

Chemical Constituents from the Roots of *Calophyllum pisiferum* Planch. & Triana and Their Cytotoxic and Antioxidant Activities

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Abstract: This is the first phytochemical investigation of the roots of *Calophyllum pisiferum* Planch. & Triana. A new 4-phenyl coumarin, calopisifuran (**1**), and a new xanthone, 1-hydroxy-4,5-dimethoxyxanthone (**2**), were isolated and identified, together with 11 known compounds, including 4-phenyl coumarin (**3–7**) and xanthones (**8–13**). Their structures were elucidated by 1D- and 2D-NMR spectra and by HR-ESI-QTOF mass spectra and were compared with the literature data for known compounds. The isolated compounds exhibited significant cytotoxic activity in the MDA-MB-231, MCF-7 and A-549 cell lines, with IC₅₀ values of 14.87, 23.56 and 43.34 µg/mL, respectively, for **10** and IC₅₀ values of 17.15, 45.76 and 85.17 µg/mL, respectively, for **1**, while the DPPH assay revealed weak antioxidant activity.

Keywords: Clusiaceae; *Calophyllum pisiferum*; 4-phenyl coumarin; xanthone; cytotoxic. © 2021 ACG Publications. All rights reserved.

1. Introduction

Calophyllum is one of the largest genera of the Clusiaceae family. The members of this genus are widely distributed throughout Asia, and some species exist in Africa, the Americas, Australasia, and the Pacific Islands [1]. This genus includes approximately 187 species, of which 17 occur in Thailand [2]. *Calophyllum* is a rich source of secondary metabolites and has been reported to contain many bioactive compounds, such as coumarins, xanthones, flavonoids, triterpenes, benzofuran, acylphloroglucinol and chromanone; in particular, coumarins and xanthones [3] are found in almost all species and are well recognized as phytochemical markers for this genus. The biological activities of these types of compounds have been reported in some of the extracted pathways, and some of the isolated compounds have also shown good pharmaceutical activities, including cytotoxic activity [4], anti-HIV activity [5], antiviral activity, antitumor-promoting activity, antimalarial activity, antibacterial activity [3], anti-inflammatory activity [6] and central nervous system (CNS) activity [7]. *Calophyllum pisiferum* Planch. & Triana, locally known as “Tung hon-bailek” in Thailand, is found only in lowland and swamp forests in southern Thailand [8], Cambodia, Indonesia, Malaysia, Myanmar and Vietnam. [9]. The wood of *C. pisiferum* has been used for the construction of dwellings, and there is no evidence for the utilization of this plant for folk medicine in Thailand.

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A literature survey showed that the chemical constituents and biological activities of this plant have not been reported. Therefore, we report herein the first isolation and structural elucidation of a new 4-phenyl coumarin compound (**1**) and a new xanthone (**2**) together with 11 known compounds (**3–13**) from the root of *C. pisiferum* (Figure 1). Some of the isolated compounds were tested for their cytotoxicity against the MCF-7, MDA-MB-231 and A-549 cell lines and for their antioxidant activities.

2. Materials and Methods

2.1. General Experimental Procedures

Melting points were determined by a Buchi melting point B-540 apparatus and were reported without correction. Optical rotations were measured on a JASCO P-1020 digital polarimeter. Ultraviolet spectra were measured in a methanol solution on a Biochrom Libra S50 UV/Vis spectrophotometer. IR spectra were measured for samples kept in the same holder with an IRTracer-100 (Shimadzu) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Bruker FTNMR Ultra Shield™ 300 and 500 MHz instruments (300 and 500 MHz for ^1H NMR and 125 and 75 MHz for ^{13}C NMR); CDCl_3 and acetone- d_6 were used as solvents, and TMS was used as the internal standard. Chemical shifts were reported in δ [ppm], and the coupling constants (J) were expressed in hertz. High-/low-resolution mass spectra were obtained by means of a mass spectrometer (Model: LCMS-IT-TOF, Shimadzu). Quick column chromatography (QCC) and column chromatography (CC) were carried out on silica gel 60 GF₂₅₄ (Merck) and silica gel 100 (Merck), respectively. Preparative thin-layer chromatography (PTLC) was performed on precoated silica gel 60 GF₂₅₄ plates (Merck); spots were detected by UV and used for analysis. The solvents used for extraction and chromatography were distilled at their boiling points prior to use.

2.2. Plant Material

Roots of *Calophyllum pisiferum* Planch. & Triana (Clusiaceae) was collected from Thung Khai, Yan Ta Khao District, Trang Province, Thailand, in December 2017. The plant was identified by Mr. Manop Poopath (Forestry Technical Officer), Forest Herbarium (BKF), and a voucher specimen (BKF No. 196969) was deposited at the Forest Herbarium (BKF), Department of National Parks, Wildlife and Plant Conservation, Chatuchak, Bangkok, Thailand.

2.3. Extraction and Isolation

The air-dried roots of *C. pisiferum*. (5.2 kg) were successively extracted with CH_2Cl_2 and acetone (2×20 L for one week) at room temperature to furnish brownish viscous crude CH_2Cl_2 (43.6 g) and acetone (10.1 g) extracts. The crude CH_2Cl_2 extract was subjected to QCC over silica gel using hexane as the first eluent, and then the polarity was increased with CH_2Cl_2 , EtOAc and acetone to give 10 fractions (F1–F10) based on TLC analysis. Fraction 3 (3.26 g) was purified by CC with 1:5 EtOAc/hexane to afford 6 subfractions (3A–3F). Subfraction 3C (473.1 mg) was purified by CC with 1:4 EtOAc/hexane to give compounds **3** (10.3 mg) and **6** (12.4 mg). Subfraction 3E (155.2 mg) was purified by CC (EtOAc/hexane, 1.5:3.5) to give **1** (5.8 mg). Fraction 5 (2.1 g) was separated by CC (EtOAc/hexane, 1:5) to afford 5 subfractions (5A–5E). Subfraction 5C (154.6 mg) was further purified by CC (acetone/hexane, 2:5) to obtain **4** (7.6 mg). Subfraction 5D (320.5 mg) was further purified by CC (EtOAc/hexane, 2.5:5) to yield **8** (27.6 mg). Fraction 6 (6.2 g) was separated by QCC over silica gel by elution with a solvent gradient from hexane to CH_2Cl_2 to MeOH to afford 6 subfractions (6A–6F). Subfraction 6B (187.2 mg) was further purified by CC (EtOAc/hexane, 2.5:3.5) to give **10** (12.1 mg) and **11** (6.3 mg). Subfraction 6D (230.6 mg) was further purified by CC (acetone/hexane, 5:3.5) followed by PTLC (acetone/hexane, 2.5:4) to give **5** (1.2 mg) and **7** (3.8 mg).

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Subfraction 8F (315.7 mg) was separated by CC (acetone/hexanes, 3:5) to afford **13** (12.4 mg), and subfraction 8H (96.4 mg) was purified by CC (EtOAc/hexanes, 1.5:3.5) to afford **2** (1.8 mg)

The crude acetone extract was subjected to QCC and eluted with a gradient of hexane–acetone to afford 8 fractions (FA1–FA8). Fraction A4 (3.7 g) was isolated by CC (acetone/hexanes, 1:3.5) to afford 6 subfractions (A4A–A4F). Fraction A6 (2.3 g) was separated by CC (acetone/hexane, 2.5:3) to afford 5 subfractions (A6A–A6E). Subfraction A6C (168.8 mg) was further purified by CC (acetone/hexane, 4:5) to yield **12** (3.5 mg). Fraction A8 (1.3 g) was separated by CC (acetone/hexane, 3.5:4) to afford 4 subfractions (A8A–A8D). Subfraction A6C (107.6 mg) was further purified by CC (acetone/hexane, 4:5) to give **9** (3.2 mg).

Calopisifuran (1): White solid; $[a]_D^{25} = +0.3$ (*c* 0.05, MeOH); R_f 0.11 (EtOAc/hexane, 1.5:3.5); UV (MeOH) λ_{\max} ($\log \epsilon$) 235 (3.32), 297 (4.06), 350 (3.24) and 370 (3.57) nm; IR (neat) ν_{\max} 3431, 1742, 1712 and 1597 cm^{-1} . ^1H NMR (CDCl_3 , 500 MHz) and ^{13}C NMR (CDCl_3 , 125 MHz) spectroscopic data are provided in Table 1; HRESI–TOFMS: m/z 361.0721 $[\text{M}-\text{H}]^+$ (Calcd. for $[\text{C}_{22}\text{H}_{18}\text{O}_5]^-$, 361.0726).

1-Hydroxy-4,5-dimethoxyxanthone (2): Yellow solid; $[a]_D^{25} = +0.7$ (*c* 0.05, MeOH); R_f 0.10 (EtOAc/hexanes, 1.5:3.5); UV (MeOH) λ_{\max} ($\log \epsilon$) 227 (4.01), 255 (3.63), 317 (2.65) and 352 (3.86) nm; IR (neat) ν_{\max} 3175, 1655 and 1589 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) and ^{13}C NMR (CDCl_3 , 75 MHz) spectroscopic data are provided in Table 1; HRESI–TOFMS: m/z 273.0149 $[\text{M}+\text{H}]^+$ (Calcd. for $[\text{C}_{15}\text{H}_{12}\text{O}_5]^+$, 273.0154).

2.4. Bioassays

2.4.1. Cytotoxicity Assay

The cytotoxicity was measured by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [10]. The breast cancer cell line MCF-7, human breast adenocarcinoma cell line MDA-MB-231 and human lung carcinoma cell line A-549 were obtained from the American Type Culture Collection. Briefly, the cells were seeded at a density of 7×10^3 cells/well in 96-well plates for 24 h. The cells were then treated with various concentrations of the isolated compounds and incubated for 24 h, and then the MTT formazan performance was measured at 570 nm. Doxorubicin and ellipticine were used as standard drugs.

2.4.2. Antioxidant Assay

The antioxidant effect of the isolated compounds was determined using the 2,2'-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay [11]. Trolox was used as a positive control. The scavenging activity was estimated based on the percentage of DPPH radicals scavenged by using the following equation:

$$\text{Scavenging effect (\%)} = \frac{\text{control absorbance} - \text{sample absorbance}}{\text{control absorbance}} \times 100$$

3. Results and Discussion

The CH_2Cl_2 and acetone extracts from the roots of *C. pisiferum* were subjected to repeated QCC over silica gel and PTLC to obtain a new 4-phenyl coumarin, namely, calopisifuran (**1**); a new xanthone, 1-hydroxy-4,5-dimethoxyxanthone (**2**); five known 4-phenyl coumarins, isomammeigin (**3**) [12], ponnalide (**4**) [13], 3,4-dihydro-5-hydroxy-2,2-dimethyl-6-(2-methylbutanoyl)-4-oxo-10-phenyl-2H-pyrano[2,3-f]chromen-8-one (**5**) [13], mammae A/AA deshydrocyclo F (**6**) [14], and 8,9-dihydro-5-hydroxy-6-(2-methylbutanoyl)-4-phenyl-8-(prop-1-en-2-yl)furo[2,3-h]chromen-2-one (**7**) [13]; and six known xanthone compounds, mangostin (**8**) [15], macluraxanthone (**9**) [16], osajaxanthone (**10**) [17], tophyllin A (**11**) [18], 1-hydroxy-3,7-dimethoxyxanthone (**12**) [19], and 1,3-dihydroxy-7-

methoxyxanthone (**13**) [20]. The known compounds were identified by comparison with NMR data from the literature (Figure 1).

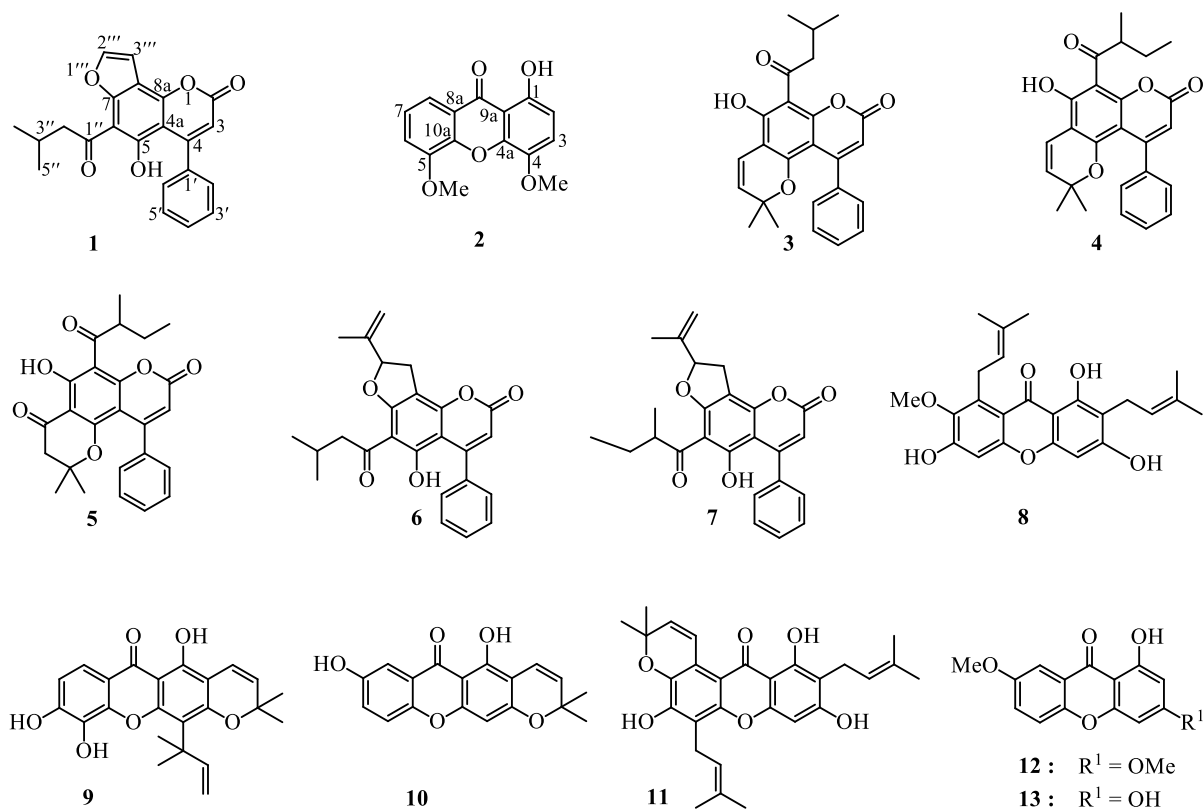


Figure 1. Structures of compounds **1–13** from *C. pisiferum*.

3.1. Structure Elucidation

Compound (**1**) was isolated as a white solid, and the HRESI–TOFMS spectrum exhibited an $[M-H]^+$ ion at m/z 361.0721, which corresponded to the molecular formula $C_{22}H_{18}O_5$ and supported the identification as an unusual type of 4-phenylcoumarin chromophore [14]. The 1H and ^{13}C NMR spectra of **1** (Table 1) displayed resonances of a chelated hydroxyl group at δ_H 14.60, (s, 5-OH), revealing the presence three signals of five aromatic protons in the free phenyl group at δ_H 7.44, br d, 2H (H-2' and H-6', δ_C 127.7), 7.35, m, 2H (H-3' and H-5', δ_C 127.2) and 7.42, m, 1H (H-4' δ_C 128.4), and one singlet aromatic proton at δ_H 6.16, (s, H-3) was observed for the olefinic proton of a C-4-substituted α -pyrone ring system (4-phenyl coumarin core structure). The 1H and ^{13}C NMR spectra (Table 1) also exhibited a methine proton at δ_H 2.29 (1H, sep, $J = 6.5$, H-3'', δ_C 25.0), a methylene proton at δ_H 3.12, (2H, d, $J = 6.5$ Hz, H₂-2'', δ_C 51.7), two methyl protons at δ_H 1.02 (6H, d, $J = 6.5$ Hz, Me-4'' and Me-5'', δ_C 22.7) and a carbonyl carbon at δ_C 204.3 (C-1''), and all these signals indicated the presence of a 3-methyl-1-oxobutyl group, confirming the side chain structure determined from COSY correlation data (Figure 2) and its location at C-6 determined from the HMBC (Figure 2) correlations of H₂-2'' (δ_H 3.12) with C-6 (δ_C 103.9). The spectra also showed doublet signals of two weakly coupled olefinic protons [δ_H 7.66, 1H, d, $J = 2.0$ Hz (H-2''') and 7.15, 1H, d, $J = 2.0$ Hz (H-3''')], thus suggesting the presence of a furan moiety. The locations of furan ring associated with C-7 and C-8 were determined by the HMBC correlations of H-2''' (δ_H 7.66) with the carbons at C-7 (δ_C 156.1) and C-8 (δ_C 109.8). Furthermore, the selected HMBC correlations of a chelated hydroxyl group at δ_H 14.60 (s, 5-OH) showed correlations to the carbons at C-4a (δ_C 104.9), C-5 (δ_C 163.0) and C-6 (δ_C 103.9), which, together with the NOESY correlation (Figure 2) between 5-OH and H-6', confirmed the position of a chelated hydroxyl group and a 3-methyl-1-oxobutyl group at C-5 and C-6,

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respectively. Additional evidence to support the isomer structure of **1** was obtained from the difference between their ^{13}C NMR data and those of isodisparfuran (Table S1, supplementary data) [14]. Therefore, compound **1** was named calopisifuran.

Compound (**2**) was obtained as a yellow solid with a molecular ion peak $[\text{M}+\text{H}]^+$ at m/z 273.0149 in the HRESI–TOFMS spectrum, which suggested a chemical formula of $\text{C}_{15}\text{H}_{12}\text{O}_5$; in addition, the UV and IR spectra of this newly isolated compound had characteristic signals of a xanthone chromophore [21]. The ^1H NMR spectrum (Table 1) showed a chelated hydroxyl group at δ_{H} 12.81 (s, 1-OH), aided by the HMQC (Table 1) and COSY (Figure 2) spectra, which exhibited two *ortho*-doublet signals at δ_{H} 7.06 (d, $J = 9.0$ Hz, δ_{C} 106.0) and 7.33 (d, $J = 9.0$ Hz, δ_{C} 120.9), and the positions of these *ortho* couples were placed at H-2 and H-3, respectively, due to the HMBC correlations (Figure 2) of a chelated hydroxyl group (1-OH) with C-1 (δ_{C} 150.7), C-2 (δ_{C} 106.0) and C-9a (δ_{C} 109.2) and NOESY correlations (Figure 2) of a methoxy proton at δ_{H} 3.96 (δ_{C} 57.2) with an aromatic proton at δ_{H} 7.33 of H-3 (4-OMe \leftrightarrow H-3). The remaining peaks indicated three adjacent aromatic protons in the ABM pattern at δ_{H} 7.25 (dd, $J = 8.5, 2.0$ Hz, H-6, δ_{C} 116.1), 7.32 (t, $J = 8.5$ Hz, H-7, δ_{C} 123.4) and 7.85 (dd, $J = 8.5, 2.0$ Hz, H-8, δ_{C} 116.9) and methoxy groups at δ_{H} 4.04 (δ_{C} 56.5). This methoxy group was located at C-5, as determined from the HMBC correlation (Figure 2) with C-5 (δ_{C} 148.5) and confirmed by the positions in the ABM aromatic proton system of H-6 at δ_{H} 7.25 correlated with C-5 (δ_{C} 148.5), H-7 at δ_{H} 7.32 correlated with C-5 (δ_{C} 148.5) and C-8a (δ_{C} 118.5) and H-8 at δ_{H} 7.85 correlated with C-6 (δ_{C} 116.1) and C-9 (δ_{C} 183.0) and the NOESY correlations between 5-OMe and H-6, as shown in Figure 2. Furthermore, a comparison of the carbon chemical shift of 1-hydroxy-4,5-dimethoxyxanthone in compound **2** was different from that of 1,8-dihydroxy-2-methoxyxanthone (Table S2, supplementary data) [22]. Thus, from the above data, the structure of compound **2** was elucidated as 1-hydroxy-4,5-dimethoxyxanthone.

Table 1. ^1H and ^{13}C NMR spectral data for compounds **1** and **2**

Position	1 ^a		2 ^b	
	δ_{H} (J in Hz)	δ_{C} (type)	δ_{H} (J in Hz)	δ_{C} (type)
1				150.7 (C)
2		159.3 (C)	7.06, d (9.0)	106.0 (CH)
3	6.16, s	114.4 (CH)	7.33, d (9.0)	120.9 (CH)
4		156.8 (C)		142.8 (C)
4a		104.9 (C)		149.8 (C)
5		163.0 (C)		148.5 (C)
6		103.9 (C)	7.25, dd (8.5, 2.0)	116.1 (CH)
7		156.1 (C)	7.32, t (8.5)	123.4 (CH)
8		109.8 (C)	7.85, dd (8.5, 2.0)	116.9 (CH)
8a		153.5 (C)		118.5 (C)
9				183.0 (C)
9a				109.2 (C)
10a				147.0 (C)
1'		139.0 (C)		
2', 6'	7.44, br d	127.7 (CH)		
3', 5'	7.35, m	127.2 (CH)		
4'	7.42, m	128.4 (CH)		
1''		204.3 (C)		
2''	3.12, d (6.5)	51.7 (CH ₂)		
3''	2.29, sep (6.5)	25.0 (CH)		
4'', 5''	1.02, d (6.5)	22.7 (CH ₃)		
2'''	7.66, d (2.0)	143.9 (CH)		
3'''	7.15, d (2.0)	104.7 (CH)		
1-OH			12.81, s	
5-OH	14.60, s			
4-OMe			3.96, s	57.2 (CH ₃)
5-OMe			4.04, s	56.5 (CH ₃)

^a Recorded at 500 MHz in CDCl_3 .

^b Recorded at 300 MHz in CDCl_3 .

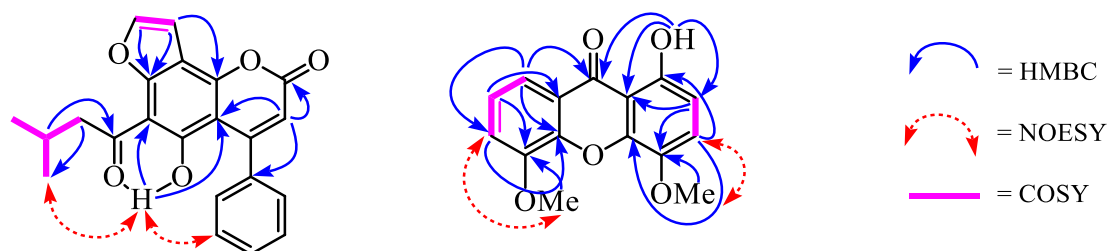


Figure 2. The key COSY, NOESY and HMBC correlations for calopisifuran (**1**) and 1-hydroxy-4,5-dimethoxyxanthone (**2**)

3.2. Cytotoxicity and Antioxidant Activity

Evaluations of the cytotoxic effects of compounds **1**, **3**, **6**, **8**, **10** and **13** (Table 2) against the breast cancer cell line MCF-7, the human breast adenocarcinoma cell line MDA-MB-231 and the human lung carcinoma cell line A-549 were performed by MTT assay, with doxorubicin and ellipticine as the positive controls. Compound **10** was found to possess the highest potency, showing moderate cytotoxicity against the MDA-MB-231, MCF-7 and A-549 cell lines, with IC_{50} values of 14.87, 23.56 and 43.34 $\mu\text{g/mL}$, respectively. New compound **1** exhibited cytotoxicity against the MDA-MB-231, MCF-7 and A-549 cell lines with IC_{50} values of 17.15, 45.76 and 85.17 $\mu\text{g/mL}$, respectively. Compound **6** exhibited cytotoxicity against the MDA-MB-231, MCF-7 and A-549 cell lines with IC_{50} values of 23.14, 40.23 and 65.77 $\mu\text{g/mL}$, respectively. In addition, compounds **3**, **8** and **13** exhibited weak to no cytotoxicity. In addition, compounds **3**, **4**, **6**, **8**, **10**, **11** and **13** were evaluated for their antioxidant properties and the ability to scavenge a stable DPPH free radical. The results revealed that all of the tested compounds, exhibited weak antioxidant activity, with DPPH radical scavenging percentages of 34.56, 46.23, 45.78, 11.23, 8.65, 0.84 and 49.54%, respectively.

Table 2. Cytotoxic activities of some isolated compounds from *C. pisiferum*

Compounds	Cytotoxic activity (IC_{50} , $\mu\text{g/mL}$)			% Radical scavenging ability
	MCF-7	MDA-MB-231	A-549	DPPH
1	45.76 \pm 1.49*	17.15 \pm 0.94*	85.17 \pm 1.02*	ND
3	>100	>100	>100	11.23 \pm 1.01*
4	ND	ND	ND	8.65 \pm 0.47*
6	40.23 \pm 1.01*	23.14 \pm 0.41*	65.77 \pm 1.43*	0.84 \pm 0.03*
8	85.33 \pm 0.99*	76.17 \pm 0.52*	94.65 \pm 0.44*	34.56 \pm 1.16*
10	23.56 \pm 0.61*	14.87 \pm 0.79*	43.34 \pm 0.59*	46.23 \pm 0.68*
11	ND	ND	ND	49.54 \pm 0.91*
1	>100	89.32 \pm 0.48*	>100	45.78 \pm 0.58*
Doxorubicin	2.30 \pm 0.12	ND	2.50 \pm 0.18	ND
Ellipticine	ND	1.70 \pm 0.17	ND	ND
Trolox (IC_{50} ; mg/L)	ND	ND	ND	77.70 \pm 1.00

*Statistically significant difference between the positive control and sample, $p < 0.05$ (mean \pm SD of three determinations); ND = not determined

4. Conclusion

In this study, a new 4-phenyl coumarin (**1**) and a new xanthone (**2**), along with eleven known compounds (**3–13**), were isolated from the roots of *C. pisiferum* for the first time, and all the compounds were characterized by means of spectroscopic methods and by comparison with previously reported data. New compound **1** and compound **10** showed significant cytotoxicity against the MDA-MB-231 cell line, whereas the remaining compounds showed weak antioxidant activity.

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Supporting Information

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

Disclosure Statement

The authors declare that we have no conflicts of interest in this paper.

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