Notes

Bioactive Iridoids and a New Lignan from *Allamanda cathartica* and *Himatanthus fallax* from the Suriname Rainforest[1]

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Bioassay-guided fractionation of the EtOAc extract of both *Allamanda cathartica* and *Himatanthus fallax* (Apocynaceae) using the Sc-7 yeast strain resulted in the isolation of the weakly cytotoxic isoplumericin and plumericin. In addition, the new lignan 7(*R*)-methoxy-8-*epi*-matairesinol and three known compounds, plumieride, matairesinol, and pinoresinol, were isolated from *H. fallax*.

As previously described,[2] we have embarked on a program to discover and develop potential therapeutic agents from the Surinamese rainforest and, in the process, to provide economic arguments for the preservation of this valuable resource. Plant collections under this program are being made independently by Conservation International, Suriname, and by the Missouri Botanical Garden, with the former collecting on an ethnobotanical basis and the latter on a phytochemical basis. Plant extracts are prepared at Bedrijf Geneesmiddelen Voorziening Suriname (BGVS). Work at Virginia Polytechnic Institute and State University (VPI&SU) is centered around the discovery of potential anticancer agents, and the Sc-7 strain of *Saccharomyces cerevisiae* (yeast) is used as a primary assay tool in this work. This strain shows growth inhibition by cytotoxic agents,[3] and activities are expressed as IC_{12} values, which are the dosages needed to produce an inhibition zone of 12 mm under defined conditions.[2]

As a part of our collaborative work, the plants *Allamanda cathartica* L. and *Himatanthus fallax* (Muell. Arg.) Plumel (Apocynaceae) were collected from the central region of Suriname as part of the phytochemical collection strategy by Missouri Botanical Garden. An EtOAc extract of *A. cathartica* had an IC_{12} value of 690 μg/mL, and a similar extract of *H. fallax* had an IC_{12} value of about 3320 μg/mL against the Sc-7 yeast strain, and fractionation studies were initiated.

Previous work on *A. cathartica* has included the isolation of the iridoid lactones plumericin and isoplumericin[4] and of plumieride coumarate and plumieride coumarate glucoside.[5] Plumericin and isoplumericin have also been isolated from *Allamanda doniana*,[6] while the occurrence of iridoids in various *Allamanda* sp. has been surveyed.[7] Studies on *Himatanthus* sp. have included the isolation of plumericin and isoplumericin, from *H. phagedaenica*,[8] and *H. obovatus*.[6]

Table 1. ^{13}C-NMR Data (δ values) for Compounds **1** and **2**[a]

carbon	compound **1**	compound **2**
1	101.7	102.3
3	152.6	152.7
4	108.9	109.4
5	38.2	38.4
6	141.1	141.1
7	126.1	126.4
8	104.9	104.6
9	53.7	53.7
10	83.8	80.3
11	125.7	127.4
12	167.4[b]	168.2[b]
13	148.2	145.3
14	14.8	16.1
*C*OOCH$_3$	166.7[b]	166.7[b]
COO*C*H$_3$	51.6	51.7

[a] Obtained in $CDCl_3$. Assignments made by a combination of DEPT and HETCOR data and comparison with the spectrum of plumenoside.[10] [b] The signals in each column may be interchanged.

Fractionation of *A. cathartica* involved liquid−liquid partition, in which the bioactivity went successively into the aqueous MeOH phase of a hexane−80% aqueous MeOH partition and into the $CHCl_3$ phase of a $CHCl_3$−60% aqueous MeOH partition. Purification on a Sephadex LH-20 column yielded the active material in a CH_2Cl_2−hexane (4:1) fraction, and final purification by vacuum liquid chromatography (VLC) over Si gel with Me_2CO−hexane as eluent, by column chromatography over Si gel, and by preparative TLC gave the two active products **1** (7 mg) and **2** (60 mg), with IC_{12} values of 42 and 74 μg/mL, respectively.

The structures of the two compounds were elucidated as isoplumericin (**1**) and plumericin (**2**) on the basis of their spectroscopic data, and specifically by comparison of their ^{1}H-NMR data with those in the literature.[9] Complete assignments for the ^{13}C-NMR spectra of both compounds (Table 1) were made for the first time, utilizing DEPT and HETCOR experiments as well as comparison with the ^{13}C-NMR data of plumenoside.[10] As noted above, both compounds have previously been isolated from *A. cathartica*.[4]

Fractionation of *H. fallax* followed lines similar to that

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Table 2. ^{1}H- and ^{13}C-NMR Data (δ values) for Compound **6**[a]

position	δ_H[b]	δ_C[c]
1		133.4 (0)[d]
2	6.85 (m)	108.3 (1)
3		145.2 (0)[e]
4		146.5 (0)[f]
5	6.85 (m)	114.4 (1)
6	6.85 (m)	118.7 (1)
7	5.23 (d, J = 7.2)	82.3 (1)
8	3.08 (dd, J = 7.2, 8.7)	55.9 (1)
9		172.5 (0)
1′		131.3 (0)[d]
2′	6.66(m)	111.2 (1)
3′		144.1 (0)[e]
4′		146.4 (0)[f]
5′	6.85 (m)	114.3 (1)
6′	6.67 (m)	121.2 (1)
7′	2.55 (dd, J = 10.6, 13.7, β)	34.5 (2)
	2.76 (dd, J = 5.3, 13.7, α)	
8′	2.91 (m)	44.2 (1)
9′	3.79 (dd, J = 6.7, 8.7, β)	72.9 (2)
	4.08 (dd, J = 6.4, 8.7, α)	
7 OCH_3	3.67	51.8 (3)
3,3′ OCH_3	3.87, 3.88	55.8 (3), 55.9 (3)
4,4′ OH	5.52, 5.60	

[a] Obtained in $CDCl_3$. [b] J in Hz. [c] Carbon type as determined by DEPT spectra: 0 = quaternary, 1 = methine, 2 = methylene, 3 = methyl. [d,e,f] Signals for carbons with similar shifts may be interchanged.

of *A. cathartica*, and yielded six products. Two were identified again as the compounds **1** and **2**, and three inactive known compounds were identified as plumieride (**3**), pinoresinol (**4**), and matairesinol (**5**) based on comparison of their mps, $[\alpha]_D$, UV, and ^{1}H- and ^{13}C-NMR spectra with those in the literature.[10−13] The last compound was identified as the new lignan **6**, 7(*R*)-methoxy-8-*epi*-matairesinol, on the basis of the evidence outlined below.

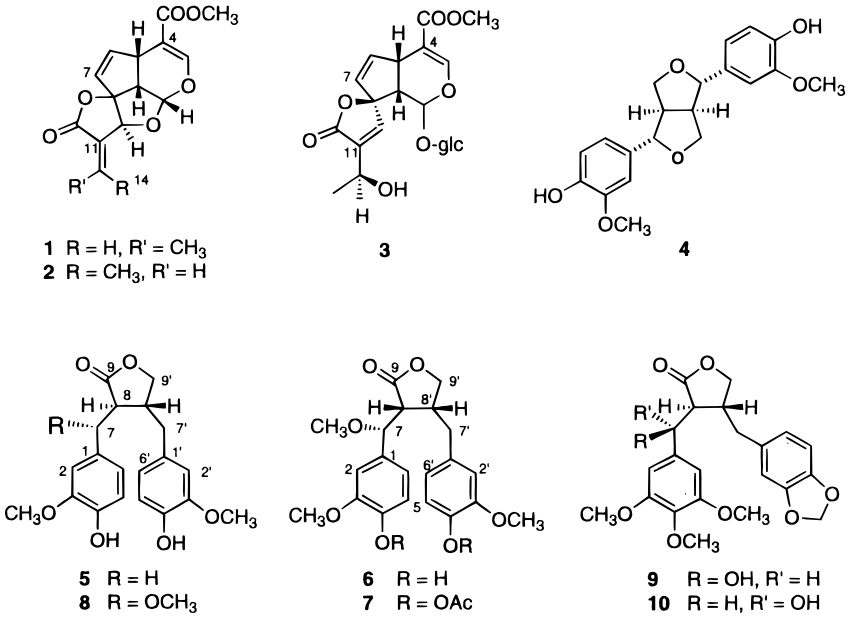
The HREIMS of **6** showed an M^+ at *m/z* 388.152, consistent with the molecular formula $C_{21}H_{24}O_7$. Its ^{13}C-NMR spectrum (Table 2) indicated the presence of three OMe groups, a lactone carbonyl (δ_c 172.5 ppm), and 12 aromatic carbon resonances, six of which were fully substituted. The remaining carbons (1 CH_2, 1 CH_2O, 2 CH, and 1 OCH) supported the assignment of **6** as a diaryl butyrolactone-type lignan.[13] The ^{1}H- and ^{13}C-NMR assignments (Table 2) were made on the basis of ^{1}H−^{1}H decoupling in different solvents, TOCSY, DEPT, and HETCOR experiments. The oxygenated CH group (δ_H 5.23 ppm, δ_C 82.3 ppm) was assigned to position 7 based on the coupling of its proton with H-8 (3.08 ppm, dd, J = 7.2, 8.7 Hz) rather than with H-8′ (2.91 ppm, m). The C-7 substituent was assigned as a methoxyl group (δ_H 3.67, δ_C 51.8) rather than a hydroxyl group, based on the fact that the chemical shift of H-7 was essentially unchanged after acetylation of **6** to form its diacetate **7**. This assignment was further supported by correlations of the C-7 OMe group with the two H-7′ protons and with H-8′ in a NOESY experiment. The chemical shifts of the aryl carbons supported a 4,4′-dihydroxy-3,3′-dimethoxy substitution.[14] The NOE correlations of the two resolved aryl protons at δ 6.66 and 6.67 with H-7′β and H-7′α assign them to the 2′ and 6′ positions, respectively.

The CD spectrum of **6** was similar to those of the rare cis-fused-type lignans.[15] To determine the stereochemistry at position 7 compound **6** was allowed to epimerize in 3% methanolic KOH solution.[16] The resulting epimer **8** had a CD spectrum similar to those of the more common trans-fused lignans, particularly those with the 7-position oxygenated as in podorhizol (**9**).[16,17] The C-7 methoxyl group was assigned the α-configuration based on comparison of the $J_{7,8}$ value of **8** (7.9 Hz) with those of epipodorhizol (**10**) with a 7α-OH group (7.7−7.9 Hz) and its 7β-OH isomer podorhizol (**9**) (1.6−2.9 Hz) (Chart 1).[18−20]

Isoplumericin and plumericin are known to have antifungal, algicidal, and barnicidal activities,[5,6,21] and, in addition, plumericin possesses antimicrobial activity.[22] In a cytotoxicity assay with the Madison lung carcinoma (M109) cell line, compounds **1** and **2** showed IC_{50} values of 25 and 100 μg/mL, respectively, suggesting that these compounds are not potent enough to be considered as development candidates.

The group of rare spirolactone-containing iridoids exemplified by plumericin and isoplumericin seems to be restricted in its occurrence to the family Apocynaceae, and mainly to the two genera *Allamanda* and

Chart 1



Plumeria,[7] although plumericin has also been reported from *Nerium indicum*.[23] Although lignans are known to occur in the Apocynaceae,[24] this is the first isolation of lignan derivatives from a *Himatanthus* species.

Experimental Section

General Experimental Procedures. The CD spectrum was recorded on a JASCO J720 spectropolarimeter. NMR spectra were recorded in $CDCl_3$ on a Varian Unity 400 NMR instrument at 399.951 MHz for ^1H and 100.578 MHz for ^{13}C, using standard Varian pulse sequence programs. LRMS were taken on a VG 7070 E-HF at VPI&SU, and exact mass measurements were obtained at the Nebraska Center for Mass Spectrometry. Other conditions were as previously described.[25]

Yeast Bioassay. The bioassay was carried out as previously described.[2]

Plant Collection and Extraction of *A. cathartica* and *H. fallax*. Leaves of *A. cathartica* and stems of *H. fallax* were collected in July 1994, near Asindopo Village, Suriname, and were assigned collection numbers EV1887 and EV1874, respectively. Voucher specimens are preserved at the National Herbarium of Suriname and at the herbarium of the Missouri Botanical Garden. Extraction of ca. 500 g of dried EV1887 at BGVS yielded 27.4 g of EtOAc extract as BGVS E-940241, and extraction of ca. 500 g of dried EV1874 at BGVS yielded 16.5 g of EtOAc extract as BGVS E-940200.

Isolation of Plumericin (1) and Isoplumericin (2) from *A. cathartica*. The bioactive EtOAc extract (IC_{12} 690 μg/mL, 27.4 g) was dissolved in 250 mL of 80% aqueous MeOH and defatted with hexane (150 mL × 4). The aqueous MeOH fraction was diluted with H_2O until a 60% aqueous MeOH mixture was produced, and this was then partitioned with $CHCl_3$ (150 mL × 4) to afford 6.0 g of the bioactive $CHCl_3$-soluble extract. This fraction was purified by chromatography on Sephadex LH-20 (5 × 50 cm) using the solvents hexane−CH_2Cl_2 (1:4, 1 L), CH_2Cl_2−Me_2CO (3:2, 1 L), CH_2Cl_2−Me_2CO (1:4, 1 L), and MeOH (2 L). The active fraction (0.5 g) eluted with hexane−CH_2Cl_2 (1:4) was separated on a Si gel column (25 g) eluted with 1% Me_2CO in $CHCl_3$, then with 2% Me_2CO in $CHCl_3$, and finally with MeOH. Fractions 6 and 7, eluted with 1% Me_2CO in $CHCl_3$ (43 mg), were separated by preparative TLC (Si gel, 10% Me_2CO in $CHCl_3$) to obtain isoplumericin (**1**, 7 mg). Fractions 8−12 (2% Me_2CO in $CHCl_3$, 75 mg) were crystallized from CH_2Cl_2−MeOH to afford plumericin (**2**, 60 mg).

Isolation of Plumericin (1), Isoplumericin (2), Plumieride (3), Pinoresinol (4), Matairesinol (5), and 7(*R*)-Methoxy-8-*epi*-matairesinol (6) from *H. fallax*. The bioactive EtOAc extract was treated as above, and the active fraction, eluted with hexane−CH_2Cl_2 (1:4; 1.2 g) from the Sephadex LH-20 chromatography (5 × 50 cm column), was crystallized from CH_2Cl_2−MeOH to afford 0.4 g of inactive crystals. The bioactive supernatant (0.8 g) (IC_{12} 890 μg/mL) was fractionated by VLC (3.5 cm × 4.5 cm, 30 g Si gel) eluted with hexane−Me_2CO mixtures. The bioactive fraction eluted with 20% Me_2CO in hexane (161 mg) was further purified using a Si gel (15 g) flash column eluted with 5% Me_2CO in $CHCl_3$. The active fractions (32 mg) were separated by preparative TLC (Si gel, 10% Me_2CO in $CHCl_3$) to obtain isoplumericin (**1**, 1.2 mg) and plumericin (**2**, 2.6 mg).

Fractions eluted with 50% Me_2CO in hexane (110 mg) were subjected to preparative TLC (Si gel, 20% Me_2CO in $CHCl_3$) to afford **6** (12 mg, R_f 0.65). The more polar band (15 mg, R_f 0.5) provided pinoresinol (**4**, 6 mg) and matairesinol (**5**, 5 mg) after HPLC separation (C_{18} Si gel, MeOH−H_2O, 1: 1).

Fractions eluted from Sephadex LH-20 with CH_2Cl_2−Me_2CO, 3:2 (0.5 g), were chromatographed by VLC (Si gel, hexane−Me_2CO−MeOH mixtures), and fractions eluted with Me_2CO (250 mg) were further purified by preparative TLC (Si gel, $CHCl_3$−MeOH 85:15) to afford plumieride (**3**, 150 mg).

Isoplumericin (1): colorless needles, mp 199−200 °C (CH_2Cl_2−MeOH) (lit.[9] mp 200.5−201.5 °C); $[\alpha]^{26}_D$ +189° (*c* 0.61, $CHCl_3$) (lit.[9] $[\alpha]^{29}_D$ +216.4°); ^{13}C-NMR data, see Table 1.

Plumericin (2): colorless needles, mp 205−206 °C (CH_2Cl_2−MeOH) (lit.[9] mp 211.5−212.5 °C); $[\alpha]^{26}_D$ +173° (*c* 1.10, $CHCl_3$) (lit.[9] $[\alpha]^{26}_D$ +197.3°); ^{13}C-NMR data, see Table 1.

Plumieride (3): colorless crystals; mp 225−226 °C (MeOH) (lit.[26] mp 224−225 °C); $[\alpha]^{26}_D$ −68° (*c* 0.90, MeOH) (lit.[26] $[\alpha]^{26}_D$ −114°(H_2O)).

Pinoresinol (4): yellowish gum; $[\alpha]^{26}_D$ +70° (*c* 0.60, MeOH) (lit.[27] $[\alpha]^{26}_D$ +64°).

Matairesinol (5): yellowish gum; $[\alpha]^{26}_D$ −45° (*c* 1.0, MeOH) (lit.[13] $[\alpha]^{26}_D$ −50°).

(7*R*)-Methoxy-8-*epi*-matairesinol (6): white crystals, mp 160−162 °C (C_6H_6); $[\alpha]^{26}_D$ +29.57°(*c* 0.71, MeOH); UV (MeOH) λ_{max} (ϵ) 214 (11 600), 225 (4900), 280 (4400) nm; (NaOMe) λ_{max} (ϵ) 214 (1200), 245 (6000), 294 (4200) nm; CD (MeOH, *c* 0.1) λ_{max} ($\Delta\epsilon$) 218 (−2.6), 240 (+2.4), 253 (−1.2), 279 (+3.8) nm; ^1H and ^{13}C NMR in $CDCl_3$, see Table 2; ^1H NMR (C_6D_6) δ 6.39 (1H, d, J = 1.9 Hz, H-2′) 6.48 (1H, dd J = 1.9, 8 Hz, H-6′), 6.93 (1H, d, J = 8 Hz, H-5′), 6.94 (1H, m, H-2), 6.97 (1H, dd J = 1.9, 8 Hz, H-6), 7.01 (1H, d J = 8 Hz, H-5); EIMS *m*/*z* 388 (M^+, 58), 249 (12), 191(20), 180 (74), 151 ($C_8H_7O_3$, 57), 137 ($C_8H_9O_2$, 75), 122 ($C_7H_6O_2$, 9), 99 ($C_5H_7O_2$, 100), 77 (6); HREIMS *m*/*z* 388.152 (M^+), calcd for $C_{21}H_{24}O_7$, 388.152.

7(*R*)-Methoxy-8-*epi*-matairesinol Diacetate (7). Compound **6** (2.0 mg) in pyridine (2.0 mL) was treated with Ac_2O (0.2 mL) for 24 h at room temperature. Evaporation of the resulting solution under a stream of argon yielded chromatographically homogeneous **7** (2.0 mg): ^1H NMR ($CDCl_3$) δ 1.86 (3H, s, $COCH_3$), 2.55 (1H, dd, J = 10.4, 13.5 Hz, H-7′β), 2.65 (1H, m , H-8′), 2.76 (1H, dd, J = 5.3, 13.5 Hz, H-7′α), 3.05 (1H, dd, J = 7.2, 8.7 Hz, H-8), 3.28 (3H, s, OCH_3-7), 3.30 (6H, s, 2 × OCH_3), 3.84 (1H, dd, J = 6.4, 8.8 Hz, H-9′β), 3.94 (1H, dd, J = 6.7, 8.8 Hz, H-9′α), 5.59 (1H, d, J = 7.2 Hz, H-7β), 6.13 (1H, d, J = 1.9 Hz, H-2′), 6.49 (2H, m, H-6, H-6′), 6.90 (1H, d, J = 8 Hz, H-5′), 7.00 (1H, br s, H-2), 7.1 (1H, d, H-5).

7(*R*)-Methoxymatairesinol (8). Compound **6** (4 mg) was dissolved in 3% methanolic KOH (3 mL), and the solution was allowed to stand at room temperature for 3 days. The solution was then neutralized with HOAc and extracted with $CHCl_3$. The $CHCl_3$ layer was then washed with 5% aqueous Na_2CO_3 followed by H_2O, dried, and evaporated to give a product that was homogeneous on TLC but was shown by ^1H-NMR

spectroscopy to be a mixture of two components. Separation of the mixture by HPLC (C_{18} Si gel, MeOH−H_2O, 45:55) afforded 1.0 mg of the epimer **8** and 1.3 mg of unepimerized **6**. Compound **8** showed the following spectral characteristics: CD (MeOH, *c* 0.09) λ_{max} ($\Delta\epsilon$) 238 (+0.74), 247 (−7.9), 279 (+0.83); ^{1}H NMR ($CDCl_3$) δ 2.63 (1H, dd, J = 8.2, 13.7 Hz, H-7′β), 2.78 (1H, dd, J = 5.8, 13.7 Hz, H-7′α), 3.08 (2H, m, H-8, H-8′), 3.20 (3H, s, OCH_3-7), 3.62 (1H, t, J = 8.4 Hz, H-9′β), 3.86, 3.87 (3H each, s, 2 × OCH_3), 4.32 (1H, dd, J = 6.7, 8.7 Hz, H-9′α), 5.19 (1H, d, J = 7.9 Hz, H-7β), 5.49, 5.54 (1H each, br s, 2 OH), 6.67 (2H, m, H-2′, H-6′), 6.72 (1H, dd, J = 1.9, 8.2 Hz, H-5′), 6.82 (3H, m, H-2, H-5, H-6); ^{1}H NMR (C_6D_6) δ 2.32 (1H, dd, J = 8.4, 13.7 Hz, H-7′β), 2.52 (1H, dd, J = 6.7, 13.7 Hz, H-7′α), 3.10 (3H, s, OCH_3-7), 2.94 (1H, dd, J = 6.9, 8.6 Hz, H-8), 3.14, 3.20 (3H each, s, 2 × OCH_3), 3.45 (1H, dd, J = 10.8, 18.0 Hz, H-9′β), 4.32 (1H, t, J = 8.4 Hz, H-9′α), 5.06 (1H, d, J = 8.4 Hz, H-7β), 5.35, 5.43 (1H each, br s, 2 OH), 6.43 (1H, d, J = 1.8 Hz, H-2′), 6.49 (1H, dd, J = 1.9, 7.9 Hz, H-6′), 6.78 (1H, dd, J = 1.8, 8.2 Hz, H-6), 6.96 (2H, m, H-2, H-5′), 7.10 (1H, d, J = 8 Hz, H-5).

Cytotoxicity Assay. The M109 cytotoxicity assays were performed as previously described.[2]

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References and Notes

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