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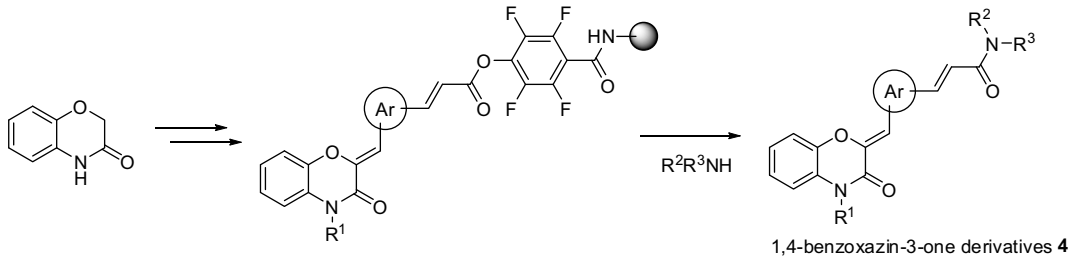
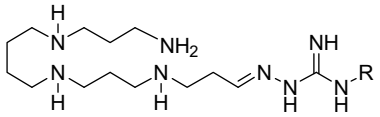
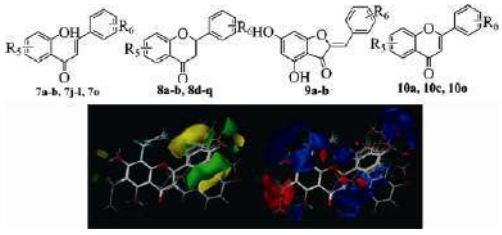


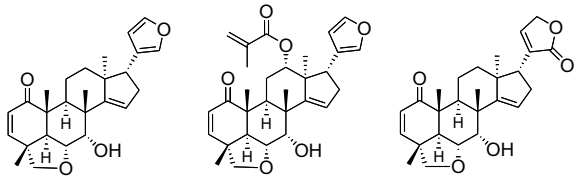
1,4-benzoxazin-3-one derivatives **4**



R= H, or alkyl groups



A series of flavonoid derivatives were designed, synthesized as vasorelaxant agents. Some were found to possess potent vasorelaxant activity. CoMFA analysis was carried out, and a statistically reliable QSAR model (r^2=0. 872 and q^2=0. 496) was established.



COVER

Histone acetylation plays an important role in the regulation of gene transcription. Chromatin with a low histone acetylation level is condensed due to charge-charge interactions between the positively charged histones and the negatively charged DNA. Acetylation reduces the charge-charge interactions between the histones and the DNA and results in relaxation of the chromatin and activation of gene transcription. Recent discoveries indicate that multiple subtypes of histone acetyl transferases exist. Small molecule inhibitors of histone acetyl transferases provide tools for pharmacological studies and ultimately provide starting points for drug discovery. This issue reports studies by Dekker *et al.* and Gorsuch *et al.* on histone acetyl transferase inhibitors with an isothiazolones core structure. [Dekker, F. J.; Ghizzoni, M.; van der Meer, N.; Wisastra, R.; Haisma, H. J. *Bioorg. Med. Chem.* **2009,** *17*, 459; Gorsuch, S.; Bavetsias, V.; Rowlands, M. G.; Aherne, G. W.; Workman, P.; Jarman, M.; McDonald, E. *Bioorg. Med. Chem.* **2009, *17,*** 466.]

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Ceramicines B–D, new antiplasmodial limonoids from *Chisocheton ceramicus*

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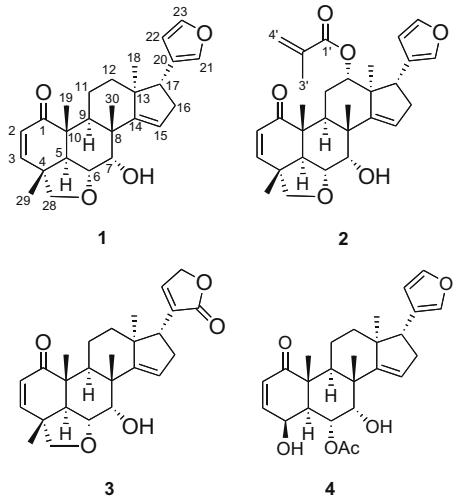
ABSTRACT

Three new limonoids, ceramicines B–D (**1**–**3**), have been isolated from the bark of *Chisocheton ceramicus*. Structures and stereochemistry of **1**–**3** were fully elucidated and characterized by 2D NMR analysis. Ceramicines exhibited a moderate antiplasmodial activity.

1. Introduction

Limonoids, highly oxidative unique secondary metabolites obtained from Meliaceae are produced by a unique biosynthetic route through tetranortriterpenoid nucleus.[1,2] Insecticidal, insect antifeedant, antibacterial, antifungal, antimalarial, anticancer, and antiviral activities have been reported for many limonoids.[3] Especially, malaria caused by parasites of the genus *Plasmodium* is one of the leading infectious diseases in many tropical and some temperate regions.[4] The emergence of widespread chloroquine-resistant and multiple-drug-resistant strains of malaria parasites leads to the need for the development of new therapeutic agents against malaria.[5]

Recently, we have isolated cassiarin A with an unprecedented tricyclic skeleton and a potent antiplasmodial activity from the leaves of *Cassia siamea*.[6] Previous investigations on limonoids from Meliaceae have led to the isolation of several unique tetranortriterpenoids.[7] In continuation of our antiplasmodial research on *Chisocheton ceramicus* belonging to Meliaceae family, we have isolated three new limonoids, ceramicines B–D (**1**–**3**) together with ceramicine A (**4**),[7b] which showed a moderate antiplasmodial activity. Herein, we report the structure elucidation and antiplasmodial activity of ceramicines B–D (**1**–**3**) from *C. ceramicus*.



1 **2** **3** **4**

1.1. Structures of ceramicines B–D (1–3)

The crude ethanol extract of bark was partitioned between $CHCl_3$, *n*-BuOH, and water. Chromatographic purification of the chloroform soluble fraction by a silica gel column (hexane/EtOAc and toluene/EtOAc solvent system) led to isolation of three new limonoids, ceramicines B (**1**, 147.4 mg, 0.074% yield), C (**2**,

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44.4 mg, 0.022% yield), and D (**3**, 15.0 mg, 0.0075% yield), together with ceramicine A.[7b]

Ceramicine B {**1**, $[\alpha]_D^{20}$ +30 (*c* 1.0, $CHCl_3$)} was obtained as a colorless solid and was revealed to have the molecular formula $C_{26}H_{32}O_4$, by HRESITOFMS [*m/z* 409.2370 $(M+H)^+$, Δ −0.9 mmu]. IR absorptions implied the presence of an α,β-unsaturated ketone (1669 cm^{-1}) and a hydroxyl (3535 cm^{-1}) groups. UV spectrum (219 nm) indicated the presence of an unsaturated carbonyl group. ^1H and ^{13}C NMR data (Tables 1 and 2, respectively) revealed 26 carbon resonances due to one carbonyl, two sp^2 quaternary carbons, four sp^3 quaternary carbons, six sp^2 methines, five sp^3 methines, four sp^3 methylenes, and four methyls. Among them, three sp^3 carbons (δ_C 72.5, 73.8, and 79.8) and two sp^2 methines (δ_C 139.7 and 142.6) were ascribed to those bearing an oxygen atom.

Five partial structures **a** (from C-2 to C-3), **b** (from C-5 to C-7), **c** (from C-9, C-11 to C-12), **d** (from C-15 to C-17), and **e** (from C-22 to C-23) were deduced from ^1H–^1H COSY analysis of **1** in $CDCl_3$ (Fig. 1). The presence of an enone group in ring A was supported by HMBC correlations as shown in Figure 1. HMBC correlations for H-3 and H_3-19 of C-1 (δ_C 202.9), for H_3-29 of C-5 (δ_C 47.7), and for H-7, H_3-19, and H_3-30 of C-9 (δ_C 35.9) gave rise to the connectivity of partial structures **a**, **b**, and **c** through C-4, C-8, and C-10 atoms. Connection between partial structures **c** and **d** could be assigned by HMBC correlations for H_3-18 of C-12 (δ_C 33.1), C-13 (δ_C 47.0), C-14 (δ_C 159.8), and C-17 (δ_C 51.9). The presence of a β-furyl ring at C-17 was also assigned by the HMBC correlations as shown in Figure 1. In addition, HMBC correlations for H-7 and H_2-28 of C-6 (δ_C 73.8) indicated the presence of a tetrahydrofuran ring at C-4–C-6 and C-28. Thus, ceramicine B (**1**) was concluded to be a new limonoid possessing cyclopenta[*a*]phenanthren ring system with a β-furyl ring at C-17 and a tetrahydrofuran ring.

The relative stereochemistry of **1** was elucidated by ROESY correlations as shown in computer-generated 3D drawing (Fig. 2). ROESY correlations of H-6/Hb-28, H_3-19, and H_3-30, H-7/H-15, and H-12/H-17 together with the ^3J proton coupling constants ($^3J_{H\text{-}5/H\text{-}6}$ =12.4 Hz and $^3J_{H\text{-}6/H\text{-}7}$ = 3.8 Hz) suggested that each of H-6, H-7, and H-17 adopts a β-configuration. Furthermore, the α configurations of H-5 and H-9 was indicated by ROESY correlation of H-5/H-9.

Table 1
^1H NMR data [δ_H (*J*, Hz)] of ceramicines B–D (**1**–**3**) in $CDCl_3$ at 300 K

	1	2	3
2	5.83 (d, 9.6 Hz)	5.82 (d, 9.6 Hz)	5.73 (d, 9.6 Hz)
3	6.95 (d, 9.6 Hz)	6.95 (d, 9.6 Hz)	6.91 (d, 9.6 Hz)
5	2.73 (d, 12.4 Hz)	2.69 (d, 12.4 Hz)	2.59 (d, 12.4 Hz)
6	4.28 (dd, 12.4, 3.8 Hz)	4.28 (dd, 12.4, 3.8 Hz)	4.19 (dd, 12.4, 3.8 Hz)
7	4.23 (d, 3.8 Hz)	4.25 (d, 3.8 Hz)	4.10 (d, 3.8 Hz)
9	2.40 m	2.61 m	2.26 m
11a	2.52 m	2.48 m	2.40 m
11b	1.80 m	2.29 m	1.69 m
12a	1.89 m	5.13 m	1.81 m
12b	1.60 m		1.60 m
15	5.59 br s	5.69 m	5.47 br s
16a	2.55 m	2.57 m	2.53 m
16b	2.40 m	2.43 m	2.25 m
17	2.85 m	3.04 m	2.76 m
18	0.82 s	1.08 s	0.79 s
19	1.17 s	1.16 s	1.07 s
21	7.25 s	7.14 s	
22	6.29 (d, 1.6 Hz)	6.23 (d, 1.6 Hz)	7.21 (dd, 1.8, 1.8 Hz)
23	7.37 (d, 1.6 Hz)	7.28 (d, 1.6 Hz)	4.77 (br s)
28a	3.63 (d, 7.3 Hz)	3.63 (d, 7.3 Hz)	3.54 (d, 7.3 Hz)
28b	3.79 (d, 7.3 Hz)	3.79 (d, 7.3 Hz)	3.69 (d, 7.3 Hz)
29	1.34 s	1.33 s	1.25 s
30	1.13 s	1.13 s	1.03 s
3′		1.76 s	
4′		5.86, 5.47 (s)	

Table 2
^{13}C NMR data (δ_C) of ceramicines B–D (**1**–**3**) in $CDCl_3$ at 300 K

	1	2	3
1	202.9	202.4	203.3
2	130.2	130.0	129.8
3	151.0	151.9	151.2
4	41.9	41.8	41.7
5	47.7	47.6	47.4
6	73.8	73.7	73.7
7	72.5	72.0	72.1
8	47.2	46.5	46.9
9	35.9	36.5	35.3
10	47.2	47.1	47.1
11	17.7	26.8	17.4
12	33.1	77.8	32.7
13	47.0	51.6	47.1
14	159.8	156.5	158.9
15	120.4	122.7	120.0
16	34.3	36.5	33.8
17	51.9	50.6	50.6
18	21.5	16.0	21.3
19	14.3	14.1	14.0
20	124.5	124.3	133.5
21	139.7	140.3	174.8
22	111.0	111.7	147.1
23	142.6	141.2	70.3
28	79.8	79.8	79.5
29	20.1	20.1	19.8
30	26.0	26.5	25.9
1′		167.1	
2′		136.4	
3′		18.0	
4′		125.9	

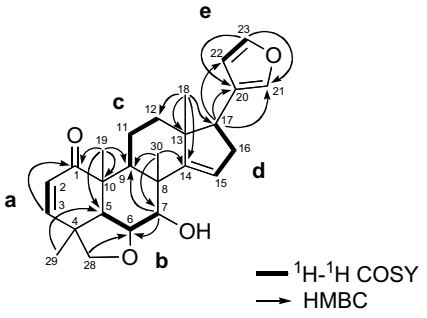

Figure 1. Selected 2D NMR correlations for ceramicine B (**1**).

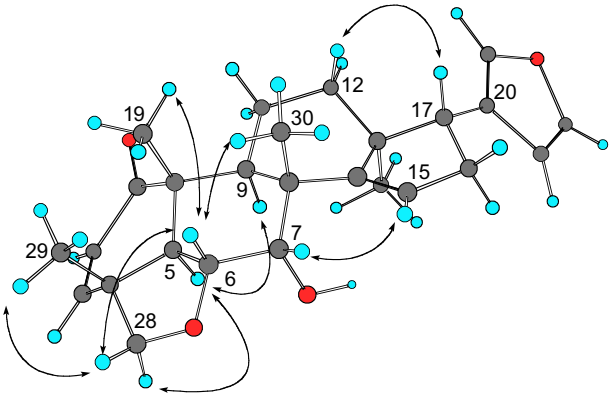

Figure 2. Selected ROESY correlations for ceramicine B (**1**).

HRESITOFMS data [*m/z* 515.2397 $(M+Na)^+$, Δ −1.3 mmu] of ceramicine C {**2**, $[\alpha]_D^{20}$ +47 (*c* 1.0, $CHCl_3$)} established the molecular

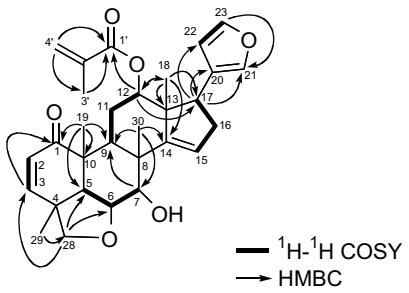

Figure 3. Selected 2D NMR correlations for ceramicine C (**2**).

formula to be $C_{30}H_{36}O_6$, which was larger than that of ceramicine B (**1**) by a $C_4H_4O_2$ unit. ^{1}H and ^{13}C NMR data (Tables 1 and 2) of **2** were analogous to those of **1**, although H-12 (δ_H 5.13) and C-12 (δ_C 77.8) bearing an oxygen atom were observed for **2**. The presence of methacrylic acid (δ_H 1.76, 5.47, and 5.86; δ_C 18.0, 125.9, 136.4, and 167.1) at C-12 was confirmed by HMBC correlations for H_3-3′ and H-12 of C-1′ (δ_C 167.1) and H_2-4′ of C-1′ and C-3′ (δ_C 18.0).

The gross structure of **2** was elucidated by 2D NMR (^{1}H–^{1}H COSY, HMQC, and HMBC) data shown in Figure 3. Analysis of ROESY spectrum (Fig. 4), suggested that the relative stereochemistry of H-12 and H-17 to be β through correlations among H-12, H-17, and H_3-30.

Ceramicine D (**3**), colorless amorphous solid, $[\alpha]_D^{20}$ +38 (*c* 1.0, $CHCl_3$), was shown to have the molecular formula of $C_{26}H_{32}O_5$ by HRESITOFMS [*m*/*z* 425.2306, $(M+H)^+$, Δ −2.2 mmu], which was larger than that of ceramicine B by 16 mmu. ^{1}H and ^{13}C NMR data of **3** were analogous to those of ceramicine B, although the β-furyl ring signals for ceramicine B were lacking for **3**. The presence of an α,β-unsaturated-γ-lactone ring instead of the β-furyl ring at C-17 was deduced by the ^{1}H [δ_H 4.77 (br s, H-23) and 7.21 (dd, *J* = 1.8, 1.8 Hz, H-22)] and ^{13}C [δ_C 133.5 (C-20), 174.8 (C-21), 147.1 (C-22), and 70.3 (C-23)] signals.[8] HMBC correlations for H-17 of C-20, C-21, and C-22 indicated the presence of β-substituted-γ-lactone ring (Fig. 5). The gross structure of **3** was elucidated by 2D NMR (^{1}H–^{1}H COSY, HMQC, and HMBC) data, and the relative stereochemistry of **3** was assigned as the same as that of ceramicine B by ROESY correlations shown in Figure 6.

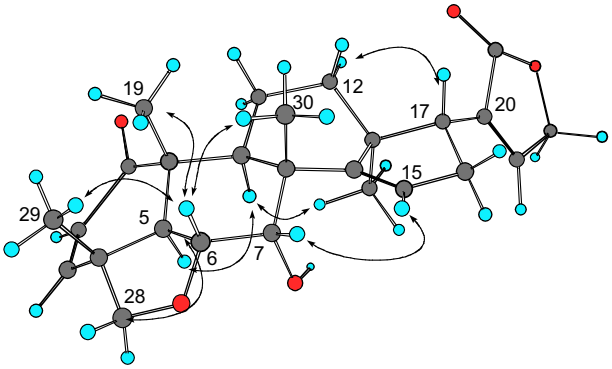

Figure 6. Selected ROESY correlations for ceramicine D (**3**).

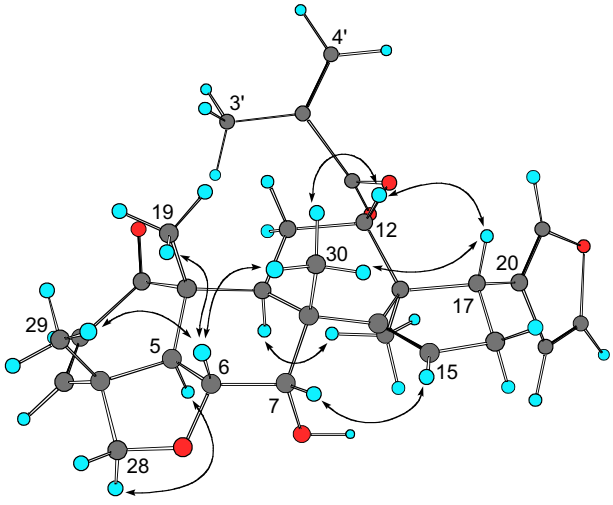

Figure 4. Selected ROESY correlations for ceramicine C (**2**).

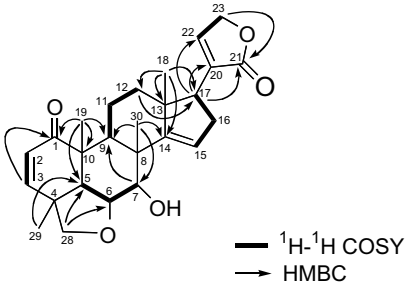

Figure 5. Selected 2D NMR correlations for ceramicine D (**3**).

1.2. Antiplasmodial activity

Malaria caused by parasites of the genus *Plasmodium* is one of the leading infectious diseases in many tropical and some temperate regions.[4] The emergence of widespread chloroquine-resistant and multiple-drug-resistant strains of malaria parasites leads to the need for the development of new therapeutic agents against malaria.[5] Ceramicine B (**1**) showed a potent in vitro antiplasmodial activity against *Plasmodium falciparum* 3D7 (IC_{50} **1**: 0.23 μg/ml),[9] whereas ceramicines C (**2**) and D (**3**) did a moderate activity and ceramicine A (**4**) did a weak activity (IC_{50} **2**, 2.38 μg/ml; **3**, 2.15 μg/ml; **4**, 44.22 μg/ml). Ceramicines B–D (**1**–**3**) showed a weak cytotoxicity on P388 cells (IC_{50} 15 μg/ml for **1**; 5.5 μg/ml for **2**; 27 μg/ml for **3**). These compounds belong to two groups with a tetrahydrofuran ring at C-4–C-6 and C-28 and without this function. In comparison of antiplasmodial activity among these compounds, ceramicines B (**1**)–D (**3**) with a tetrahydrofuran ring showed a potent activity, whereas ceramicine A (**4**) without this function exhibited a relatively weak activity.

2. Experimental

2.1. General methods

^{1}H and 2D NMR spectra were recorded on a 400 MHz spectrometers at 300K, while ^{13}C NMR spectra were measured on a 100 MHz spectrometer. Each NMR sample of ceramicines B–D (**1**–**3**) were prepared by dissolving 3.0 mg in 250 μl of $CDCl_3$ in 2.5 mm micro cells (Shigemi Co., Ltd) and chemical shifts were reported using residual $CDCl_3$ (δ_H 7.21 and δ_C 77.0) as an internal standard. Standard pulse sequences were employed for the 2D NMR experiments. ^{1}H–^{1}H COSY, HOHAHA, and ROESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1 K data points for each of 256 t_1 increments. ROESY and HOHAHA spectra in the phase sensitive mode were measured with a mixing time of 800 and

30 ms, respectively. For HMQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1 K data points were collected. For HMBC spectra with *Z*-axis PFG, a 50 ms delay time was used for long-range C–H coupling. Zero-filling to 1K for F_1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation.

2.2. Material

The barks of *C. ceramicus* were collected at Pahang, Malaysia in 1996. The botanical identification was made by Mr. Teo Leong Eng, Faculty of Science, University of Malaya. Voucher specimens are deposited in the Herbarium of Chemistry Department, University of Malaya.

2.3. Extraction and isolation

The dried ground barks of *C. ceramicus* (200 g) were extracted successively with ethanol and the extract (10.5 g) was partitioned with 10% aq MeOH and $CHCl_3$. The $CHCl_3$-soluble materials were subjected to a silica gel column (hexane/EtOAc, 1:0 → 0:1), in which a fraction eluted with hexane/EtOAc (7:3) was further purified on a silica gel column with toluene/EtOAc (4:1) to afford ceramicine B (**1**, 147.4 mg, 0.074% yield) as colorless solids. The fraction eluted with hexane/EtOAc (3:2) was purified on a silica gel column with toluene/EtOAc (4:1) to obtain ceramicine C (**2**, 44.4 mg, 0.022% yield). The fraction eluted with hexane/EtOAc (2:3) was purified on a silica gel column with toluene/EtOAc (3:2) to give ceramicine D (**3**, 15 mg, 0.0075% yield).

2.3.1. Ceramicine B (1)

Colorless solid; $[\alpha]_D^{20}$ +30 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3535, 3457, 2969, 2927, 2862, 1720, 1669, 1457, 1387, and 1247 cm^{-1}; UV (MeOH) λ_{max} 219 (ε 9300) nm; CD (MeOH) λ_{max} 340 (θ −3300) and 220 nm (θ +30,800); ^1H and ^{13}C NMR data (Tables 1 and 2); HRESITOFMS *m/z* 409.2370 (M+H; calcd for $C_{26}H_{32}O_4$, 409.2379).

2.3.2. Ceramicine C (2)

Colorless solid; $[\alpha]_D^{20}$ +47 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3448, 2932, 1711, 1677, 1451, 1389, 1248, and 1160 cm^{-1}; UV (MeOH) λ_{max} 219 (ε 9400) nm; CD (MeOH) λ_{max} 334 (θ −2700) and 220 nm (θ +29600); ^1H and ^{13}C NMR data (Tables 1 and 2); HRESITOFMS *m/z* 515.2397 (M+Na; calcd for $C_{30}H_{36}O_6Na$, 515.2410).

2.3.3. Ceramicine D (3)

Colorless solid; $[\alpha]_D^{20}$ +38 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3435, 2929, 1750, 1677, 1459, 1388, and 1249 cm^{-1}; UV (MeOH) λ_{max} 222 (ε 10,000) nm; CD (MeOH) λ_{max} 338 (θ −2100) and 223 nm (θ +17,900); ^1H and ^{13}C NMR data (Tables 1 and 2); HRESITOFMS *m/z* 425.2306 (M+H; calcd for $C_{26}H_{32}O_5$, 425.2328).

2.4. Antiplasmodial activity

Human malaria parasites were cultured according to the method by Trager et al.[9] The antimalarial activity of the isolated compounds was determined by the procedure described by Budimulja et al. [10] In brief, Stock solution of the samples were prepared in DMSO (final DMSO concentrations of <0.5%) and were diluted to the required concentration with complete medium (RPMI-1640 supplemented with 10% human plasma, 25 mM Hepes and 25 mM $NaHCO_3$) until the final concentration of samples at well culture plate are: 10, 1, 0.1, 0.01, 0.001 μg/ml. The malarial parasite *P. falciparum* 3D7 clone was propagated in a 24-well culture plate in the presence of a wide range of concentrations of each compound. The growth of the parasite was monitored by making a blood smear fixed with MeOH and stained with Geimsa stain. The antimalarial activity of each compound was expressed as an IC_{50} value, defined as the concentration of the compound causing 50% inhibition of parasite growth relative to an untreated control.

The percentage of growth inhibition was expressed according to following equation: Growth inhibition% = 100 − [(test parasitaemia/control parasitemia) × 100. Chloroqine: IC_{50} = 0.0061 μg/ml.

2.5. Cytotoxicity

P-388. murine leukemia cells were maintained in RPMI-1640 medium supplemented with 5% fetal calf serum and kanamycin (100 μg/ml). The cells (3×10^3 cells/well) were cultured in Corning disposable 96-well plates containing 100 μl of growth medium per well and were incubated at 37 °C in a humidified atmosphere of 5% CO_2. Various drug concentrations (10 μl) were added to the cultures at day one after the transplantation. At day three, 20 μl MTT solution (5 mg/ml) per well was added to each cultured medium. After a further 4 h of incubation, 100 ml of 10% SDS–0.01 N HCl solution was added to each well and the formazan crystals in each well were dissolved by stirring with a pipette. The optical density measurements were made using a micropipette reader (Tohso MPR-A4i) with a two wavelength system (550 and 700 nm). In all experiments, three replicate wells were used to determine each point.

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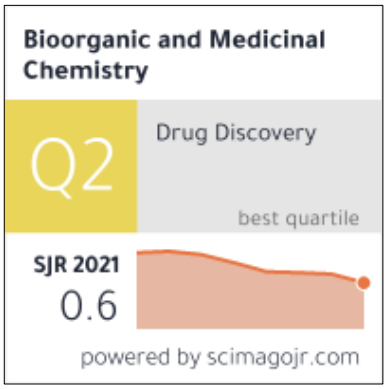

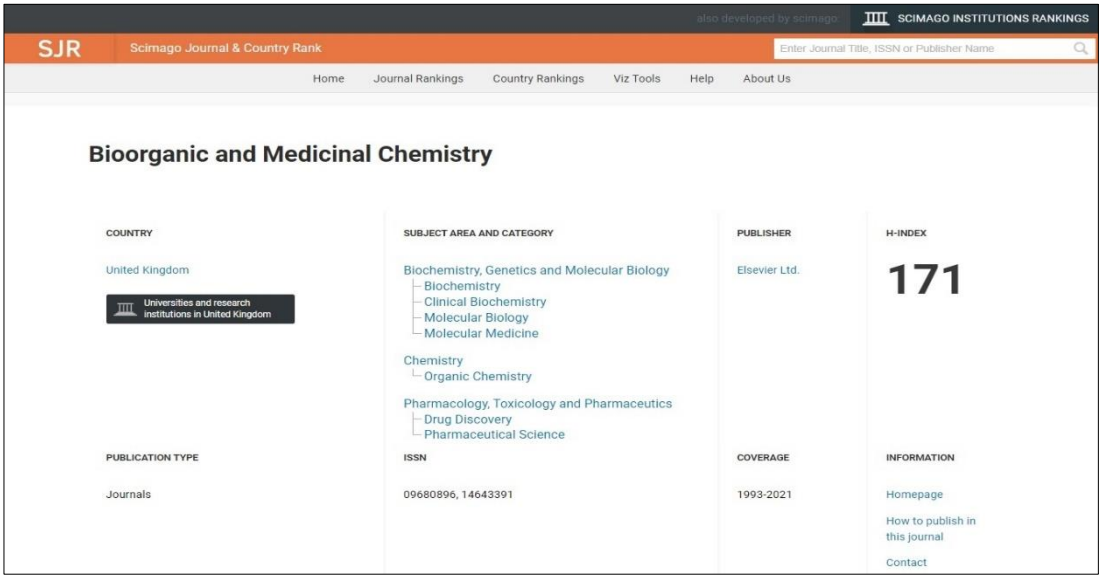

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