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2-Phenylnaphthalenes and a polyoxygenated cyclohexene from the stem and root extracts of *Uvaria cherrevensis* (Annonaceae)

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Abstract

Three new 2-phenylnaphthalene derivatives, cherrevenaphthalenes A-C (1-3), and a new polyoxygenated cyclohexene derivative, (-)-uvaribonol F (4) together with six known compounds, 5-10, were isolated from the stem and root extracts of *Uvaria cherrevensis* (Annonaceae). The structures of all isolated compounds were elucidated by spectroscopic analysis. The structures of 3 and 4 were further confirmed by single crystal X-ray diffraction methods. Compound 2 exhibited modest antiplasmodial activity against the *P. falciparum* strains TM4/ 8.2 and K1CB1 with IC₅₀ values of 18.8 ± 3.63 and 23.4 ± 4.08 µM, respectively, and weak cytotoxicity to a Vero cell line. Furthermore, compound 4 displayed cytotoxic activity against a KB cell line with an IC₅₀ value of 22.1 ± 0.42 µM but was non-cytotoxic to the Vero cell line. Compound 5 revealed stronger cytotoxicity towards the KB cell line, with an IC₅₀ value of 5.05 ± 0.86 µM and was nearly equally cytotoxic to the Vero cell line

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**2-Phenyl-naphthalenes and a polyoxygenated cyclohexene from the stem and root extracts of *Uvaria cherrevensis*
(Annonaceae)**

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Abstract: Three new 2-phenylnaphthalene derivatives, cherrevenaphthalenes A-C (**1-3**), and a new polyoxygenated cyclohexene derivative, (–)-uvaribonol F (**4**) together with six known compounds, **5-10**, were isolated from the stem and root extracts of *Uvaria cherreensis* (Annonaceae). The structures of all isolated compounds were elucidated by spectroscopic analysis. The structures of **3** and **4** were further confirmed by single crystal X-ray diffraction methods. Compound **2** exhibited modest antiplasmodial activity against the *P. falciparum* stains TM4/8.2 and K1CB1 with IC₅₀ values of 18.8±3.63 and 23.4±4.08 µM, respectively, and weak cytotoxicity to a Vero cell line. Furthermore, compound **4** displayed cytotoxic activity against a KB cell line with an IC₅₀ value of 22.1±0.42 µM but was non-cytotoxic to the Vero cell line. Compound **5** revealed stronger cytotoxicity towards the KB cell line, with an IC₅₀ value of 5.05±0.86 µM and was nearly equally cytotoxic to the Vero cell line.

Keywords: *Uvaria cherreensis*, Annonaceae, phenylnaphthalene, polyoxygenated cyclohexene, antiplasmodial activity, cytotoxic activity

1. Introduction

The plant *Uvaria* belongs to the Annonaceae family which is widely distributed in tropical and subtropical regions. Around 110 species have been found in the world and 26 of these in Thailand [1,2]. *Uvaria cherrevensis* (synonymous *Ellipeiopsis cherrevensis*) [2,3] was collected in the North of Thailand. The roots of this plant have been used as a traditional medicine for the treatment of urinary disorders [4]. Previous reports on the phytochemical studies on this plant revealed various types of secondary metabolites, especially alkaloids, flavonoids and polyoxygenated cyclohexenes [4,5], some of which presented significant pharmaceutical activities such as antimalarial and antimicrobial activities [4]. Some of the isolated compounds from the *Uvaria* genus have shown interesting biological activities, for example, 2-hydroxy-1,8-pyrenedione isolated from *U. lucia* showed strong cytotoxicity against human promyelocytic leukemia [6] and uvarins B and C isolated from *U. siamensis* presented strong antiplasmodial activities [7]. Therefore, *Uvaria* plants are important species to search for novel bioactive compounds. We report here the results of our phytochemical investigation of the stem and root extracts of *Uvaria cherrevensis*. This has resulted in the

isolation and characterization of three new 2-phenylnaphthalene derivatives (**1-3**) and a new polyoxygenated cyclohexene (**4**), together with six known compounds (**5-10**). The results of the testing of the isolated compounds against the *Plasmodium falciparum* strains, TM4/8.2 and K1CB1 (sensitive and multidrug resistant strains) and their cytotoxic activities against KB (oral cavity cancer) and Vero cell lines (African green monkey kidney cells) are also reported.

2. Experimental

2.1. General experimental procedures

Melting points were determined on a Stuart SMP10 melting point apparatus and are uncorrected. Optical rotations were measured in MeOH at the sodium D-line on a Rudolph Research Analytical Autopol I polarimeter. UV-vis absorption spectra were measured in MeOH with a Thermo Scientific Evolution 210 UV-vis spectrophotometer. Circular dichroism (CD) measurements were made using a Jasco J-810 spectropolarimeter using a quartz cell. The CD spectra shown were obtained after subtraction of the solvent spectra. The infrared (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrophotometer. The NMR spectra were recorded using either a 400 MHz Bruker or a 500 MHz Varian UNITY INOVA spectrometer. Chemical shifts were recorded in parts per million (δ) in CDCl_3 (δ_{H} 7.26 and δ_{C} 77.0 ppm) and/or acetone- d_6 (δ_{H} 2.05 and δ_{C} (CO) 206.2 and (CH₃) 29.8 ppm), with TMS as an internal reference. The HRESIMS data was obtained on a Bruker Daltonics mass spectrometer. X-ray diffraction data were collected on a SuperNova four-circle diffractometer equipped with a CCD area detector. Crystallographic data had been deposited in the Cambridge Crystallographic Data Centre. Thin-layer chromatography (TLC) was performed on silica

gel 60 GF₂₅₄ (Merck). Column chromatography (CC) was carried out on Sephadex LH-20 with MeOH or silica gel (Merck) type 100 (62-400 μm) and type 60 (5-40 μm) for quick column chromatography (QCC). Solvents for extraction and chromatography were distilled prior to use.

2.2 Plant Material

The stems and roots of *Uvaria cherrevensis* were collected from Doi Suthep National Park, Chiang Mai, Thailand in August 2015. This plant was identified by Dr. Tanawat Chaowasku, CMUB Herbarium, Chiang Mai University, Thailand, where a voucher specimen has been deposited (specimen no. T.Ritthiwigrom5).

2.3 Extraction and isolation

The air dried stems and roots of *U. cherrevensis* (2.3 kg) were extracted with acetone (8 L) over a period of 3 d at room temperature and removal of the solvent under reduced pressure afforded a dark green viscous oil (64.36 g). The oil was dissolved in CH_2Cl_2 (300 ml) to provide the CH_2Cl_2 soluble fraction (26.21 g) as a dark green viscous oil. The CH_2Cl_2 fraction was separated by QCC over silica gel by elution with a solvent gradient from hexanes (100%) to EtOAc (100%) to MeOH (100%) to provide six fractions (Fractions 1-6). Fraction 3 (836.0 mg) was separated by CC over silica gel by elution with CH_2Cl_2 to give seven subfractions (3A-3G). Subfraction 3B (26.0 mg) was fractionated by CC over silica gel by elution with acetone/hexanes (1:4) to furnish three subfractions (3B1-3B3). The second subfraction (13.0 mg) was purified by CC over Sephadex LH-20 with 100% MeOH to yield compounds **1** (5.0 mg) and **3** (4.0 mg) as a yellow solid and as red crystals, respectively. Compound **2** (9.8 mg) was isolated as a yellow solid from subfraction 3D (35.4 mg) after FCC over silica gel by elution with acetone/hexanes (1:9). Fraction 4 (1.70 g) was fractionated by CC over silica gel by elution with acetone/hexanes (1:4) to give five subfractions (4A-4E).

Subfraction 4B (336.8 mg) was separated by CC over Sephadex LH-20 with 100% MeOH to yield compound **9** (7.0 mg) as an orange solid. Compound **5** (4.0 mg) was obtained as brown solid from subfraction 4D (381.0 mg) after CC over Sephadex LH-20 with 100% MeOH. Fraction 5 (2.63 g) was fractionated by FCC over silica gel by elution with acetone/hexanes (3:7) to give four subfractions (5A-5D). Subfraction 5B (476.1 mg) was separated by CC over silica gel by elution with EtOAc/CH₂Cl₂ (1:9) to provide five subfractions (5B1-5B5). The second subfraction (125.4 mg) was purified by CC over silica gel by elution with MeOH/CH₂Cl₂ (1:99) to provide compound **10** (29.5 mg) as a yellow solid. Compound **8** (31.4 mg) was isolated as a yellow viscous oil from subfraction 5B4 (68.0 mg) after FCC over silica gel by elution with acetone/hexanes (1:4). Fraction 6 (1.99 g) was fractionated by FCC over silica gel by elution with acetone/hexanes (3:7) to afford four subfractions (6A-6D). Subfraction 6B (115.0 mg) was separated by CC over Sephadex LH-20 with 100% MeOH to receive three subfractions (6B1-6B3). The second subfraction (57.7 mg) was purified by FCC over silica gel by elution with MeOH/CH₂Cl₂ (1:99) to provide compounds **4** (13.0 mg) and **7** (39.1 mg) as colorless crystals and a yellow viscous oil, respectively. Fraction 6C (324.7 mg) was fractionated by CC over silica gel by elution with MeOH/CH₂Cl₂ (2:98) to provide five subfractions (6C1-6C5). Compound **6** (41.1 mg) was isolated as a white solid from subfraction 6C4 (65.9 mg) after CC over Sephadex LH-20 with 100% MeOH. A schematic for the isolation of compounds from the crude CH₂Cl₂ extract from this plant is provided in the Supplementary data.

Cherrevenaphthalene A (**1**): yellow solid; mp 171-172 °C; UV (MeOH) λ_{max} (log ϵ) 262 (4.5), 292 (4.0) 352 (3.2) nm; IR (neat) ν_{max} 3418, 2925, 1619, 1505, 1404 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆) and ¹³C NMR (100 MHz, acetone-*d*₆) see Table 1; HRESIMS m/z 295.0967 [M-H]⁻, calcd for C₁₈H₁₅O₄, 295.0970.

Cherrevenaphthalene B (**2**): yellow solid; mp 178-179 °C; UV (MeOH) λ_{max} (log ϵ) 214 (3.9), 253 (4.0), 316 (4.2) nm; IR (neat) ν_{max} 3386, 2926, 2853 1608, 1514 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (100 MHz, CDCl_3) see Table 1; HRESIMS m/z 297.1136 $[\text{M}-\text{H}]^-$, calcd for $\text{C}_{18}\text{H}_{17}\text{O}_4$, 297.1127.

Cherrevenaphthalene C (**3**): red crystal; mp 206-207 °C; UV (MeOH) λ_{max} (log ϵ) 279 (4.0), 318 (3.7), 397 (3.6) nm; IR (neat) ν_{max} 3357, 2925, 1684, 1647, 1573, 1521, 1261 cm^{-1} ; ^1H NMR (500 MHz, acetone- d_6) and ^{13}C NMR (125 MHz, acetone- d_6) see Table 2; HRESIMS m/z 333.0729 $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{18}\text{H}_{14}\text{O}_5\text{Na}$, 333.0739; Crystallographic data (CCDC 1539198).

(-)-Uvaribonol F (**4**): colorless crystal; mp 149-150 °C; $[\alpha]_D^{20}$ -12.5 (c 0.5, MeOH); UV (MeOH) λ_{max} (log ϵ) 229 (2.8), nm; CD (MeOH,) λ_{max} ($\Delta\epsilon$) 229 (-2.0) nm; IR (neat) ν_{max} 3391, 1744, 1719, 1369, 1274, 1250, 1216 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR(125 MHz, CDCl_3) see Table 3; HRESIMS m/z 365.1233 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{18}\text{H}_{21}\text{O}_8$, 365.1236; Crystallographic data (CCDC 1539199).

2.4 Bioactivity Assays

The antiplasmodial activity testing (TM4/8.2, a wild type sensitive strain and K1CB1, multidrug resistant strain) was carried out using a modified Microdilution Radioisotope Techniques [8]. Cycloguanil and pyrimethamine were used as the reference substances [9]. KB cells (human mouth epidermal carcinoma cells) and normal Vero cells (kidney epithelial cells of African green monkey, *Cercopithecus aethiops*) [10] were evaluated using the sulforhodamine B (SRB) assay [11]. Doxorubicin, ellipticine and WR99210 (1,6-dihydro-6,6-dimethyl-1-[3-(2,4,5-trichlorophenoxy)propoxy]-1,3,5-triazine-2,4-diamine) were used as the standard compounds. Both assays performed at the bioassay laboratory, BIOTEC, NSTDA, Thailand.

3. Results and Discussion

The CH₂Cl₂ extract of the stems and roots of *U. cherrevensis* was separated and provided three new 2-phenylnaphthalene derivatives, cherrevenaphthalenes A-C (**1-3**), and a new polyoxygenated cyclohexene derivative, (–)-uvaribonol F (**4**) along with six known compounds; 2-hydroxy-3-methoxy-6-(4'-hydroxyphenyl)naphthalene (**5**) [7], (–)-zeylenol (**6**) [12], (+)-sootepenol A (**7**) [13], (–)-ellipieiopsol B (**8**) [5], 2',4'-dihydroxy-3'-(2-hydroxybenzyl)-6'-methoxychalcone (**9**) [4] and 5-*O*-methyldichamanetin (**10**) [14]. (Fig. 1) The structures of these isolated compounds were elucidated using spectroscopic methods especially 1D and 2D NMR spectroscopy and X-ray crystallography. All isolated compound were evaluated for their antimalarial activities against the *Plasmodium falciparum*, TM4/8.2 and K1CB1 (sensitive and multidrug resistant strains); and cytotoxicities against KB (oral cavity cancer) and Vero cell lines (African green monkey kidney cells).

Compound **1** was isolated as a yellow solid with mp 171-172 °C and demonstrated a molecular formula of C₁₈H₁₆O₄ as assigned from the HRESIMS ion peak at m/z 295.0967 [M-H][–] (calcd 295.0970). The UV spectrum displayed maximal absorption bands at $\lambda_{\max}$ 262, 292 and 352 nm and the IR spectrum revealed absorption bands of a hydroxy group (3418 cm^{–1}), and an aromatic (1619 and 1505 cm^{–1}) ring system, indicating the possibility of a naphthalene nucleus [7,15]. The ¹H NMR spectrum (Table 1) demonstrated resonances for three aromatic protons of a 1,2,4-trisubstitued benzene [δ_{H} 8.13 (1H, *d*, *J* = 2.0 Hz), 7.70 (1H, *d*, *J* = 8.4 Hz) and 7.61 (1H, *dd*, *J* = 8.4 and 2.0 Hz)], four aromatic protons of a *para*-disubstitued benzene [δ_{H} 7.60 and 6.96 (each, 2H, *d*, *J* = 8.6 Hz)], an isolated aromatic proton (δ_{H} 7.06, 1H, *s*) and two methoxy groups [δ_{H} 4.04 and 3.98 (each 3H, *s*)]. Compound **1** showed resonances for eight quaternary (δ_{C} 157.8, 150.9, 148.5, 141.2, 136.5, 133.5, 131.0 and 125.0), eight methine [δ_{C} 128.9 (2C), 127.6, 125.6, 118.9, 116.6 (2C) and 106.4] and two methoxy (δ_{C} 61.4 and 61.2) carbons

in the ^{13}C NMR and DEPT 135 spectra (Table 1). The aromatic protons of the 1,2,4-trisubstituted benzene at δ_{H} 8.13, 7.70 and 7.61 were assigned to H-8, H-5 and H-6, respectively, due to their multiplicities and the HMBC correlations of H-8 to C-1 (δ_{C} 148.5), C-6 (δ_{C} 125.6), C-10 (δ_{C} 131.0) and C-1' (δ_{C} 133.5); of H-5 to C-4 (δ_{C} 106.4), C-7 (δ_{C} 136.5) C-9 (δ_{C} 125.0), and C-10; and of H-6 to C-8 (δ_{C} 118.9), C-10 and C-1'. The methoxy group resonating at δ_{H} 4.04 was located at C-1 on the basis of the HMBC cross peak between these methoxy protons with C-1 as well as the HMBC correlation of H-8 with C-1. The singlet aromatic proton at δ_{H} 7.06 was assigned to H-4 according to its HMQC cross peak with C-4 (δ_{C} 106.4) together with the HMBC correlations of H-4 with C-2 (δ_{C} 141.2), C-3 (δ_{C} 150.9), C-5 (δ_{C} 127.6) and C-9. The substituent at C-3 was identified as a hydroxy group because of its ^{13}C NMR chemical shift, thus the remaining methoxy group resonating at δ_{H} 3.98 was located at C-2 because of the relative high field ^{13}C NMR chemical shift of C-2 due to its two-*ortho* oxygenated aromatic substituents and its HMBC correlation to C-2. The *para*-disubstituted aromatic ring was attached at C-7 (δ_{C} 136.5) of the naphthalene unit according to the HMBC correlations of the aromatic protons H-2' and H-6' with C-7. The hydroxy group was assigned as the substituent at C-4' based on its ^{13}C NMR chemical shift. Compound **1** (cherrevenaphthalene A) was thus elucidated as 3-hydroxy-1,2-dimethoxy-7-(4'-hydroxyphenyl)naphthalene.

Compound **2** was obtained as a yellow solid (mp 178-179 °C) which showed a $[\text{M}-\text{H}]^-$ ion at m/z 297.1136 in the HRESIMS, consistent with a molecular formula of $\text{C}_{18}\text{H}_{17}\text{O}_4$ (calcd 297.1127). The spectroscopic data of **2** were similar to those of **1** (Table 1), except for the three aromatic proton resonances of the 1,2,4-trisubstituted benzene in **1** were replaced with resonances for two coupled methylene groups at δ_{H} 2.82 and 2.64 (each 2H, *brt*, $J = 8.5$ Hz) and one olefinic proton (δ_{H} 6.97) in **2**. The two coupled methylene group resonances at δ_{H} 2.82 and 2.64

were assigned to H₂-5 and H₂-6, respectively, supported by the HMBC correlations between H₂-5 and C-9 (δ_C 121.2) and C-10 (δ_C 131.8), and between H₂-6 and C-7 (δ_C 135.8) and C-8 (δ_C 116.3). The olefinic proton, H-8 (δ_H 6.97, *brs*) showed HMBC cross peaks with C-1 (δ_C 148.5), C-6 (δ_C 26.3) and C-10 to confirm its location at C-8. Therefore, cherrevenaphthalene B (**2**) was characterized as 3-hydroxy-1,2-dimethoxy-7-(4'-hydroxyphenyl)-5,6-dihydronaphthalene.

Compound **3** was obtained as a red crystals with a mp 206-207 °C, and had the molecular formula C₁₈H₁₄O₅ by HRESIMS [found *m/z* 333.0729 (calcd for 333.0739) [M+Na]⁺]. The UV spectrum showed absorption bands at $\lambda_{\max}$ 279, 318 and 397 nm and the IR spectrum indicated hydroxyl (3357 cm⁻¹), two carbonyl (1684 and 1647 cm⁻¹) and aromatic (1573 and 1521 cm⁻¹) groups. The ¹H NMR spectroscopic data (Table 1) of compound **3** were close to those of compound **1**. The main difference was the absence of the singlet aromatic proton resonance in ¹H NMR spectrum in **1** and the presence two carbonyl carbons at δ_C 178.2 and 177.4 instead of two aromatic carbons in the ¹³C NMR spectrum of **3**. The aromatic proton, H-5 (δ_H 7.97) showed a HMBC correlation with the carbonyl carbon resonating at δ_C 177.4, indicating that this carbonyl carbon was located at C-4. Thus, the remaining carbonyl carbon at δ_C 178.2 was assigned to C-3. A single crystal X-ray diffraction analysis (Fig. 2) confirmed the structure of compound **3**. Therefore, compound **3** (cherrevenaphthalene C) was determined as 3,4-dimethoxy-7-(4'-hydroxyphenyl)naphthalene-1,2-dione.

Compound **4** was obtained as colorless crystals (mp 149-150 °C) with a specific rotation of $[\alpha]_D^{20}$ -12.5 (*c* 0.5, MeOH). Its molecular formula, C₁₈H₂₀O₈, was deduced from HRESIMS. The UV, IR, ¹H and ¹³C NMR spectral data (Table 2) were almost the same as those of (+)-

uvaribolnol F which was isolated from the stem extracts of *U. boinana* [16] and were identical to that of synthetic (–) **4** reported earlier [17]. The absolute configuration and structure of (–) **4** was determined as (1*S*,2*R*,3*S*,4*R*)-3,4-diacetate-2-(benzoyloxymethyl)-1,2,3,4,-tetrolcyclohex-5-ene by X-ray crystallography (Fig. 3). Compound **4** showed a negative Cotton effect at 229 nm ($\Delta\epsilon$ –2.0) (Supplementary information) further supporting its similar configuration to (–)-6-acetylzeylenol and (–)-zeylenol [18].

The isolated compounds were evaluated for their antimalarial activities against *Plasmodium falciparum*, TM4/8.2 and K1CB1 (sensitive and multidrug resistant strains) and cytotoxicities against the KB (oral cavity cancer cell line) human and noncancerous Vero cell lines (African green monkey kidney cell line) (Table 3). The phenylanthranols exhibited antimalarial activity better than the flavonoids while the polyoxygenated cyclohexenes were all most inactive in this assay. However, the activity was dependent on the position of the substituent groups. In terms of cytotoxicity, the polyoxygenated cyclohexene which contained an acetyl group at the C-2 position, exhibited the highest cytotoxicity against KB cells and was not toxic to Vero cells while the phenylanthranols and flavonoids showed activity against both KB and Vero cells. Compounds **1**, **2** and **5** exhibited modest antiplasmodial activity against the *P. falciparum* strains TM4/8.2 and K1CB1 with IC₅₀ values of 18.8 to 24.2 μ M. These compounds showed different levels of cytotoxicities to KB and Vero cell lines. Compound **2**, having a saturated bond between the C-5 and C-6 positions, demonstrated less cytotoxic activities when compare with compound **1**. While compound **5** without a substituent at the C-1 position was toxic to both KB and Vero cells with IC₅₀ values about 5 μ M. Compounds **1** and **2** carrying a methoxy substituent at the C-1 position were less cytotoxic against both cell lines when compared to compound **5**. Compound **3** with modifications at C-3 and C-4 exhibited weaker antimalarial activity and was not cytotoxic. The effects of the different substitutions at C-1, C-3 and C-4 on the biological activities of

these compounds suggests that chemical modification at these and other positions may lead to improvement in their antimalarial and/or anticancer activity with less toxicity to Vero cells. Compound **4** displayed cytotoxic activity against the KB cell line with an IC₅₀ value of 22.1±0.42 µM, but was non-cytotoxic to Vero cells. Compounds **6-8** were inactive in all assays. Compound **9** showed significant cytotoxicity to KB and Vero cell lines but exhibited weak antiplasmodial activity. Compound **10** showed weak cytotoxicity to Vero cells. The cytotoxicity against Vero cells of most of the isolated compounds may suggest that this plant may be quite toxic.

Conflict of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://>

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Table 1 NMR data (400 MHz) of cherrevenaphthalenes A and C in acetone-*d*₆ and B in CDCl₃ (**1-3**)

Position	1			2			3^a		
	δ_{C} , type	δ_{H} , (<i>J</i> in Hz)	HMBC	δ_{C} , type	δ_{H} , (<i>J</i> in Hz)	HMBC	δ_{C} , type	δ_{H} , (<i>J</i> in Hz)	HMBC
1	148.5, C			148.5, C			155.9, C		
2	141.2, C			138.2, C			139.5, C		
3	150.9, C			148.0, C			178.2, C		
4	106.4, CH	7.06, s	2, 3, 5, 9	109.9, CH	6.56, s	2, 3, 5, 9	177.4, C		
5	127.6, CH	7.70, d (8.4)	4, 7, 9, 10	28.5, CH ₂	2.82, brt (8.5)	4, 6, 7, 9, 10	129.0, CH	7.97, d (8.0)	4, 7, 9
6	125.6, CH	7.61, dd (8.4, 2.0)	8, 10, 1'	26.3, CH ₂	2.64, brt (8.5)	5, 7, 8, 10	127.1, CH	7.78, dd (8.0, 1.5)	8, 10
7	136.5, C			135.8, C			147.5, C		
8	118.9, CH	8.13, d (2.0)	1, 6, 10, 1'	116.3, CH	6.97, brs	1, 6, 10, 1'	122.6, CH	8.05, d (1.5)	1, 10
9	125.0, C			121.2, C			133.8, C		
10	131.0, C			131.8, C			126.3, C		
1'	133.5, C			134.4, C			130.2, C		
2'/6'	128.9, CH	7.60, d (8.6)	7, 2', 4', 6'	126.6, CH	7.44, d (8.7)	7, 2', 3', 4', 6'	128.5, CH	7.67, d (9.0)	7, 2', 4', 6'
3'/5'	116.6, CH	6.96, d (8.6)	1', 3', 4', 5'	115.4, CH	6.84, d (8.7)	1', 3', 4', 5'	116.0, CH	7.01, d (9.0)	1', 3', 4', 5'
4'	157.8, C			155.0, C			158.6, C		
OCH ₃ (1)	61.4, CH ₃	4.04, s	1	61.2, CH ₃	3.87, s	1	61.2, CH ₃	4.39, s	1
OCH ₃ (2)	61.2, CH ₃	3.98, s	2	61.1, CH ₃	3.92, s	2	60.2, CH ₃	3.87, s	2

^aRecorded at 500 MHz

Table 2 NMR data (500 MHz in CDCl₃) of (–) uvaribonol F (**4**)

Position	4		
	δ_C , type	δ_H , (<i>J</i> in Hz)	HMBC
1	75.2, C		
2	71.7, CH	5.50, d (6.5)	1, 2-CO, 3, 4
3	70.6, CH	5.59, brd (6.5)	2, 3-CO, 5
4	127.3, CH	5.78, brdd (10.0, 2.5)	2, 5, 6
5	129.0, CH	5.96, brdd (10.0, 3.0)	1, 3, 4, 6
6	69.1, CH	4.28, d (3.0)	1, 4, 7
7	66.2, CH ₂	4.66, d (12.0) 4.54, d (12.0)	1, 2, 6, 7-CO
1'	129.2, C		
2'	129.8, CH	8.06, d (7.5)	4', 6', 7-CO
3'	128.6, CH	7.47, d (7.5)	1', 7-CO
4'	133.6, CH	7.60, t (7.5)	2', 6'
5'	128.6, CH	7.47, d (7.5)	1', 7-CO
6'	129.8, CH	8.06, d (7.5)	2', 4', 7-CO
2-Ac	20.8, CH ₃	2.12, s	2-CO
3-Ac	20.9, CH ₃	2.00, s	3-CO
2-CO	170.44, C		
3-CO	170.39, C		
7-CO	167.2, C		

Table 3 Antimalarial and cytotoxic activities of the isolated compounds (IC₅₀, μ M)

Compounds	Antimalarial activity against <i>P. falciparum</i>		Cytotoxic activity	
	TM4/8.2	K1CB1	KB	Vero cells
1	21.1±3.14	24.2±4.55	30.7±3.69	17.5±2.11
2	18.8±3.63	23.4±4.08	^a	39.1±4.81
3	40.4±9.34	^a	^a	^a
4	^a	^a	22.1±0.42	^a
5	22.3±0.81	23.4±4.41	5.05±0.86	5.47±0.10
9	32.4±7.31	^a	13.8±1.07	6.99±1.28
10	^a	^a	^a	38.6±7.95
Cycloguanil ^b	0.059±0.022	6.38±2.23	^a	^a
Pyrimethamine ^b	0.13±0.05	30.6±6.00	^a	32.9±10.3
Doxorubicin ^c			0.56	
Ellipticine ^c				0.4
WR99210 ^c			2.68±0.18	7.62±1.19

^a Inactive at >50 μ M. ^b Reference drugs for antiplasmodial activity.^c Positive control for cytotoxic assay. Compounds **6–8** were inactive in all assays.

Fig. 1. Isolated compounds from the stem and root extracts of *U. cherrevensis*.

Fig. 2. X-ray structure of compound 3

Fig. 3. X-ray structure of compound **4**