

## A New Cynaropicrin Derivative from *Cynara Scolymus* L.

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**Abstract:** A new sesquiterpene lactone **1a** along with other four known compounds **1b**, **2**, **3** and **4** were isolated from fresh leaves of *Cynara scolymus* L. using ordinary chromatographic techniques. The structures of the isolated compounds were determined via spectroscopic analysis.

**Keywords:** *Cynara scolymus*; sesquiterpene lactones; dihydrocynaropicrin; tetrahydrocynaropicrin; pinoselinol; luteolin. © 2020 ACG Publications. All rights reserved.

### 1. Introduction

Globe artichoke (*Cynara cardunculus* var. *scolymus* Fiori), formerly *Cynara scolymus* L., Asteraceae family, is an ancient herbaceous perennial plant, originating from the Mediterranean area. It's cultivated, worldwide, for its leaves, the large immature capitula with edible fleshy bracts and receptacle [1]. In addition of being consumed as a food, *C. scolymus* is recognized as herbal medicine [2]. Leaves which are rich in polyphenols are mostly utilized in nutraceuticals for the production of commercial extracts [3]. Flower heads and roots are used as prebiotic ingredient in functional foods due to their inulin content [3]. Several health promoting effects of artichoke extracts have been demonstrated including hepatoprotective [4], choleric [5], anticholestatic [6], antioxidative [7], hypolipidemic [8], antispasmodic [9], antimicrobial [10] and antihypercholesterolemic effects [11]. Additionally, artichoke extracts have shown antitumor [12], analgesic and anti-inflammatory [13] activities. Phytochemical studies of *C. scolymus* revealed the presence of several classes of compounds such as caffeoylquinic acids derivatives, sesquiterpene lactones, flavonoids, saponins, phenolic acids [14] and the sesquiterpene glycosides; cynarascosides A, B, and C [8]. Whereas, anthocyanins were present only in the capitula of this plant [15]. Chlorogenic acid and 1,5-dicaffeoylquinic acids are the predominant compounds among hydroxycinnamates of *C. scolymus* [2]. A published review on the sesquiterpene lactone cynaropicrin, indicated that it contributes to approximately 80% of the characteristic bitterness of artichoke, reported to have vital biological activities as anti-HCV, antiparasitic, antihyperlipidemic, antifeedant, antiphotaging, antioxidant, antibacterial, anti-inflammatory, anti-gastritis and antitumor [16].

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Owing to the valuable biological activities of *C. scolymus*, this study aims to revisit this plant to explore the presence of additional sesquiterpene lactones and other constituents that may contribute to such biological activities.

## 2. Materials and Methods

### 2.1. General

Rotary flash evaporator (Büchi, Switzerland), UV lamp 254 and 366 nm, Desaga (Germany), UV-visible spectrophotometer, Shimadzu 1601 PC, model TCC240 (Shimadzu, Kyoto, Japan), Mass spectrometry (HRAM/MS) spectra were obtained using a Thermo Scientific UPLC RS Ultimate 3000-Q Exactive hybrid quadrupole-Orbitrap mass spectrometer combines high-performance quadrupole precursor selection with high-resolution, accurate-mass (HR/AM) Orbitrap™ detection, Infra-red spectrophotometer, Thermo Scientific Nicolet™ iS™10 FT-IR Spectrometer (Thermo Fisher scientific Co., Madison, WI, USA), Thin-layer chromatography (TLC) was performed using pre-coated silica gel 60 GF<sub>254</sub> (20 x 20 cm, 0.2 mm thick) on aluminum sheets (Merck, Darmstadt, Germany) and pre-coated reversed phase C<sub>18</sub> silica gel glass plates, Partisil® KC<sub>18</sub>F Silica gel 60A with fluorescent indicator (5 x 20 cm, 200 µm layer thickness). Vanillin-sulfuric acid (5%), 5% aluminum chloride, ferric chloride spray reagents. Nuclear magnetic resonance spectra (<sup>1</sup>H NMR, <sup>13</sup>C NMR, APT and other 2D spectra) were recorded with Bruker Avance III spectrophotometer at 400 MHz for proton and at 100 MHz for carbon. For column chromatography; glass columns of different dimensions were used, normal phase chromatography was carried out using silica gel G 60-230 (Merck, Darmstadt, Germany) packed by the wet method in the stated solvent, gel permeation chromatography was carried out using Sephadex LH-20 (SIGMA-ALDRICH, Missouri, USA) in a medium pressure column and reversed phase chromatography was performed using phase-bonded octadecylsilyl-silica gel (RP-C<sub>18</sub>, BAKERBOND® Octadecyl, C<sub>18</sub>) 40 µm, Prep LC Packing (Phillipsburg, NJ, USA).

### 2.2. Plant Material

The plant material was collected in February 2017, from Agricultural Research Center farm, Dakahlia, Egypt. The plant identity was confirmed by Prof. Dr. Ibrahim Mashaly, Department of Botany, Faculty of Science, Mansoura University, Egypt. A voucher specimen 02-17-CS-Mansoura was deposited at the Herbarium of Faculty of Pharmacy, Mansoura University. The leaves were collected, milled and kept for phytochemical investigations.

### 2.3. Extraction and Isolation

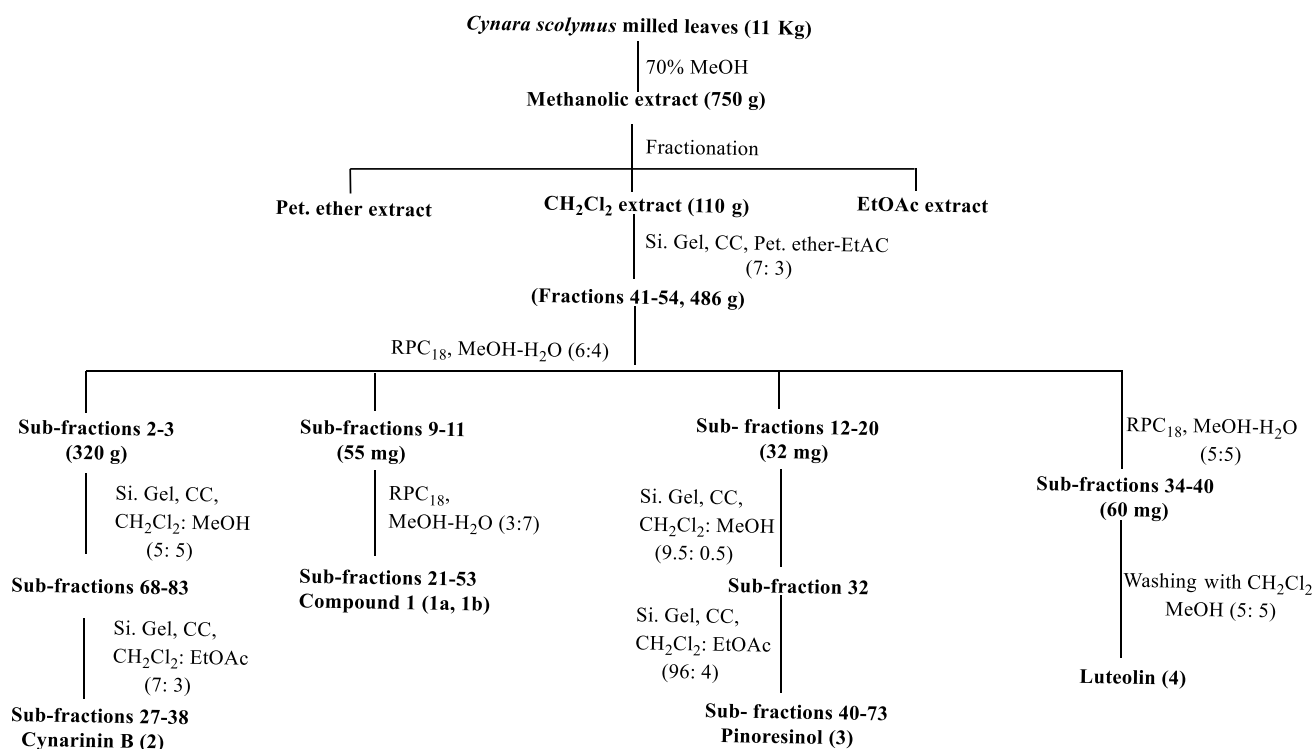
In the present study, the CH<sub>2</sub>Cl<sub>2</sub> fraction (110 g) of MeOH extract was coarsely fractionated over a silica gel column (20 x 4.5 cm i.d., 215 g) using gradient elution with petroleum ether-EtOAc, mixtures up to 100 v/v EtOAc. The effluents, 250 mL each, were collected, concentrated and similar fractions were combined into 17 groups. Four selected groups were used for the isolation of compounds **1-4** as outlined in Figure 1.

Fractions 41-54 (Gr.1), 486 mg, eluted with petroleum ether-EtOAc (70: 30 v/v) displayed 3 major spots, R<sub>f</sub> 0.71, 0.57 and 0.51, using MeOH-water (6: 4 v/v) as a solvent system and RP-C<sub>18</sub> silica gel glass plates. The fraction was rechromatographed over a RP-C<sub>18</sub> column (15 x 4.5 cm i.d., 200 g) and eluted with gradient elution with MeOH-H<sub>2</sub>O mixtures starting with MeOH-H<sub>2</sub>O (40: 60 v/v) till 100 % MeOH. The effluents, 10 mL fraction each, were collected and screened by TLC. Similar fractions were collected. Sub-fractions 2-3 (Gr.1A), 320 mg, eluted with MeOH- H<sub>2</sub>O (40: 60 v/v), displayed three spots, R<sub>f</sub> 0.19, 0.32 and 0.43, using CH<sub>2</sub>Cl<sub>2</sub>- MeOH (9.5: 0.5 v/v) as a solvent system and normal silica gel plate, two of them are major spots. The collected fraction was rechromatographed over normal silica column (35 x 2 cm i.d., 200 g) and eluted with gradient elution with CH<sub>2</sub>Cl<sub>2</sub>- MeOH

mixtures, (100: 0 v/v) till (0: 100 v/v). The effluents (20 mL) were collected and screened by TLC. Similar fractions were collected; sub-fractions 68-83, 64.4 mg, eluted with CH<sub>2</sub>Cl<sub>2</sub>- MeOH (50: 50 v/v) were collected and further purified over normal silica gel column (18 x 0.7 cm i.d., 2.5 g) and gradient-eluted with CH<sub>2</sub>Cl<sub>2</sub>- EtOAc mixtures, (100: 0 v/v) till (0: 100 v/v). The effluents (100 mL) were collected and screened by TLC. Similar fractions were collected; sub-fractions 27-38, eluted with CH<sub>2</sub>Cl<sub>2</sub>- EtOAc (7: 3 v/v), were collected and further purified over Sephadex LH20 column using isocratic elution with 100% CH<sub>2</sub>Cl<sub>2</sub> to afford compound **2** (Fr.1- 6), 40 mg.

Sub-fractions 9-11 (Gr.1B), 55 mg, eluted with MeOH- H<sub>2</sub>O mixtures (40: 60 v/v) displayed one major spot, R<sub>f</sub> 0.29 using MeOH- H<sub>2</sub>O mixtures (5: 5 v/v) as a solvent system and C<sub>18</sub> silica gel glass plates. The fraction was re-purified on RP-C<sub>18</sub> column using gradient elution starting with MeOH- H<sub>2</sub>O (30: 70 v/v) till (33: 67 v/v) and fractions of 10 mL were collected to afford compound **1** (sub-fractions 21-53), 45 mg. Sub-fractions 12-20 (Gr.1C), 32 mg, eluted with MeOH- H<sub>2</sub>O (40: 60 v/v), were re-chromatographed over normal silica column (16 x 0.7 cm i.d., 2 g) and gradient-eluted with CH<sub>2</sub>Cl<sub>2</sub>- MeOH mixtures, (100: 0 v/v) to (80: 20 v/v). The effluents, 10 mL fraction each, were collected and screened by TLC. Similar fractions were collected; sub-fraction 32, 8 mg, eluted with CH<sub>2</sub>Cl<sub>2</sub>- MeOH (9.5: 0.5 v/v), was further purified over normal silica column (5 x 0.5 cm i.d., 0.5 g) and eluted with gradient elution with CH<sub>2</sub>Cl<sub>2</sub>-EtOAc mixtures started with 100% CH<sub>2</sub>Cl<sub>2</sub> till (95: 5 v/v). The effluents (1 mL) were collected and screened by TLC. Similar fractions were collected; sub-fractions 40-73, eluted with CH<sub>2</sub>Cl<sub>2</sub>- EtOAc (96: 4 v/v) were collected to afford compound **3**, 4.5 mg.

Sub-fractions 34-40 (Gr.1D), 60 mg, eluted with MeOH- H<sub>2</sub>O (50: 50 v/v), displayed one major spot, R<sub>f</sub> 0.63 using CH<sub>2</sub>Cl<sub>2</sub>- MeOH (9.5: 0.5 v/v) as a solvent system and normal silica gel plate and acquired yellow color after heating with vanillin/sulfuric acid. The formed precipitate washed three times with CH<sub>2</sub>Cl<sub>2</sub>- MeOH mixture (5:5 v/v) to afford compound **4**, 40 mg.



**Figure 1.** Isolation procedures of compounds **1- 4**

We were able to identify a new cynaropicrin derivative (**1a**) from the CH<sub>2</sub>Cl<sub>2</sub> fraction of the methanol extract of fresh *C. scolymus* leaves. This new derivative was isolated as a mixture with the known sesquiterpene lactone, 11,13-dihydrocynaropicrin (**1b**) [17]. Different techniques were used in isolation including repeated column chromatography using silica gel, RP-C<sub>18</sub> or Sephadex LH-20. Extensive 1D and 2D NMR spectroscopic analyses were applied for the structural elucidation.

Moreover, the isolation procedures afforded three other known compounds; the sesquiterpene lactone cynarinin B (**2**), the lignan pinoresinol (**3**) and the flavonoid luteolin (**4**).

### 3. Results and Discussion

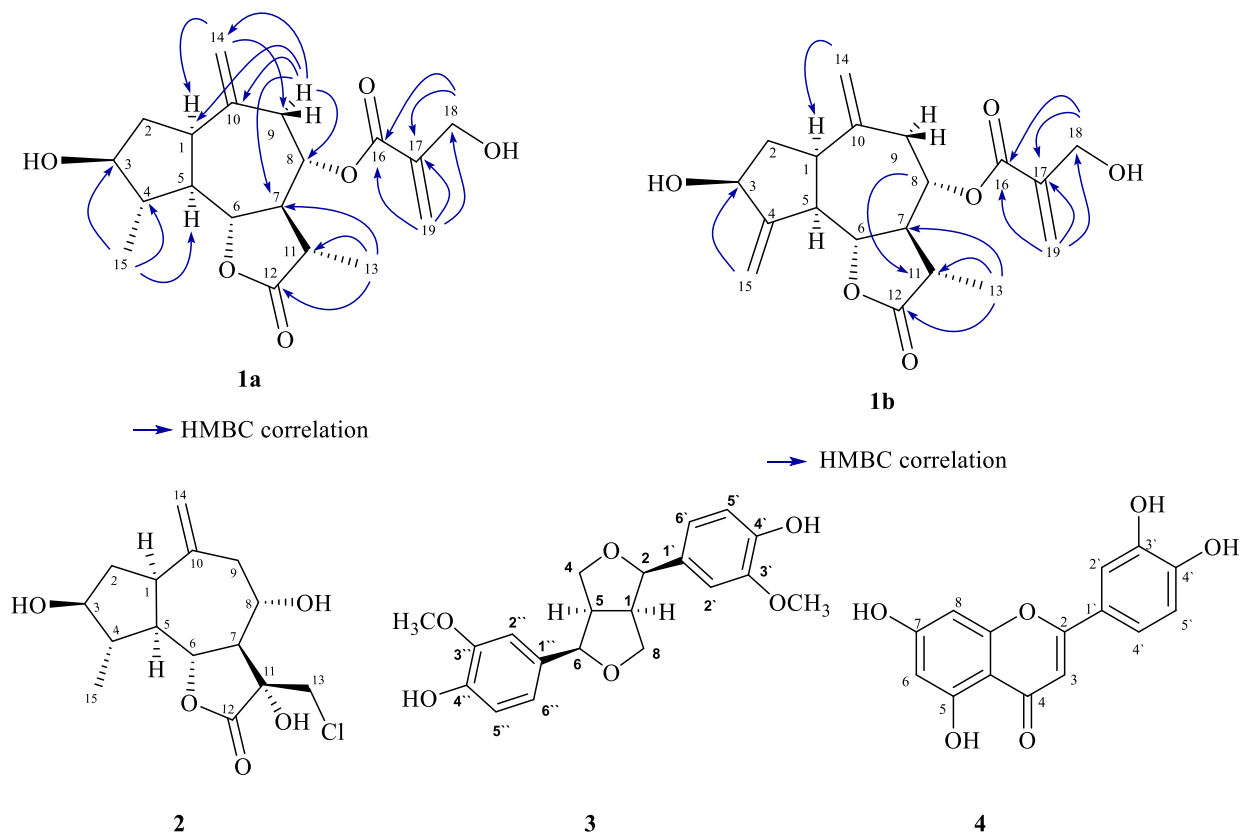
#### 3.1. Structure Elucidation

Compound **1** (20 mg) was obtained as a transparent to slightly yellowish viscous oil. Careful examination of the  $^1\text{H}$ - and APT spectra and correlating the data from them with that obtained from both HSQC and HMBC suggested the presence of three methyls, eleven methylenes, thirteen methines, and nine quaternary carbons, two of them are  $\gamma$ -lactone carbonyls. This data suggests that **1** is a mixture of two sesquiterpene lactones **1a** and **1b**. This was further supported by data obtained from HRMS that showed clear two molecular ion peaks at  $m/z$  395.1710 and 393.1550 [ $\text{M}^+ \text{HCOO}^-$ ] (calcd. 395.1706 and 393.1549), respectively. So, we suggested that one of the derivatives is the dehydro form of the other one and this is supported by the dehydration process occurring during the biosynthetic pathway of this series of compounds due to activity of NADP enzyme [18]. Data from 1D and 2D spectra revealed that one of the two compounds (**1a**, Figure 2) possesses 19 carbons established for two methyls, five methylenes, seven methines, and four quaternary carbons. The resonance at  $\delta_c$  176.6 was assigned to a  $\gamma$ -lactone carbonyl carbon (C-12). The two methyl signals at  $\delta_c$  15.4 and 18.3 corroborated to the proton signals at  $\delta_H$  1.25 (3H, s) and 1.19 (3H, *br.s*) were assigned by HSQC experiment (Figure S10) and further confirmed by HMBC experiment (Figure 2 and S12) to  $\text{CH}_3$ -13 and  $\text{CH}_3$ -15, respectively. The  $^1\text{H}$  NMR spectrum displayed two broad singlets at  $\delta_H$  5.10 (1H) and 5.11 (1H) attributable to a pair of vinylic hydrogens of an exomethylene group ( $\text{H}_2$ -14) which were assigned to the carbon resonance at  $\delta_c$  116.3 (C-14), based on HSQC correlation with C-14 and HMBC correlations between these protons (i.e.  $\text{H}_2$ -14) and carbon signals at  $\delta_c$  42.3 (C-1) and 42.4 (C-9). Three oxygenated carbons were displayed by APT spectrum at  $\delta_c$  78.0, 81.0 and 76.9, were assigned to C-3, C-6 and C-8, respectively. These spectroscopic data were consistent with those of a guaianolide-type sesquiterpene lactone. The downfield shift of H-8 at  $\delta_H$  4.94 (1H, *br.s*) and the deshielded C-8 at  $\delta_c$  76.9 evidenced the acylation of the hydroxyl group at this position [19]. The presence of four carbon resonances at  $\delta_c$  165.2 (C=O), 139.9 (C), 126.3 ( $\text{CH}_2$ ) and 62.0 ( $\text{CH}_2\text{OH}$ ) were assigned to C-16, C-17, C-19 and C-18, respectively of the acyl moiety at C-8. HSQC spectrum correlated the proton singlet at  $\delta_H$  4.35 (2H) to the hydroxymethylene C-18 and the broad singlet at  $\delta_H$  5.94 (2H) to the exomethylene C-19. The proton signal  $\text{H}_2$ -18 showed HMBC correlations with C-16 and C-17, whereas the proton signal  $\text{H}_2$ -19 showed HMBC correlations with C-16, C-17 and C-18 (Figure 2) confirming their assignments. Therefore, the ester's side chain at C-8 was defined as 4-hydroxymethacrylate.

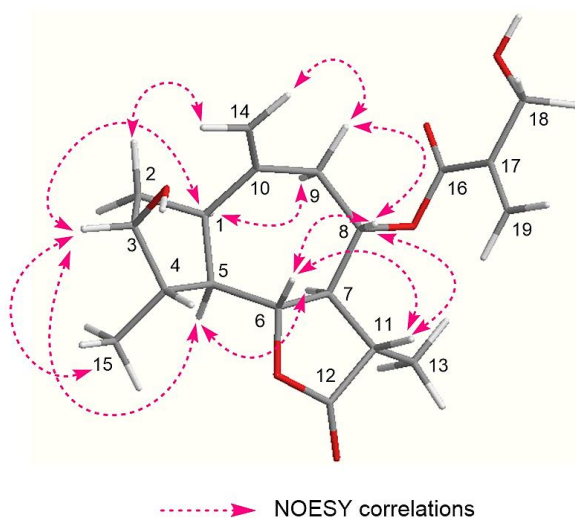
The stereochemical configuration was related to cynaropicrin [20, 21], meanwhile the NOESY correlations allowed the determination of H-13 and 1-15 orientation. NOESY correlations (Figure 3) between H-11 at  $\delta_H$  2.50 (1H, *m*) with H-8  $\delta_H$  4.94 (1H, *br.s*) and H-6  $\delta_H$  4.04 (1H, *t*,  $J = 8.0$ ) allowed the determination of  $\text{CH}_3$ -13 as  $\alpha$ -oriented. NOESY correlation between H-3 at  $\delta_H$  3.71 (1H, *br.s*) with H-1 at  $\delta_H$  2.62 (1H, *m*), H-5 at  $\delta_H$  1.95 (1H, *m*) and  $\text{CH}_3$ -15 at  $\delta_H$  1.19 (3H, *br.s*), allowed the determination of  $\text{CH}_3$ -15 as  $\alpha$ -oriented. The absence of NOESY correlations (Figure 3) between H-6 at  $\delta_H$  4.04 (1H, *t*,  $J = 8.0$  Hz) and both of H-5 at  $\delta_H$  1.95 (1H, *m*) and H-7 at  $\delta_H$  2.20 (1H, *m*) indicated that the cycloheptene ring and the  $\gamma$ -lactone ring were *trans*-fused. The spectral data of **1a** were highly similar to the previously reported data for cynaropicrin [22, 23] except for the methyl substitutions at C-4 and C-11 instead of exomethylene groups in cynaropicrin.

Based on the collective spectral data of the residual peaks after subtracting the identified peaks, the second compound **1b** was almost similar to those published for a semi-synthesized cynaropicrin derivative [17]. Careful examination of spectral data of **1b** confirmed the presence of guaianolide-type sesquiterpene lactone nucleus with a 4-hydroxymethacrylate side chain at  $\delta_c$  76.3 (C-8), two exomethylene groups at  $\delta_c$  112.4 (C-15) and 117.4 (C-14), a hydroxyl group at  $\delta_c$  73.5 (C-3) and a carbon resonance at  $\delta_c$  15.4 (C-13) assigned to the methyl group at C-11. The vinylic hydrogens of the exomethylene group  $\text{CH}_2$ -14 was assigned to the overlapped signal at  $\delta_H$  5.03, and the broad singlet at  $\delta_H$  5.14 as revealed from HSQC spectrum and from  $^3\text{J}$ -HMBC correlation with C-1 ( $\delta_c$  44.2). Additionally, the methylene carbon at  $\delta_c$  112.4, correlated in HSQC spectrum with a pair of broad

singlets at  $\delta_H$  5.33 and 5.40 (H<sub>2</sub>-15), showed HMBC correlation with carbon signal at  $\delta_C$  73.5 (C-3) confirming its assignment.



**Figure 2.** Structure of the isolated compounds from *Cynara scolymus* L.



**Figure 3.** Significant NOESY correlations of **1a**

From the previous data and by comparison with the reported ones, compound **1** was confirmed to be a mixture of two sesquiterpene lactones; the first (**1a**) is 4,11,13,15-tetrahydrocynaropicrin, which is a new compound and the second one (**1b**), 11,13-dihydrocynaropicrin, is a known one that was

previously semi-synthesized from cynaropicrin [17] and is reported here for the first time as a natural compound. The structures of the remaining compounds **2**, **3** and **4** (Figure 2) were elucidated by comparing their  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data with those reported in the literature as cynarinin B (**2**) [24], pinoresinol (**3**) [25] and luteolin (**4**) [26].

**Table 1.** APT (at 100 MHz) and  $^1\text{H}$  NMR (at 400 MHz) data for compounds **1a** and **1b** in  $\text{CDCl}_3$

C/H No.	<b>1a</b>		<b>1b</b>	
	APT, $\delta_{\text{C}}$ in ppm	$\delta_{\text{H}}$ in ppm, $J$ in Hz	APT, $\delta_{\text{C}}$ in ppm	$\delta_{\text{H}}$ in ppm, $J$ in Hz
1	42.3 (CH)	2.81 (1H, <i>m</i> )	44.2 (CH)	2.92 (1H, <i>m</i> )*
2	38.1 (CH <sub>2</sub> )	1.74 (1H, <i>m</i> , 2 $\beta$ )* 2.12 (1H, <i>m</i> , 2 $\alpha$ )*	38.7 (CH <sub>2</sub> )	1.75 (1H, <i>m</i> , 2 $\beta$ )* 2.31 (1H, <i>m</i> , 2 $\alpha$ )
3	78.0 (CH)	3.71 (1H, <i>br.s</i> )	73.5 (CH)	4.54 (1H, <i>br.s</i> )
4	47.0 (CH)	1.89 (1H, <i>br.s</i> )	152.6 (CH)	1.89 (1H, <i>br.s</i> )
5	50.9 (CH)	1.95 (1H, <i>m</i> )	50.5 (CH)	2.82 (1H, <i>m</i> )
6	81.0 (CH)	4.04 (1H, <i>t</i> , $J=8.0$ )	78.9 (CH)	4.16 (1H, <i>t</i> , $J=8.0$ )
7	55.8 (CH)	2.20 (1H, <i>m</i> )	53.3 (CH)	2.29 (1H, <i>m</i> )
8	76.9 (CH)	4.94 (1H, <i>br.s</i> )	76.3 (CH)	5.03 (1H, <i>br.s</i> )
9	42.4 (CH <sub>2</sub> )	2.18 (1H, <i>m</i> , 9 $\alpha$ )* 2.82 (1H, <i>m</i> , 9 $\beta$ )*	40.3 (CH <sub>2</sub> )	2.27 (1H, <i>m</i> , 9 $\alpha$ )* 2.75 (1H, <i>m</i> , 9 $\beta$ )*
10	142.0 (C)	---	142.0 (C)	---
11	41.4 (CH)	2.50 (1H, <i>m</i> )	41.3 (CH)	2.50 (1H, <i>m</i> )
12	176.6 (C)	---	178.0 (C)	---
13	15.4 (CH <sub>3</sub> )	1.25 (3H, <i>s</i> )	15.4 (CH <sub>3</sub> )	1.25 (3H, <i>s</i> )
14	116.3 (CH <sub>2</sub> )	5.11 (1H, <i>br.s</i> , 14b) 5.10 (1H, <i>br.s</i> , 14a)	117.4 (CH <sub>2</sub> )	5.14 (1H, <i>br.s</i> , 14b) 5.03 (1H, <i>br.s</i> , 14a)
15	18.3 (CH <sub>3</sub> )	1.19 (3H, <i>br.s</i> )	112.4 (CH <sub>2</sub> )	5.33 (1H, <i>br.s</i> , 15b) 5.40 (1H, <i>br.s</i> , 15a)
16	165.2 (C)	---	165.2 (C)	---
17	139.3 (C)	---	139.3 (C)	---
18	62.0 (CH <sub>2</sub> )	4.35 (2H, <i>br.s</i> )	62.0 (CH <sub>2</sub> )	4.35 (2H, <i>br.s</i> )
19	126.3 (CH <sub>2</sub> )	5.94 (2H, <i>br.s</i> )	126.3 (CH <sub>2</sub> )	6.27 (2H, <i>br.s</i> )

\*Overlapping signals

## Supporting Information

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

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