

# New Tricyclic Alkaloids, Cassiarins G, H, J, and K from Leaves of *Cassia siamea*

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## New Tricyclic Alkaloids, Cassiarins G, H, J, and K from Leaves of *Cassia siamea*

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Four new alkaloids, cassiarins G, H, J, and K (1–4) which showed moderate antiplasmodial activity against *Plasmodium falciparum* 3D7, were isolated from the leaves of *Cassia siamea* (Leguminosae) and the structures of 1–4 were elucidated by 1D- and 2D-NMR analysis and X-ray crystallographic analysis.

**Key words** alkaloid; *Cassia siamea*; cassiarin; antiplasmodial activity; *Plasmodium falciparum* 3D7

*Cassia siamea* LAM. (Leguminosae), has been widely used in traditional medicine, particularly for the treatment of periodic fever and malaria in Indonesia.<sup>1,2)</sup> Cassiarin A,<sup>3)</sup> an unprecedented tricyclic alkaloid exhibiting potent antimalarial activity against *P. falciparum* *in vitro* as well as *P. berghei in vivo*,<sup>4)</sup> was isolated from the leaves of *C. siamea* and has attracted the attention of synthetic organic chemists<sup>5–7)</sup> as well as pharmacologists.<sup>8)</sup> Recently, we have also reported the synthesis of a series of a hydroxyl and a nitrogen-substituted derivatives of cassiarins A and B and their antimalarial activity against *P. falciparum* *in vitro* as well as a vasorelaxation activity.<sup>9)</sup> Furthermore, we isolated a novel biaryl tetracyclic alkaloid, cassirin F and achieved its total synthesis.<sup>10)</sup> In our continuing investigation of the pharmacologically and structurally unique alkaloids from this plant, we have isolated four new alkaloids possessing tricyclic skeleton. We herein report the structure elucidation of these alkaloids and antiplasmodial activity against *P. falciparum* 3D7.

The crude basic fraction obtained by a conventional procedure from the MeOH extract of the leaves of *C. siamea*, was purified by repeated chromatography to afford new alkaloids, cassiarins G (1; 0.0064%), H (2; 0.00008%), J (3; 0.0022%), and K (4; 0.0012%), along with cassiarins A and B<sup>3)</sup> and 5-acetyl-7-hydroxy-2-methylchromone.<sup>11)</sup>

Cassiarin G (1) was obtained as yellowish needles (mp 213–218°C) and showed the molecular formula, C<sub>14</sub>H<sub>13</sub>NO<sub>4</sub>, which was determined by high resolution-electrospray ionization-time-of-flight-mass spectrometry (HR-ESI-TOF-MS) [*m/z* 260.0921, (M+H)<sup>+</sup>, –0.2 mmu]. IR absorptions implied the presence of hydroxy and/or amino (3116 cm<sup>–1</sup>) and carbonyl (1673 cm<sup>–1</sup>) functionalities. <sup>1</sup>H- and <sup>13</sup>C-NMR data are

presented in Table 1. The <sup>13</sup>C-NMR spectrum revealed 14 carbon signals due to one carbonyl carbon, six *sp*<sup>2</sup> and one *sp*<sup>3</sup> quaternary carbons, three *sp*<sup>2</sup> methines, and three methyl groups. Among them, four *sp*<sup>2</sup> quaternary carbons (δ<sub>C</sub> 144.0, 152.0, 155.4, 168.9), one *sp*<sup>3</sup> quaternary carbon (δ<sub>C</sub> 106.8), and one *sp*<sup>3</sup> methyl carbon (δ<sub>C</sub> 50.5) were ascribed to those bearing a nitrogen or an oxygen atom.

A partial structure, C-10 to C-12 was deduced from analysis of the <sup>1</sup>H–<sup>1</sup>H correlation spectroscopy (COSY) spectrum including a long range coupling from H<sub>3</sub>-12 to H-10. The heteronuclear multiple bond connectivity (HMBC) correlations for H-10 of C-4a (δ<sub>C</sub> 110.2) and C-5 (δ<sub>C</sub> 142.0), H-6 of C-10 (δ<sub>C</sub> 121.7), and H-8 of C-4a, C-6 (δ<sub>C</sub> 103.0), and C-7 (δ<sub>C</sub> 168.9) gave rise to 3-methylisoquinolin-6-ol core, which is the same as the partial structure of cassiarin A. The other partial structure was assigned by HMBC correlations for H<sub>3</sub>-9 and H<sub>3</sub>-13 of C-2 and H<sub>3</sub>-9 of C-3 (δ<sub>C</sub> 189.0) and the downfield chemical shifts of C-2 (δ<sub>C</sub> 106.8) and C-8a (δ<sub>C</sub> 155.4) suggested the presence of an ether linkage between C-2 and C-8a to form a 2-methyl-2-methoxy-3-carbonylpyran ring. Thus, cassiarin G (1) was assigned to be a 2-methoxycassiarin A-3-one (Fig. 1). The proposed structure inferred by spectroscopic analysis was confirmed by X-ray crystallographic analysis (Fig. 2). 1 was found as a racemic form base on X-ray crystallographic information.

Cassiarin H (2) showed the molecular formula, C<sub>19</sub>H<sub>21</sub>NO<sub>6</sub>, which was determined by HR-ESI-TOF-MS [*m/z* 360.1441, (M+H)<sup>+</sup>, –0.6 mmu]. IR absorptions implied the presence of carbonyl (1726, 1683 cm<sup>–1</sup>) functionality. The gross structure of 2 was elucidated by analyses of 2D-NMR data including <sup>1</sup>H–<sup>1</sup>H COSY, heteronuclear multiple quantum coherence

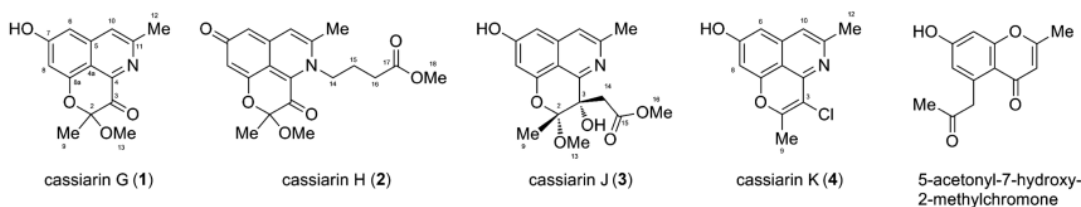


Chart 1

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Table 1.  $^1\text{H}$ -NMR Data [ $\delta_{\text{H}}$  ( $J$ , Hz)] and  $^{13}\text{C}$ -NMR Data [ $\delta_{\text{C}}$ ] of Cassiarins G, H, J, and K (1–4) in Methanol- $d_4$  at 300 K<sup>a)</sup>

Position	1		2		3		4	
	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2		106.8		102.2		107.1		157.4
3		189.0		187.0		76.1		113.7
4		152.0		137.5		156.9		148.4
4a		110.2		115.9		111.0		112.8
5		142.0		141.4		141.0		139.9
6	6.88 (1H, brs)	103.0	6.33 (1H, d, 1.8)	106.5	6.83 (1H, brs)	103.1	6.57 (1H, brs)	102.5
7		168.9		183.5		167.9		163.0
8	6.79 (1H, brs)	107.6	6.58 (1H, d, 1.8)	116.6	6.74 (1H, brs)	107.3	6.54 (1H, brs)	100.5
8a		155.4		153.2		154.4		155.2
9	1.71 (3H, s)	14.9	1.79 (3H, s)	17.4	1.76 (3H, s)	15.5	2.41 (3H, s)	18.2
10	7.70 (1H, s)	121.7	7.40 (1H, s)	121.8	7.57 (1H, s)	120.3	6.91 (1H, s)	115.3
11		144.0		145.1		141.0		153.8
12	2.73 (3H, s)	19.7	2.72 (3H, s)	20.1	2.65 (3H, s)	20.3	2.45 (3H, s)	23.9
13	3.25 (3H, s)	50.5	3.42 (3H, s)	51.3	3.20 (3H, s)	50.6		
14a			4.40 (2H, t, 8.5)	49.9	2.87 (1H, d, 13.2)	43.6		
14b					3.00 (1H, d, 13.2)			
15a			1.90 (1H, m)	27.0		170.7		
15b			2.14 (1H, m)					
16			2.51 (2H, m)	31.2	3.40 (3H, s)	52.4		
17				174.5				
18			3.69 (3H, s)	52.3				

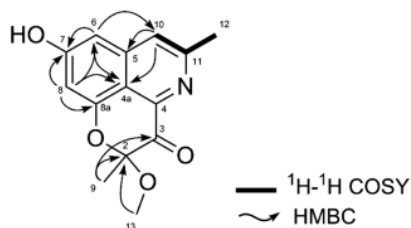
a)  $\delta$  in ppm.

Fig. 1. Selected 2D-NMR Correlations for Cassiarin G (1)

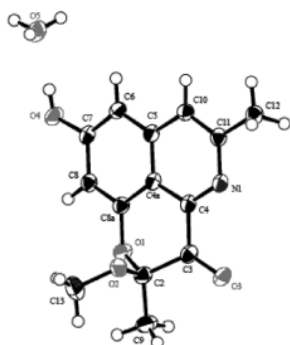


Fig. 2. An ORTEP Drawing for Cassiarin G (1)

(HMQC), and HMBC spectra in methanol- $d_4$  (Fig. 3). The  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR (Table 1) spectra of **2**, which is like a combination of those of cassiarins B and G, indicated that **2** was concluded to be a 2-methoxycassiarin B-3-one. Due to the no optical rotation and Cotton effects, **2** might be racemic form.

Cassiarin J (**3**) showed the molecular formula,  $\text{C}_{17}\text{H}_{19}\text{NO}_6$ , which was determined by HR-ESI-TOF-MS [ $m/z$  332.1107,

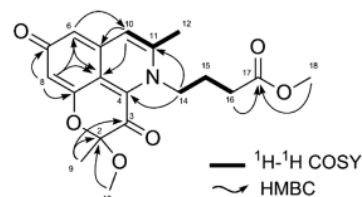


Fig. 3. Selected 2D-NMR Correlations for Cassiarin H (2)

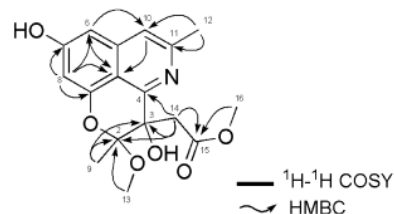


Fig. 4. Selected 2D-NMR Correlations for Cassiarin J (3)

( $\text{M}-\text{H}$ )<sup>-</sup>,  $-2.0$  mmu]. IR absorptions implied the presence of hydroxy and/or amino ( $3370\text{ cm}^{-1}$ ) and carbonyl ( $1632\text{ cm}^{-1}$ ) functionalities.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra are presented in Table 1. The gross structure of **3** was elucidated by analyses of 2D-NMR data including  $^1\text{H}$ - $^1\text{H}$  COSY, HMQC, and HMBC spectra in methanol- $d_4$  (Fig. 4). The structure of **3** resembled those of **1** except for the chemical shift and a moiety of C-3 ( $\delta_{\text{C}}$  76.1). The presence of a methylacetate and hydroxyl moiety at C-3 was supported by HMBC correlations for  $\text{H}_2$ -14 of C-2 ( $\delta_{\text{C}}$  107.1), C-3, C-4 ( $\delta_{\text{C}}$  156.9), and C-15 ( $\delta_{\text{C}}$  170.7) and  $\text{H}_3$ -16 of C-15. Thus, cassiarin J (**3**) was concluded to be methyl 3-hydroxy-2-methoxy-3-cassiarin A-acetate. The relative configuration of **3** was elucidated by rotating frame Overhauser

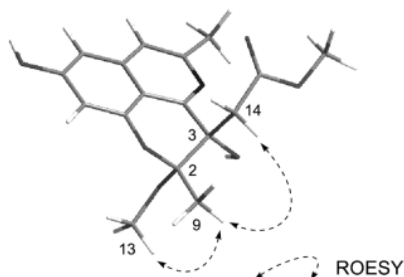


Fig. 5. Most Stable Conformation of Cassiarin J (3) by Monte Carlo Conformational Search and the Selected ROESY Correlations

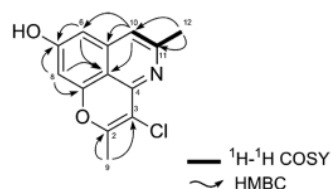


Fig. 6. Selected 2D-NMR Correlations for Cassiarin K (4)

enhancement spectroscopy (ROESY) correlations as depicted in the computer-generated three-dimensional drawing (Fig. 5). The ROESY correlations for H<sub>3</sub>-9/H<sub>3</sub>-13 and H<sub>2</sub>-14 suggested the methyl at C-2 and the hydroxy at C-3 took equatorial orientations as in Fig. 5. The energetically most stable conformation of **3** found in the Monte Carlo conformational search<sup>12)</sup> satisfied with the above-mentioned ROESY correlations. No optical rotation and Cotton effects indicated **3** might be racemic form.

Cassiarin K (**4**) showed the molecular formula, C<sub>13</sub>H<sub>10</sub>NO<sub>2</sub>Cl, which was determined by HR-ESI-TOF-MS [*m/z* 248.0474, (M+H)<sup>+</sup>, -0.4mmu]. IR absorption implied the presence of hydroxy and/or amino (3420cm<sup>-1</sup>) functionality. The gross structure of **4** was elucidated by analyses of 2D-NMR data including <sup>1</sup>H-<sup>1</sup>H COSY, HMQC, and HMBC spectra in methanol-*d*<sub>4</sub> (Fig. 6). The <sup>1</sup>H- and <sup>13</sup>C-NMR (Table 1) spectra of **4** are similar to those of cassiarin A except for the absence of H-3. The C-3 resonance of **4** was observed as a quaternary carbon at δ 113.7 as expected for a chlorine-bearing carbon resonance. Cassiarin K (**4**) is the first halogenated cassiarin analogue, has a structure in which H-3 of cassiarin A is substituted by a chlorine atom.

Biogenetically, cassiarins G, H and J (**1**–**3**) could be derived through oxidation of 5-acetonyl-7-hydroxy-2-methylchromone.

Cassiarin J (**3**) showed moderate *in vitro* antiplasmodial activity against *P. falciparum* 3D7 (IC<sub>50</sub> **3**: 0.3 μM). Whereas cassiarins G, H, and K (IC<sub>50</sub> **1**: >50 μM; **2**: >50 μM; **4**: 1.4 μM) were less active than cassiarin J (**3**), although they contained the similar cassiarin A-type skeleton.

## Experimental

**General Experimental Procedures** 1D- and 2D-NMR spectra were recorded on a Bruker AV 400, Inova500, and Bruker AVANCE 700 spectrometers and chemical shifts were referenced to the residual solvent peaks (δ<sub>H</sub> 3.31 and δ<sub>C</sub> 49.0 for methanol-*d*<sub>4</sub>). Standard pulse sequences were employed for

the 2D-NMR experiments. <sup>1</sup>H-<sup>1</sup>H COSY and ROESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1K data points for each of 256 *t*<sub>1</sub> increments. ROESY spectra in the phase sensitive mode were measured with a mixing time of 800 ms. For HMQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1K 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*<sub>1</sub> and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation.

**Material** Leaves of *C. siamea* were collected at Purwodadi Botanical Garden in 2007. The botanical identification was made by Ms. Sri Wuryanti, Purwodadi Botanical Garden, Indonesia. A voucher specimen has been deposited at Purwodadi Botanical Garden, Pasuruan, Indonesia.

**Extraction and Isolation** The leaves of *C. siamea* (0.5 kg) were extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. The aqueous layer was adjusted at pH 9 with saturated Na<sub>2</sub>CO<sub>3</sub> aq. and extracted with CHCl<sub>3</sub>. CHCl<sub>3</sub>-soluble alkaloidal materials were roughly separated by silica gel column chromatography (CHCl<sub>3</sub>/MeOH, 1:0→0:1) to give seven fractions (1–7). The fraction 4 was rechromatographed over SiO<sub>2</sub> (CHCl<sub>3</sub>/MeOH, 1:0→0:1), ODS (MeOH/H<sub>2</sub>O, 40:60→100:0), and then purified by ODS HPLC (MeOH/0.1% TFA aq, 40:60) to afford cassiarin G (**1**, 0.0064%), cassiarin H (**2**, 0.00008%), cassiarin J (**3**, 0.0022%), and cassiarin K (**4**, 0.0012%) together with cassiarin A and 5-acetonyl-7-hydroxy-2-methylchromone.

Cassiarin G (**1**): Yellowish needles (mp 213–218°C) crystal solid; IR (KBr) *v*<sub>max</sub> 3116, 2316, and 1673 cm<sup>-1</sup>; UV (MeOH) *λ*<sub>max</sub> 213 (ε 16300), 243 (19600), 269 (10900), and 325 (2100) nm; <sup>1</sup>H- and <sup>13</sup>C-NMR, see Table 1; ESI-MS *m/z* 260 (M+H)<sup>+</sup>; HR-ESI-TOF-MS *m/z* 260.0921 [(M+H)<sup>+</sup>], (Calcd for C<sub>14</sub>H<sub>14</sub>NO<sub>4</sub>, 260.0923).

Cassiarin H (**2**): Yellow amorphous solid; IR (film) *v*<sub>max</sub> 1726 and 1683 cm<sup>-1</sup>; UV (MeOH) *λ*<sub>max</sub> 215 (ε 2135), 238 (1978), 312 (1424), 387 (443), and 496 (310) nm; <sup>1</sup>H- and <sup>13</sup>C-NMR, see Table 1; ESI-MS *m/z* 360 (M+H)<sup>+</sup>; HR-ESI-TOF-MS *m/z* 360.1441 [(M+H)<sup>+</sup>], (Calcd for C<sub>19</sub>H<sub>22</sub>NO<sub>6</sub>, 360.1447).

Cassiarin J (**3**): Yellow amorphous solid; IR (film) *v*<sub>max</sub> 3370 and 1632 cm<sup>-1</sup>; UV (MeOH) *λ*<sub>max</sub> 242 (ε 16100), 289 (2600), and 327 (sh, 1600) nm; <sup>1</sup>H- and <sup>13</sup>C-NMR, see Table 1; ESI-MS *m/z* 334 (M+H)<sup>+</sup>; HR-ESI-TOF-MS *m/z* 332.1127 [(M+H)<sup>+</sup>], (Calcd for C<sub>17</sub>H<sub>18</sub>NO<sub>6</sub>, 332.1107).

Cassiarin K (**4**): Yellow amorphous solid; IR (KBr) *v*<sub>max</sub> 3420 cm<sup>-1</sup>; UV (MeOH) *λ*<sub>max</sub> 201 (ε sh, 5500), 219 (7300), and 336 (1500) nm; <sup>1</sup>H- and <sup>13</sup>C-NMR, see Table 1; ESI-MS *m/z* 248 (M+H)<sup>+</sup>; HR-ESI-TOF-MS *m/z* 248.0474 [(M+H)<sup>+</sup>], (Calcd for C<sub>13</sub>H<sub>11</sub>NO<sub>2</sub>Cl, 248.0478).

**Antiplasmodial Activity** Human malaria parasites were cultured according to the method of Trager and Jensen.<sup>13)</sup> The antimalarial activity of the isolated compounds was determined by the procedure described by Budimulya *et al.*<sup>14)</sup> In brief, stock solutions of the samples were prepared in dimethyl sulfoxide (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 *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulfonic acid (HEPES) and 25 mM NaHCO<sub>3</sub>) until the final concentrations of

samples in culture plate wells were 10; 1; 0.1; 0.01; 0.001  $\mu\text{g}/\text{mL}$ . The malarial parasite *P. falciparum* 3D7 clone was propagated in a 24-well culture plates. 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  $\text{IC}_{50}$  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 following equation:  $\text{growth inhibition \%} = 100 - [(\text{test parasitaemia}/\text{control parasitaemia}) \times 100]$ . Chloroquine:  $\text{IC}_{50}$  0.011  $\mu\text{M}$ .

**X-Ray Crystallography** Measurement was made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated  $\text{CuK}\alpha$  radiation. Crystal data of cas-siarin G: A yellow, block, triclinic,  $\text{C}_{14}\text{H}_{15}\text{NO}_5$ ,  $M=277.28$ , crystal dimensions 0.12 $\times$ 0.12 $\times$ 0.05 mm, space group P-1 (#2),  $a=7.22313(13)\text{ \AA}$ ,  $b=9.79354(18)\text{ \AA}$ ,  $c=10.3279(7)\text{ \AA}$ ,  $V=629.94(5)\text{ \AA}^3$ ,  $Z=2$ ,  $D_{\text{calc}}=1.462\text{ g/cm}^3$ . Of the 21093 reflections that were obtained, 2292 were unique ( $R_{\text{int}}=0.026$ ). The structure was solved by direct methods.  $R1=0.0371$  ( $I>2.00\sigma(I)$ ). All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL-97. The refined fractional atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). CCDC 848465 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/deposit>, or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: +44 1223 336 033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).

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GENERAL COMMENTS

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