Aristolactams and Dioxoaporphines from *Fissistigma balansae* and *Fissistigma oldhamii*

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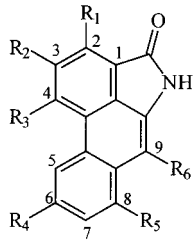
Investigation of extracts of *Fissistigma balansae* and *Fissistigma oldhamii* resulted in the isolation of 11 aristolactams—stigmalactam (**1**), piperolactam A (**2**), piperolactam C (**3**), aristolactam AII (**4**), aristolactam AIIIa (**5**), aristolactam BII (**6**), aristolactam BIII (**7**), aristolactam FII (**8**), goniothalactam (**9**), enterocarpam I (**10**), and velutinam (**11**)—as well as two dioxoaporphines, noraristolodione (**12**) and norcepharadione B (**13**). The new compound **1** was identified by spectral data interpretation. Compounds **1**−**13** were subjected to antiplatelet aggregation testing.

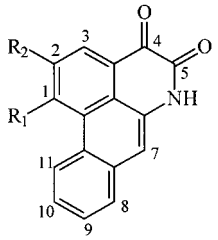
In previous work, *Fissistigma* species (Annonaceae) have been found to contain many bioactive natural substances, including aporphines,[1,2] oxoaporphines,[3−6] morphinandienones,[5] phenanthrenes,[2,4] a hydro-oxadiazine,[7] protoberberines,[2,8] tetrahydroprotoberberines,[2,8] and flavonoids and chalcones.[9,10] However, aristolactam and dioxoaporphine constituents have not been reported previously from this genus.

F. balansae (A. DC.) Merr. is a climbing shrub found in the southern part of mainland China and Vietnam.[11] *F. oldhamii* (Hemsl.) Merr. is a perennial climbing shrub indigenous to the broad-leafed tree zone of Taiwan.[12] The roots and stems of the latter species have been used in folk medicine to treat hepatomegaly, inflammation, cancer, and rheumatism, in Taiwan and southern China.[13] The crude extracts of these two plants showed significant activity in an antiplatelet aggregation assay. As part of our continuing investigation on the phytochemical and bioactive principles of Annonaceous plants, 11 aristolactams—stigmalactam (**1**), piperolactam A (**2**), piperolactam C (**3**), aristolactam AII (**4**), aristolactam AIIIa (**5**), aristolactam BII (**6**), aristolactam BIII (**7**), aristolactam FII (**8**), goniothalactam (**9**), enterocarpam I (**10**), and velutinam (**11**)—and two dioxoaporphines, noraristolodione (**12**) and norcepharadione B (**13**), were isolated from these two species. Among them, **1** is a new compound. We report herein the isolation, structure identification, and antiplatelet aggregation activities of these isolates.

Stigmalactam (**1**) was obtained as brownish yellow needles with mp 276−278 °C. The molecular formula, $C_{18}H_{15}O_5N$, was confirmed by HRMS measurement (*m*/*z* 325.0948 $[M]^+$, calcd 325.0950). The UV spectrum exhibited absorptions at 234, 254, 304, and 314 nm, which corresponded to a phenanthrene chromophore.[14] The presence of a phenolic hydroxyl group was indicated by the IR absorption at 3435 cm^{-1} and a UV spectral bathochromic shift in alkaline solution. The IR spectrum also showed absorptions for NH (3220 cm^{-1}) and C=O (1714 cm^{-1}) groups, respectively. Compound **1** exhibited physical and spectral features similar to those of other known aristolactams (**2**−**11**) from this genus. Therefore, it was determined that **1** possesses an aristolactam skeleton. In the ^1H NMR spectrum, an ABX pattern was observed at δ 8.64 (1H, d, J = 2.8 Hz), 7.72 (1H, d, J = 8.8 Hz), and 7.09 (1H, dd, J = 8.8, 2.8 Hz), attributable to H-5, H-8, and H-7, respectively. The other signals, including δ 7.17 (1H, s), 3.99 (3H, s), 4.19 (3H, s), and 4.41 (3H, s), were assigned to H-9, CH_3O-3, CH_3O-4, and CH_3O-2, respectively, and



1	R_1=R_2=R_3=OCH_3	R_4=OH	R_5=R_6=H
2	R_2=OCH_3	R_3=OH	R_1=R_4=R_5=R_6=H
3	R_1=R_2=R_3=OCH_3		R_4=R_5=R_6=H
4	R_3=OCH_3	R_2=OH	R_1=R_4=R_5=R_6=H
5	R_3=OCH_3	R_2= R_4=OH	R_1=R_5=R_6=H
6	R_2=R_3=OCH_3		R_1=R_4=R_5=R_6=H
7	R_2=R_3=R_4=OCH_3		R_1=R_5=R_6=H
8	R_1=R_3=OCH_3	R_2=OH	R_4=R_5=R_6=H
9	R_2=R_3=OCH_3	R_4=OH	R_1=R_5=R_6=H
10	R_3=R_5=R_6=OCH_3	R_2=OH	R_1= R_4=H
11	R_2=R_3=OCH_3	R_5=OH	R_1=R_4=R_6=H



12	R_1=OCH_3	R_2=OH
13	R_1=OCH_3	R_2=OCH_3

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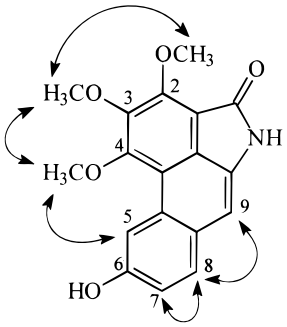

Figure 1. NOESY correlations for **1**.

Table 1. Effects of Compounds **1**−**13** on Platelet Aggregation Induced by Thrombin, AA, Collagen, and PAF in Washed Rabbit Platelets[a]

compound[b]	aggregation (%)			
	thrombin	AA	collagen	PAF
1	91.9 ± 0.2*	14.2 ± 0.9***	10.1 ± 1.5***	70.8 ± 2.8***
2	84.3 ± 4.5	0.0 ± 0.0***	0.0 ± 0.0***	84.1 ± 2.0*
3	83.7 ± 3.9	7.8 ± 6.8***	0.0 ± 0.0***	6.1 ± 5.0***
4	90.0 ± 0.6*	86.3 ± 1.0	82.5 ± 1.0***	78.3 ± 4.5*
5	90.6 ± 1.4	56.9 ± 9.6**	39.6 ± 7.3***	80.7 ± 1.3***
6[c]				
7	89.3 ± 1.4	71.9 ± 1.4***	0.0 ± 0.0***	60.6 ± 13.8*
8	83.9 ± 3.5*	8.5 ± 3.2***	9.7 ± 3.2***	6.7 ± 2.9***
9	89.8 ± 1.1	13.6 ± 0.9***	10.5 ± 2.7***	67.3 ± 3.1***
10	86.5 ± 5.5	2.2 ± 1.1***	15.2 ± 1.6***	43.0 ± 11.3***
11	92.1 ± 0.2	37.5 ± 16.3**	18.4 ± 1.4***	87.3 ± 2.2
12	88.7 ± 1.0*	65.8 ± 2.3***	40.6 ± 7.7***	82.5 ± 3.0*
13[c]				
aspirin		0.0 ± 0.0	87.8 ± 1.5	90.4 ± 1.1
control	91.7 ± 03	89.6 ± 1.3	90.1 ± 0.9	89.9 ± 0.9

[a] Platelets were preincubated with DMSO (0.5%, control) or a test compound at 37 °C for 3 min, then thrombin (0.1 U/mL), AA (10 μM), collagen (10 μg/mL), or PAF (2 ng/mL) was added. Percentages of aggregation are presented as mean ±S.E. (n = 3−5); *p <0.05, **p <0.01, ***p <0.001 as compared with the respective control. [b] Dose was 100 μg/mL. [c] Promoted platelet aggregation.

were confirmed by 2D NMR experiments. The NOESY spectrum of **1** showed correlations between CH_3O-2/CH_3O-3, CH_3O-3/CH_3O-4, CH_3O-4/H-5, and H-7/H-8, as well as between H-8/H-9 (Figure 1). The ^{13}C NMR spectrum showed the expected four methines, 11 quaternary carbons (including a carbonyl carbon at δ 167.9), and three methoxyl signals. On the basis of these results, **1** was established structurally as 10-amino-6-hydroxy-2,3,4-trimethoxyphenanthrene-1-carboxylic acid lactam, which has been given the trivial name, stigmalactam.

The known compounds **2**−**13** were identified by comparison of physical and spectroscopic data (UV, IR, NMR and MS) with literature values.[14−21] The antiplatelet effects of compounds **1**−**13** were studied on the aggregation of washed rabbit platelets induced by thrombin (0.1 U/mL), arachidonic acid (AA) (10 μM), collagen (10 μg/mL), or platelet-activating factor (PAF) (2 ng/mL). The results are shown in Table 1. At a concentration of 100 μg/mL, compounds **2**, **3**, and **7** completely inhibited platelet aggregation induced by collagen, and **2** also showed complete inhibition of AA-induced platelet aggregation. Compounds **1**, **8**, **9**, and **10** were strong inhibitors of platelet aggregation induced by AA and collagen, and **8** also exhibited strong inhibition of PAF-induced platelet aggregation. Compound **3** showed strong inhibitory effects on platelet aggregation induced by AA and PAF, while compound **11** showed strong inhibition of platelet aggregation induced by collagen. Both compounds **5** and **12** showed significant inhibition of platelet aggregation induced by collagen, with **5** exhibiting significant inhibition of AA-induced platelet aggregation and **12** showing slight but significant inhibition of AA-induced platelet aggregation. Compounds **7** and **10** significantly inhibited PAF-induced platelet aggregation, and **7** showed weak but significant inhibition of AA-induced platelet aggregation. Compounds **6** and **13**, on the other hand, promoted the platelet aggregation caused by these inducers. Moreover, compounds **1**, **2**, **8**, **9**, and **10** showed significant inhibitory effects against AA and collagen at 50 μM and even at 20 μM (Table 2).

Table 2. Effects of Compounds on Platelet Aggregation Induced by AA and Collagen in Washed Rabbit Platelets[a]

compound	(μg/mL)	aggregation (%)	
		AA	collagen
1	50	18.8 ± 4.3***	30.8 ± 8.7***
	20	46.4 ± 15.3**	72.9 ± 1.1***
2	50	14.7 ± 3.9***	22.2 ± 8.0***
	20	83.5 ± 1.1**	84.2 ± 1.1***
3	50	89.4 ± 1.2	82.0 ± 2.8**
7	50	86.6 ± 1.0**	59.1 ± 11.6*
8	50	16.5 ± 1.8***	14.5 ± 0.7***
	20	52.5 ± 10.9**	41.5 ± 8.3***
	10	85.4 ± 1.3**	81.7 ± 0.5***
9	50	50.4 ± 12.4**	17.3 ± 2.3***
	20	81.6 ± 2.6**	75.9 ± 0.7***
	10	85.9 ± 2.1	83.0 ± 1.3***
10	50	13.5 ± 6.2***	25.8 ± 1.9***
	20	46.4 ± 15.3**	72.9 ± 1.1***
	10	83.5 ± 3.3	83.7 ± 0.9***
11	50	77.5 ± 5.5	65.4 ± 7.8**
12	50		72.0 ± 5.2**
	20		84.7 ± 0.5***
	control	89.6 ± 1.3	90.1 ± 0.9

[a] Platelets were preincubated with DMSO (0.5%, control) or a test compound at 37 °C for 3 min, then AA (10 μM) or collagen (10 μg/mL) was added. Percentages of aggregation are presented as mean ±S.E. (n = 3−5); *p <0.05, **p <0.01, ***p <0.001 as compared with the respective control.

Exogenous AA can be converted into prostaglandin endoperoxides by platelet cyclooxygenase and then, in turn, these are converted by thromboxane synthase to thromboxane A_2, which is an important mediator for platelet aggregation. Collagen may also trigger platelet aggregation by increasing the formation of thromboxane A_2.[22] Aspirin is a cyclooxygenase inhibitor,[23] and it can completely inhibit AA-induced platelet aggregation, but not aggregation by other inducers. Thus, the mechanism of antiplatelet effects of these aristolactams and dioxoaporphines appears to be different from that of aspirin. The antiplatelet effects of the present isolates may be due to the inhibition of thromboxane A_2 formation because the types of platelet aggregation induced by AA and collagen were the most easily inhibited.

From the results obtained, the following structure−activity conclusions can be drawn in terms of antiplatelet effects. First, the aristolactams containing three oxygenated substituents in ring A and no substitution in ring D (such as **3** and **8**) led to the strong inhibition of PAF-induced platelet aggregation. When a hydroxyl group was present in ring D (as in **1**), the antiplatelet activity was reduced. Second, aristolactams or dioxoaporphines containing two methoxyl groups in ring A and no substitution in ring D (as in **6** and **13**) promoted the platelet aggregation caused by these inducers. If the 4-methoxyl group was substituted by a hydroxyl group (as in **2**), this increased the inhibitory effects on platelet aggregation induced by AA and collagen. If a 3-methoxyl group was present instead of a hydroxyl group (as in **4** or **12**), it only slightly increased

the antiplatelet activity. Third, none of the tested compounds significantly inhibited thrombin-induced platelet aggregation. Finally, like previous antiplatelet-aggregation data for aporphines,[24−27] small changes in the aristolactam skeleton resulted in quite different activities.

Experimental Section

General Experimental Procedures. Melting points were determined using a Yanagimoto micromelting point apparatus and are uncorrected. The UV spectra were obtained on a Hitachi 200-20 spectrophotometer, and IR spectra were measured on a Hitachi 260-30 spectrophotometer. ^{1}H NMR (400 MHz) and NOESY spectra were obtained on a Varian NMR spectrometer. FABMS and EIMS were collected on a JEOL JMS-SX/SX 102A mass spectrometer or Quattro GS/MS spectrometer having a direct inlet system. HREIMS were measured on a JEOL JMS-HX 110 mass spectrometer. Si gel 60 (Merck, 230−400 mesh) was used for column chromatography. Precoated Si gel plates (Merck, Kieselgel 60 F_{254}, 0.20 mm) were used for analytical TLC, and precoated Si gel plates (Merck, Kieselgel 60 F_{254}, 0.50 mm) were employed for preparative TLC. The spots were detected by spraying with Dragendorff's reagent or 50% H_2SO_4 and then heating on a hot plate.

Plant Material. The twigs of *F. balansae* were collected from Xishuangbanna, Kunming, the southern part of Yunnan Province, People's Republic of China, in May 1995. A voucher specimen is deposited in the Laboratory of Phytochemistry, Kunming Institute of Botany, Academia Sinica, Kunming, People's Republic of China. The stems of *F. oldhamii* were collected from Wulai, Taipei Hsien, Taiwan, in December 1981. A voucher specimen is deposited in the Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung, Taiwan.

Extraction and Isolation. Twigs of *F. balansae* (2.14 kg) were extracted repeatedly with EtOH at room temperature and the solvent evaporated under reduced pressure. The EtOH extract (144.5 g) was then partitioned to yield $CHCl_3$, *n*-BuOH, and aqueous solutions, respectively. The $CHCl_3$ solution was extracted with 3% HCl to give a neutral $CHCl_3$ layer and an acidic aqueous solution. The neutral $CHCl_3$ layer was concentrated and chromatographed over Si gel 60 and eluted with $CHCl_3$−EtOAc−MeOH mixtures of increasing polarity to give 14 fractions. Fraction 7, which eluted with acetone−*n*-hexane (1:4), was further separated and purified by Si gel column chromatography and preparative TLC (Si gel, acetone−*n*-hexane, 1:2) to give **3** (4 mg) (acetone−*n*-hexane, 1:4, R_f = 0.46), **6** (5.5 mg) (acetone−*n*-hexane, 1:4, R_f = 0.37), **7** (3 mg) (acetone−*n*-hexane, 1:4, R_f = 0.33), **13** (5 mg) (acetone−*n*-hexane, 1:4, R_f = 0.29), **2** (10 mg) (acetone−*n*-hexane, 1:4, R_f = 0.21), and **12** (4.5 mg) (acetone−*n*-hexane, 1:4, R_f = 0.14), respectively. Fractions 8−10, eluting with acetone−*n*-hexane (1:3), were further separated and purified by Si gel column chromatography and preparative TLC (Si gel, acetone−*n*-hexane, 1:1) to afford **9** (3 mg) (acetone−*n*-hexane, 1:4, R_f = 0.13) and **5** (5 mg) ($CHCl_3$−MeOH, 6:1, R_f = 0.58), respectively.

The crude MeOH extract (78 g) of the stems of *F. oldhamii* (1.25 kg) was directly chromatographed over Si gel 60 and eluted with $CHCl_3$−MeOH mixtures of increasing polarity to give 30 fractions. Fraction 9, eluted with $CHCl_3$−MeOH (100:1), was further separated and purified by Si gel column chromatography and preparative TLC (Si gel, $CHCl_3$−MeOH, 12:0.5) to afford **7** (10 mg), **8** (3.5 mg) ($CHCl_3$−MeOH, 12:0.5, R_f = 0.43), and **4** (4 mg) ($CHCl_3$−MeOH, 20:1, R_f = 0.47), respectively. Fractions 13−27, eluting with *n*-hexane−EtOAc (1:3), was further separated and purified by Si gel column chromatography and preparative TLC (Si gel, *n*-hexane−EtOAc 9:1), to afford **2** (10 mg), **11** (5 mg) (acetone−*n*-hexane, 1:4, R_f = 0.29), **10** (10 mg) (acetone−*n*-hexane, 1:4, R_f = 0.21), and **1** (4.5 mg) (acetone−*n*-hexane, 1:4, R_f = 0.14), respectively.

Stigmalactam (1): brownish yellow needles; mp 276−278 °C; UV (EtOH) λ_{max} (log ϵ) 234 (4.58), 254 (4.56), 304 (4.30), 314 (4.32) nm; IR (neat) ν_{max} 3435, 3220, 1714, 1464, 1404, 1377, 1271, 1047 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.99 (3H, s, CH_3O-3), 4.19 (3H, s, CH_3O-4), 4.41 (3H, s, CH_3O-2), 7.09 (1H, dd, J = 2.8, 8.8 Hz, H-7), 7.17 (1H, s, H-9), 7.72 (1H, d, J = 8.8 Hz, H-8), 8.64 (1H, d, J = 2.8 Hz, H-5); ^{13}C NMR (CD_3OD, 100 MHz) δ 61.4 (CH_3O-4), 62.1 (CH_3O-3), 63.2 (CH_3O-2), 108.0 (C-9), 112.2 (C-5), 117.2 (C-4b), 117.5 (C-7), 126.8 (C-1), 127.2 (C-4a), 128.6 (C-10a), 129.3 (C-8a), 131.1 (C-8), 133.0 (C-10), 147.5 (C-3), 151.2 (C-6), 156.9 (C-2), 158.7 (C-4), 167.9 (CO); EIMS *m/z* [M$^+$] 325 (71), 310 (21), 296 (12), 252 (33), 196 (35), 131 (44), 91 (100); HREIMS *m/z* 325.0948 (calcd for $C_{17}H_{13}O_4N$ 325.0950).

Piperolactam A (2): yellow powder; mp >300 °C; EIMS *m/z* [M$^+$] 265; identified by comparison with literature values.[13]

Piperolactam C (3): yellow crystals; mp 189−190 °C; EIMS *m/z* [M$^+$] 309; identified by comparison with literature values.[13]

Aristolactam AII (4): pale yellow powder; mp 270−272 °C; EIMS *m/z* [M$^+$] 265; identified by comparison with literature values.[14,15]

Aristolactam AIIIa (5): yellow crystals; mp > 300 °C; EIMS *m/z* [M$^+$] 281; identified by comparison with literature values.[13]

Aristolactam BII (6): pale yellow crystals; mp 264−265 °C; EIMS *m/z* [M$^+$] 279; identified by comparison with literature values.[14,15]

Aristolactam BIII (7): yellow-green powder; mp 264−265 °C; EIMS *m/z* [M$^+$] 309; identified by comparison with literature values.[14,15]

Aristolactam FII (8): pale orange powder; mp 226−227 °C; EIMS *m/z* [M$^+$] 295; identified by comparison with literature values.[16]

Goniothalactam (9): yellow powder; mp 238−240 °C; EIMS *m/z* [M$^+$] 295; identified by comparison with literature values.[17]

Enterocarpam I (10): pale yellow needles; mp 214−215 °C; EIMS *m/z* [M$^+$] 325; identified by comparison with literature values.[18]

Velutinam (11): brownish yellow needles; mp 268−269 °C; EIMS *m/z* [M$^+$] 295; identified by comparison with literature values.[19]

Noraristolodione (12): orange needles; mp >300 °C; EIMS *m/z* [M$^+$] 293; identified by comparison with literature values.[13,20]

Norcepharadione B (13): orange needles; mp >300 °C; EIMS *m/z* [M$^+$] 307; identified by comparison with literature values.[13]

Platelet Aggregation Bioassays. The platelet aggregation assays were carried out according to the previous literature.[24−27]

Data Analysis. The experimental results are expressed as means ± S. E. and accompanied by the number of observations. A one-way analysis of variance (ANOVA) was used for multiple comparison, and if there was significant variation between treatment groups, then the mean values for inhibitors were compared with those for control by

Student's *t*-test, and *p* values of less than 0.05 were considered to be statistically significant.[28]

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