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Chrobisiamone A, a new bischromone from *Cassia siamea* and a biomimetic transformation of 5-acetonyl-7-hydroxy-2-methylchromone into cassiarin A

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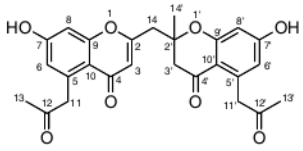
ABSTRACT

A new bischromone, chrobisiamone A (**1**) with an antiplasmodial activity has been isolated from the leaves of *Cassia siamea* and the structure was elucidated by 2D NMR analysis. Cyclization of 5-acetonyl-7-hydroxy-2-methylchromone (**2**) in the presence of ammonium acetate resulted in generation of cassiarin A (**3**) with an unprecedented tricyclic skeleton, supporting a biogenetic pathway proposed for **3**.

Malaria caused by parasites of the genus *Plasmodium* is one of the leading infectious diseases in many tropical and some temperate regions.[1] 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.[2]

Cassia siamea (Leguminosae), have been widely used in traditional medicine, particularly for the treatment of periodic fever and malaria in Indonesia.[3] So far some chromone derivatives, such as anhydrobarakol,[4] 5-acetonyl-7-hydroxy-2-methylchromone,[5] 2-methyl-5-propyl-7,12-dihydroxychromone-12-*O*-β-D-glucopyranoside,[6] and cassiadinine,[7] have already been isolated from the bark, leaves, and flowers of *C. siamea*. We have isolated cassiarins A (**3**) and B with an unprecedented tricyclic skeleton and a potent antiplasmodial activity from the leaves of *C. siamea* and proposed a biogenetic path for cassiarin A (**3**) generated from 5-acetonyl-7-hydroxy-2-methylchromone (**2**).[8] Recently, the first total synthesis of cassiarin A (**3**) was completed via sequential alkynylation of arenes with Sonogashira coupling and 6-*endo*-dig-cyclization of phenolic oxygens to the resulting alkynes in 51% overall yield in seven steps.[9] On continuing search for chemical constituents of *C. siamea*, we have isolated a new bischromone, chrobisiamone A (**1**) with an antiplasmodial activity. This letter describes the isolation and structural elucidation of **1**, and a biomimetic transformation of 5-acetonyl-7-hydroxy-2-methylchromone (**2**) into cassiarin A (**3**).



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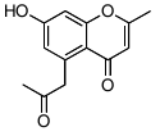

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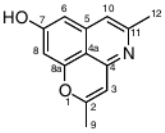

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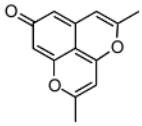

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The leaves of *C. siamea* (300 g), which were collected at the Purwodadi Botanical Garden, Pasuruan, Indonesia (2005), were

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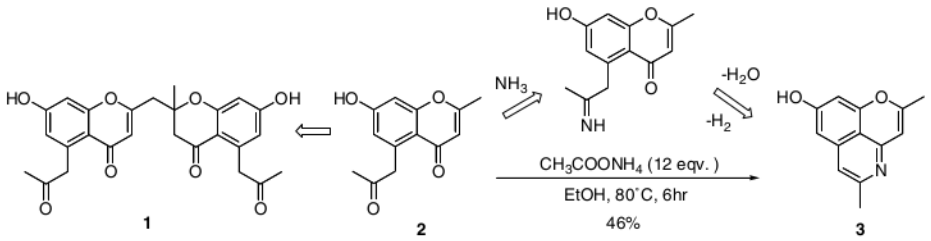

Scheme 1. Biomimetic transformation and plausible biogenetic path for chrobisiamone A (**1**) and cassiarin A (**3**).

Table 1
^{1}H [δ_H (J, Hz)] and ^{13}C NMR data (δ_C) of chrobisiamone A (**1**) in CD_3OD at 300 K

	δ_H	δ_C
2		165.5
3	6.00 (1H, s)	113.8
4		180.6
5		139.4
6	6.61 (1H, d, 2.2)	120.2
7		164.1
8	6.68 (1H, d, 2.2)	102.9
9		161.1
10		115.1
11	4.17 (2H, s)	50.5
12		208.2
13	2.31 (3H, s)	30.9
14a	3.06 (1H, d, 14.0)	43.3
14b	2.93 (1H, d, 14.0)	
2′		80.7
3′	2.74 (2H, s)	49.0[a]
4′		192.6
5′		140.7
6′	6.20 (1H, d, 2.4)	115.9
7′		165.9
8′	6.25 (1H, d, 2.4)	103.8
9′		165.2
10′		112.5
11′a	3.88 (1H, d, 17.1)	50.7
11′b	3.96 (1H, d, 17.1)	
12′		208.7
13′	2.26 (3H, s)	30.8
14′	1.50 (3H, s)	25.7

[a] Overlapped with CD_3OD.

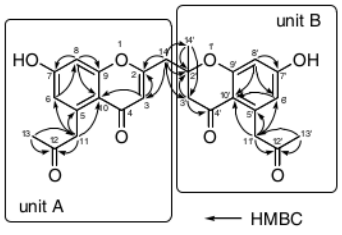

Figure 1. Selected 2D NMR correlations of chrobisiamone A (**1**) in CD_3OD.

extracted with MeOH, and the extract was partitioned with $CHCl_3$ and H_2O. $CHCl_3$-soluble materials were subjected to a silica gel column ($CHCl_3$/MeOH/AcOEt, 1:0:0 → 0:1:0), in which a fraction eluted by $CHCl_3$/MeOH/AcOEt (1:1:0) was further purified on an LH-20 column with $CHCl_3$/MeOH (1:1) to afford chrobisiamone A (**1**, 0.00013%) together with 5-acetonyl-7-hydroxy-2-methylchromone (**2**),[5] cassiarins A (**3**) and B,[8] anhydrobarakol (**4**),[4] and 4-(*trans*)-acetyl-3,6,8-trihydroxy-3-methyldihydro-naphthalenone.[10]

Chrobisiamone A (**1**), colorless solid, $[\alpha]_D^{20}$ −19 (*c* 0.33, MeOH), showed the molecular formula, $C_{26}H_{24}O_8$, which was determined by HRESIMS [*m*/*z* 465.1549, $(M+H)^+$, Δ −0.2 mmu]. IR absorptions implied the presence of OH and/or NH (3100 cm^{-1}) and ketone (1720 and 1670 cm^{-1}) functionalities. UV absorptions at 238 (ε 17,500), 250 (14,400), and 282 (13,500) indicated a conjugated aromatic ring system. ^{1}H and ^{13}C NMR data are presented in Table 1. The ^{13}C NMR spectrum revealed 26 carbon signals due to 13 sp^2 quaternary carbons, one sp^3 quaternary carbon, five sp^2 methines, four methylenes, and three methyls. Among them, six quaternary carbons (δ_C 80.7, 161.1, 164.1, 165.2, 165.5, and 165.9) and four carbonyl carbons (δ_C 180.6, 192.6, 208.2, and 208.7) were ascribed to those bearing an oxygen atom.

The gross structure of **1** was deduced from extensive analyses of the two-dimensional NMR data, including the ^{1}H–^{1}H COSY and HMBC spectra in CD_3OD (Fig. 1). The HMBC spectrum revealed connectivities of two chromone structures (C-1 ∼ C-10 and C-1′ ∼ C-10′) and two acetonyl groups (C-11 ∼ C-13 and C-11′ ∼ C-13′) classed into two units A and B as shown in Figure 1.

The presence of two acetonyl groups at C-5 and C-5′ was supported by HMBC correlations for H_2-11 (δ_H 4.17) of C-5 (δ_C 134.1), C-6 (δ_C 120.2), and C-10 (δ_C 115.1), and H_2-11′ (δ_H 3.88 and 3.96) of C-5′ (δ_C 140.7), C-6′ (δ_C 115.9), and C-10′ (δ_C 112.5) as shown in Figure 1. HMBC correlations for H_2-14 (δ_H 2.93 and 3.06) of C-2 (δ_C 165.5), C-2′ (δ_C 80.7), C-3 (δ_C 113.8), and C-3′ (δ_C 49.0), H_3-14′ (δ_H 1.50) of C-2′ and C-3′ gave rise to the connectivity of two partial structures A and B through C-14 and C-2′ atoms. Thus, chrobisiamone A (**1**) was concluded to be an unique dimeric ring system consisting of 5-acetonyl-7-hydroxy-2-methylchromone and 5-acetonyl-7-hydroxy-2-methyl-2,3-hydrochromone.[11]

A plausible biogenetic pathway for chrobisiamone A (**1**) and cassiarin A (**3**) was proposed as shown in Scheme 1. Chrobisiamone A (**1**) might be derived from 5-acetonyl-7-hydroxy-2-methylchromone (**2**) by Michael addition of the chromone carbanion of C-14 to C-2′ of a second chromone. Treatment of 5-acetonyl-7-hydroxy-2-methylchromone (**2**) with ammonium acetate as the nitrogen source caused ring cyclization giving cassiarin A (**3**) in 46% yield. This biomimetic transformation might support a biogenetic pathway proposed for cassiarin A (**3**), which might be derived through an imine intermediate of **2** followed by cyclization.

Chrobisiamone A (**1**), 5-acetonyl-7-hydroxy-2-methylchromone (**2**), and anhydrobarakol (**4**) showed a moderate in vitro antiplasmodial activity[12] against parasite *Plasmodium falciparum* 3D7 (IC_{50} **1**: 2.6 μg/ml; **2**: 4.5 μg/ml; **4**: 7.8 μg/ml).

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