

Article

## A New Prenylated Flavanone from *Derris trifoliata* Lour.

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**Abstract:** A new flavanone, 4',5,7-trihydroxy-6,8-di-(2-hydroxy-3-methylbut-3-enyl)-flavanone, was isolated from the aerial parts of *Derris trifoliata*, together with eleven known compounds: rotenone, tephrosin, 12a-hydroxyrotenone, deguelin, 6a,12a-dehydro-rotenone, dehydrodeguelin, 7a-O-methyldeguelol, 7a-O-methylellyptanol, 5,7,3',4'-tetrahydroxy-6,8-diprenylisoflavone, daidzein and 4'-hydroxy-7-methoxyflavanone. 7a-O-Methylellyptanol was isolated for the first time from the genus *Derris*. Their structures were characterized on the basis of spectral data. Eight of the isolated compounds were found to be significantly toxic to brine shrimp (LC<sub>50</sub> range 0.06–9.95 µg/mL). The new compound showed weak toxicity (LC<sub>50</sub> = 211.31 µg/mL).

**Keywords:** *Derris trifoliata*; aerial part; prenylated flavanone; rotenoids; brine shrimp toxicity

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## 1. Introduction

*Derris trifoliata* Lour., a mangrove associate occurring in the tropical regions of Asia and East Africa [1], belongs to the Leguminosae, subfamily Papilionoideae. *D. trifoliata* is a poisonous plant, used locally for catching fish, and nowadays also used extensively for the control of insect pests [2]. Different parts of the plant were used in traditional medicine for treatment of wounds, calculus, rheumatism and dysmenorrhea and asthma [3]. Extracts and metabolites from this plant have been found to possess significant larvicidal, pesticidal, cytotoxic, anti-fungal, anti-inflammatory, antimicrobial, nitric oxide inhibitory, and cancer chemopreventive activities [4–7]. Previous phytochemical investigations on *D. trifoliata* show that flavonoids, including rotenoids, are the most characteristic compounds of this plant [8].

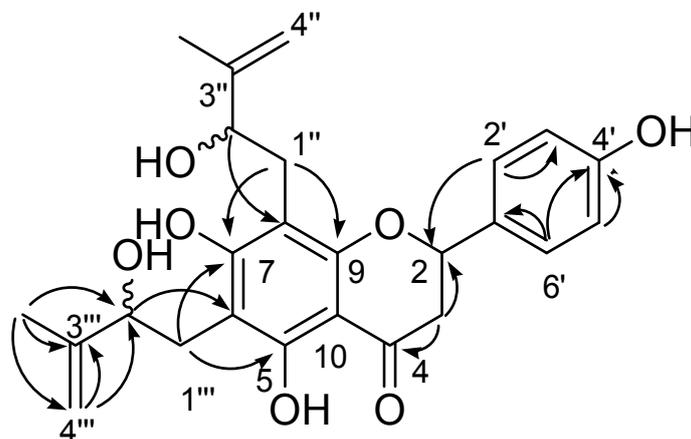
The brine shrimp lethality assay (BSLA) is considered a useful tool for assessment of toxicity, and has been widely used in chemical ecology studies on chemical defense in plants. The extract from aerial part of *D. trifoliata* was found to be toxic to brine shrimp ( $LC_{50} = 10.00 \mu\text{g/mL}$ ) [9]. However, to the best of our knowledge, there are no reports on brine shrimp toxicity of compounds from *D. trifoliata*. As a part of our search for chemical defence compounds of mangrove plants in South China, a chemical investigation of the brine shrimp toxic extract from *D. trifoliata* has been carried out. In this study, we report the structural elucidation of a new prenylated flavanone, together with 11 known compounds from the aerial part of *D. trifoliata*, as well as their toxicity against brine shrimp.

## 2. Results and Discussion

Compound **1**, a light yellow, optically active oil ( $[\alpha]_D^{20} -17.3^\circ$ , MeOH; c 0.3) oil, gave a molecular ion peak at  $m/z$  440.1795 in the HREIMS, indicating a molecular formula of  $C_{25}H_{28}O_7$  (calc. 440.1835). The  $^1\text{H-NMR}$  spectrum of **1** showed three proton resonances at  $\delta_H$  2.76 (1H, m), 3.04 (1H, m), and 5.29 (1H, m), assignable to the typical H-2 and H-3 of a flavanone skeleton. The signals of H-3 overlapped with those of protons of other two methylenes ( $\delta_H$  2.82, 2H, m; and  $\delta_H$  2.95, 2H, m), but could be distinguished by HSQC spectra. In addition, resonances for an AA'XX' spin system that is comprised of four protons ( $\delta_H$  6.82, 2H, d,  $J = 8.5$  Hz, H-3', 5' and  $\delta_H$  7.25, 2H, d,  $J = 8.5$  Hz, H-2', 6') assignable to a 4-substituted B-ring were observed. Furthermore, together with HSQC spectrum, the 1D NMR ( $^{13}\text{C}$ ,  $^1\text{H}$  and DEPT) spectra of **1** revealed the presence of one ketone ( $\delta_C$  196.5, C-4), six aromatic carbons ( $\delta_C$  160.4, C-5;  $\delta_C$  106.5, C-6;  $\delta_C$  163.9, C-7;  $\delta_C$  105.2, C-8;  $\delta_C$  158.9, C-9;  $\delta_C$  102.6, C-10), two olefinic methylenes ( $\delta_H$  4.99, 1H, d,  $J = 7.5$  Hz, H-4''a,  $\delta_H$  4.85, 1H, s, H-4''b,  $\delta_C$  110.3, C-4'';  $\delta_H$  4.90, 1H, d,  $J = 7.5$  Hz, H-4a,  $\delta_H$  4.78, 1H, s, H-4b,  $\delta_C$  110.2, C-4), two quaternary olefinic carbons ( $\delta_C$  146.8, C-3'';  $\delta_C$  147.0, C-3), two methyls ( $\delta_H$  1.69, 3H, s, H-5'',  $\delta_C$  18.4, C-5'';  $\delta_H$  1.83, 3H, s, H-5,  $\delta_C$  18.3, C-5), two oxygenated methines ( $\delta_H$  4.28, 1H, t,  $J = 7.0$  Hz, H-2,  $\delta_C$  77.0, C-2'';  $\delta_H$  4.28, 1H, t,  $J = 7.0$  Hz, H-2'',  $\delta_C$  77.0, C-2), and a hydroxyl ( $\delta_H$  12.41, 1H, s, OH-5). Comparison of the 1D NMR spectral data of compound **1** with those of 6-(2-hydroxy-3-methyl-3-butenyl)-8-prenyleriodictyol suggested that **1** was a flavnanone with two isoprenyls on ring A [10]. In the HMBC spectrum of **1**, the correlations from H-4 to C-2, 3, from H-5 to C-3, 4, and 2, and from H-1 to C-2, 3 confirmed the identity of the 2-hydroxy-3-methylbut-3-enyl moiety. The partial structure of another 2-hydroxy-3-methylbut-3-enyl in **1** was confirmed by HMBC correlation peaks of H-4'' with C-2'', 3'';

H-5'' with C-3, 4; and H-1 with C-2, 3. Moreover, the substitution pattern of ring A was unambiguously established by HMBC correlations (Figure 1), which gave evidence for the placement of the two isoprenyls at C-6 and C-8, respectively. Thus, **1** was characterized as 4',5,7-trihydroxy-6,8-di-(2-hydroxy-3-methylbut-3-enyl)-flavanone. The absolute configuration of **1** was not determined.

**Figure 1.** Structure of compound **1** and selected HMBC correlations.



Besides the new compound, 11 known compounds: Rotenone (**2**) [11], tephrosin (**3**) [12], 12a-hydroxyrotenone (**4**) [13], deguelin (**5**) [12], 6a,12a-dehydrorotenone (**6**) [11], dehydrodeguelin (**7**) [12], 7a-*O*-methyldeguelol (**8**) [14], 7a-*O*-methylelloptanol (**9**) [15], 5,7,3',4'-tetrahydroxy-6,8-diprenylisoflavone (**10**) [16], daidzein (**11**) [17], and 4'-hydroxy-7-methoxyflavanone (**12**) [18], were isolated from the plant and their structures elucidated by comparing their spectroscopic data with those reported in literature. As far as know, 7a-*O*-methylelloptanol is isolated for first time from the genus *Derris*.

Prenyl substitution is common among all known classes of flavonoids in *D. trifoliata*. However, the prenylation pattern in **1** is relatively rare. To the best of our knowledge, besides **1**, only two other flavonoids, 6,3'-di-(2-hydroxy-3-methylbut-3-enyl)-flavone, and 3,5'-di-(2-hydroxy-3-methylbut-3-enyl)-4,2',4'-trihydroxychalcone, were found to contain two 2-hydroxy-3-methylbut-3-enyls [19], and additionally compound **1** is the first flavonoid with two such groups on the same aromatic ring.

Results of the brine shrimp lethality assay on three crude extracts and nine isolated compounds are shown in Table 1. Eight flavonoids exhibited significant brine shrimp toxicity ( $LC_{50} < 30 \mu\text{g/mL}$ ) [20]. The  $LC_{50}$  value obtained in present study for **2** was similar to those reported in literature: 0.049~1.8  $\mu\text{g/mL}$  for rotenone [21,22]. The  $LC_{50}$  values for **3** and **4** reported here were somewhat lower than literature data, 2.2  $\mu\text{g/mL}$  for tephrosin, and 1.9  $\mu\text{g/mL}$  for 12a-hydroxyrotenone [10]. The brine shrimp toxicity of compounds **1**, **5**–**8**, and **12** had never been reported in literature. The rotenonoids with  $sp^3$  hybridization at C-6a and C-12a, namely compounds **2**–**5**, showed extreme toxicity with  $LC_{50}$  values less than 1  $\mu\text{g/mL}$ , and this is consistent with the previously reported cytotoxic effects of compounds from *D. trifoliata* [14].

**Table 1.** The mean LD<sub>50</sub> values ± S.D for crude extracts and compounds screened against brine shrimp larvae (*Artemia salina*).

Extract/Compound	LC <sub>50</sub> ± S.D. (µg/mL)
Petroleum ether extract	7.61 ± 1.62
Ethyl acetate extract	5.78 ± 1.18
<i>n</i> -Butanol extract	>500.00
Compound <b>1</b>	211.31 ± 12.5
Rotenone	0.06 ± 0.03
Tephrosin	0.24 ± 0.05
12a-Hydroxyrotenone	0.37 ± 0.15
Deguelin	0.73 ± 0.12
6a,12a-Dehydrorotenone	9.95 ± 1.05
Dehydrodeguelin	5.32 ± 0.6
7a- <i>O</i> -Methyldeguelol	2.75 ± 0.76
4'-Hydroxy-7-methoxyflavanone	3.97 ± 0.63

### 3. Experimental

#### 3.1. General

Optical rotations were measured on a Jasco 1020 polarimeter. NMR spectra were obtained on a Bruker AVANCE 500 spectrometer (operating at 500 MHz for <sup>1</sup>H-NMR, 125 MHz for <sup>13</sup>C-NMR). HREIMS spectra were recorded on a Finnigan MAT TSQ 700 mass spectrometer. UV spectra were obtained in a Beckman DU-640 UV spectrophotometer. Semipreparative HPLC was carried out using a Phenomenex Luna 5 µL C18 100A ODS column (250 × 20 mm) on a system comprised of a Waters 600E Multisolvant Delivery System and a Waters 996 Photodiode Array Detector.

#### 3.2. Plant Material

The aerial parts of *D. trifoliata* were collected in September 2008 from the mangrove area of Sanya, Hainan Province, Southern China. The material was identified by Prof. Si Zhang, Key Laboratory of Marine Bio-resources Sustainable Utilization, South China Sea Institute of Oceanology, Chinese Academy of Sciences. A voucher specimen (No. GKLMMM22) is deposited at the herbarium of South China Sea Institute of Oceanology.

#### 3.3. Extraction and Isolation

The dry powdered aerial part of *D. trifoliata* (7.0 kg) was extracted three times with ethanol-water (1:1, v/v, 40 L) at room temperature for 10 days. The pooled extracts were evaporated in *vacuo*. The resulting residue was suspended in H<sub>2</sub>O, and subsequently extracted with petroleum ether, ethyl acetate, and *n*-BuOH (7.5 L, room temperature, 10 h). After removal of solvent, the ethyl acetate extracts (65 g) was fractionated into 10 fractions (Fr-I~Fr-X) by column chromatography using a gradient of mixtures of CHCl<sub>3</sub>-MeOH (100:1 to 65:35). Fr-III (3.5 g) was subjected to a column chromatography eluting with a gradient of petroleum ether-ethyl acetate (5:1 to 2:1) to give four fractions (Fr-III-A~Fr-III-D). Fr-IV (2.5 g) was separated by column chromatography (petroleum ether-ethyl acetate (5:1 to 2:1 2.0 L))

to give four fractions (Fr-IV-A~Fr-IV-D). Fractions Fr-III-B (300mg), Fr-III-D (362 mg), and Fr-IV-A (400 mg) were further separated by semipreparative HPLC (linear gradient within 40 min from MeOH-H<sub>2</sub>O 7:3 to 10:0), respectively, to give **1** (7.0 mg; t<sub>R</sub> = 14.5 min), **2** (14.0 mg; t<sub>R</sub> 16.8 min), **3** (40.0 mg; t<sub>R</sub> 18.1 min), **4** (20.0 mg; t<sub>R</sub> 16.4 min), **5** (3.5 mg; t<sub>R</sub> 17.9 min), **6** (2.5 mg; t<sub>R</sub> 24.4 min), **7** (2.5 mg; t<sub>R</sub> 26.4 min), **8** (4.0 mg; t<sub>R</sub> 10.9 min), and **9** (5.0 mg; t<sub>R</sub> 21.4 min). Fr-V (5.3 g) was separated by column chromatography over a silica gel using gradient elution of CHCl<sub>3</sub>-ethyl acetate (9:1 to 7:3) to give four fractions (Fr-V-A~Fr-V-D). Fr-V-A (250 mg) and Fr-V-B (120 mg) were further purified by semipreparative HPLC with linear gradient within 40 min from MeOH-H<sub>2</sub>O from 1:1 to 1:0 to afford **10** (2.5 mg; t<sub>R</sub> 32.6 min), **11** (4.0 mg; t<sub>R</sub> 8.7 min) and **12** (4.3 mg; t<sub>R</sub> 13.7 min).

*4',5,7-Trihydroxy-6,8-di-(2-hydroxy-3-methylbut-3-enyl)-flavanone (1)*: A light yellow oil, [α]<sub>D</sub><sup>20</sup> −17.3° (MeOH; c 0.3), HREIMS *m/z*: 440.1795 [M]<sup>+</sup>; UV (MeOH) λ<sub>max</sub> nm: 298.3, 345.9; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ<sub>H</sub> = 5.29 (1H, m, H-2), 2.76 (1H, m, H-3a), 3.04 (1H, m, H-3b), 6.82 (2H, d, *J* = 8.5 Hz, H-3', 5'), 7.25 (2H, d, *J* = 8.5 Hz, H-2', 6'), 2.82 (1H, m, H-1''a), 3.08 (1H, m, H-1''b), 4.31 (1H, t, *J* = 7.0 Hz, H-2''), 4.99 (1H, d, *J* = 7.5 Hz, H-4''a), 4.85 (1H, s, H-4''b), 1.69 (3H, s, H-5''), 2.82 (1H, m, H-1a), 3.08 (1H, m, H-1b), 4.28 (1H, t, *J* = 7.0 Hz, H-2), 4.90 (1H, d, *J* = 7.5 Hz, H-4a), 4.78 (1H, s, H-4b), 1.83 (3H, s, H-5''), 12.41 (1H, s, OH-5); <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ<sub>c</sub> = 78.8 (C-2), 43.0 (C-3), 196.5 (C-4), 160.4 (C-5), 106.5 (C-6), 163.9 (C-7), 105.2 (C-8), 158.9 (C-9), 102.6 (C-10), 130.5 (C-1') 127.7 (C-2',6'), 115.6 (C-3',5'), 156.3 (C-4'), 29.4 (C-1''), 77.0 (C-2'', C-2, interchangeable with C-2), 146.8 (C-3''), 110.3 (C-4''), 18.4 (C-5''), 28.6 (C-1), 77.0 (C-2, interchangeable with C-2''), 147.0 (C-3), 110.2 (C-4), 18.3 (C-5).

### 3.4. Brine Shrimp Assay

Toxicity against brine shrimp was evaluated using the method reported by Wanyoike [20]. Artificial seawater was prepared by dissolving sea salt (38 g) in distilled water (1 L). The 60-mm culture dishes were used for hatching. To seawater (50 mL), brine shrimp eggs (10 mg) were added. The culture dish was placed in the light incubator at 25 °C for 48 h. The larvae were attracted to one side of the vessel with a light source and collected with pipette. Nauplii were separated from eggs by aliquoting them three times in small beakers containing seawater. The brine shrimp are then put in wells of a 96 flat-bottom well plate (Nunc Microwell plate). Each column (12 per plate) contains a two-fold dilution series representing 8 doses. Potassium dichromate was used as a positive control, as well as the solvent DMSO was used as a negative control. Each sample was repeated six times (columns) in each experiment. After 24 hours of exposure to the samples, the number of died and total (determined after killing by freezing) brine shrimp for each well were determined. The data were analyzed by probit regression (SPSS) to calculate the LC<sub>50</sub>.

## 4. Conclusions

A new prenylated flavanone **1** was isolated from aerial parts of *D. trifoliata*, and its structure was elucidated on the basis of spectroscopic analysis as 4',5,7-trihydroxy-6,8-di-(2-hydroxy-3-methylbut-3-enyl)-flavanone. Among the isolated compounds, all rotenoids **2–9**, and a flavanone **12** exhibited significant toxicity against brine shrimp, while the new flavanone **1** showed low brine shrimp lethality.

## Supplementary Materials

Supplementary materials can be accessed at: <http://www.mdpi.com/1420-3049/17/1/657/s1>.

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*Sample Availability:* Samples of compounds **1–12** are available from the authors.

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