

# Antiplasmodial indole alkaloids from *Leuconotis griffithii*

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## Antiplasmodial indole alkaloids from *Leuconotis griffithii*

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**Abstract** A new indole alkaloid, leucoridine A *N*-oxide (1), consisting of two units of a strychnan type of skeleton, was isolated from the leaves of *Leuconotis griffithii*. Its structure was elucidated by various spectroscopic means such as NMR and MS, and also by chemical means. Antiplasmodial activity against *Plasmodium falciparum* 3D7 of indole alkaloids isolated from *L. griffithii* was investigated.

**Keywords** Leucoridine A *N*-oxide · Indole alkaloids · *Leuconotis griffithii* · Antiplasmodial activity

In our search for new bioactive alkaloids from tropical plants in Malaysia and Indonesia, we have reported a series of bisindole alkaloids, bisnicalaterines A–C from *Hunteria zeylanica* and cassiarins from *Cassia siamea*, with potent vasorelaxant and antiplasmodial activities [1–4]. *Leuconotis griffithii* (Retz.) Gardner ex Thwaites is a member of

the Apocynaceae family in Malaysia and Indonesia [5]. The species of *Leuconotis* have been known to produce monoterpene indole alkaloids [6, 7], whose skeletons are similar to those found in *Alstonia* and *Kopsia* species [8]. In addition to our previously reported bisleucocurine A (2) [9], a new bisindole alkaloid leucoridine A *N*-oxide (1), consisting of two strychnan skeletons, has been isolated from the leaves of *L. griffithii* together with leucoridine A (3) [10], anhydropereirine (4) [11], leuconicine B (5) [12], and melohenine A (6) [13] (Fig. 1). This paper describes the isolation and structure elucidation of the new strychnan dimer leucoridine A *N*-oxide (1) and the antiplasmodial activity of alkaloids isolated from *L. griffithii* leaves.

Leucoridine A *N*-oxide (1) was isolated as a yellow amorphous solid and the molecular formula  $C_{38}H_{44}N_4O$  was determined by HRESIMS [ $m/z$  573.3619 (M+H)<sup>+</sup>,  $\Delta$  +2.6 mmu]. <sup>1</sup>H and <sup>13</sup>C NMR data (Table 1) suggested the presence of twelve sp<sup>3</sup> methylenes, six sp<sup>3</sup> methines, two methyls, three sp<sup>3</sup> quaternary carbons, eight sp<sup>2</sup> methines, and seven sp<sup>2</sup> quaternary carbons. Among them, five sp<sup>3</sup> methylenes ( $\delta_C$  51.9;  $\delta_H$  3.11 and 4.63,  $\delta_C$  52.3;  $\delta_H$  3.25 and 3.64,  $\delta_C$  53.3;  $\delta_H$  3.35 and 3.60,  $\delta_C$  67.8;  $\delta_H$  3.77 and 4.46, and  $\delta_C$  72.5;  $\delta_H$  4.04 and 4.08), two sp<sup>3</sup> methines ( $\delta_C$  63.3;  $\delta_H$  4.54, and  $\delta_C$  82.8;  $\delta_H$  4.13), and four sp<sup>2</sup> quaternary carbon ( $\delta_C$  148.4,  $\delta_C$  150.9,  $\delta_C$  153.7, and  $\delta_C$  186.5) were attached to a nitrogen atom. Comparison of <sup>1</sup>H and <sup>13</sup>C NMR data of 1 with those of 3 showed that except for the downfield shift of signals ascribed to position 3, 5 and 21, the two are quite similar, suggesting 1 as the *N*-oxide derivative of 3.

The gross structure of 1 was confirmed from extensive analyses of the two-dimensional NMR data, including the <sup>1</sup>H–<sup>1</sup>H COSY, HSQC, and HMBC spectra in CD<sub>3</sub>OD (Fig. 2). The <sup>1</sup>H–<sup>1</sup>H COSY and HSQC spectra revealed connectivities of eight partial structures a (C-5 to C-6),

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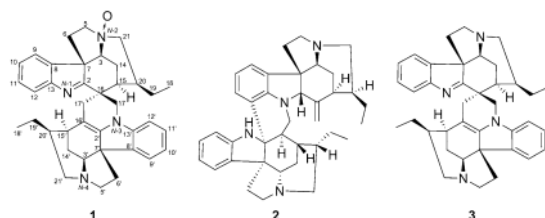
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**b** (C-9 to C-12), **c** (C-3, C-14 to C-15), **d** (C-18 to C-21), **e** (C-5' to C-6'), **f** (C-9' to C-12'), **g** (C-3', C-14' to C-15'), and **h** (C-18' to C-21'), as shown in Fig. 2. These partial structures were classified into two units, A and B.

In unit A, the presence of an indoline ring (C-2, C-7–C-13, and N-1) was revealed by the HMBC correlations of H-6 to C-2 ( $\delta_C$  186.5) and C-8 ( $\delta_C$  146.4), H-9 to C-7 ( $\delta_C$



**Fig. 1** Structures of **1–3**

**Table 1**  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of leucoridine A N-oxide (**1**) in  $\text{CD}_3\text{OD}$  at 300 K

$[\delta_{\text{H}} (J, \text{Hz})]$	$[\delta_{\text{C}}]$	$[\delta_{\text{H}} (J, \text{Hz})]$	$[\delta_{\text{C}}]$	
2	186.5	2'	148.4	
3	4.13 (1H, br. s)	82.8	3' 4.54 (1H, br. s)	63.3
5	4.04 (1H, m)	72.5	5' 3.35 (1H, m)	53.3
	4.08 (1H, m)		3.60 (1H, m)	
6	2.39 (1H, dd, 14.9, 6.4)	32.1	6' 1.86 (1H, m)	38.2
	3.03 (1H, m)		2.57 (1H, m)	
7	61.9	7'	50.2	
8	146.4	8'	134.4	
9	7.65 (1H, d, 7.3)	122.1	9' 7.30 (1H, d, 7.9)	121.1
10	7.34 (1H, t, 7.3)	128.4	10' 6.93 (1H, t, 7.9)	122.7
11	7.38 (1H, t, 7.3)	130.1	11' 7.21 (1H, t, 7.9)	129.5
12	7.42 (1H, d, 7.3)	121.4	12' 7.11 (1H, d, 7.9)	111.6
13	153.7	13'	150.9	
14	1.35 (1H, m)	27.5	14' 1.70 (1H, m)	30.8
	2.21 (1H, m)		2.12 (1H, m)	
15	2.24 (1H, br. s)	42.5	15' 2.63 (1H, br. s)	33.5
16	48.1	16'	111.6	
17	3.11 (1H, d, 10.4)	51.9	17' 2.30 (1H, d, 16.7)	46.9
	4.63 (1H, dd, 10.4, 2.5)		2.87 (1H, br. d, 16.7)	
18	1.08 (3H, t, 7.4)	12.9	18' 1.08 (3H, t, 7.4)	11.7
19	1.64 (1H, m)	27.0	19' 1.75 (1H, m)	25.8
	1.72 (1H, m)		1.82 (1H, m)	
20	2.42 (1H, m)	41.6	20' 2.00 (1H, m)	39.7
21	3.77 (1H, dd, 14.4, 5.2)	67.8	21' 3.25 (1H, m)	52.3
	4.46 (1H, br t, 14.4)		3.64 (1H, m)	

61.9) and C-13 ( $\delta_C$  153.7), and H-10 and H-12 to C-8. The connection between C-3 of partial structure **c** and C-7 was deduced from the correlation of H-3 to C-8. The linkage between partial structure **c** and **d** through C-15 and C-20 was suggested by the correlation of H-19 to C-15 ( $\delta_C$  42.5). The HMBC cross peaks of H<sub>2</sub>-17 to C-2, C-15 and C-16 suggested the connections among C-2, C-15, and C-17 through C-16 ( $\delta_C$  48.1). Finally, HMBC correlations of H-3 to C-21 ( $\delta_C$  67.8), H-5 to C-3 ( $\delta_C$  82.8) and C-21, and the relatively downfield chemical shift of C-3, C-5, and C-21 established the connections among C-3, C-5, and C-21 through a nitrogen atom (N-2) and the presence of an N-oxide in unit A.

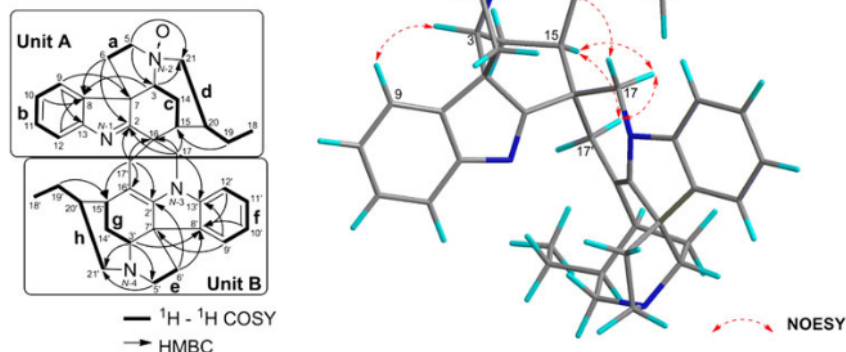
The chemical shift of the remaining carbons suggested that unit B was a similar structure to unit A. The presence of an indoline ring (C-2', C-7' to C-13', and N-3) and the connectivity of partial structure **e** and the indoline ring were revealed by the HMBC correlations of H-9' to C-7' ( $\delta_C$  50.2) and C-13' ( $\delta_C$  150.9), H-10' and H-12' to C-8' ( $\delta_C$  134.4), H<sub>2</sub>-6' to C-2' ( $\delta_C$  148.4), and C-8'. HMBC correlations of H-3' to C-5' ( $\delta_C$  53.3) and C-21' ( $\delta_C$  52.3), H-5' to C-21' established the connections among C-3', C-5', and C-21' through a nitrogen atom (N-4). The connection between C-3' of partial structure **g** and C-7' was deduced from the correlation of H-3' to C-8'. HMBC cross peaks of H-19' to C-15' ( $\delta_C$  33.5) suggested the linkage between C-15' and C-20', and finally the connections among C-2', C-15', and C-17' through C-16' ( $\delta_C$  111.6) were deduced from the HMBC correlations of H<sub>2</sub>-17' to C-2', C-15', and C-16', completing the structure of unit B.

Finally, the linkages between units A and B from C-16 to C-17' and C-17 to N-3 were provided by the HMBC correlations of H-17 to C-13' and H-17' to C-16. Thus, the gross structure of **1** was assigned to be leucoridine A N-oxide, as shown in Fig. 2.

The relative configuration of **1** was confirmed to be the same as **3** by NOESY correlations and coupling constant data. In unit A, the NOESY correlations of H-17b/H-21b and H-3/H-9 and the values of  $J_{20-21a}$  and  $J_{20-21b}$  suggested that C-6 and C-17 were  $\beta$ -oriented, while H-3, H-15, and H-20 were  $\alpha$ -oriented. The relative configurations at C-3', 7', 15', and 20' of unit B were the same as unit A. Finally, the NOESY correlations of H-17'b/H-15 and H-17a were used to deduce the relative configuration of the total molecule. The structure of **1** was also confirmed by chemical conversion to **3** by the use of sodium hydrogen sulfite in methanol.

Antimalarial activities of **1–6** against *Plasmodium falciparum* 3D7 were evaluated (Table 2). **1**, **2**, and **5** showed potent antimalarial activity ( $\text{IC}_{50}$  0.09, 0.007, and 0.06  $\mu\text{M}$ , respectively) with a good selectivity (SI 248, 543, and 280, respectively). Although the antiplasmodial activity of some strychnan-related bisindole alkaloids is known [14], this is

**Fig. 2** Selected 2D NMR correlations for leucoridine A *N*-oxide (**1**)



**Table 2** Antiplasmodial activity of **1–6** against *Plasmodium falciparum* 3D7

Antiplasmodial activity (IC <sub>50</sub> μM)	Cytotoxic activity (IC <sub>50</sub> μM) <sup>a</sup>	SI
<b>1</b>	0.09	22.33
<b>2</b>	0.007	3.8
<b>3</b>	2.36	16.3
<b>4</b>	0.11	9.78
<b>5</b>	0.06	16.82
<b>6</b>	>50	>50

<sup>a</sup> Against HL-60

SI selectivity index

**23** the first report on the antiplasmodial activity of bisindole alkaloids having skeletons as in **1** or **2**.

## **15** Experimental section

### General experimental procedures

UV spectra were recorded on a Shimadzu UVmini-1240 spectrophotometer and IR spectra on a JASCO FT/IR-4100 spectrophotometer. High-resolution ESI MS were obtained on a LTQ Orbitrap XL (Thermo Scientific). <sup>1</sup>H and 2D NMR spectra were recorded on a Bruker AV 700 spectrometer, and chemical shifts were referenced to the residual solvent peaks ( $\delta_{\text{H}}$  3.31 and  $\delta_{\text{C}}$  49.0 for CD<sub>3</sub>OD). Standard pulse sequences were employed for the 2D NMR experiments.

### Material

The leaves of *L. griffithii* collected at Mersing, Malaysia, in 2001. The botanical identification was made by Mr. Teo

Leong Eng, Faculty of Science, University of Malaya. The voucher specimen (Herbarium No. KL 4976) was deposited at the Herbarium of the Department of Chemistry, University of Malaya, Kuala Lumpur, Malaysia.

### Extraction and isolation

The leaves of *L. griffithii* were extracted with MeOH, and part (87 g) of the extract was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> to pH 10 and extracted with CHCl<sub>3</sub> to give an alkaloidal fraction (1.8 g). The alkaloidal fraction was subjected to a Sephadex LH-20 column to give eight fractions, and the fractions were further separated using silica gel column (CHCl<sub>3</sub>/MeOH, 1:0 → 0:1), and amino silica gel column (CHCl<sub>3</sub>/MeOH, 1:0 → 0:1). Fraction 4 yielded leucoridine A *N*-oxide (**1**, 0.5 mg, 0.0001%) and leuconicine B, fraction 6 gave bis-leucocurine A, fraction 7 gave leucoridine A together with melohenine A, and fraction 8 yielded anhydropereirine.

### Leucoridine A *N*-oxide (**1**)

Yellow amorphous solids,  $[\alpha]_{\text{D}}^{22} +140$  (*c* 0.4, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  204 ( $\epsilon$  48500) and 261 (sh, 14000); CD (MeOH)  $\lambda_{\text{max}}$  205 ( $\Delta\epsilon$  +12.41), 215 (0), 218 (−4.56), 223 (0), 229 (+3.37), 243 (+3.95), 267 (+3.07), 311 ( $\Delta$  +3.80) nm; <sup>1</sup>H and <sup>13</sup>C NMR data see Table 1; HRESIMS [*m/z* 573.3619 (M+H)<sup>+</sup>, calc. for C<sub>38</sub>H<sub>45</sub>N<sub>4</sub>O, 573.3593].

### Chemical conversion of leucoridine A *N*-oxide (**1**) to leucoridine A (**3**)

To a solution of leucoridine A *N*-oxide (**1**, 0.1 mg) in MeOH (0.1 ml) was added Na<sub>2</sub>SO<sub>3</sub> (1.0 mg) and the mixture was kept at room temperature. After 12 h, the

mixture was partitioned with  $\text{CHCl}_3$  to obtain a reaction product (0.1 mg) whose spectral properties (MS,  $^1\text{H}$  NMR and CD) are identical to those of **3**.

#### Antiplasmodial activity

Human malaria parasites were cultured according to the method of Trager and Jensen [15]. The antimalarial activity of the isolated compounds was determined using the procedure of Budimulya et al. [16]. In brief, stock solutions 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  $\text{NaHCO}_3$ ) until the final concentrations of samples in culture plate wells were 10, 1, 0.1, 0.01, and 0.001  $\mu\text{g}/\text{ml}$ . The malarial parasite *P. falciparum* 3D7 clone was propagated in 24-well culture plates. The growth of the parasite was monitored by making a blood smear fixed with MeOH and stained with Giemsa stain. The antimalarial activity of each compound was expressed as an  $\text{IC}_{50}$  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 the following equation: growth inhibition % =  $100 - [(\text{test parasitaemia}/\text{control parasitemia}) \times 100]$ . Chloroquine:  $\text{IC}_{50}$  0.011  $\mu\text{M}$ .

#### Cytotoxic activity

HL-60 human promyelocytic leukemia cells were maintained in RPMI-1640 medium. The growth medium was supplemented with 10% fetal calf serum and 1% penicillin–streptomycin. The cells ( $5 \times 10^3$  cells/well) were cultured in Nunc disposable 96-well plates containing 90  $\mu\text{l}$  of growth medium per well and were incubated at  $37^\circ\text{C}$  in a humidified incubator with 5%  $\text{CO}_2$ . 10  $\mu\text{l}$  of samples were added to the cultures at 24 h of incubation. After 48 h of incubation with the samples, 15  $\mu\text{l}$  of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (5 mg/ml) were added to each of the wells. The cultures were incubated for another 3 h before the cells supernatant was removed. After the removal of the cells supernatant, 50  $\mu\text{l}$  of dimethyl sulfoxide (DMSO) was added to each well. The formazan crystal formed was dissolved by re-suspension by pipette. The optical density was measured using a microplate reader (Bio-Rad, USA) at 550 nm with reference wavelength at 700 nm. In all experiment, three replicates were used. Cisplatin was used as positive control ( $\text{IC}_{50}$ : 0.87  $\mu\text{M}$  for HL-60).

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