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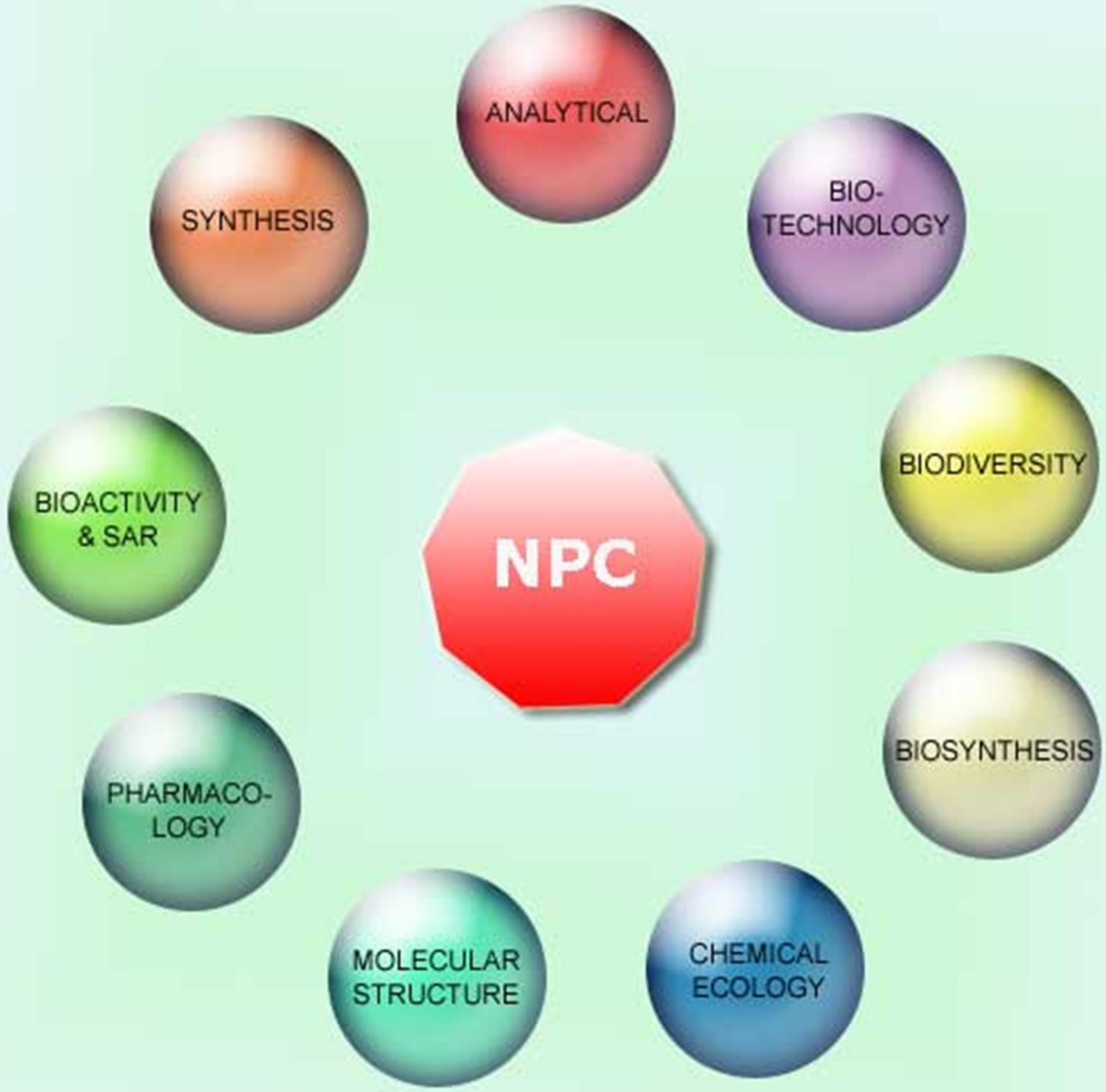

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Antiplasmodial Quinones from the Rhizomes of *Kniphofia foliosa*

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Extracts of the rhizomes of *Kniphofia foliosa* exhibited antiplasmodial activities against the chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *Plasmodium falciparum* with IC_{50} values of 3–5 μg/mL. A phenyloxanthrone, named 10-acetonylknipholone cyclooxanthrone (**1**) and an anthraquinone-anthrone dimer, chryslandicin 10-methyl ether (**2**), were isolated from the rhizomes, along with known quinones, including the rare phenylanthraquinone dimers, joziknipholones A and B. The structures of these compounds were determined based on spectroscopic data. This is the second report on the occurrence of the dimeric phenylanthraquinones in nature. In an *in vitro* antiplasmodial assay of the isolated compounds, activity was observed for phenylanthraquinones, anthraquinone-anthrone dimers and dimeric phenylanthraquinones, with joziknipholone A being the most active. The new compound, 10-acetonylknipholone cyclooxanthrone, also showed anti-plasmodial activity. In an *in vivo* assay, knipholone anthrone displayed marginal antimalarial activity.

Keywords: *Kniphofia foliosa*, Rhizomes, 10-Acetonylknipholone cyclooxanthrone, Chryslandicin 10-methyl ether, Joziknipholones A and B, Knipholone anthrone, Malaria.

Malaria still remains a public health and economic problem in the world mainly due to increase in resistance of the pathogens to the conventional drugs [1]; this makes the search for new agents a vital and urgent task [2]. Phenylanthraquinones and anthraquinone-anthrone dimers are among the many classes of compounds identified with antiplasmodial activities [3,4]. These compounds are found in some genera of the family Asphodelaceae, including *Bulbine* and *Kniphofia* [3,4].

Kniphofia foliosa is used medicinally for the treatment of abdominal cramps and for wound healing [3]. The plant is known to elaborate monomeric [5] and dimeric anthraquinones [3,6], and phenylanthraquinones [4,7], some of which exhibit diverse biological activities [3,4,8,9]. We report here the isolation and structural elucidation of two new anthraquinone derivatives (**1** and **2**, Figure 1) along with known compounds from the rhizomes of *K. foliosa*. The anti-plasmodial activities of some of the isolated compounds are also reported.

Compound **1** ($C_{27}H_{22}O_8$) exhibited a UV spectrum (λ_{max} 284, 360 and 412 nm) which suggested a phenylanthrone moiety [7]. Furthermore, comparison of the ^{1}H and ^{13}C NMR spectra (Table 1) with knipholone anthrone (**3**) [7] indicated that this compound also contains a chrysophanol anthrone moiety with the three aromatic protons of ring C resonating at δ_H 7.45 (dd, J = 1.2, 7.8 Hz, H-5), 7.62 (t, J = 7.8 Hz, H-6) and 7.02 (dd, J = 1.2, 7.8 Hz, H-7). In ring A, a singlet at δ_H 6.98 was assigned to H-2 with the methyl being placed at C-3 (δ_C 147.4), as expected biogenetically, requiring a substituent at C-4 (δ_C 118.8), which, as in knipholone anthrone (**3**), was established (Table 1) to be an acetylphloroglucinol methyl ether [7]. The signals for the methylene group at C-10, which were observed in **3** [7] are missing; instead, the presence of a quaternary carbon signal at δ_C 76.7 was observed which showed that this sp^3 carbon is oxygenated. Furthermore, in the ^{1}H and ^{13}C NMR spectra (Table 1), the presence of two geminal protons (δ_H 3.17, d, J = 15.0 Hz; and δ_H 2.87, *d*, J = 15.0 Hz, showing HSQC correlation with the signal at δ_C 51.1 for CH_2-1"), a carbonyl signal (δ_C 203.7 for C-2") and a highly shielded methyl signal (δ_H 1.64, *s*; δ_C 31.7 for CH_3 -3") showed the presence of an acetonyl substituent at C-10, and its placement was confirmed from the HMBC spectrum, which showed correlation between the methylene protons of the acetonyl group and C-10 (δ_C 76.7). The molecular ion peak at *m/z* 474.1303 (corresponding to $C_{27}H_{22}O_8$) and lack of OH signals (except for the chelated hydroxyl groups), even in acid free solvent, is in agreement with cyclization involving C-10 and 6'-OH, as in kinipholone cyclooxanthrone [10]; consequently, the new compound was characterized as 10-acetonylknipholone cyclooxanthrone (**1**).

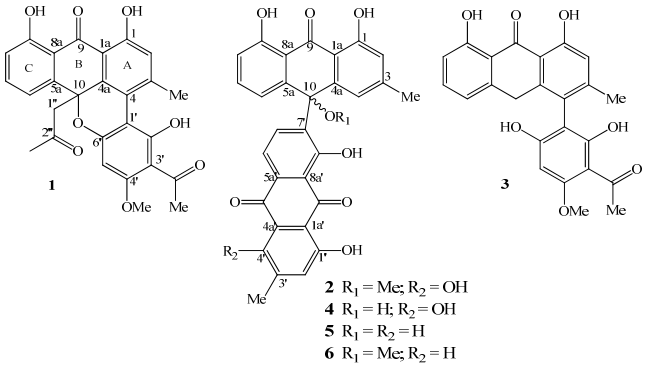

Figure 1: Anthraquinone derivatives from *Kniphofia foliosa.*

Table 1: ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR data together with HMBC correlation of compounds **1** and **2** (in ppm, CD_2Cl_2).

	1			**2**		
C/H	δ_H m (*J* in Hz)	δ_C	HMBC	δ_H m (*J* in Hz)	δ_C	HMBC
1		160.6			162.1	
1a		111.3			114.4	
2	6.98 s	120.6	C-1,C-1a, C-4a, CH_3-3	6.70 d (1.8)	117.8	C-1a
3		147.4			148.7	
4		118.8		6.53 d (1.8)	120.7	
4a		136.8			148.7	
5	7.45 dd (1.2, 7.8)	117.3	C-6, C-7 , C-8a, C-10	6.69 dd (8.4, 1.2)	119.2	C-6
5a		142.7			144.3	
6	7.62 t (7.8)	136.8	C-5, C-5a, C-8	7.35 t (8.4)	136.7	C-8
7	7.02 dd (1.2, 7.8)	118.2	C-5, C-8, C-8a	6.86 dd (8.4, 1.2)	117.6	C-5
8		162.2			162.1	
8a		114.7			116.1	
9		192.6			192.8	
10		76.7			75.1	
1'		105.6			158.4	
1'a					115.5	
2'		163.0		7.01 brs	128.9	
3'		107.6			141.7	
4'		163.9			157.6	
4'a					113.8	
5'	6.42 s	92.9	C-1', C-3', C-4, C-4', C-6', 3'-C=O	7.95 d (8.4)	118.9	C-10'
5'a					138.0	
6'		159.3		8.60 d (8.4)	132.5	C-8'
7'					132.6	
8'					162.9	
8'a					116.4	
9'						
10'					186.0	
1"	3.17 d (15.0),2.87 d (15.0)	51.1	C-4, C-5a, C-10, 2"-C=O			
2"						
3"						
3- CH_3	2.39 s	23.8	C-2, C-3, C-4	2.18 s	22.2	C-2, C-3, C-4
3'-CH_3	2.72 s	33.4	C-3', 3'-C=O	2.25 s	22.3	C-2', C-3', C-4'
3"-CH_3	1.64 s	31.7	C-1", 2"-C=O			
10-OCH_3				2.78 s	50.5	C-10
4'-OCH_3	4.00 s	56.3	C-4', C-5'			
1-OH	11.62		C-1, C-1a, C-2,	11.94 s		
8-OH	12.05		C-7, C-8, C-8a	12.16 s		
1'-OH				12.18 s		
4'-OH				13.41 s		
8'-OH				12.28 s		
2'-OH	15.08		C-1', C-2', C-3', 3'-C=O			
3'-CO		204.6				
2"-CO		203.7				

This compound appears to have been formed through the acetonation of knipholone cyclooxanthrone, a compound which was recently isolated from the roots of this plant [10]. There are examples of compounds reported from plants containing a three carbon substituent, including acetonides, probably derived from propanoyl-CoA [11]; however, there still exists controversy as to whether acetonides are true natural products or artifacts formed during extraction and isolation [12].

The UV spectrum (λ_{max} 262, 295, 370sh, 388, 500, 522sh and 537 nm) and the $[M+1]^+$ ion at *m/z* 539.1895 (molecular formula $C_{31}H_{22}O_9$) in the MS of **2** suggested that it is an anthraquinone-anthrone dimer, as in chryslandicin (**4**) [6]. In support of this, the ^{1}H NMR spectrum (Table 1) showed the presence of five chelated hydroxyl and two aromatic methyl groups of a dimer. As in compound **4** [6], one half of the dimer (**2**) was readily identified as chrysophanol oxanthrone, which is connected to the other half at C-10 (Table 1). For the other half of the molecule, the presence of the biogenetically expected methyl group (δ_H 2.25, δ_C 22.3) at C-3' and a singlet at δ_H 7.01 assigned to H-2', suggested that C-4' is substituted with a hydroxyl group (δ_H 13.41), as in islandicin [13]. The ABX pattern expected for ring C in islandicin is now replaced by a pair of deshielded *ortho*-coupled protons (*J* = 8.4 Hz) at δ_H 7.95 (H-5') and 8.60 (H-6'), which is consistent with C-7' as the point of attachment of the islandicin moiety to chrysophanol oxanthrone. This new compound is therefore a dimer comprised of chrysophanol oxanthrone and islandicin moieties with a methoxyl (δ_H 2.78; δ_C 50.5) substituent at C-10, i.e. 10-methoxy-10-(islandicin-7'-yl)chrysophanol anthrone; the trivial name chryslandicin 10-methyl ether is suggested by relating it with the co-metabolite chryslandicin (**4**) [3,6]. Refluxing a sample of **4** in acidic methanol gave **2**, which confirmed that the new compound is indeed a 10-methyl ether derivative of **4**. The CD spectrum of **2** displayed a negative Cotton effect at 272 nm, however the absolute configuration at C-10 has not been determined.

The other known compounds were identified as the anthraquinone monomers chrysophanol [13], aloe-emodin acetate [5], islandicin [13], deoxyerythrolaccin [14] and laccaic acid D [15]; the anthraquinone dimers asphodelin [16] and chryslandicin (**4**) [6]; the phenylanthraquinone, knipholone [7], the phenylanthrone knipholone anthrone (**3**) [7]; the rare dimeric phenylanthraqunones joziknipholones A and B [17] and a minor phenolic 3,4-dihydroxy-benzoic acid [15]. This is only the second report on the occurrence of the dimeric phenylanthraqunones joziknipholones A and B in nature having been isolated from the roots of *Bulbine frutescens* [17]. The occurrence of these compounds in *Bulbine* and *Kniphofia* species supports the previous assertion that these two genera are closely related [4]. Deoxyerythrolaccin, laccaic acid D, asphodelin and 3,4-dihydroxybenzoic acid are reported here for the first time from the genus.

The crude extracts of the rhizomes of *K. foliosa* showed anti-plasmodial activities against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum* (Table 2). The isolated compounds were also tested and one of the new compounds, 10-acetonylknipholone cyclooxanthrone (**1**), exhibited significant activity (IC_{50} 3.1±1.2 mg/mL) against the W2 strain of

Table 2: *In vitro* antiplasmodial activities of crude extracts and pure compounds obtained from *Kniphofia foliosa* against *Plasmodium falciparum*.

Sample	IC_{50} values (µg/mL±SD)		
	D6	W2	Other strains
Crude extracts			
K. foliosa (rhizomes, extract I)	3.4±0.4	4.8±0.2	
K. foliosa (rhizomes, extract II)	4.7±0.5	4.1±0.8	
K. foliosa (roots extract) [10]	8.9±1.5	11.3±0.01	3.8 (3D7) [3]
Monomeric anthraquinones			
Chrysophanol	NT	NT	>5 [4]
Aloe-emodin	NT	NT	>5 (K1) [4], >18.5 (K1), 18.5 (NF54) [4]
Dimeric anthraquinones/anthrones			
Chryslandicin (**4**)	2.1±0.5	1.5±0.3	0.54 (3D7) [3]
10-Hydroxy-10-(chrysophanol-7'-yl)chrysophanol anthrone (**5**)	1.7±0.2	0.7±0.2	0.26 (3D7) [3]
10-Methoxy-10-(chrysophanol-7'-yl)chrysophanol anthrone (**6**) [10]	4.1±1.5	1.2±0.1	
Asphodelin	8.2±1.7	6.4±1.4	
Phenylanthraquinones/anthrones			
Knipholone	10.1±0.2	8.0±0.5	1.70 (NF54), 1.06 (K1) [4],
Isoknipholone	8.6±1.6	7.9±1.2	0.12 (K1) [4]
Knipholone anthrone (**3**)	4.1±0.8	3.6±0.9	0.38 (K1), 0.42 (NF54), 0.15 (K1) [4]
10-Acetonylknipholone cyclooxanthrone (**1**)	4.4±1.5	3.1±1.2	
Knipholone cyclooxanthrone [10]	4.0±0.7	6.1±1.6	
Dimeric phenylanthraquinones			
Joziknipholone A	0.4±0.1	0.3±0.1	0.2 (K1) [17]
Joziknipholone B	2.5±0.6	1.5±0.2	0.3 (K1) [17]
Naphthalene derivatives			
Dianellin [10]	5.5±1.20	3.3±0.2	
2-Acetyl-1-hydroxy-8-methoxy-3-methylnaphthalene			15.5 (3D7) [3]
Standard drugs			
Chloroquine	0.007±0.001	0.2±0.03	
Mefloquine	0.03±0.01	0.0025±0.0004	

NT = Not Tested.

P. falciparum. The dimeric phenylanthraquinone, joziknipholone A showed the highest activity with IC_{50} values of 0.4±0.1 µg/mL (against D6) and 0.3±0.1 µg/mL (against W2), while moderate activity was observed for its atropisomer, joziknipholone B (Table 2). Similarly, good activities have been reported for joziknipholones A and B, isolated from *Bulbine frutescens*, against the K1 strain of *P. falciparum* [17]. It was, however, noted that the activities observed for the monomeric phenylanthraquinones knipholone, isoknipholone and knipholone anthrone (**3**) against the D6 and W2 strains, in the SYBR Green I assay, were lower compared with what has been reported against the K1 and NF54 strains (Table 2). These phenylanthraquinones were isolated as scalemic or nearly as racemic mixtures [4]; it will, therefore, be interesting to test the pure enantiomeric forms (or at least the enantiomerically enriched forms) in order to find out the relationship between configuration and antiplasmodial activity. It has already been reported that the anticancer activity of phenylanthraquinones is related to the configuration at the biaryl axis [4].

The major compound of this plant, knipholone anthrone (**3**) [7], which has been reported to show *in vitro* antiplasmodial activity [4], was tested in an *in vivo* 4-day *Plasmodium berghei* ANKA suppressive test [18] at 100 mg/kg/day; however, only marginal activity (30.1% chemosuppression) was observed. In light of this preliminary data and the cytotoxicity observed for some phenylanthraquinones/anthrones, including knipholone anthrone (**3**) [4], more comprehensive *in vivo* testing of these compounds is necessary to establish whether the observed antiplasmodial activities may be due to general cytotoxicity or not.

Wube *et al.* [3] have reported that the anthraquinone-anthrone dimers **4** and **5** (Figure 1) showed good antiplasmodial activities against the 3D7 strain of *P. falciparum* with low cytotoxicity (high selectivity index). These compounds, along with the related dimer (**6**), are also active against the D6 and W2 strains of *P. falciparum* (Table 2), supporting the assertion that this class of compounds may constitute a new class of antimalarial lead structures, provided that they also show *in vivo* activities. Asphodelin, which is 4,7'-bichrysophanol, did not show good antiplasmodial activity (Table 2), suggesting that a 10-7'-anthrone-anthraquinone linkage is important for good antiplasmodial activity.

Experimental

General: Analytical TLC: Merck pre-coated silica gel 60 F_{254} plates. CC on oxalic acid impregnated silica gel 60 (70-230 mesh). UV spectra on a Specord S600, Analytik Jena AG, Germany. HREI-MS on a Micromass GC-TOF micro mass spectrometer (Micromass, Wythenshawe, Waters Inc., UK). NMR on a Bruker Avance 600 spectrometer. COSY, HSQC and HMBC spectra were acquired using the standard Bruker software.

Plant material: The rhizomes of *K. foliosa* were collected from the Chemistry Department, Addis Ababa University garden in November, 2009. For authentication refer to [7].

Extraction and isolation: The air-dried and ground rhizomes of *K. foliosa* (1.4 kg) were extracted successively with CH_2Cl_2/CH_3OH; 1:1 (3X2L) and CH_3OH (3X2L). The concentrated CH_2Cl_2/CH_3OH; 1:1 extract (labeled as extract I, 45 g) was subjected to CC on oxalic acid impregnated silica gel (400 g) whilst eluting with *n*-hexane containing an increasing gradient of EtOAc, which afforded 35 fractions each of *ca.* 250 mL. The 2% EtOAc in *n*-hexane eluent was separated on Sephadex LH-20 (eluent, CH_2Cl_2/CH_3OH; 1:1) and by preparative TLC (eluent, 70% CH_2Cl_2 in *n*-hexane) to yield **2** (3 mg). The 4% EtOAc eluent was further separated by CC on oxalic acid impregnated silica gel (eluting with 10% CH_2Cl_2 in *n*-hexane) to give chrysophanol (5 mg), asphodelin (7 mg), aloe-emodin actetate (4 mg) and **4** (9 mg). The 6-8% EtOAc eluents were combined and crystallized to give knipholone (60 mg). The 10% EtOAc eluent was purified on Sephadex LH-20 (eluent, CH_2Cl_2/CH_3OH; 1:1) to give deoxyerythrolaccin (5 mg); similarly, the 15% EtOAc eluent gave **1** (7 mg).

The CH_3OH extract was partitioned between EtOAc and water; the EtOAc layer was concentrated (labeled as extract II, 27 g) and fractionated by CC on oxalic acid impregnated silica gel (400 g) whilst eluting with mixtures of *n*-hexane and EtOAc with increasing polarities. The 1% EtOAc in *n*-hexane eluent was further separated by CC on Sephadex LH-20 (eluent, CH_2Cl_2/CH_3OH; 1:1), which gave chrysophanol (10 mg) and islandicin (2 mg). CC on Sephadex LH-20 (eluent, CH_2Cl_2/CH_3OH; 1:1) of the combined fractions eluted with 2% to 4% EtOAc in *n*-hexane gave chryslandicin (20 mg). Similar treatment of the 8% EtOAc eluent and subsequent

fractional crystallization gave knipholone (75 mg) and knipholone anthrone (**3**, 56 mg). The 10% EtOAc eluent was further purified on Sephadex LH-20 (eluent, CH_2Cl_2/CH_3OH; 1:1), followed by PTLC (eluent, 5% CH_3OH in CH_2Cl_2) to give joziknipholone A (38 mg) and joziknipholone B (23 mg). The 15% EtOAc eluent was purified on Sephadex LH-20 (eluent, CH_2Cl_2/CH_3OH; 1:1) to give laccaic acid D (22 mg) and 3,4-dihydroxybenzoic acid (21 mg).

10-Acetonylknipholone cyclooxanthrone (**1**)
Pale yellow amorphous solid.
UV $\lambda_{max}(CHCl_3)$ nm: 284, 360, 423.
^{1}H (600 MHz, CD_2Cl_2): Table 1.
^{13}C NMR (150 MHz, CD_2Cl_2): Table 1.
EIMS m/z (70 eV, rel. int.): 474 (11, $[M]^+$), 418 (23), 183 (13).
TOF HREIMS: *m/z* $[M]^+$ calcd for $C_{27}H_{22}O_8$ 474.1315; found 474.1303.

Chryslandicin 10-methyl ether (**2**)
Red amorphous solid.
UV λ_{max} $(CHCl_3)$ nm: 262, 295, 370sh, 388, 500, 522sh, 537.
CD $(CHCl_3)$:$\Delta\varepsilon_{272}$ = -3.0 cm^2 mol^{-1}.
^{1}H NMR (600 MHz, CD_2Cl_2): Table 1.
^{13}C NMR (150 MHz, CD_2Cl_2): Table 1.
EIMS *m/z* (70 eV, rel. int.): 546 (32), 391 (44), 279 (70), 253 (80), 111 (72), 97 (82), 83 (70), 71 (86), 57 (98), 43 (94).
TOF-HREIMS: *m/z* $[M+1]^+$ calcd for $C_{31}H_{23}O_9$ 539.1342; found 539.1395.

Conversion of chryslandicin (4) into chryslandicin 10-methyl ether (2): To a methanolic solution of **4** (4 mg), 3 drops of concentrated hydrochloric acid were added and the mixture refluxed on a water bath for 5 h. The reaction mixture was concentrated, diluted with water and partitioned with EtOAc. The organic layer was concentrated and separated by preparative TLC (eluent, CH_2Cl_2/*n*-hexane; 7:3) to give **2** (2 mg) and unreacted **4** (1 mg).

Antiplasmodial assay: Drug susceptibility was tested by the malaria SYBR Green I-based *in vitro* assay technique [19] against the Indochina W2 (chloroquine-resistant) and the Sierra Leone D6 (chloroquine-sensitive) strains of *Plasmodium falciparum.*

4-Day* Plasmodium berghei *ANKA suppressive test: The four day suppressive test described by [18] was adopted and the details are described in [19].

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