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Antiplasmodial Diterpenoids and a Benzotropolone from *Petradoria pumila*

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Abstract

An extract of *Petradoria pumila* from the Natural Products Discovery Institute was found to have moderate antiplasmodial activity, with an IC₅₀ value between 5 and 10 µg/mL. The four new diterpenoids petradoriolides A – D (**1** – **4**), the new benzotropolone petradoriolone (**5**), and the two known lignans **6** – **7** were isolated after bioassay-directed fractionation. The structures and stereochemistries of the new compounds were determined by interpretation of NMR spectroscopy, mass spectrometry and ECD spectra. Among these compounds, petradoriolide C (**3**) displayed the most potent antiplasmodial activity, with an IC₅₀ value of 7.3 µM.

Graphical Abstract

Malaria is a serious and widespread disease, and is estimated to have caused 429,000 deaths in 2015, with nearly 70% of these deaths occurring in children under 5 years old.¹ Natural

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ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge on the ACS Publications website.

Structures of reference compounds **S1** – **S10**; NMR comparisons of petradoriolides A (**1**) and B (**2**) with known reference compounds; characterization data for compounds **6** – **7**, literature references for reference compounds **S1** – **S10**; ¹H NMR, gHSQC, gHMBC, and NOESY spectra for petradoriolides A – D (**1** – **4**); ¹H NMR, gHSQC and gHMBC spectra for compounds **5** – **7**

products have played key roles in antimalarial therapy, with the natural product quinine and its analogues such as chloroquine providing effective therapies for many years. Unfortunately *Plasmodium falciparum*, the most significant malaria parasite, had developed resistance to chloroquine by 1960.² The natural product artemisinin now provides effective treatment,³ usually as part of an artemisinin-based combination therapy (ACT),⁴ but *P. falciparum* has already developed resistance to artemisinin in the Greater Mekong subregion.⁵ Therefore, there is a continuing need to develop new antimalarial drugs. Our research is focused on potential antimalarial agents from plant sources, based on the fact that the two most important antimalarial drugs are plant-derived natural products.

This paper reports the results of a study of *Petradoria pumila* (Nutt.) Greene (Asteraceae) from the Natural Products Discovery Institute (NPDI) Repository for new antiplasmodial natural products. *P. pumila* is the only specie in the genus *Petradoria*; it is known by the common name rock goldenrod, and is native to the southwestern USA.⁶ This plant was selected for study after its detanninized dichloromethane extract showed moderate antiplasmodial activity against the chloroquine-resistant Dd2 strain of *P. falciparum*. The Asteraceae family is a rich source of bioactive compounds, including antimalarial sesquiterpenes and diterpenes.^{7–9} However, there are no reports on the chemistry or antiplasmodial activity of *P. pumila*, so this extract was selected for investigation.

RESULTS AND DISCUSSION

A dichloromethane (DCM) extract of the stems and roots of *P. pumila* was subjected to C₁₈ SPE to afford active MeCN and MeOH fractions, with IC₅₀ values against the drug-resistant Dd2 strain of *Plasmodium falciparum* of about 3 and 5 µg/mL, respectively. The MeCN fraction was separated by chromatography on a silica gel open column to generate 14 sub-fractions. The active sub-fractions were separated by C₁₈ reversed phase HPLC to yield the four new diterpenoids petradoriolide A–D (**1–4**), the new benzotropolone petradoriolone I (**5**) and the two known lignans **6** and **7**. The less active MeOH fraction was also fractionated, but failed to yield any pure active compounds.

Petradoriolide A (**1**) was isolated as a pale yellow powder. Its positive ion HRESIMS revealed a peak for a sodiated molecular ion at m/z 385.2364, corresponding to a molecular formula of C₂₂H₃₄O₄. Its ¹H and ¹³C NMR data (Table 1) displayed signals for six methyl

groups (δ_{H} 1.58, H-16; 1.20, H-17; 1.03, H-18; 1.01, H-19; 1.14, H-20; 2.03, H-2'), five alkyl methylenes (δ_{H} 2.64 and 2.30, H-2; 1.82 and 1.65, H-3; 1.80 and 1.51, H-6; 1.96 and 1.40, H-7; 2.41 and 1.85, H-11), two alkyl methines (δ_{H} 1.44, H-5; 1.72, H-9), one oxygen-bearing methine (δ_{H} 3.88, H-12) and one terminal olefin (δ_{H} 6.05, dd, 17.6, 11.0, H-14; 5.21, dd, 11.0, 0.8 and 5.15, dd, 17.6, 0.8, H-15). The presence of an acetoxy group was confirmed by 2J -HMBC correlations between H-2' and C-1' (δ_{C} 170.0). The remaining 20 carbons, two oxygens, and 31 protons could be assigned to a compound with either an 8,12-epoxylabdane (**1**)¹⁰ or an 8,13-epoxylabdane (**1a**) skeleton¹¹ (Figure 1).

Structures **1** and **1a** are both consistent with 2J -HMBC correlations between H-5 and C-6 (δ_{C} 22.0), H-7 and C-6, H-9 and C-8 (δ_{C} 81.5), and with 3J -HMBC correlations between H-2 and C-4 (δ_{C} 32.0), H-3 and C-5 (δ_{C} 53.9), H-7 and C-5, H-9 and C-5, H-9 and C-7 (δ_{C} 39.7), H-11 and C-8, H-11 and C-13 (δ_{C} 82.8), and H-15 and C-13 (Figure 2). The positions of the five methyl groups in either structure could be assigned by 3J -HMBC correlations between H-14 and C-16 (δ_{C} 19.4), H-17 and C-7, H-17 and C-9 (δ_{C} 53.0), H-18 and C-3 (δ_{C} 39.0), H-18 and C-5, H-18 and C-19 (δ_{C} 31.4), H-19 and C-3, H-19 and C-5, H-19 and C-18 (δ_{C} 23.7), H-5 and C-20 (δ_{C} 15.2), and H-9 and C-20. The carbonyl group was assigned to the C-1 position, based on 3J -HMBC correlations between H-20 and C-1 (δ_{C} 215.8) and H-3 and C-1. The acetoxy group was assigned to C-13 in **1** or C-12 in **1a** on the basis of 2J -HMBC correlations between H-12 and C-11 (δ_{C} 26.3), and H-12 and C-13, and 3J -HMBC correlations between H-12 and C-16. The identification of **1** as the correct isomer was then made on the basis of the chemical shift of H-12 (3.89 ppm, dd, J = 10.2, 5.1 Hz), which is more shielded than the 4.2 ppm predicted for the esterified oxymethine of **1a**. In addition, the $J_{11,12}$ coupling constants of 10.1 and 5.9 Hz were consistent with the values of 9.5 and 5 Hz observed for the related compound 13-hydroxy-8 α ,12 β -epoxylabd-14-ene,¹² and the ^1H NMR shifts of H-11 (1.85 and 2.41 ppm) were consistent with the shifts of 1.89 and 2.81 ppm observed for these protons in the related compound scapairrin D.¹³

The relative configuration of petradoriolide A (**1**) was assigned as (5*S**,8*R**,9*R**,10*S**12*S**,13*R**) based on NOESY correlation between H-2b and H-20, H-5 and H-9, H-7 and H-9, H-3-17 (δ_{H} 1.20) and H-6b (δ_{H} 1.51), H-3-20 (δ_{H} 1.14) and H-6b (δ_{H} 1.51), and between H-9 and H-12 (Figure 3). The relative configurations of C-12 and C-13 were assigned tentatively by the NOESY correlation between H-12 and H-3-16, consistent with an internuclear distance of 2.4 Å in an energy-minimized structure, and this conclusion was confirmed by comparisons with the chemical shifts of the relevant carbons of the known compounds (8*R*,12*R*,13*S*)-13-acetoxy-8,12-epoxy-labd-14-ene and (8*R*,12*S*,13*R*)-13-acetoxy-8,12-epoxy-labd-14-ene.¹⁰ The chemical shifts of C-12 and C-17 of the (12*S*,13*R*) isomer, at 85.3 and 25.1 ppm respectively, agreed well with the values for the corresponding carbons in **1**. The chemical shifts of C-12 and C-17 of the (12*R*,13*S*) isomer were 80.3 and 21.3 ppm respectively. Details of these comparisons are provided in Table S2 (Supporting Information).

The absolute configuration of petradoriolide A was determined by electronic circular dichroism. The negative $n-\pi^*$ Cotton effect at 304 nm (Figure 4) indicated its absolute configuration to be (5*S*,8*R*,9*R*,10*S*,12*S*,13*R*).¹⁴ The structure of petradoriolide A (**1**) was thus assigned as (5*S*,8*R*,9*R*,10*S*,12*S*,13*R*)-13-acetoxy-8,12-epoxy-1-oxolabd-14-ene.

Petradoriolide B (**2**) was isolated as a pale yellow powder. Its positive ion HRESIMS revealed a peak for a sodiated molecular ion at m/z 343.2225, corresponding to a molecular formula of $C_{20}H_{32}O_3$. The difference of 42 Da between the molecular weights of **1** and **2** suggested that **2** was a deacetylated product of **1**. This was supported by the absence of the chemical shifts of the acetate group at δ_C 170.0 (C), 22.1 (CH₃) and δ_H 2.03 (CH₃). This assignment was confirmed by the HMBC correlations shown in Figure 2. The relative configuration of petradoriolide B (**2**) was assigned as (5*S**,8*R**,9*R**,10*S**,12*S**,13*S**) by the observation of the same NOESY correlations as observed for compound **1** (Figure 3), and additionally by comparisons of the chemical shifts of C-12, C-14, C-16 and C-17 with those of related known compounds in the literature^{10, 12, 15, 16} (Table S1, Supporting Information). The absolute configuration of petradoriolide B (**2**) was determined by electronic circular dichroism (Figure 5) to be the same as that of petradoriolide A (**1**). Its structure was thus assigned as (5*S*,8*R*,9*R*,10*S*,12*S*,13*S*)-8,12-epoxy-13-hydroxy-1-oxolabd-14-ene.

Petradoriolide C (**3**) was isolated as a pale yellow powder. Its positive ion HRESIMS revealed a peak for a sodiated molecular ion at m/z 387.2504, corresponding to a molecular formula of $C_{22}H_{36}O_4$. The difference of 2 Da between the molecular weights of **1** and **3** suggested that **3** was a dihydro product of **1**, and this was confirmed by the change of chemical shift for C-1 from δ_C 215.8 (C) in **1** to δ_C 72.8 (CH) in **3** and by the HMBC correlations shown in Figure 2. The relative configuration of petradoriolide C (**3**) was assigned as (1*S**,5*S**,8*R**,9*R**,10*S**,12*S**,13*R**) based on the NOESY correlations shown in Figure 3, with the correlation between H-1 and H-20 establishing the configuration at C-1. The absolute configuration of compound **3** was assumed to be the same as those of compound **1**. The structure of petradoriolide C (**3**) was thus assigned as (1*S*,5*S*,8*R*,9*R*,10*S*,12*S*,13*R*)-13-acetoxy-8,12-epoxy-1-hydroxylabd-14-ene.

Petradoriolide D (**4**) was isolated as a pale yellow powder. Its positive ion HRESIMS revealed a peak for a sodiated molecular ion at m/z 345.2421, corresponding to a molecular formula of $C_{20}H_{34}O_3$. The difference of 42 Da between the molecular weights of **3** and **4** suggested that **4** was the deacetylated product of **3**. This was confirmed by the absence of the signals at δ_C 170.0 (C), 22.4 (CH₃) and δ_H 2.03 (CH₃), and by the HMBC cross-peaks shown in Figure 2. The relative configuration of compound **4** was assigned as (1*S**,5*S**,8*R**,9*R**,10*S**,12*S**,13*S**) based on the NOESY correlations shown in Figure 3, with the correlation between H-1 and H-20 establishing the configuration at C-1. The absolute configuration of **4** was also inferred from that of **2**. The structure of petradoriolide D (**4**) was thus assigned as (1*S*,5*S*,8*R*,9*R*,10*S*,12*S*,13*S*)-8,12-epoxy-1,13-dihydroxylabd-14-ene.

It is noteworthy that the configurations of the two acetates **1** and **3** at C-13 are the opposite of those of the corresponding alcohols. This raises the intriguing possibility that the acetates are biosynthesized by a process involving inversion of configuration, rather than by simple acetylation of a hydroxyl group.

Petradoriolone (**5**) was isolated as a yellowish oil. Its positive ion HRESIMS revealed a peak for a protonated molecular ion at m/z 201.0920 and for a sodiated molecular ion at m/z 223.0743, both corresponding to a molecular formula of $C_{13}H_{12}O_2$. The ¹H NMR and HSQC data (Table 2) displayed signals for a methoxy group (δ_H 4.01), a methyl group (δ_H

2.73, H-9), and six aromatic methines (δ_{H} 7.62, H-1; 7.43, H-2; 7.53, H-3; 7.32, H-5; 7.04, H-8; 7.64, H-9).

The benzocyclohepten-7-one skeleton was confirmed by 3J -HMBC correlations between H-1 and C-9 (δ_{C} 142.1), H-1 and C-4a (δ_{C} 132.5), H-2 and C-4 (δ_{C} 137.5), H-2 and C-9a (δ_{C} 133.5), H-6 and C-7 (δ_{C} 181.7), H-6 and C-8 (δ_{C} 131.5), H-5 and C-4, H-5 and C-9a, H-5 and C-7, H-8 and C-6 (δ_{C} 156.9), H-8 and C-9a, H-9 and C-1 (δ_{C} 132.6), H-9 and C-4a, H-9 and C-7 and 2J -HMBC correlations between H-5 and C-6.¹⁷ The methyl and methoxy groups were assigned to C-4 and C-6 respectively, as determined by 3J -HMBC correlations between Me and C-3 (δ_{C} 132.9), Me and C-4a, and OMe and C-6 (Figure 6). The structure of petradoriolone I (**5**) was thus assigned as 6-methoxy-4-Emethylbenzotropolone.

Compounds **6** and **7** were identified as known arylcoumaran neolignans,^{18, 19} with later reassignments of the relative configurations of C-7' and C-8' of compound **6**²⁰ and the absolute configuration of compound **6** confirmed by ECD data.²¹ Compound **6** was identified as (7*E*)-(7'*R*,8'*S*)-4'-hydroxy-3',5-dimethoxy-4,7'-epoxy-8',3-neolig-7-en-9,9'-diyl diacetate. Compound **7** was identified as (7*E*)-(7'*R*,8'*S*)-4'-hydroxy-3',5-dimethoxy-4,7'-epoxy-8',3-neolig-7-en-9,9'-diyl di-3-methylbutanoate by comparison of its spectroscopic data with those of **6** and with literature data.²²

All isolated compounds were tested for antiparasmodial activity against the Dd2 strain of *P. falciparum* (Table 3). Petradoriolide C (**3**) displayed moderate antiparasmodial activity, with an IC₅₀ value of 7.3 μM . The new diterpenoids petradoriolide A-D (**1-4**) and petradoriolone I (**5**) were also tested for antiproliferative activity against the A2780 ovarian cancer cells. None of them displayed significant activity, all having IC₅₀ values higher than 20 μM .

EXPERIMENTAL SECTION

General Experimental Procedures

Optical rotations were recorded on a JASCO P-2000 polarimeter. UV and IR spectroscopic data were measured on a Shimadzu UV-1201 spectrophotometer and a MIDAC M-series FTIR spectrophotometer, respectively. ECD spectra were obtained on a JASCO J-815 circular dichroism spectrometer. NMR spectra were recorded in CDCl₃ on Bruker Avance 500 or 600 spectrometers. The chemical shifts are given in δ (ppm), and coupling constants (*J*) are reported in Hz. Mass spectra were obtained on an Agilent 6220 LC-TOF-MS in the positive ion mode.

Antiparasmodial Bioassays

The effect of each fraction and pure compound on parasite growth of the *P. falciparum* Dd2 strain was measured in a 72 h growth assay in the presence of drug as described previously.⁹ Briefly, ring stage parasite cultures (100 μL per well, with 1% hematocrit and 1% parasitemia) were grown for 72 h in the presence of increasing concentrations of the drug in a 5% CO₂, 5% O₂, and 90% N₂ gas mixture at 37 °C. After 72 h in culture, parasite viability was determined by DNA quantitation using SYBR Green I. The half-maximum inhibitory concentration (IC₅₀) calculation was performed with GraphPad Prism using nonlinear

regression curve fitting. The IC₅₀ values are the average of three independent determinations with each determination in duplicate and are expressed $\pm$ SEM.

In vitro Antiproliferative Activity Against A2780 Cells

The A2780 ovarian cancer cell line antiproliferative bioassay was performed at Virginia Tech as previously reported.^{23, 24} The A2780 cell line is a drug-sensitive ovarian cancer cell line.²⁵ Paclitaxel was used as the positive control.

Plant Material

Stem and root material of a small shrub identified as *Petradoria pumila* (Nutt.) Greene was collected on May 26, 2001. The plant material was collected and identified by Daniel Atha with Michael Windham and Molly Windham. The plant material was collected 50 meters south of Utah Highway 121 at mile marker 28, about 12 miles west of Vernal, Uinta County, Utah, at an altitude of 1,687 m (5,535 ft). A voucher specimen is deposited at the New York Botanical Number under barcode 01269145.

Extraction and Isolation

The dried and powdered collection of stems and roots of *Petradoria pumila* was exhaustively extracted with EtOH in two 24-hour percolation steps followed by partition into hexanes, DCM, and aqueous sub-fractions. For purposes of fractionation and purification, the DCM fraction designated 112461–09G was shipped to Virginia Tech for bioassay-guided isolation. A 340 mg portion of this extract was detanninized by dissolving it in MeOH and filtering it through a 12 $\times$ 3.5 cm polyamide column. The filtrate was evaporated and subjected to a 12 $\times$ 3.5 cm C₁₈ SPE column with elution with MeCN (150 mL) followed by MeOH (150 mL) to afford MeCN and MeOH fractions with IC₅₀ values of 3 and 5 μ g/mL. The MeCN fraction was separated by chromatography on an open silica gel column with CHCl₃:MeOH 9:1 to generate 14 subfractions (**1.1**–**1.14**). Fraction **1.2** (12.0 mg) with an IC₅₀ value of 8 μ g/mL was purified by HPLC on a C₁₈ column using MeOH:H₂O from 70:30 to 100:0 in 30 mins to yield compound **7** (0.6 mg) with a retention time of 24.2 min. Fraction **1.4** (6.0 mg) with an IC₅₀ value of 5 μ g/mL was separated by HPLC on a C₁₈ column using a MeOH and H₂O gradient from 70% MeOH to 100% MeOH in 30 mins to yield compound **6** (0.7 mg) and compound **1** (1.1 mg) with retention times of 11.2, 21.5 and 25.4 min. Fraction **1.7** (8.0 mg) with an IC₅₀ value of 3 μ g/mL was separated by HPLC on a C₁₈ column using a MeOH:H₂O gradient from 50% MeOH to 100% MeOH in 40 mins to yield compound **5** (2.0 mg) and compound **2** (1.0 mg) with retention times of 19.1 and 32.0 min. Fraction **1.9** (14.3 mg) with an IC₅₀ value of 5 μ g/mL was purified by HPLC on a C₁₈ column using MeOH:H₂O from 60:40 to 100:0 in 30 mins and then MeOH alone for 10 min to yield compound **3** (1.1 mg) with a retention time of 31.2 min. Fraction **1.11** (7.2 mg) with an IC₅₀ value of 2.5 μ g/mL was purified by HPLC on a C₁₈ column using MeO:H₂O from 60:40 to 100:0 in 30 mins to yield compound **4** (0.6 mg) with a retention time of 28.3 min. The active MeOH fraction was also fractionated by C₁₈ HPLC but failed to yield any pure compounds.

Petradoriolide A (**1**): yellow powder; $[\alpha]_D^{21} +16.9$ (c 6.5×10^{-4} g/mL, MeOH); UV (c 0.248 mM, MeOH) $\lambda_{\max}$ (e) 220 nm (6167), 295 nm (4926); ECD (c 0.248 mM, MeOH)

$\epsilon_{304} - 0.8$; HRESIMS m/z 385.2364 $[M+Na]^+$ (calcd. for $C_{22}H_{34}NaO_4^+$, 385.2349); 1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$), see Table 1.

Petradoriolide B (2): yellow powder; $[\alpha]_D^{21} +24.1$ (c 2.9×10^{-4} g/mL, MeOH); UV (c 0.604 mM, MeOH) λ_{max} (e) 206 nm (2528), 279 nm (415); ECD (c 0.604 mM, MeOH) $\epsilon_{298} - 0.17$; HRESIMS m/z 343.2225 $[M+Na]^+$ (calcd. for $C_{20}H_{32}NaO_3^+$, 343.2244); 1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$), see Table 1.

Petradoriolide C (3): yellow powder; $[\alpha]_D^{21} +12.1$ (c 1.65×10^{-4} g/mL, MeOH); HRESIMS m/z 387.2504 $[M+Na]^+$ (calcd. for $C_{22}H_{36}NaO_4^+$, 387.2506); 1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$), see Table 1.

Petradoriolide D (4): yellow powder; $[\alpha]_D^{21} +34.0$ (c 2.35×10^{-4} g/mL, MeOH); HRESIMS m/z 345.2421 $[M+Na]^+$ (calcd. for $C_{20}H_{34}NaO_3^+$, 345.2400); 1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$), see Table 1.

Petradoriolone I (5): yellow oil; HRESIMS m/z 223.0743 $[M+Na]^+$ (calcd. for $C_{13}H_{12}NaO_2^+$, 223.0730) and 201.0920 $[M+H]^+$ (calcd. for $C_{13}H_{13}O_2^+$, 201.0910); 1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$), see Table 2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Possible structures **1** and **1a**

Figure 2.
Selected 3J -HMBC correlations of petradoriolides A-D (**1–4**).

Figure 3.
Selected NOESY correlations for compounds **1** – **4**.

Figure 4.
The ECD spectrum of petradoriolide A (**1**)

Figure 5.
The ECD spectrum of petradoriolide B (2).

Figure 6.
HMBC correlations of petradoriolone I (**5**).

Table 1.

NMR Spectroscopic Data for Compounds 1–4 in CDCl₃ (500 MHz)

	1		2		3		4	
position	δ_{H} (J in Hz)	δ_{C} , type	δ_{H} (J in Hz)	δ_{C} , type	δ_{H} (J in Hz)	δ_{C} , type	δ_{H} (J in Hz)	δ_{C} , type
1		215.8, C		215.7, C	3.50 m	72.8, CH	3.52 m	72.4, CH
2a	2.30 ddd 15.3, 9.1, 4.9	35.0, CH ₂	2.29 ddd 15.4, 8.9, 4.9	35.1, CH ₂	1.47 m	26.2, CH ₂	1.51 m	26.0, CH ₂
2b	2.64 ddd 15.3, 8.6, 4.8		2.67 ddd 15.4, 8.9, 4.9		2.11 m		2.11 m	
3a	1.82 m	39.0, CH ₂	1.82 m	39.2, CH ₂	1.63 m	35.6, CH ₂	1.59 m	35.4, CH ₂
3b	1.65 m		1.65 ddd 13.9, 8.9, 4.9		1.20 m		1.20 m	
4		32.0, C		32.3, C		33.1, C		33.1, C
5	1.44 m	53.9, CH	1.42 m	54.3, CH	1.42 m	48.7, CH	1.45 m	48.4, CH
6a	1.80 m	22.0, CH ₂	1.80 m	21.8, CH ₂	1.79 m	21.4, CH ₂	1.81 dd 13.7, 3.5	21.2, CH ₂
6b	1.51 m		1.50 m		1.32 m		1.33 m	
7a	1.96 dt 12.1, 3.1	39.7, CH ₂	1.95 dt 12.1, 3.2	39.9, CH ₂	1.93 m	40.8, CH ₂	1.92 dt 12.0, 3.2	40.4, CH ₂
7b	1.40 m		1.41 m		1.46 m		1.44 dt 12.0 3.0	
8		81.5, C		81.2, C		81.7, C		81.6, C
9	1.72 m	53.0, CH	1.76 m	53.4, CH	2.02 m	53.2, CH	2.06 dd 13.0, 5.3	53.1, CH
10		50.1, C		50.1, C		40.0, C		40.1, C
11a	2.41 dt 11.0, 5.5	26.3, CH ₂	2.40 ddd 11.0, 5.1, 5.1	25.9, CH ₂	1.74 m	24.5, CH ₂	1.76 m	23.6, CH ₂
11b	1.85 m		1.88 ddd 13.4, 11.0, 10.2		1.69 m		1.72 m	
12	3.88 dd 10.1, 5.5	85.4, CH	3.89 dd 10.2, 5.1	85.2, CH	3.93 dd 9.8, 6.0	85.7, CH	3.91 dd 9.7, 5.9	85.1, CH
13		82.8, C		73.1, C		83.3, C		73.1, C
14	6.05 dd 17.6, 11.0	140.1, CH	5.98 dd 17.3, 10.7	145.0, CH	6.05 dd 17.6, 11.1	140.4, CH	5.97 dd 17.3, 10.7	144.6, CH
15a	5.21 dd 11.0, 0.8	114.4, CH ₂	5.30 dd 17.3, 1.3	112.8, CH ₂	5.20 dd 11.1, 1.0	114.6, CH ₂	5.30 dd 17.3, 1.3	112.5, CH ₂
15b	5.15 dd 17.6, 0.8		5.11 dd 10.7, 1.3		5.15 dd 17.6, 1.0		5.11 dd 10.7, 1.3	
16	1.58 s	19.4, CH ₃	1.20 s	23.2, CH ₃	1.58 s	19.4, CH ₃	1.19 s	23.2, CH ₃
17	1.20 s	25.3, CH ₃	1.21 s	25.6, CH ₃	1.18 s	25.5, CH ₃	1.20 s	25.5, CH ₃
18	1.03 s	23.7, CH ₃	1.03 s	23.4, CH ₃	0.84 s	20.9, CH ₃	0.84 s	21.0, CH ₃
19	1.01 s	31.4, CH ₃	1.00 s	32.2, CH ₃	0.91 s	33.4, CH ₃	0.91 s	33.3, CH ₃
20	1.14 s	15.2, CH ₃	1.14 s	15.2, CH ₃	0.87 s	17.0, CH ₃	0.86 s	16.8, CH ₃
1'		170.0, C				170.0, C		
2'	2.03 s	22.1, CH ₃			2.03	22.4, CH ₃		

Table 2.NMR Spectroscopic Data for Petradoriolone (5) in CDCl₃ (500 MHz)

position	δ_{H} (J in Hz)	δ_{C} , type	position	δ_{H} (J in Hz)	δ_{C} , type
1	7.62 d 8.0	132.6, CH	7		181.7, C
2	7.43 dd 8.0, 7.5	127.7, CH	8	7.04 d 13.0	131.5, CH
3	7.53 d 7.5	132.9, CH	9	7.64 d 13.0	142.1, CH
4		137.5, C	9a		133.5, C
4a		132.5, C	6-OMe	4.01	55.8, CH ₃
5	7.32 s	111.7, CH	4-Me	2.73	21.8, CH ₃
6		156.9, C			

Table 3.

Biological Activities of compounds 1 – 7

Compound	<i>P. falciparum</i>	
	Dd2 IC ₅₀ (μM)	A2780 IC ₅₀ (μM)
1	NA	> 50
2	> 20	> 50
3	7.3 ± 0.6	> 50
4	> 20	> 50
5	> 20	> 50
6	NA	NT
7	> 20	NT
Artemisinin	0.0085 ± 0.3	NT
Paclitaxel	NT	0.013 ± 0.001