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Isolation of antiplasmodial anthraquinones from *Kniphofia ensifolia,* and synthesis and structure-activity relationships of related compounds

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Abstract

Bioassay-guided separation of the South African plant *Kniphofia ensifolia* for antiplasmodial activity led to the isolation of two new anthraquinones, named kniphofiones A and B (**3, 4**), together with three known bioactive anthraquinone monomers (**1**, **2** and **5**), and four known bisanthraquinones (**6–9**). The structures of the two new compounds were elucidated based on analyses of their 1D and 2D NMR spectra and mass spectrometric data. The dimeric compounds **6** and **7** displayed the strongest antiplasmodial activity among all the isolated compounds, with IC_{50} values of 0.4 ± 0.1 and 0.2 ± 0.1 μM, respectively. The two new compounds displayed modest activities, with IC_{50} values of 26 ± 4 and 9 ± 1 μM, respectively. Due to the synthetic accessibility of the new compounds and the increased activity shown by the dimeric compounds, a structure-activity relationship study was conducted. As a result, one analogue of kniphofione B (**4**), the caffeic acid derivative of aloe-emodin, was found to have the highest activity among all the aloe-emodin derivatives, with an IC_{50} value of 1.3 ± 0.2 μM.

Keywords

Anthraquinone; Antiplasmodial acitivity; *Kniphofia ensifolia*; Structure-activity relationship

1. Introduction

Malaria remains one of the major infectious diseases that threaten human lives. According to the latest available estimates from the WorldaHealthaOrganization (WHO), there were about 219 million cases of malaria and an estimated 660,000 deaths from malaria in 2010, with about 90% of all of these deaths occurring in sub-Saharan Africa.[1] Although current anti-

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Notes

The authors declare that there are no competing financial interest.

malarial therapies, including mefloquinone and its analogues[2] and artemisinin combination therapy combined with insecticide-treated bed nets[3] have achieved significant success in controlling the spread of the disease, malaria still remains a burden to humanity due to increasing drug resistance and the lack of multistage therapies to target the complex life cycle of the parasites. The recent emergence of resistance to artemisinin in the Cambodia–Thailand border area is particularly troubling.[4] A continuing search for new anti-malarial drugs is thus important to the overall goal of eradicating this scourge of mankind.

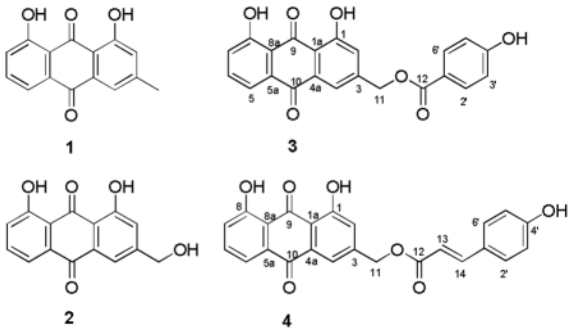
As part of a collaborative research project established between Virginia Tech and the Institute for Hepatitis and Virus Research (IHVR) and its the Natural Products Discovery Institute (NPDI),[5] we are searching for antiproliferative and antimalarial natural products in the plant extract library of the NPDI. An investigation for antiproliferative compounds from this library yielded several homoisoflavonones and bufadienolides with strong antiproliferative activity,[6] and the present work reports the first results from our investigation of extracts with antimalarial activity.

Screening of over 6,900 extracts from the NPDI collection led to the identification of a dichloromethane extract of *Kniphofia ensifolia* Baker (Asphodelaceae)[7] as an extract with promising antiplasmodial activity against the drug-resistant Dd2 strain of *Plasmodium falciparum*, with an IC_{50} value of ~ 6 μg/mL. Members of the Asphodelaceae family are widely distributed in Africa, central and western Europe, the Mediterranean basin, Central Asia, and Australia.[8] The genus *Kniphofia* is a rich source of anthraquinones, flavonoids and alkaloids, which are well-known for their broad range of bioactivities, including anticancer and antimalarial activities.[9] Although the genus *Kniphofia* has been well explored, the phytochemistry of *K. ensifolia* has not previously been investigated, and its extract of was thus selected for bioassay-guided fractionation to isolate its bioactive components.

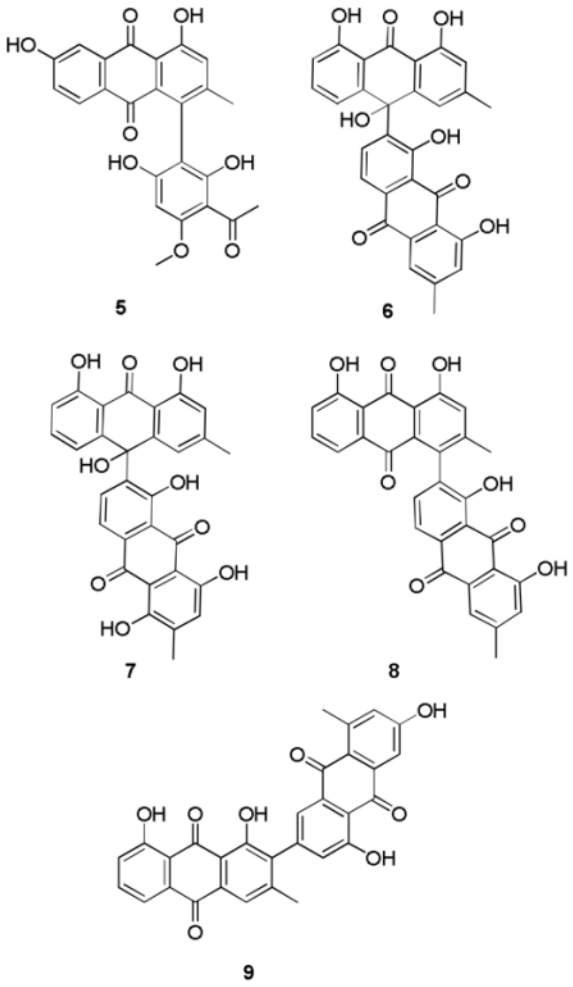
2. Results and discussions

2.1. Isolation and structure elucidation of bioactive anthraquinones

An EtOH extract of the whole plant of *K. ensifolia* was subjected to liquid-liquid partitioning to give an antiplasmodial CH_2Cl_2 fraction (IC_{50} = ~ 6.0 μg/mL). Bioassay-guided separation of the CH_2Cl_2 fraction, including Sephadex LH-20 size-exclusion chromatography, normal-phase silica gel chromatography, and C_{18} reverse-phase HPLC, yielded two new anthraquinones, named kniphofiones A and B (**3**, **4**), two known strongly active anthraquinones (**6**, **7**), and five other known anthraquinones (**1**, **2**, **5**, **8**, **9**). The structure elucidation of the new compounds is reported herein.



Compounds **1**, **2** and **5–9** were identified as chrysophanol (**1**),[10] aloe-emodin (**2**),[11] knipholone (**5**),[12] 10-(chrysophanol-7′-yl)-10-hydroxychrysophanol-9-anthrone (**6**),[9b] chryslandicin (**7**),[13] asphodeline (**8**),[14] and microcarpin (**9**)[15] respectively, by comparison of their experimental and reported physical and spectroscopic data with literature data.



Kniphofione A (**3**) was isolated as a yellow-orange powder. Its negative ion HR-ESI-MS revealed a peak for a deprotonated molecular ion at *m/z* 389.0688 $[M-H]^-$, corresponding to a molecular formula of $C_{22}H_{14}O_7$. Its IR spectrum exhibited absorption bands at 3390 and 1673 cm^{-1}, indicating the presence of hydroxy and conjugated carbonyl groups. The presence of two chelated hydroxy groups was further confirmed by two singlet signals located at δ_H 12.09 and 12.12 in the ^1H NMR spectrum (Table 1). In addition, a set of three coupled aromatic protons in the ABC-type spin system [δ_H 7.90 (1H, dd, *J* = 7.9, 1.6 Hz), 7.73 (1H, dd, *J* = 8.0, 7.9 Hz) and 7.39 (1H, dd, *J* = 8.0, 1.6 Hz)], two *meta*-coupled doublets located at δ_H 7.87 and 7.34 (both, 1H, *J* = 1.6), as well as methylene protons on an oxygen-bearing carbon at δ_H 5.44 (2H, singlet), were similar to the corresponding signals of aloe-emodin (**2**) and of aloe-emodin-type anthraquinones.[11, 16] The observation of two carbonyl carbon resonances located at δ_C 192.7 and 181.6, as well as a methylene carbon signal at δ_C 64.9 (C-11) in the ^{13}C NMR spectrum, corroborated its structure as an aloe-emodin derivative. The basic skeleton of 1,8-dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione was confirmed by the HMBC correlations between H-2 and C-1a, H-4 and C-10, H-6 and C-8, H-7 and C-8a, and H-11 and C-2 (Figure 1).

Furthermore, the presence of a *para*-hydroxybenzoate group was suggested by the presence of two doublets at δ_H 8.07 and 6.92 (2H each, *J* = 8.8 Hz) in the ^1H NMR spectrum, and a set of five carbon signals at δ_C 165.8 (C-12), 159.6 (C-4′), 132.0 (C-2′/6′), 121.8 (C-1′), and 113.9 (C-3′/5′), in the ^{13}C NMR spectrum.[17] The structure of the *para*-hydroxybenzoate

group and its connection to C-11 was further confirmed by the HMBC correlations between H-2′/H-6′ and C-12, H-6′/H-2′ and C-4′, and H_2-11 and C-12. Hence, the structure of compound **3** was assigned as (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-4-hydroxybenzoate.

Kniphofione B (**4**) was obtained as a light yellow oil. Its molecular formula was deduced to be $C_{24}H_{16}O_7$, based on its protonated molecular ion peak at *m/z* 417.0986 $[M+H]^+$ and a sodiated molecular ion peak at *m/z* 439.0806 $[M+Na]^+$ in its positive ion HR-ESI-MS. The ^{1}H-NMR spectrum of compound **4** displayed splitting patterns in the aromatic region similar to that of compound **3**, suggesting they have related structures. Comparison of the ^{13}C NMR spectroscopic data of **4** with those of **3** (Table 1) indicated that both compounds shared the same aloe-emodin-type anthraquinone skeleton, but differed in the acyl group attached to C-11. The presence of a *trans para*-hydroxycinnamate group in **4**, as opposed to the *para*-hydroxybenzoate group in **3**, was indicated by the presence of two doublets at δ_H 7.50 and 6.88 (2H each, J = 8.8 Hz) in the ^{1}H NMR spectrum, a set of five carbon signals at δ_C 166.7 (C-12), 159.5 (C-4′), 130.0 (C-2′/6′), 126.9 (C-1′), and 114.4 (C-3′/5′) in the ^{13}C NMR spectrum, and *trans*-coupled doublet proton signals at δ_H 6.43 and 7.75 (both, 1H, J = 15.9 Hz). The latter signals corresponded by HMQC to the two methine carbon resonances at δ_C 114.4 (C-13) and 145.8 (C-14).[18] The two carbons of the carbon-carbon double bond in the cinnamate group were assigned to C-13 and C-14, based on the HMBC crosspeaks between H-13 and C-1′, H-6′ and C-14, and H-14 and C-12 (Figure 2).

The structure of compound **4** was thus determined as (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)-methyl-3-(4-hydroxyphenyl) acrylate.

2.2. Biological activities and structure-activity relationships

All the isolated compounds were tested for antiproliferative activity against the A2780 ovarian cancer cell line and for antiplasmodial activity against the Dd2 chloroquine-resistant strain of *P. falciparum*. As listed in Table 2, the known dimeric compounds (**6** and **7**) displayed the highest antiplasmodial activity, with IC_{50} values of 0.4 ± 0.1 and 0.2 ± 0.1 μM, respectively. In addition, both of these dimeric compounds showed modest antiproliferative activity against the A2780 human ovarian cancer cell line, with IC_{50} values of 6 ± 1 and 4 ± 1 μM, respectively. However, their antiproliferative activity and lack of synthetic accessibility decreased their appeal as lead compounds for potential new antimalarial agents.

For these reasons, the two modestly active new compounds (**3** and **4**, IC_{50} = 26 ± 4 and 9 ± 1 μM, respectively) were more attractive for a study of structure-activity relationships due to their low cytotoxicities (IC_{50} > 60 μM to the A2780 ovarian cancer cell line) and synthetic accessibility. Both compounds are C-11 acylated derivatives of aloe-emodin (**2**), and so a number of C-11 acylated aloe-emodin derivatives were prepared by standard methods to determine the feasibility of developing derivatives with improved antiplasmodial activity.

Antiplasmodial activity data on the isolated natural products showed that compound **4**, the *para*-hydroxy cinnamate derivative of aloe-emodin (**2**), is about six times more potent than **2**, and this compound was thus selected as the lead compound for the present SAR study. Various acyl derivatives of aloe-emodin were then prepared by reaction of the commercially available natural product aloe-emodin (**2**) with a variety of organic acids, with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) as the coupling reagent. The reaction products were purified by column chromatography and their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy, as well as by HR-ESI-MS. The resulting compounds and their antiplasmodial activities are listed in Table 3. All the compounds were also tested for

antiproliferative activity against A2780 cells, but none of them had IC_{50} values less than 60 μM.

Inspection of the results of this study led to the following conclusions:

i. Acetylation of the primary alcohol of aloe-emodin slightly increased antiplasmodial activity, while acetylation of the hydrogen-bonded hydroxy group had the reverse effect.

The C-11 monoacetate (**10**, IC_{50} = ~ 42 μM) displayed slightly better antiplasmodial activity than aloe-emodin (IC_{50} = ~ 55 μM), while the mixture of the C-1, C-11 and C-8, C-11 diacetates (**11**, IC_{50} = ~ 60 μM) was slightly less potent than aloe-emodin. This result suggested that the presence of the hydrogen-bonded hydroxy groups might be important for antiplasmodial activity, and so acylation of the primary alcohol (C-11) of aloe-emodin was selected as the modification of choice for investigation.

ii. The phenyl group and the non-aromatic carbon-carbon double bond are both important functional groups for increasing the antiplasmodial activity.

To explore whether acylation of the primary alcohol might increase potency, the C-11 crotonate, benzoate, phenylpropionate and cinnamate derivatives were synthesized. Cinnamate **15** (IC_{50} = 18.4 ± 2.4 μM) displayed the highest activity among the four; benzoate **12** (IC_{50} = 31.5 ± 1.5 μM), phenylpropionate **14** (IC_{50} = ~ 36 μM), and crotonate **13**, (IC_{50} = ~ 45 μM) were all less potent. Although cinnamate **15** displayed the highest activity among all four acylated derivatives, it was only approximately half as potent as the 4-hydroxy-cinnamate **4** (kniphofione B), indicating that the hydroxy group at the C-4′ of the phenyl group is a contributor to the higher activity.

iii. The position and number of oxygenations on the phenyl group influences antiplasmodial activity.

The influence of the type of oxygenation at C-4′ of the phenyl ring on antiplasmodial activity was investigated by the synthesis of 4-methoxybenzoate **16** (IC_{50} = 22 ± 2 μM), 4-methoxycinnamate **17** (IC_{50} = 5 ± 1 μM), 4-acetoxycinnamate **18** (IC_{50} = 12 ± 2 μM), and 4-acetoxybenzoate **19** (IC_{50} = 30 ± 2 μM). 4-Methoxycinnamate derivative **17** was more potent than kniphofione B (**4**) and **18**, with hydroxycinnamate and acetoxycinnamate groups, respectively. Similar results were observed for the corresponding benzoate derivatives. The methoxy group is thus important for activity and was selected as the oxygenated moiety for further study.

Compounds **22** and **23** were then synthesized to investigate the influence of the number of methoxy groups on the phenyl ring of the cinnamate on potency. The 3,4-dimethoxycinnamate **22** (IC_{50} = 1.3 ± 0.2 μM) was more potent than both the 4-methoxycinnamate **17** (IC_{50} = 5 ± 1 μM) and the 3,4,5-trimethoxy-cinnamate **23** (IC_{50} = 2.7 ± 0.4 μM), suggesting that two methoxy groups on the cinnamate provides the best potency.

Finally, to understand what effect the positions of the methoxy groups on the cinnamate phenyl ring might have, 2,3-dimethoxy-cinnamate (**26**), 2,4- dimethoxy-cinnamate (**25**), 2,5-dimethoxy-cinnamate (**27**), and 3,5-dimethoxy-cinnamate (**24**) were synthesized and evaluated. 3,4-Dimethoxy-cinnamate (**22**) was the most potent of these compounds, and a similar response was observed from 3,4-methylenedioxy-cinnamate **28** (IC_{50} = 1.9 ± 0.3 μM), suggesting that alkylation on the 3′ and 4′ positions of the phenyl group favorably influences antiplasmodial activity.

In summary, this SAR study showed that esterification of the primary hydroxyl group of aloe-emodin (**2**) with various carboxylic acids increased its antiplasmodial activity, with the most potent analogue being the 3,4-dimethylcaffeic acid derivative (**22**), with an IC_{50} value of 1.3 ± 0.2 μM (Table 3). This analogue displays approximately 7 and 20 times the potency of the two new natural products **3** and **4**, and over 40 times than that of aloe-emodin (**2**).

Although aloe-emodin (**2**) has previously been identified as an anticancer agent,[19] and might thus be thought to have little potential for development as an antiplasmodial agent, our bioassay data indicated that acylation of the primary alcohol of aloe-emodin resulted in the increase of antiplasmodial activity (Dd2 assay), accompanied by a decrease of antiproliferative activity (A2780 assay). As an example, acylation of the C-11 hydroxyl group of aloe-emodin to give the *p*-coumaroyl derivative **4** increases its antiplasmodial activity sixfold while decreasing its antiproliferative activity to the A2780 cell line at least twofold. This observation indicates that further modifications of the C-11 hydroxyl group of aloe-emodin have the potential to yield antiplasmodial agents with little or no antiproliferative activity.

3. Experimental Section

3.1. General Experimental Procedures

UV and IR spectroscopic data were measured on a Shimadzu UV-1201 spectrophotometer and a MIDAC M-series FTIR spectrophotometer, respectively. NMR spectra were recorded in $CDCl_3$ 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 and negative ion mode.

3.2. Antiproliferative Bioassays (A2780 assay)

Antiproliferative activities were obtained at Virginia Tech against the drug-sensitive A2780 human ovarian cancer cell line as previously described.[20]

3.3. Antiplasmodial Bioassays (Dd2 assay)

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 with minor modifications.[21] Briefly, ring stage parasite cultures (200 μL per well, with 1% hematocrit and 1% parasitemia) were then grown for 72 h in the presence of increasing concentrations of the drug in a 5.05% CO_2, 4.93% O_2, and 90.2% N_2 gas mixture at 37 °C. After 72 h in culture, parasite viability was determined by DNA quantitation using SYBR Green I (50 μL of SYBR Green I in lysis buffer at 0.4 μL of SYBR Green I/mL of lysis buffer). The half-maximum inhibitory concentration (IC_{50}) calculation was performed with GraFit software using nonlinear regression curve fitting. IC_{50} values are the average of three independent determinations with each determination in duplicate and are expressed ± SEM.

3.4. Plant Material

Plant collection of *K. ensifolia* Baker (Asphodelaceae) was made in April 1999 on top of Mariepskop in the Pilgrims Rest district, State of Mpumalanga, South Africa, by Prof. P. C. Zietsman under the auspices of the New York Botanical Garden, accession number Z03796a. A voucher specimen is deposited in the New York Botanical Garden and also at BLFU (Bloemfontein Free University, South Africa)

3.5. Extraction and Isolation

The dried and powdered whole plant (100 g) of *Kniphofia ensifolia* was exhaustively extracted with EtOH (2 × 1 L) in two 24-hour percolation steps; successive partition of the concentrated extract with hexanes and CH_2Cl_2 gave an active CH_2Cl_2 fraction. A 0.75 g sample of the original EtOH extract, designated 60031-9D, was shipped to Virginia Tech for bioassay-guided isolation. A 0.60 g portion of this sample (IC_{50} = ~ 6.0 μg/mL against *P. falciparum* strain Dd2) was suspended in aqueous MeOH (MeOH-H_2O 9:1, 100 mL), and extracted with hexanes (3 × 100 mL). The aqueous layer was diluted to 60% MeOH (v/v) with H_2O and extracted with CH_2Cl_2 (3 × 150 mL). The hexanes fraction was evaporated in vacuo to leave 107.7 mg of material with an IC_{50} value of 5 ~ 10 μg/mL. The residue from the CH_2Cl_2 fraction (20.7 mg) was the most active fraction with an IC_{50} value of 2.5 ~ 5 μg/mL. The remaining aqueous MeOH fraction had an IC_{50} value of greater than 10 μg/mL. The hexanes and CH_2Cl_2 fractions were combined due to the similarity of their TLC patterns.

The combined hexanes and CH_2Cl_2 fractions were divided into five fractions by Sephadex LH-20 size exclusion open column chromatography. The most active fraction (F4, 28.6 mg) had an IC_{50} value of 2.5 μg/mL. Fraction F4 was then applied to a silica gel column eluted with hexanes: EtOAc = 7:3 to give six fractions. Fraction 4-1 was evaporated to give compound **1** (0.3 mg, IC_{50} = ~ 58 μM) and fractions 4–5 were evaporated to give compound **5** (2.6 mg, IC_{50} = 1.1 ± 0.2 μM). The most active fraction 4-2 (1.8 mg, IC_{50} = 0.27 μg/mL), was subjected to HPLC on a C_{18} column using a MeCN and H_2O gradient as the solvent system to yield the four known active compounds **6** (0.3 mg, IC_{50} = 0.43 ± 0.14 μM), **7** (0.9 mg, IC_{50} = 0.20 ± 0.08 μM), **8** (0.3 mg, IC_{50} = 10.2 ± 1.6 μM) and **9** (0.3 mg, IC_{50} = 9.6 ± 1.8 μM), with retention times of 21.3, 26.0, 28.5 and 31.2 min, respectively. HPLC of fraction 4-3 (2.2 mg, IC_{50} = 4.3 μg/mL) on a C_{18} column gave compounds **2** (0.5 mg, IC_{50} = ~ 55 μM) **3** (0.7 mg, IC_{50} = 25.6 ± 3.6 μM) and **4** (1.0 mg, IC_{50} = 8.9 ± 1.2 μM), with retention times of 8.5, 18.0 and 21.2 min, respectively.

3.6. (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-4-hydroxybenzoate (3, kniphofione A)

Yellow-orange powder. UV (MeOH) λ_{max} (ε) 257 (1.6), 289 (0.5), 432 (0.5); IR ν_{max} cm^{-1}: 3390, 2915, 2343, 1673, 1621, 1450, 1277, 1110 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$), and ^{13}C NMR (150 MHz, $CDCl_3$), see Table 1; HR-ESI-MS *m/z* 389.0688 $[M-H]^-$ (calcd for $C_{22}H_{13}O_7$, 389.0667).

3.7. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-(4-hydroxyphenyl) acrylate (4, kniphofione B)

Yellow-orange powder. UV (MeOH) λ_{max} (ε) 259 (1.2), 289 (1.4), 310 (0.9), 433 (0.6); IR ν_{max} cm^{-1}: 3390, 2916, 2362, 1706, 1627, 1603, 1450, 1268, 1161 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$), and ^{13}C NMR (150 MHz, $CDCl_3$), see Table 1; HR-ESI-MS *m/z* 439.0806 $[M+Na]^+$ (calcd for $C_{24}H_{16}NaO_7$, 439.0788) and 417.0986 $[M+H]^+$ (calcd for $C_{24}H_{17}O_7$, 417.0969).

3.8. General procedure for synthesis of ester derivatives of aloe-emodin[22]

Substituted benzoic acids or cinnamic acids (0.1 mmol) in dry CH_2Cl_2 (0.2 mL) were treated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, 20.6 mg, 0.1 mmol) and DMAP (1.0 mg, 0.006 mmol). The mixtures were stirred at room temperature for 5 minutes. Aloe-emodin (**2**, 5.4 mg, 0.02 mmol) was added, and stirring was continued at room temperature until the starting compound was consumed. The resulting solution was diluted with EtOAc (10 mL) and concentrated on a rotary evaporator. The final benzoate and

cinnamate derivatives of aloe-emodin were purified by using preparative TLC (silica gel, 500 m; hexane/EtOAc, 4:1).

3.9. (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl acetate (10)

Yellow-orange powder; HR-ESI-MS *m/z* 313.0711 $[M+H]^+$ (calcd for $C_{17}H_{13}O_6$, 313.0707); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.01 (s, 1H), 11.98 (s, 1H), 7.78 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.63 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.25 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.20 (d, *J* = 1.6 Hz, 1H), 5.12 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 192.7, 181.5, 170.5, 162.8, 162.6, 146.4, 137.3, 133.9, 133.51, 124.8, 122.4, 120.2, 118.5, 115.8, 115.3, 64.7, 20.8.

3.10. Mixture of (1-acetoxy-8-hydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl acetate and (8-acetoxy-1-hydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl acetate (11)

Yellow-orange powder; HR-ESI-MS *m/z* 355.0815 $[M+H]^+$ (calcd for $C_{19}H_{15}O_7$, 355.0812); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.57 (s, 1H), 12.55 (s, 1H), 8.28 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.22 (d, *J* = 1.0 Hz, 1H), 7.82 (dd, *J* = 8.0, 7.9 Hz, 1H), 7.81 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.75(d, *J* = 1.6 Hz, 1H), 7.66 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.43 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.40 (d, *J* = 1.8 Hz, 1H), 7.26 (d, *J* =1.0 Hz, 1H), 5.24 (s, 2H), 5.17 (s, 2H), 2.48 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H).

3.11. (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl benzoate (12)

Yellow-orange powder; HR-ESI-MS *m/z* 375.0866 $[M+H]^+$ (calcd for $C_{22}H_{15}O_6$, 375.0863); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.11 (s, 1H), 12.06 (s, 1H), 8.12 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.61 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.49 (t, *J* = 7.8, 2H), 7.32 (dd, *J* = 8.4, 1.0 Hz, 1H),, 5.46 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.5, 166.0, 162.8, 162.6, 146.6, 137.3, 133.9, 133.8, 133.5, 130.1, 129.8, 128.6, 124.8, 122.4, 120.2, 118.5, 115.8, 115.3, 65.1.

3.12. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-but-2-enoate (13)

Yellow-orange powder; HR-ESI-MS *m/z* 339.0865 $[M+H]^+$ (calcd for $C_{19}H_{15}O_6$, 339.0863); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.09 (s, 1H), 12.07 (s, 1H), 7.85 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.29 (d, *J* = 1.6 Hz, 1H), 7.10 (dd, *J* = 15.5, 7.0 Hz, 1H), 5.96 (dd, *J* = 15.6, 1.6 Hz, 1H), 1.94 (dd, *J* = 6.9, 1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.6, 166.4, 162.8, 162.6, 146.8, 146.4, 137.3, 133.8, 133.6, 124.8, 122.3, 121.9, 120.2, 118.4, 115.8, 115.2, 64.4, 18.2.

3.13. (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-phenylpropanoate (14)

Yellow-orange powder; HR-ESI-MS *m/z* 403.1146 $[M+H]^+$ (calcd for $C_{24}H_{19}O_6$, 403.1176); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.07 (s, 1H), 12.06 (s, 1H), 7.85 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.76 (d, *J* = 1.6 Hz, 1H), 7.70 (dd, *J* = 8.3, 7.8 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.29 (d, *J* = 1.6 Hz, 1H), 7.28 (m, 2H), 7.21 (m, 3H), 5.18 (s, 2H), 3.01 (d, *J* = 7.8 Hz, 2H), 2.77 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.5, 172.4, 162.8, 162.6, 146.4, 140.1, 137.3, 133.9, 133.5, 128.6, 128.3, 126.4, 124.8, 122.5, 120.2, 118.6, 115.8, 115.3, 64.7, 35.7, 30.9.

3.14. (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl cinnamate (15)

Yellow-orange powder; HR-ESI-MS *m/z* 401.1031 $[M+H]^+$ (calcd for $C_{24}H_{17}O_6$, 401.1020); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.03 (s, 1H), 12.00 (s, 1H), 7.79 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.73 (d, *J* = 16.0 Hz, 1H), 7.64 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.50 (m, 2H), 7.35 (m, 3H), 7.27 (d, *J* = 1.6 Hz, 1H), 7.25 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 5.27 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.6, 166.4, 162.8, 162.6, 146.7, 146.2, 137.3, 134.1, 133.9, 133.6, 130.6, 129.0, 128.3, 124.8, 122.4, 120.2, 118.6, 117.0, 115.4, 115.3, 64.7.

3.15. (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-4-methoxybenzoate (16)

Yellow-orange powder; HR-ESI-MS *m/z* 405.0971 $[M+H]^+$ (calcd for $C_{23}H_{17}O_7$, 405.0969); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.10 (s, 1H), 12.07 (s, 1H), 8.08 (d, *J* = 8.9 Hz, 2H), 7.88 (d, *J* = 1.5 Hz, 1H), 7.85 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.70 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.37 (d, *J* = 1.5 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 5.42 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.6, 165.7, 164. 9, 162.8, 162.6, 146.9, 137.3, 134.1, 133.6, 131.9, 124.8, 122.3, 121.7, 120.2, 118.5, 115.8, 115.3, 113.8, 64.8, 55.5.

3.16. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-(4-methoxyphenyl) acrylate (17)

Yellow-orange powder; HR-ESI-MS *m/z* 431.1133 $[M+H]^+$ (calcd for $C_{25}H_{19}O_7$, 431.1125); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.02 (s, 1H), 12.00 (s, 1H), 7.79 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.78 (d, *J* = 1.6 Hz, 1H), 7.68 (d, *J* = 16.0 Hz, 1H), 7.63 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 1.6 Hz, 1H), 7.25 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.34 (d, *J* = 16.0 Hz, 1H), 5.26 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.6, 166.7, 162.8, 161.7, 159.8, 146.9, 145.8, 137.3, 133.9, 133.6, 130.0, 126.9, 124.8, 122.4, 120.2, 118.5, 118.2, 115.8, 115.3, 114.4, 64.6, 55.5.

3.17. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-(4-acetoxy phenyl)acrylate (18)

Yellow-orange powder; HR-ESI-MS *m/z* 459.1079 $[M+H]^+$ (calcd for $C_{26}H_{19}O_8$, 459.1074); ^1H NMR (600 MHz, $CDCl_3$) δ_H 12.09 (s, 1H), 12.06 (s, 1H), 7.86 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.85 (d, *J* = 1.6 Hz, 1H), 7.76 (d, *J* = 16.0 Hz, 1H), 7.70 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 5.33 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 192.8, 181.6, 169.2, 166.3, 162.9, 162.7, 152.5, 146.7, 145.1, 137.4, 134.0, 133.7, 132.0, 129.5, 124.9, 122.6, 122.3, 120.3, 118.7, 117.3, 115.9, 115.4, 64.9, 21.2.

3.18. (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl 4-acetoxybenzoate (19)

Yellow-orange powder; HR-ESI-MS *m/z* 433.0935 $[M+H]^+$ (calcd for $C_{24}H_{17}O_8$, 433.0918); ^1H NMR (600 MHz, $CDCl_3$) δ_H 12.09 (s, 1H), 12.05 (s, 1H), 8.15 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.70 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.36 (d, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.22 (d, *J* = 8.9 Hz, 2H), 5.44 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 192.7, 181.6, 167.7, 164.3, 162.8, 162.6, 158.4, 143.5, 137.4, 134.1, 133.5, 131.5, 127.0, 124.9, 122.5, 121.9, 120.3, 118.6, 115.7, 115.3, 65.3, 21.3.

3.19. (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl 3,4-dimethoxybenzoate (20)

Yellow-orange powder; HR-ESI-MS *m/z* 435.1084 $[M+H]^+$ (calcd for $C_{24}H_{19}O_8$, 435.1074); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.10 (s, 1H), 12.06 (s, 1H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.78 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.77 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 5.43 (s, 2H), 3.96 (s, 6H) ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.6, 165.8, 162.8, 162.6, 153.4, 148.8, 146.9, 137.3, 133.91, 133.5, 124.8, 124.0, 122.4, 121.8, 120.2, 118.5, 115.8, 115.3, 112.1, 110.4, 65.0, 56.1.

3.20. (1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3,4,5-trimethoxybenzoate (21)

Yellow-orange powder; HR-ESI-MS *m/z* 465.1187 $[M+H]^+$ (calcd for $C_{25}H_{21}O_9$, 465.1180); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.09 (s, 1H), 12.05 (s, 1H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.7 Hz, 1H), 7.35 (s, 2H), 7.33 (d, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 5.44 (s, 2H), 3.93 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.5, 165.7, 162.8, 162.6, 159.8, 153.1, 146.6, 137.4, 134.0, 133.5, 124.8, 124.3, 122.5, 120.2, 118.5, 115.8, 115.4, 107.1, 65.2, 61.0, 56.3.

3.21. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-(3,4-dimethoxyphenyl)acrylate (22)

Yellow-orange powder; HR-ESI-MS *m/z* 461.1245 $[M+H]^+$ (calcd for $C_{26}H_{21}O_8$, 461.1231); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.02 (s, 1H), 11.99 (s, 1H), 7.78 (d, *J* = 1.6 Hz, 1H), 7.78 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.66 (d, *J* = 15.9 Hz, 1H), 7.63 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.27 (d, *J* = 1.6 Hz, 1H), 7.25 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.07 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.02 (d, *J* = 1.9 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 5.26 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.7, 166.7, 162.8, 162.7, 151.4, 149.3, 146.9, 146.1, 137.3, 133.9, 133.6, 127.1, 124.8, 123.0, 122.4, 120.2, 118.5, 115.8, 115.3, 114.6, 111.0, 109.6, 64.6, 56.0, 55.9.

3.22. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-(3,4,5-trimethoxyphenyl)acrylate (23)

Yellow-orange powder; HR-ESI-MS *m/z* 491.1352 $[M+H]^+$ (calcd for $C_{27}H_{23}O_9$, 491.1337); ^1H NMR (500 MHz, $CDCl_3$) δ_H 12.04 (s, 1H), 11.99 (s, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 7.79 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.64 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.63 (d, *J* = 15.9 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.26 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.73 (s, 2H), 6.39 (d, *J* = 15.9 Hz, 1H), 5.27 (s, 2H), 3.84 (s, 6H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.7, 181.6, 166.3, 162.8, 162.6, 153.5, 146.7, 146.1, 140.4, 137.3, 133.9, 133.5, 129.6, 124.8, 122.4, 120.2, 118.5, 116.2, 115.8, 115.3, 105.4, 64.7, 61.0, 56.2.

3.23. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-(3,5-dimethoxyphenyl)acrylate (24)

Yellow-orange powder; HR-ESI-MS *m/z* 461.1224 $[M+H]^+$ (calcd for $C_{26}H_{21}O_8$, 461.1231); ^1H NMR (600 MHz, $CDCl_3$) δ_H 12.09 (s, 1H), 12.06 (s, 1H), 7.86 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.85 (d, *J* = 1.6 Hz, 1H), 7.70 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.70 (d, *J* = 15.9 Hz, 1H), 7.33 (d, *J* = 1.6 Hz, 1H), 7.32(dd, *J* = 8.4, 1.1 Hz, 1H), 6.70 (d, *J* = 2.2 Hz, 2H), 6.52 (t, *J* = 2.3 Hz, 1H), 6.51(d, *J* = 15.9 Hz, 1H), 5.33 (s, 2H), 3.83 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 192.8, 181.7, 166.4, 162.7, 161.2, 146.8, 146.3, 137.5, 136.1, 134.1, 133.7, 124.9, 122.6, 120.3, 118.7, 117.7, 116.0, 115.5, 106.2, 103.2, 77.2, 64.9, 55.5.

3.24. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-(2,4-dimethoxy phenyl)acrylate (25)

Yellow-orange powder; HR-ESI-MS *m/z* 461.1212 $[M+H]^+$ (calcd for $C_{26}H_{21}O_8$, 461.1231); ^1H NMR (600 MHz, $CDCl_3$) δ_H 12.08 (s, 1H), 12.07 (s, 1H), 8.01 (d, *J* = 16.1 Hz, 1H), 7.85 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.85 (d, *J* = 1.6 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.7 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.34 (d, *J* = 2.3 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.54 (d, *J* = 16.1 Hz, 1H), 6.53, 6.53, 6.52 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.47 (d, *J* = 2.3 Hz, 1H), 5.32 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 192.7, 181.6, 167.3, 163.0, 162.6, 160.1, 147.2, 146.8, 141.6, 137.2, 133.8, 133.6, 130.9, 124.7, 122.4, 120.1, 118.6, 118.3, 116.4, 115.9, 114.8, 105.3, 98.5, 64.4, 55.5.

3.25. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-(2,3-dimethoxy phenyl)acrylate (26)

Yellow-orange powder; HR-ESI-MS *m/z* 461.1242 $[M+H]^+$ (calcd for $C_{26}H_{21}O_8$, 461.1231); ^1H NMR (600MHz, $CDCl_3$) δ_H 12.08 (s, 1H), 12.06 (s, 1H), 8.12 (d, *J* = 16.2 Hz, 1H), 7.86 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.70 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.34 (d, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.20 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.59 (d, *J* = 16.2 Hz, 1H), 5.34 (s, 2H), 3.89 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 192.7, 181.5, 166.6, 162.8, 162.6, 153.2, 148.7, 146.8, 141.0, 137.3, 133.9, 133.6, 128.3, 124.7, 124.2, 122.4, 120.2, 119.4, 118.5, 118.3, 115.8, 115.3, 114.3, 64.7, 61.4.

3.26. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methyl-3-(2,5-dimethoxy phenyl)acrylate (27)

Yellow-orange powder; HR-ESI-MS *m/z* 461.1211 $[M+H]^+$ (calcd for $C_{26}H_{21}O_8$, 461.1231); ^1H NMR (600 MHz, $CDCl_3$) δ 12.07 (s, 1H), 12.06 (s, 1H), 8.07 (d, *J* = 16.1 Hz, 1H), 7.86 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.70 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.34 (d, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.07 (d, *J* = 3.0 Hz, 1H), 6.93 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 6.62 (d, *J* = 16.1 Hz, 1H), 5.33 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 192.8, 181.7, 166.9, 163.0, 162.7, 153.7, 153.2, 147.1, 141.6, 137.4, 134.1, 133.7, 124.9, 123.8, 122.6, 120.3, 118.7, 117.8, 116.0, 115.4, 113.5, 112.7, 77.2, 64.8, 56.2.

3.27. (*E*)-(1,8-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-3-yl)methy-3-(3,4-methylene dioxyphenyl)acrylate (28)

Yellow-orange powder; HR-ESI-MS *m/z* 445.0912 $[M+H]^+$ (calcd for $C_{25}H_{17}O_8$, 445.0918); H NMR (500 MHz, $CDCl_3$) H NMR (500 MHz, $CDCl_3$) δ_H 12.09 (s, 1H), 12.07 (s, 1H), 7.86 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.70 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.69 (d, *J* = 15.9 Hz, 1H), 7.33 (d, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.07 (d, *J* = 1.7 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.02 (s, 2H), 5.32 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 192.8, 181.7, 166.7, 163.0, 162.8, 150.1, 148.6, 147.0, 141.6, 137.5, 134.0, 133.7, 128.7, 125.0, 124.9, 122.6, 120.3, 118.7, 116.0, 115.4, 115.1, 108.8, 106.8, 101.8, 64.8.

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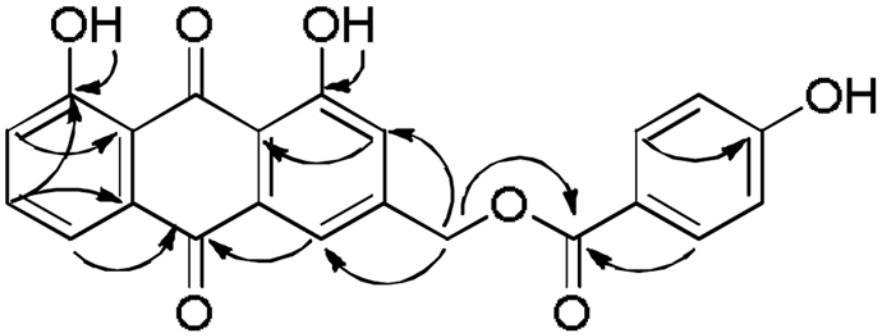


Figure 1.
HMBC correlations of compound **3**.

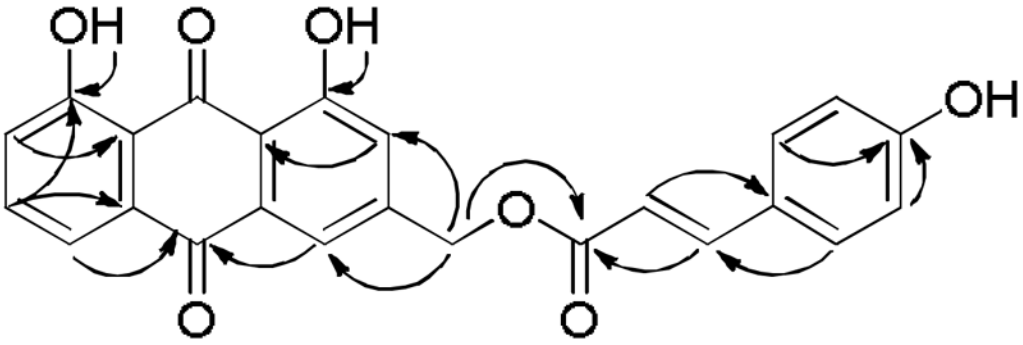


Figure 2.
HMBC correlations of compound **4**.

Table 1

NMR Spectroscopic Data for **3** and **4** in $CDCl_3$ (500 MHz)

	3		**4**	
posn	**δ_H (*J* in Hz)**	**δ_C, type**	**δ_H (*J* in Hz)**	**δ_C, type**
1	-	162.9, C	-	162.8, C
1a	-	115.3, C	-	115.2, C
2	7.87 d (1.6)	118.6, CH	7.87 d (1.6)	118.5, CH
3	-	147.0, C	-	146.9, C
4	7.34 d (1.6)	122.4, CH	7.36 d (1.6)	122.4, CH
4a	-	133.6, C	-	133.6, C
5	7.90 dd (7.9, 1.6)	120.2, CH	7.87 dd (7.9, 1.6)	120.2, CH
5a	-	134.1, C	-	133.9, C
6	7.73 dd (8.0, 7.9)	137.4, CH	7.73 dd (8.0, 7.9)	137.3, CH
7	7.39 dd (8.0, 1.6)	124.8, CH	7.35 dd (8.0, 1.6)	124.8, CH
8	-	162.7, C	-	162.8, C
8a	-	115.9, C	-	115.8, C
9	-	192.7, C	-	192.7, C
10	-	181.6, C	-	181.6, C
11	5.44 s	64.9, CH_2	5.35 s	64.6, CH_2
12	-	165.8, C	-	166.7, C
13	-	-	6.43 d (15.9)	114.4, CH
14	-	-	7.75 d (15.9)	145.8, CH
1′	-	121.8, C	-	126.9, C
2′	8.07 brd (8.8)	132.0, CH	7.50 brd (8.5)	130.0, CH
3′	6.92 brd (8.8)	113.9, CH	6.88 brd (8.5)	114.4, CH
4′	-	159.6, C	-	159.5, C
5′	6.92 brd (8.8)	113.9, CH	6.88 brd (8.5)	114.4, CH
6′	8.07 brd (8.8)	132.0, CH	7.50 brd (8.5)	130.0, CH
1-OH	12.12 s	-	12.11 s	-
8-OH	12.09 s	-	12.09 s	-

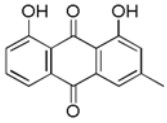
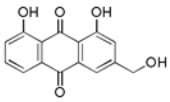
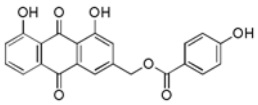
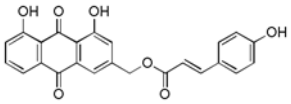
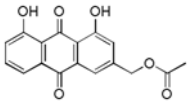
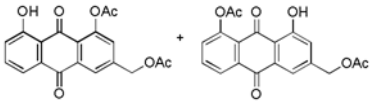
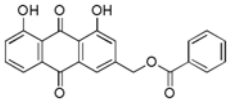
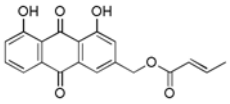
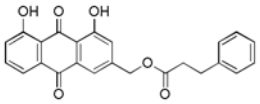
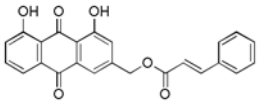
Table 2

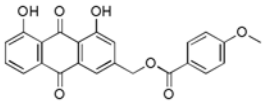
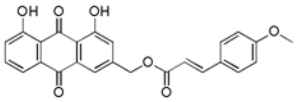
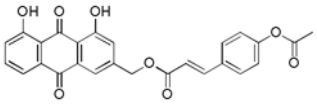
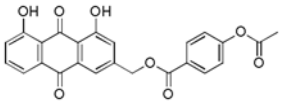
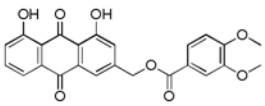
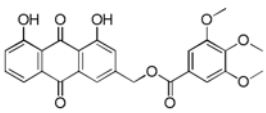
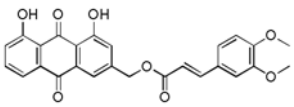
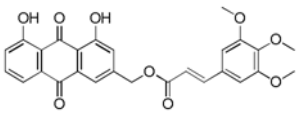
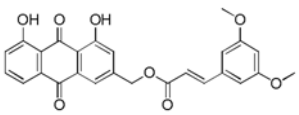
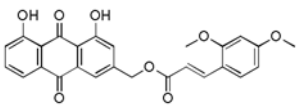
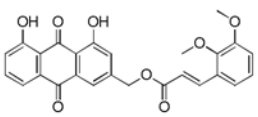
Bioactivities of the isolated anthraquinones (**1–9**).

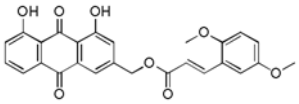
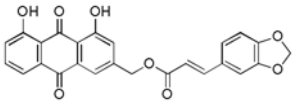
	Compound									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Artemisinin**
Dd2 IC_{50} (μM)	58	55	26 ± 4	9 ± 1	1.1± 0.2	0.4 ± 0.1	0.2 ± 0.1	10 ± 2	10 ± 2	0.007
A2780 IC_{50} (μM)	> 60	26 ± 2	> 60	> 60	8 ± 2	6 ± 1	4 ± 1	>60	>60	ND

Table 3

Antiplasmodial activity of natural and synthetic aloe-emodin derivatives

Cmpd	Structure	IC_{50} (μM)
1		~ 58
2		~ 55
3		26 ± 4
4		9 ± 1
10		~ 42
11		~ 60
12		31 ± 2
13		~ 45
14		~ 36
15		18 ± 2

Cmpd	Structure	IC_{50} (μM)
16		22 ± 2
17		5 ± 1
18		12 ± 2
19		30 ± 2
20		14 ± 2
21		16 ± 2
22		1.3 ± 0.2
23		2.7 ± 0.4
24		2.5 ± 0.9
25		6 ± 2
26		8 ± 2

Cmpd	Structure	IC_{50} (μM)
27		9 ± 2
28		1.9 ± 0.3