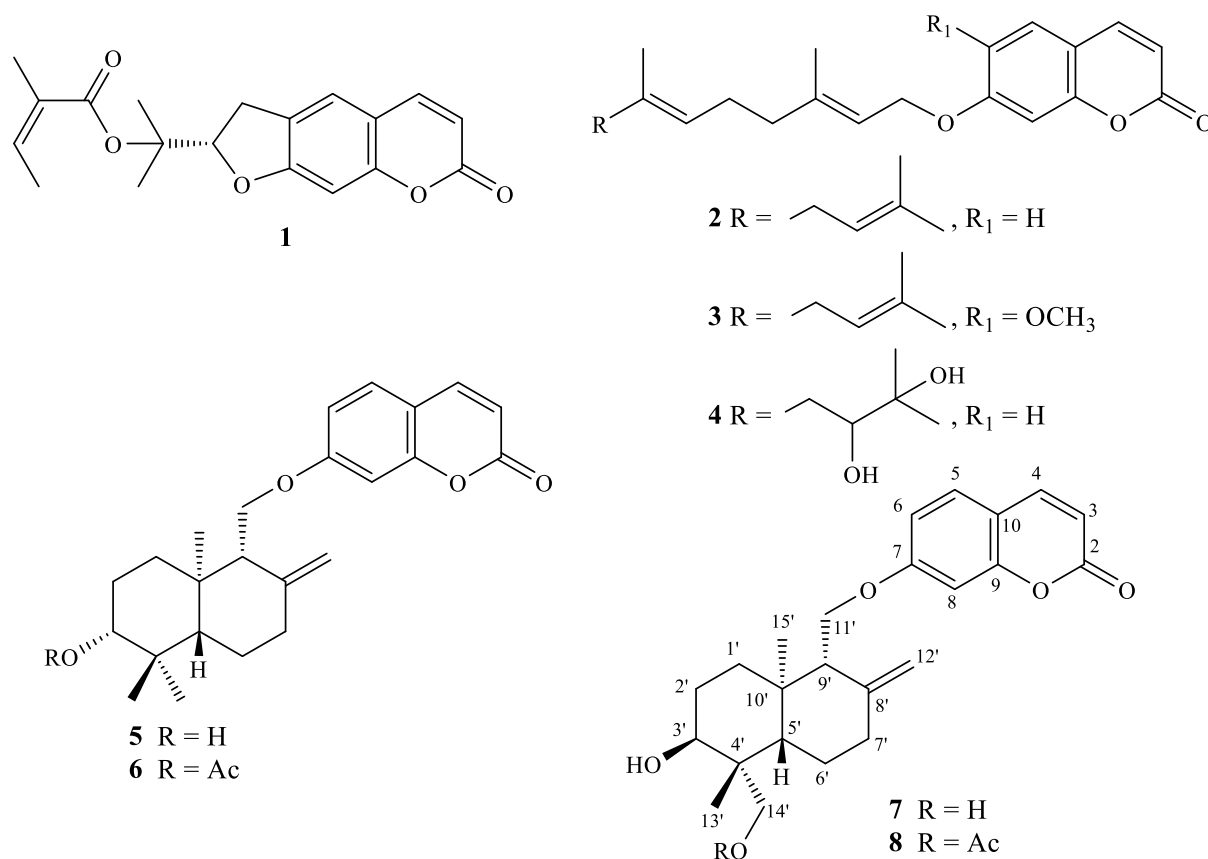
Coumarins from *Heptaptera triquetra*

Figure 1. Structures of the coumarins isolated from the dichloromethane extract of the roots of *Heptaptera triquetra*

2.4. Cytotoxicity Assay on Renal Cancer Cell Lines

The assay used for this study was a two-day, two-cell line XTT bioassay [23], an *in vitro* antitumor colorimetric assay developed by the MTP Assay Development and Screening Section. The renal cancer cell lines used were UO31 and A498. Colon cancer cell lines were COLO205 and KM12. The assay was performed as described previously [9].

3. Results and Discussion

3.1. Structure Elucidation

The fractionation of the dichloromethane extract of the roots of *H. triquetra* yielded a dihydrofuranocoumarin ester, deltoin (**1**), and known sesquiterpene coumarin ethers; umbelliprenin (**2**), farnesyloscopoletin (**3**), karatavicinol (**4**), colladonin (**5**), and colladin (colladonin acetate) (**6**), as well as a new sesquiterpene coumarin ether, 14'-hydroxybadrakemin (**7**) (Figure 1). Known coumarin derivatives were identified by comparing their spectroscopic data with those reported previously [8,9,24,25] and by direct comparison with the reference compounds where available.

The positive high-resolution electrospray ionization mass spectroscopy (HRESIMS) spectrum of new coumarin (**7**) (Supporting Information, Figure S1) displayed a protonated molecular peak at m/z 399.2168 $[M+H]^+$ ($C_{24}H_{31}O_5$, calcd. for 399.2172) confirmed a $C_{24}H_{30}O_5$ molecular formula with ten degrees of unsaturation. The 1H -NMR spectrum of **7** was almost identical to that of 14'-acetoxybadrakemin (**8**) [8] except the lack of acetyl methyl signal at δ 2.04 ppm and ca. 0.44 ppm upfield shift of the C14'a and C14'b proton doublets indicating that compound **7** is the C-14' desacetyl

derivative of the 14'-acetoxybadrakemin (**8**). The ^{13}C -NMR (Table 1) and 2D-COSY, HSQC, HMBC, and NOESY spectra (Figures 2 and 3, Supporting Information, Figures S5-S8) also confirm the structure of **7** as 14'-hydroxybadrakemin. Furthermore, 14'-hydroxybadrakemin (**7**) was prepared by the basic hydrolysis of 14'-acetoxybadrakemin (**8**) (see experimental section), semi-synthetic 14'-hydroxybadrakemin was found to be identical to that of natural compound **7**.

Table 1. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) data of 14'-Hydroxybadrakemin (**7**) (in CDCl_3).

Position	δ_{H} (in ppm, m, J in Hz)	δ_{C} (in ppm)
2	–	161.44
3	6.23; d; 9.5; 1H	113.33
4	7.62; d; 9.5; 1H	143.60
5	7.34; dd; 8.0, 2.0; 1H	128.85
6	6.82; dd; 8.0, 2.2; 1H*	113.09
7	–	162.41
8	6.81; bs, 1H*	101.45
9	–	156.03
10	–	112.59
1' α	1.53; m; 1H	32.00
1' β	1.88; m; 1H	
2' α	1.72; m; 1H**	25.86
2' β	1.93; m; 1H	
3'	3.94; bm; 1H	70.32
4'	–	43.14
5'	1.78; dd; 2.8, 13.0; 1H**	49.06
6' α	1.38; dq; 4.3, 13.0; 1H	23.79
6' β	1.74; m; 1H**	
7' α	2.44; ddd; 13.3, 4.3, 2.4; 1H	37.90
7' β	2.09; btd; 13.1, 4.8; 1H	
8'	–	146.43
9'	2.33; bdd; 6.5, 4.1; 1H	54.94
10'	–	38.70
11'a	4.21; dd; 9.7, 4.1; 1H	65.82
11'b	4.15; dd; 9.7, 7.8; 1H	
12'a	4.89; bs; 1H	107.93
12'b	4.53; bs; 1H	
13'	1.11; s; 3H	22.12
14'a	3.75; d; 11.0; 1H	66.24
14'b	3.52; d; 11.0; 1H	
15'	0.81; s; 3H	16.36

*, ** Partially overlapped signals

3.2. Chemotaxonomic Significance

The genus *Heptaptera* Marg. & Reuter has 11 species worldwide and four of them; *H. cilicica* (Boiss. & Balansa) Tutin, *H. anisoptera* (DC.) Tutin, *H. anatolica* (Boiss.) Tutin and *H. triquetra* (Vent.) Tutin are found in Türkiye [4,5]. *Heptaptera triquetra* (Vent.) Tutin is the only species growing in the European section of Türkiye [4].

Heptaptera species are known to contain sesquiterpene coumarin derivatives; however, so far, only ethers of the bi-cyclic drimanyl or acyclic farnesyl sesquiterpene derivatives with the 7-hydroxyl group of umbelliferone were isolated from the *Heptaptera* species growing in Anatolian peninsula [6-9]. In contrast, *Heptaptera triquetra*, the only species growing in the European part of Türkiye, afforded a dihydrofuranocoumarin [i.e., deltoin (**1**)] and farnesyl ether of scopoletin (**3**) in addition to the usual sesquiterpene coumarin ether derivatives. The presence of dihydrofuranocoumarin compounds in *H.*

Coumarins from *Heptaptera triquetra*

triquetra indicates that this species may have a chemotaxonomical affinity to other dihydrofuranocoumarin-bearing genera within the Apiaceae family, such as *Opopanax* [26,27] and *Smyrniopsis* [28]. Interestingly, the sesquiterpene ethers of methoxylated coumarins were mainly isolated from the roots of Asteraceae plants such as *Achillea* [29-31], *Artemisia* [31,32], and *Conyza* [24] species, the presence of a sesquiterpene ether of a methoxylated coumarin in an Apiaceae species is the first example of such an occurrence. Previously, R. Hegnauer discussed the presence of triterpenes, polyacetylenic compounds, chromones, germacranolides, and guaianolides [33] in both Asteraceae and Apiaceae plants. However, the presence of rare sesquiterpene coumarin ether of methoxylated coumarins has not been reported from the Apiaceae plants.

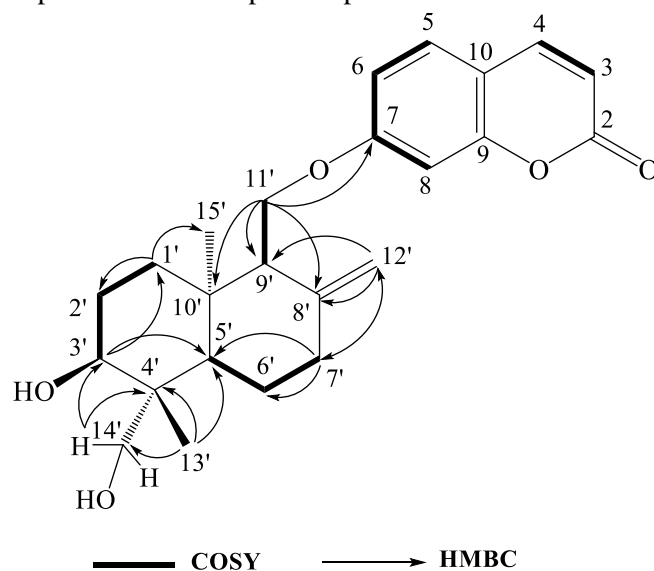


Figure 2. Key COSY and HMBC correlations of 14'-Hydroxybadrakemin (7)

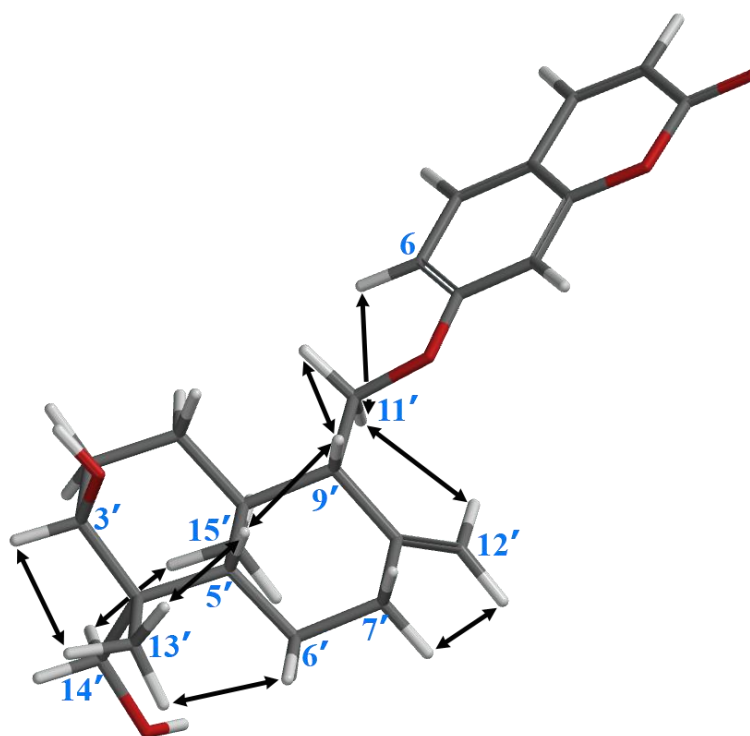


Figure 3. NOE interactions observed in the 2D NOESY spectrum of 14'-hydroxybadrakemin (7)

3.3. Cytotoxic Activity

The highest cytotoxic activities were observed in the dichloromethane extracts of the roots against KM12 and COLO205 cancer cell lines with IC₅₀ values 3.6 and 8.7 µg/mL, respectively. Whereas, both ethyl acetate and aqueous methanol extracts did not show cytotoxic activities against KM12 and COLO205 cancer cell lines up to 50 µg/mL concentrations (Table 2).

Table 2. Cytotoxic activities (IC₅₀, µg/mL) of the extracts obtained from the roots of *H. triquetra*

Extracts	CH ₂ Cl ₂	EtOAc	Aq. MeOH
COLO205	8.7	> 50	> 50
KM12	3.6	> 50	> 50

Table 3. Inhibitory concentration (IC₅₀, µM) values of coumarins isolated from *H. triquetra*

Compounds	Cytotoxic Activity (IC ₅₀ values in µM)			
	COLO205	KM12	A498	UO31
1	45	>50	>50	>50
2	>50	>50	>50	1.8
3	>50	>50	>50	>50
4	>50	>50	>50	7.6
5	19	2.5	21	0.75
6	>50	29	>50	0.39
7	>50	36.8	>50	>50

We previously reported the cytotoxic activity of umbelliprenin (**2**), karatavicinol (**4**), colladonin (**5**), and colladin (**6**), in UO31, A498, COLO205, KM12, A673, and TC32 cell lines [9]. Deltoin (**1**) exhibited weak cytotoxic activity against the COLO205 cancer cell line. 14'-hydroxybadrakemin (**7**) also showed weak cytotoxic activity against the KM12 cancer cell line. Farnesyl scopoletin (**3**) did not show cytotoxic activity against COLO205, KM12, A498, or UO31 cancer cell lines up to 50 µM concentration.

This is the first report of the cytotoxic activities of deltoin (**1**), farnesyl scopoletin (**3**), and 14'-hydroxybadrakemin (**7**) against UO31, A498, COLO205, and KM12 cell lines.

4. Conclusion

In 1970, Ban'kovski et al. reported colladin (**6**) and colladonin (**5**) from *Colladonia triquetra* (synonym of *Heptaptera triquetra*) [34]. In 2022 Kaya et al. reported umbelliprenin (**2**), colladonin (**5**), karatavicinol (**4**) and badrakemin acetate from the dichloromethane extract of the roots of *Heptaptera triquetra* [12]. In this study, farnesyl scopoletin (**3**), deltoin (**1**), and a new coumarin 14'-hydroxybadrakemin (**7**) were isolated for the first time from *H. triquetra*. Farnesyl scopoletin was earlier isolated from *Artemisia persica* and *Conyza* species (Asteraceae) [24,32] and deltoin from *Peucedanum japonicum* and *Ferula lutea* [25,35]. Recently, we reported umbelliprenin, karatavicinol, colladonin, and colladin from the dichloromethane extract of the roots of *H. cilicica* [9]. The chemotaxonomical significance of deltoin and farnesyl scopoletin in *Heptaptera triquetra* was two-fold. While the presence of deltoin highlights the bridging status of *H. triquetra* between *Heptaptera* and other dihydrofuranocoumarin-bearing genera of Apiaceae family such as *Opopanax* and *Smyrniopsis*, the presence of farnesyl scopoletin, a sesquiterpene ether of a methoxylated coumarin, corroborates the evolutionary connectivity between the Apiaceae and Asteraceae families.

Coumarins from *Heptaptera triquetra***Acknowledgments**

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Supporting Information

Supporting information accompanies this paper on <http://www.acgpubs.org/journal/records-of-natural-products>

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