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Hybrid flavan-chalcones, aromatase and lipoxygenase inhibitors, from *Desmos cochinchinensis*

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ABSTRACT

Hybrid flavan-chalcones, desmosflavans A (**1**) and B (**2**), together with three known compounds, cardamonin (**3**), pinocembrin (**4**) and chrysin (**5**), were isolated from leaves of *Desmos cochinchinensis*. Cardamonin (**3**) and chrysin (**5**) exhibited potent antioxidant activity with 15.0 and 12.2 ORAC units. Desmosflavans A (**1**) and B (**2**), pinocembrin (**4**), and chrysin (**5**) were found to be inhibitors of aromatase with respective IC_{50} values of 1.8, 3.3, 0.9, and 0.8 μM. Desmosflavan A (**1**) inhibited lipoxygenase with the IC_{50} value of 4.4 μM. Desmosflavan A (**1**) exhibited cytotoxic activity with IC_{50} values of 0.29–3.75 μg/mL, while desmosflavan B (**2**) showed IC_{50} values of 1.71–27.0 μg/mL.

1. Introduction

Plants of the genus *Desmos* belong to the family Annonaceae, and are distributed in south Asian countries. Some species of *Desmos* are used as folk medicines in China in treating malaria and rheumatism, and they are rich in flavonoids that have various biological properties such as antitumor, anti-inflammatory, antiviral and anti-HIV activities (Liao et al., 1989; Wu et al., 2003). *Desmos cochinchinensis* Lour. is a shrub widely distributed in Asia. Constituents in *D. cochinchinensis* are flavonoids (Liao et al., 1989), flavones (Wu et al., 1994), cytotoxic fatty acid (Sun et al., 1995), and cytotoxic cycloartane triterpenoids (Sun et al., 1992). *D. cochinchinensis* is native to Southern Thailand, and it is locally used as herbal medicine to relieve hangover symptoms after consumption of alcoholic beverages. Our preliminary screening demonstrated that a leaf extract of *D. cochinchinensis* (at 20 μg/mL) could inhibit 99% of an aromatase activity; this prompted us to investigate bioactive constituents of this plant. In the present study, two new hybrid flavan-chalcones (Fig. 1), namely desmosflavans A (**1**) and B (**2**), together with three known compounds, cardamonin (**3**) or 2′,4′-dihydroxy-6′-methoxychalcone, pinocembrin (**4**), and chrysin (**5**), were isolated from the leaves of *D. cochinchinensis*. Aromatase and lipoxygenase inhibitory, radical scavenging, antioxidant, and cytotoxic activities of the isolated compounds are also reported.

2. Results and discussion

2.1. Structural determination

Fractionation of the CH_2Cl_2 extract of *D. cochinchinensis* by Sephadex LH-20 and preparative TLC led to the isolation of two new hybrid flavan-chalcones, desmosflavans A (**1**) and B (**2**), together with three known compounds, cardamonin (**3**), pinocembrin (**4**), and chrysin (**5**). Known compounds **3**–**5** were identified by analysis of spectroscopic data and by comparison of their spectroscopic data with those reported in the literature (Diaz Napal et al., 2009; Jaipetch et al., 1982; Ma et al., 2007).

Desmosflavan A (**1**) was obtained as a yellow amorphous solid with the molecular formula $C_{32}H_{26}O_8$ as indicated by APCI TOF MS spectrum. The IR absorption bands at 1603 and 3194 cm^{-1} indicated the presence of carbonyl and hydroxyl groups, respectively. The ^1H NMR (600 MHz, $CDCl_3$) of desmosflavan A (**1**)

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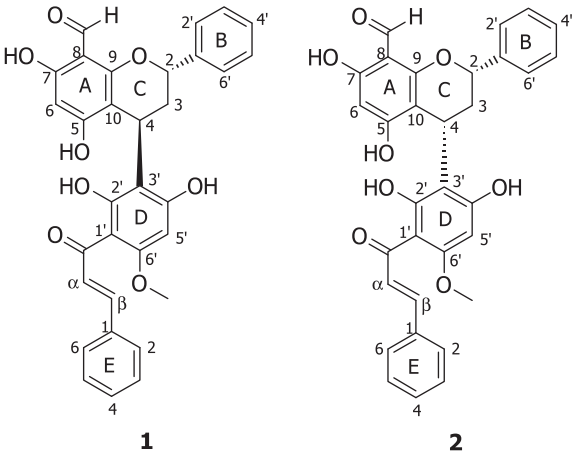

Fig. 1. Structure of the isolated compounds **1** and **2**.

displayed signals for two mono-substituted aromatic rings, a *trans* double bond, two sp^3 methines, one methylene, one aldehyde, and a methoxy group. Analysis of the ^1H NMR spectrum of **1** also indicated signals of two chelated hydroxyl protons at δ_H 15.04 (2′-OH, D) and 12.43 (7-OH, A). A coupling constant of 15.6 Hz suggested a *trans* double bond in **1**. Analysis of the ^{13}C NMR (150 MHz) and DEPT spectra also demonstrated the presence of 32 carbons in **1**, attributable to 15 sp^2 methine carbons (including one aldehyde), two sp^3 methines, one sp^3 methylene, one sp^3 methoxy, and 13 sp^2 non-protonated carbons, respectively. The HMBC correlations from protons (H-α and H-β) of a *trans* double bond to a ketone carbonyl (δ_C 193.0), H-α to C-1′ (D), and H-β to C-1 (E) and C-2/C-6 (E), suggested the presence of a chalcone unit in desmosflavan A (**1**). The ^1H NMR signal of H-5′ (D) in **1** was a singlet, implying the presence of a penta-substituted aromatic ring. The upfield shift (δ_H 5.91; δ_C 92.2) of H-5′ (D) was similar to that of a flavonoid or phloroglucinol, which contains a 1,3,5-trihydroxybenzene unit. The HMBC correlations from H-5′ (D) to C-1′, C-3′, C-4′, and C-6′; 6′-OMe to C-6′; and 2′-OH to C-1′, C-2′, and C-3′, establishing substituent positions on a penta-substituted aromatic ring D in a chalcone unit in **1**. The ^1H-^1H COSY spectrum of **1** established a partial structure H-2/H_2-3/H-4 of ring C. The chemical shift (δ_H 5.25; δ_C 76.6) of H-2 (C) suggested that it was a sp^3 methine attached to an oxygen atom, and possibly linked with an electron withdrawing group due to downfield ^1H resonance (δ_H 5.25). The HMBC correlations from H-2 (C) to C-1′ (B) and C-2′/ C-6′ (B) indicated H-2 (C) being attached to a mono-substituted aromatic ring B. Similar to a chalcone unit, H-6 (A) was a singlet, suggesting the presence of a penta-substituted aromatic ring A, and its upfield shift (δ_H 5.99; δ_C 96.2) again implied the presence of a 1,3,5-trihydroxybenzene unit. The HMBC correlations from H_2-3 (C) to C-10 (A); and H-4 (C) to C-9 (A) and C-10 (A) suggested H-4 (C) as being attached to an aromatic ring A. The above ^1H–^1H COSY and HMBC correlations also established that desmosflavan A (**1**) has a flavan unit in its molecule. The HMBC correlations from H-6 (A) to C-5, C-7, C-8,

Table 1
^1H and ^{13}C NMR spectroscopic data for compounds **1**–**2**.

Ring or position	**1**[c]		**1**[d]		**2**[c]	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
A/C						
2	5.25 (dd, 10.2, 2.6)	76.6	5.55 (t, 6.8)	75.9	5.12 (d, 11.4)	79.7
3	2.40 (dt, 14.3, 2.6); 2.34 (ddd, 14.3, 10.2, 5.5)	36.1	2.30 (m)	37.1	2.41 (q, 11.5); 2.53 (dd, 13.3, 7.6)	35.5
4	4.65 (dd, 5.5, 2.5)	25.6	4.74 (t, 3.9)	25.5	4.94 (t, 9.3)	26.1
5	–	163.0	–	164.3	–	163.7
6	5.99 (s)	96.2	5.94 (s)	94.0	5.98 (s)	97.4
7	–	165.2	–	163.8	–	164.2
8	–	106.0	–	105.1	–	106.3[b]
9	–	159.7	–	159.8	–	160.6
10	–	99.9	–	104.2	–	102.4
7-OH	12.43 (s)	–	12.40 (s)	–	12.22 (s)	–
8-CHO	10.19 (s)	192.0	10.18 (s)	191.2	10.14 (s)	192.0
B						
1′	–	139.9	–	141.5	–	139.4
2′,6′	7.37 (m)	126.0	7.44 (m)	125.8	7.45 (m)	125.9
3′,5′	7.41 (m)[a]	128.9[a]	7.40 (m)[a]	128.5[a]	7.40 (m)[a]	128.7[a]
4′	7.33 (m)	128.3	7.31 (m)	127.8	7.36 (m)	128.5
D						
1′	–	106.4	–	105.4	–	106.0[b]
2′	–	165.7	–	166.1	–	164.8
3′	–	107.6	–	110.7	–	106.8
4′	–	162.2	–	162.9	–	161.8
5′	5.91 (s)	92.2	6.16 (s)	91.3	5.94 (s)	92.6
6′	–	161.7	–	161.3	–	162.2
6′-OMe	3.91 (s)	55.9	3.95 (s)	55.3	3.89 (s)	56.0
2′-OH	15.04 (s)	–	14.91 (s)	–	15.42 (s)	–
C=O	–	193.0	–	192.4	–	193.0
α	7.90 (d, 15.6)	127.4	8.03 (d, 15.6)	127.7	7.90 (d, 15.5)	127.1
β	7.80 (d, 15.6)	142.8	7.77 (d, 15.6)	141.6	7.82 (d, 15.5)	143.4
E						
1	–	135.5	–	135.6	–	135.4
2,6	7.60 (m)	128.4	7.70 (m)	128.3	7.60 (m)	128.5
3,5	7.37 (m)[a]	128.6[a]	7.40 (m)[a]	128.9[a]	7.40 (m)[a]	128.9[a]
4	7.41 (m)	130.2	7.43 (m)	130.0	7.40 (m)	130.4

[a,b] Assignment may be interchanged in the same column.
[c] Acquired in $CDCl_3$ (600 MHz).
[d] Acquired in acetone-d_6 (400 MHz).