New antiplasmodial indole alkaloids from Hunteria zeylanica

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New antiplasmodial indole alkaloids from *Hunteria zeylanica*

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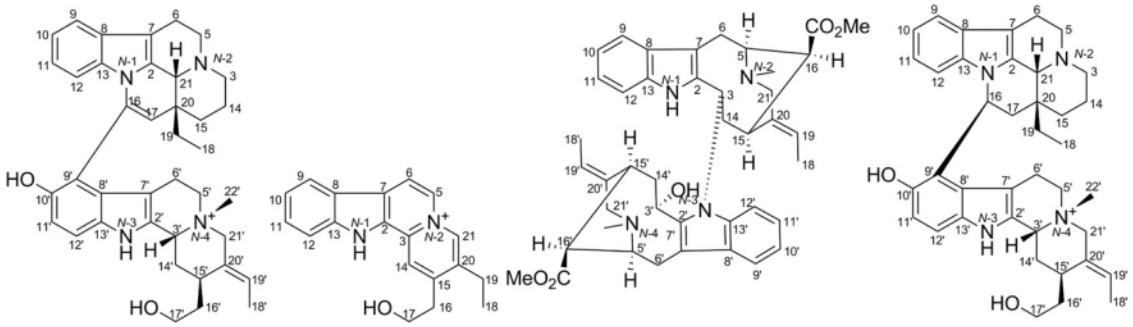
ABSTRACT

Two new indole alkaloids, bisnicalaterine D (**1**), consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (**2**) were isolated from the bark of *Hunteria zeylanica*. Their structures were elucidated by various spectroscopic data such as NMR and CD spectra. A series of bisnicalaterines and nicalaterine A showed potent antiplasmodial activity against *Plasmodium falciparum* 3D7.

In our search for new bioactive alkaloids from tropical plants in Malaysia and Indonesia, we have previously reported a series of cassiarins with potent antiplasmodial activity.[1,2] *Hunteria zeylanica* (Retz.) Gardner ex Thwaites is a member of the Apocynaceae family in Malaysia, found mostly in Pahang and Selangor,[3] and the bark and leaves have been known to produce various skeletal alkaloids depending on the area where the plants were distributed.[4–9] In our previous paper,[10,11] we have reported the isolation of new bisindole alkaloids, bisnicalaterines A–C (**3**–**5**) from *H. zeylanica*. In this Letter, we report the isolation and structure elucidation of bisnicalaterine D (**1**), a new bisindole alkaloid consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (**2**) as well as the antimalarial activity of **1**–**5** against *Plasmodium falciparum* 3D7.



bisnicalaterine D (**1**:S_a) nicalaterine A (**2**) bisnicalaterine A (**3**:R_a) bisnicalaterine B (**4**:S_a) bisnicalaterine C (**5**:R_a)

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The bark of *H. zeylanica*[12] was extracted with MeOH, and part (33 g) of the extract was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated Na_2CO_3 (aq) to pH 10 and extracted with $CHCl_3$ and *n*-BuOH subsequently. The *n*-BuOH fraction was subjected to an HP-20 column (H_2O/MeOH 0:1 to 1:0), and the 80% MeOH fraction (3.5 g) was further separated by using a Sephadex LH-20 column. Fractions containing **1** was then separated by a silica gel column ($CHCl_3$/MeOH, 9:1 to 0:1), followed by an ODS Sep-Pak (MeOH/H_2O 1:9 to 1:0) to give bisnicalaterine D (**1**, 8.1 mg, 0.003%), while purification of fractions containing **2** by an amino silica gel column ($CHCl_3$/MeOH, 9:1 to 0:1) and a silica gel column ($CHCl_3$/MeOH, 8:2) yielded nicalaterine A (**2**, 2.0 mg, 0.0008%).

Bisnicalaterine D (**1**),[13] a yellowish amorphous solid, $[\alpha]_D^{20}$ −72 (*c* 1.0, MeOH), showed a molecular formula, $C_{39}H_{47}N_4O_2$, which was determined by HRESIMS [*m*/*z* 603.3689 $(M)^+$, Δ −0.5 mmu]. IR absorption band (3430 cm^{-1}) was characteristic of amino or hydroxyl group. ^1H and ^{13}C NMR data (Table 1) suggested the presence of one sp^3 quaternary carbon, 12 sp^3 methylenes, three sp^3 methines, three methyls, eight sp^2 methines, and 12 sp^2 quaternary carbons. The ^{13}C NMR spectrum of **1** is very similar to those of bisnicalaterines B (**4**).[11] Compared to spectroscopic data of **4**, **1** has two less sp^3 carbons, two additional sp^2 carbons (δ_c 131.9 and δ_c 117.7) and also 2 amu smaller which suggests the existence of an additional double bond in **1**. The existence of a double bond between C-16 and C-17 was confirmed by the HMBC correlations of H-17 to C-16, C-19, C-20, C-21 and C-9′, H_3-18 to C-20, and H-21 to C-15. Further analysis of the two-dimensional NMR data (^1H–^1H COSY, HMQC, and HMBC spectra) revealed the gross structure of **1** as shown in Figure 1.

Table 1
^1H and ^{13}C NMR data of bisnicalaterine D (**1**) and nicalaterine A (**2**) in CD_3OD at 300 K[a]

Position	1		2	
	[δ_H (*J*, Hz)]	[δ_c]	[δ_H (*J*, Hz)]	[δ_c]
2		125.3		131.5
3a	3.37 (1H, m)	46.7		132.4
3b	3.37 (1H, m)			
5a	3.87 (1H, m)	53.1	8.69 (1H, br s)	127.3
5b	3.97 (1H, m)			
6a	3.13 (1H, m)	16.9	8.44 (1H, br s)	117.0
6b	3.30 (1H, m)			
7		108.2		123.0
8		128.7		122.3
9	7.48 (1H, d, 7.6)	119.7	8.21 (1H, d, 7.6)	122.6
10	6.97 (1H, m)	121.7	7.39 (1H, t, 7.6)	124.0
11	6.69 (1H, t, 8.3)	124.2	7.64 (1H, t, 7.6)	130.4
12	5.83 (1H, d, 8.3)	113.4	7.70 (1H, br s)	113.7
13		136.2		143.0
14a	1.83 (1H, m)	19.4	8.58 (1H, s)	121.2
14b	1.98 (1H, m)			
15a	1.68 (1H, m)	29.1		151.1
15b	1.86 (1H, m)			
16		131.9	3.22 (2H, br s)	36.2
17	5.26 (1H, s)	117.7	4.09 (2H, br s)	61.4
18	1.11 (3H, t, 7.6)	8.8	1.45 (3H, t, 7.2)	13.7
19a	1.85 (1H, m)	27.9	2.98 (2H, q, 7.2)	24.8
19b	2.00 (1H, m)			
20		39.2		139.5
21	5.22 (1H, s)	59.1	8.94 (1H, s)	135.1
2′		131.3		
3′	4.68 (1H, dd, 11.0, 3.5)	62.8		
5a′	2.93 (1H, m)	52.2		
5b′	3.76 (1H, m)			
6a′	1.53 (1H, m)	18.7		
6b′	2.93 (1H, m)			
7′		102.6		
8′		126.8		
9′		112.1		
10′		150.9		
11′	6.96 (1H, m)	114.3		
12′	7.39 (1H, d, 8.2)	114.8		
13′		133.0		
14a′	2.16 (1H, m)	36.1		
14b′	2.25 (1H, m)			
15′	3.16 (1H, m)	30.4		
16a′	1.86 (1H, m)	34.5		
16b′	1.96 (1H, m)			
17a′	3.51 (1H, m)	60.1		
17b′	3.62 (1H, m)			
18′	1.73 (3H, d, 6.9)	13.3		
19′	5.79 (1H, q, 6.9)	132.1		
20′		129.2		
21a′	3.66 (1H, m)	68.1		
21b′	4.18 (1H, br d, 13.8)			
22′	2.50 (3H, s)	48.6		

[a] δ In ppm.

The absolute structure of **1** was deduced by comparing its CD spectrum to that of bisnicalaterine B (**4**). The CD spectrum[13] of **1** showed a similar CD pattern to that of **4**,[11] thus the absolute structure of **1** was determined to be of 20*R*, 21*R*, 4′*R*, 3′*R*, 15′*R*.

Nicalaterine A (**2**),[14] a yellowish amorphous solid, showed a molecular formula, $C_{19}H_{19}N_2O$, which was determined by HRESIMS [*m*/*z* 291.1496 $(M)^+$, Δ −0.1 mmu]. IR absorption band (3430 cm^{-1}) was characteristic of amino or hydroxyl group. The UV spectrum suggested the presence of a highly conjugated ring system [λ_{max} 386 (ε 8000), 346 (8300), 291 (6900), 240 (16,100), and 235 (sh, 15,000)] as in flavopereirine.[15] ^1H and ^{13}C NMR data (Table 1) suggested the presence of three sp^3 methylenes, one methyl, eight sp^2

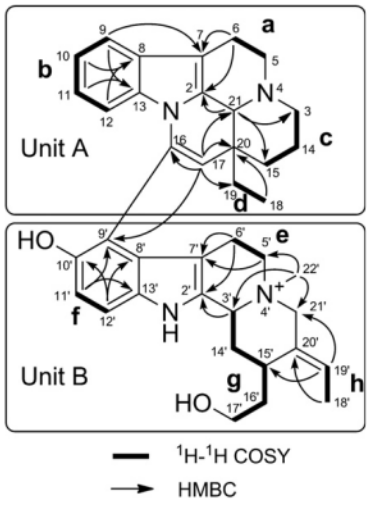

Figure 1. Selected 2D NMR correlations for bisnicalaterine D (**1**).

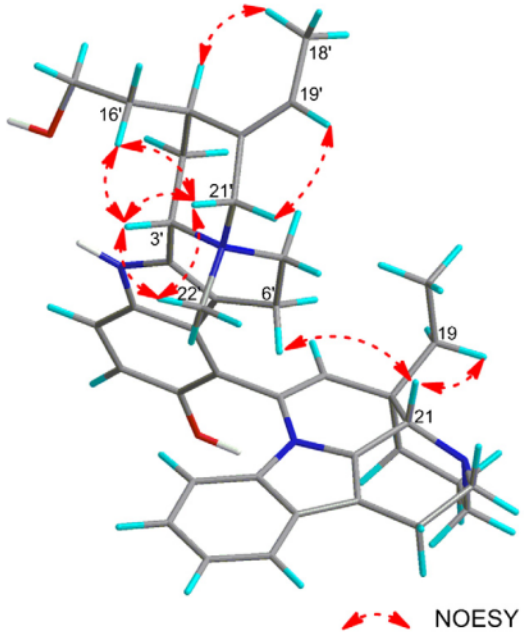

Figure 2. Selected NOESY correlations for bisnicalaterine D (**1**).

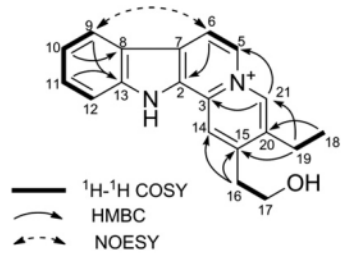

Figure 3. Selected 2D NMR correlations for nicalaterine A (**2**).

Table 2
Antiplasmodial activity of **1**–**5** against *P. falciparum* 3D7

	Antiplasmodial activity (IC_{50}, μM)	Cytotoxic activity[a] (IC_{50}, μM)	SI
1	>50	>50	–
2	0.11	>50	>450
3	4.36	16.2	3.7
4	1.13	>50	>44
5	0.05	>50	>1000

[a] Against HL-60.

methines, and seven sp^2 quaternary carbons. The HMBC correlations of H_2-19 to C-15 and C-21, H_3-18 to C-20, and H_2-16 to C-15 and C-14 allowed the attachment of the ethyl side chain (C-18 and C-19) to C-20 and the 2-hydroxyethyl side chain to C-15. Further analysis of the two-dimensional NMR data (^{1}H–^{1}H COSY, HSQC, and HMBC spectra in CD_3OD) revealed the gross structure of **2** as shown in Figure 3.

Antimalarial activity[16–18] for **1**–**5** against *P. falciparum* 3D7 was evaluated (Table 2). Nicalaterine A (**2**) and bisnicalaterine C (**5**) showed potent antimalarial activity (IC_{50} 0.11 and 0.05 μM, respectively) with a good selectivity (SI >450 and >1000, respectively). Bisnicalaterine C (**5**) with an extended conformation showed 20 times more effective than that of bisnicalaterine B (**4**) with a twisted conformation. On the other hand, bisnicalaterine D (**1**), which also possessed a twisted conformation, showed practically no antimalarial activity. It is interesting to note that the conformation around the C-16 - C-9′ bond may play important roles to show antimalarial activity.

Acknowledgments

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13. Bisnicalaterine D, yellowish amorphous solid, $[\alpha]_D^{20}$ −72 (*c* 1.0, MeOH), UV (MeOH) λ_{max} 217 (ε 16800), 249 (6100), 277.5 (5300), 302 (4100); CD (MeOH) λ_{max} 205 (Δε 5.95), 218 (−6.09), 243 (6.54), 280 (−4.22), 365 (3.07); IR (KBr) ν_{max} 3430 cm^{-1}; ^{1}H and ^{13}C NMR data see Table 1; EI-MS *m*/*z* 603 M^+; HRESIMS [*m*/*z* 603.3689 $(M)^+$, calcd for $C_{39}H_{47}N_4O_2$, 603.3694].
14. Nicalaterine A (**2**), a yellowish amorphous solid, UV (MeOH) λ_{max}, 235 (sh, 15,000), 240 (16,100), 291 (6900), 346 (8300), and 386 (ε 8000); IR (KBr) ν_{max} 3430 cm^{-1}, ^{1}H and ^{13}C NMR data see Table 1; EI-MS *m*/*z* 291 M^+; HRESIMS [*m*/*z* 291.1496 $(M)^+$, calcd for $C_{19}H_{19}N_2O$, 291.1497].
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