New Antimalarial Bis-dehydroaporphine Alkaloids from *Polyalthia debilis*†

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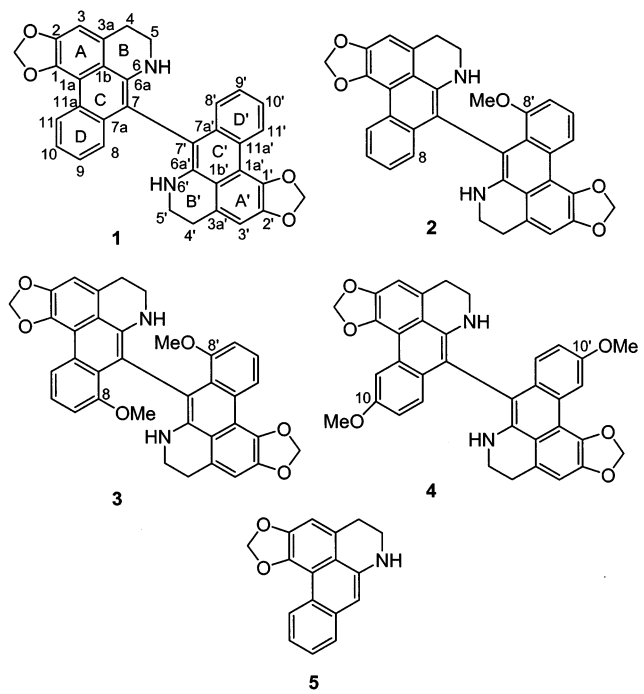
Four new dimeric aporphinoids named bidebilines A−D (**1**−**4**), bis-7,7′-dehydroanonaine (**1**), 7-dehydroanonaine-7′-dehydro-8′-methoxyanonaine (**2**), bis-7,7′-dehydro-8,8′-dimethoxyanonaine (**3**), and bis-7,7′-dehydro-10,10′-dimethoxyanonaine (**4**), were isolated from the roots of *Polyalthia debilis*. Their structures were established on the basis of spectral evidence. Compounds **3** and **4** exhibited moderate antimalarial activity with IC_{50} values of 5.4 and 4.1 μg/mL, respectively.

The Thai herbal preparation *Polyalthia debilis* (Annonaceae) is called Kon Krok in Thai. It grows widely in the northeastern part of Thailand. A water decoction of the roots is used traditionally for treatment of abdominal pain.[1] Previous phytochemical investigations on *Polyalthia* species resulted in the isolation of clerodan diterpenes,[2−4] triterpenes,[5,6] benzopyran derivatives,[7] polyacetylene compounds,[8,9] and several types of alkaloids such as azaanthracenes,[10] aporphines,[4,11,12] bisaporphines,[13−15] indolosesquiterpenes,[16] *seco*-benzyltetrahydroisoquinolines,[17] and oxoprotoberberines.[4,18] As part of our search for bioactive constituents from Thai plants, the dichloromethane extract of air-dried roots of *P. debilis* was shown to be active against *Plasmodium falciparum* (IC_{50} 1.35 μg/mL). We report herein the isolation and characterization of four new rare bis-7,7′-dehydroaporphine alkaloids named bidebilines A−D (**1**−**4**).



Results and Discussion

Four new bis-7,7′-dehydroaporphine alkaloids, bidebilines A−D (**1**−**4**), were isolated from the CH_2Cl_2 extract of air-dried roots of *P. debilis* by a combination of silica gel column chromatography and preparative TLC. Structures of **1**−**4** were elucidated by analyses of ^{1}H, ^{13}C, and MS spectral data as well as by comparison with published data.[13,15,19−21] In addition, the structures of **2** and **4** were characterized by extensive analyses of 2D NMR data.

Bidebiline A (**1**) was obtained as a yellowish solid. The molecular formula was deduced as $C_{34}H_{24}N_2O_4$ from the ESI-TOF mass spectrum [observed *m*/*z* 524.1813 $(M + H)^+$]. The UV absorption at λ_{max} 261 (log ϵ 4.65), 335 (log ϵ 4.10), and 384 (log ϵ 3.89) nm indicated the characteristics of the dehydroaporphine system with C-7 substitution.[19] Genesis of an intense fragmentation ion from the EIMS spectrum at *m*/*z* 263, $C_{17}H_{13}NO_2$ for $[M/2 + H]^+$, which was equivalent to a $[M]^+$ peak for dehydroanonaine (**5**),[20] revealed that **1** was a dimer of **5**. The IR spectrum showed absorption bands at 3380 (NH), 1626, 1597, and 949 (aromatic) cm^{-1}. The ^{1}H NMR spectrum of **1** (Table 1) exhibited only half of the number of resonance signals expected, indicating that the two monomers were symmetrical. The monomeric unit of rings A and A′ showed a signal at δ 7.03 (s, H-3, H-3′). Among four aromatic protons of rings D and D′ (generally appearing at δ 7.10−7.33), a signal of H-11 or H-11′ was exceptionally deshielded at δ 9.04 (d, J = 8.1 Hz), suggesting the anisotropic effect from ring A. The methylenedioxy protons showed a singlet signal at δ 6.27, whereas cyclic methylene resonances of H-4, H-4′ and H-5, H-5′ appeared as complex multiplet signals between δ 3.15 and 3.40. Since no signal appeared near δ 6.56, for protons at C-7 and C-7′, which is characteristic of dehydroanonaine (**5**),[20] it could be concluded that **1** was a symmetrical dimer of dehydroanonaine (**5**). As expected for a symmetrical dimer, ^{13}C NMR and DEPT spectra (Table 2) contained only 17 signals attributable to nine aromatic quarternary carbons, five aromatic methine carbons (δ 107.9, 122.4, 123.4, 127.3, 127.5), and three methylene carbons (δ 30.8, 41.2, 101.0). The carbons of two monomeric units were assigned by comparison with related compounds, 7,7′-bisdehydro-*O*-methylisopiline,[15] dehydroanonaine (**5**),[20] and urabaine.[21] Thus, the structure of **1** was identified as a bis-7,7′-dehydroanonaine for which we proposed the name of bidebiline A.

Bidebiline B (**2**) was obtained as a yellow-green solid. The molecular formula was deduced as $C_{35}H_{26}N_2O_5$ from the ESI-TOF mass spectrum [observed *m*/*z* 554.1924 $(M + H)^+$]. The EIMS showed $[M]^+$ at *m*/*z* 554 with two fragments at *m*/*z* 263 ($C_{17}H_{12}NO_2$ + H) and *m*/*z* 293 ($C_{18}H_{14}NO_3$ + H), suggesting the presence of an asymmetric dimer of a dehydroanonaine unit and a dehydromethoxyanonaine unit. The UV spectrum was also typical for a dehydroapor-

† Dedicated to Professor Yodhathai Thebtaranonth in honor of his 60th birthday.

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Table 1. ^{1}H NMR Spectral Data (δ, ppm) of Compounds **1**, **2**, **3**, and **4** in $CDCl_3$

position	**1**[a]	**2**[b]	**3**[a]	**4**[b]
3	7.03 s	7.02 br s	7.00 s	7.06 s
3′	7.03 s	7.02 br s	7.00 s	7.06 s
4	3.40−3.15 m	3.43−3.10 m	3.40−3.15 m	3.40−3.28 m
4′	3.40−3.15 m	3.43−3.10 m	3.40−3.15 m	3.40−3.28 m
5	3.40−3.15 m	3.43−3.10 m	3.40−3.15 m	3.30−3.19 m
5′	3.40−3.15 m	3.43−3.10 m	3.40−3.15 m	3.30−3.19 m
8	7.10 d (7.9)	7.24 d (7.9)		7.08 d (9.0)
8′	7.10 d (7.9)			7.08 d (9.0)
9	7.24 t (7.2)	7.19 t (7.9)	6.83 dd (8.1, 1.4)	6.95 dd (9.0, 2.6)
9′	7.24 t (7.2)	6.79 d (7.7)	6.83 dd (8.1, 1.4)	6.95 dd (9.0, 2.6)
10	7.33 t (7.1)	7.32 t (7.1)	7.25 t (8.1)	
10′	7.33 t (7.1)	7.25 t (8.0)	7.25 t (8.1)	
11	9.04 d (8.1)	9.03 d (8.1)	8.78 dd (8.1, 1.4)	8.62 d (2.6)
11′	9.04 d (8.1)	8.78 br d (8.0)	8.78 dd (8.1, 1.4)	8.62 d (2.6)
1-OCH_2O	6.27 s	6.26 d (3.3)	6.24 d (1.4)	6.30 s
1′-OCH_2O	6.27 s	6.25 s	6.24 d (1.4)	6.30 s
8-OMe			2.97 s	
8′-OMe		2.97	2.97 s	
10-OMe				3.94 s
10′-OMe				3.94 s

[a] Spectra obtained at 300 MHz. [b] Spectra obtained at 400 MHz. Figures in parentheses are coupling constants in Hz.

Table 2. ^{13}C NMR Spectral Data (δ, ppm) of Compounds **1**, **2**, **3**, and **4** in $CDCl_3$

position	**1**[a]	**2**[b]	**3**[a]	**4**[b]
1	142.1 s[c]	142.1 s	141.8 s	142.4 s
1′	142.1 s	141.9 s	141.8 s	142.4 s
1a	117.2 s	117.8 s	117.3 s	117.6 s
1a′	117.2 s	118.2 s	117.3 s	117.6 s
1b	120.7 s	117.1 s	118.5 s	119.1 s
1b′	120.7 s	118.2 s	118.5 s	119.1 s
2	145.6 s	145.5 s	144.8 s	145.6 s
2′	145.6 s	144.9 s	144.8 s	145.6 s
3	107.9 d	108.2 d	107.9 d	108.5 d
3′	107.9 d	107.6 d	107.9 d	108.5 d
3a	128.3 s	128.4 s	127.9 s	128.6 s
3a′	128.3 s	127.8 s	127.9 s	128.6 s
4	30.8 t	30.9 t	31.2 t	31.3 t
4′	30.8 t	31.1 t	31.2 t	31.3 t
5	41.2 t	41.2 t	41.5 t	41.7 t
5′	41.2 t	41.6 t	41.5 t	41.7 t
6a	140.8 s	140.8 s	138.5 s	139.2 s
6a′	140.8 s	138.6 s	138.5 s	139.2 s
7	105.7 s	111.8 s	109.0 s	106.7 s
7′	105.7 s	109.0 s	109.0 s	106.7 s
7a	133.9 s	133.8 s	125.8 s	127.9 s
7a′	133.9 s	127.9 s	125.8 s	127.9 s
8	127.5 d	126.9 d	156.3 s	125.2 d
8′	127.5 d	155.8 s	156.3 s	125.2 d
9	127.3 d	126.9 d	110.5 d	117.2 d
9′	127.3 d	110.7 d	110.5 d	117.2 d
10	122.4 d	122.2 d	120.5 d	155.9 s
10′	122.4 d	120.7 d	120.5 d	155.9 s
11	123.4 d	123.6 d	121.8 d	110.1 d
11′	123.4 d	121.9 d	121.8 d	110.1 d
11a	123.5 s	127.6 s	125.5 s	125.4 s
11a′	123.5 s	125.8 s	125.5 s	125.4 s
1-OCH_2O	101.0 t	100.8 t	100.7 t	101.4 t
1′-OCH_2O	101.0 t	100.8 t	100.7 t	101.4 t
8-OMe			56.8 q	
8′-OMe		56.7 q	56.8 q	
10-OMe				55.9 q
10′-OMe				55.9 q

[a] Spectra obtained at 75 MHz. [b] Spectra obtained at 100 MHz. [c] Multipicities were determined by analyses of the DEPT spectra.

phine alkaloid, like that of **1**. The IR spectrum also showed absorption bands at 3381 (NH), 1626, 1597, and 949 (aromatic) cm^{-1}. The ^{1}H NMR spectrum of **2** (Table 1) exhibited an overlapping signal of H-3 and H-3′ as a singlet at δ 7.02. The four aromatic protons in ring D showed a spin system similar to those of **1**. However, unlike dimer **1**, the aromatic protons of ring D′ resonated differently from those of ring D. Ring D′ of **2** possessed three aromatic protons with a methoxy group at C-8′, showing spin systems at δ 6.79 (d, J = 7.7 Hz, H-9′), 7.25 (t, J = 8.0 Hz, H-10′), and 8.78 (br d, J = 8.0 Hz, H-11′). The two methylenedioxy groups were observed as singlet and doublet signals, supporting an asymmetric structure in **2**. The aliphatic methylene protons of H-4, H-4′ and H-5, H-5′ appeared as complex multiplet signals between δ 3.10 and 3.43. The methoxy group at C-8 of ring D′, confirmed by HMBC experiment, appeared at high field (δ 2.97) due to the ring current effect as reported for beccapoline.[13] These data readily led to the conclusion that the two monomeric units were dehydroanonaine (**5**) and dehydro-8′-methoxyanonaine. The ^{13}C NMR and DEPT spectra (Table 2) also confirmed an asymmetric dimer by showing 35 signals attributable to 19 aromatic quarternary carbons, nine aromatic methine carbons (δ 107.6, 108.2, 110.7, 120.7, 121.9, 122.2, 123.6, 126.9, 126.9), six methylene carbons (δ 30.9, 31.1, 41.2, 41.6, 100.8, 100.8), and one methoxy group (δ 56.7). The assignment of ^{1}H and ^{13}C NMR were made by an HMBC experiment and also comparison with a monomer, dehydroanonaine,[20] and unit B of beccapoline.[13] On the basis of the spectral evidence, the structure of **2** was established as a 7-dehydroanonaine-7′-dehydro-8′-methoxyanonaine, for which we proposed the name bidebiline B.

Bidebiline C (**3**) was obtained as a yellow-green solid. The molecular formula was deduced as $C_{36}H_{28}N_2O_6$ from the EIMS data at m/z 584 $[M]^+$ and elemental analysis. The fragmentation ion of the mass spectrum at m/z 292 for $C_{18}H_{14}NO_3$ $[M/2]^+$ suggested a dimer of dehydromethoxyanonaine. The UV spectrum was also typical for dehydroaporphine alkaloid, like **1** and **2**. The IR spectrum showed absorption bands at 3383 (NH), 1624, 1597, and 950 (aromatic) cm^{-1}. The ^{1}H NMR spectrum (Table 1) showed half of the number of resonance signals expected, revealing that the two monomers were symmetrical as in **1**. The absence of proton signals at C-7 and C-7′ indicated that the bridge in **3** was connected via C-7 to C-7′. The monomeric unit of rings A and A′ showed a singlet signal at δ 7.00 (H-3, H-3′), and the three aromatic protons of rings D and D′ with a methoxy group at C-8 and C-8′ showed a spin pattern as observed in ring D′ of **2**. The two methylenedioxy protons appeared as doublet signals, whereas the aliphatic methylene protons of H-4, H-4′ and H-5, H-5′ were observed as complex multiplet signals. The

methoxy protons at C-8 and C-8′ appeared at high field (δ 2.97), like those of **2**. The ^{13}C NMR and DEPT spectra (Table 2) contained 18 signals attributable to 10 aromatic quarternary carbons, four aromatic methine carbons (δ 107.9, 110.5, 120.5, 121.8), three methylene carbons (δ 31.2, 41.5, 100.7), and one methoxy carbon (δ 56.8). By comparison of spectroscopic data with those of **2**, bidebiline C (**3**) was established as a symmetrical dimer, bis-7,7′-dehydro-8,8′-dimethoxyanonaine.

Bidebiline D (**4**) was obtained as a yellow-green solid. The molecular formula was deduced as $C_{36}H_{28}N_2O_6$ from the EIMS data at *m/z* 584 $[M]^+$ and elemental analysis. Genesis of an intense fragmentation ion at *m/z* 292 $C_{18}H_{14}NO_3$ for $[M/2]^+$ indicated that **4** readily fragmented into two identical halves, and this observation suggested that **4** was a dimer of a dehydromethoxyanonaine, as **3**. The UV spectrum of **4** was also typical for a dehydroaporphine alkaloid, as those of **1**−**3**. The IR spectrum showed absorption bands at 3370 (NH), 1624, 1597, and 950 (aromatic) cm^{-1}. The ^1H NMR spectrum of **4** (Table 1) exhibited half of the number of resonance signals as expected for a symmetrical dimer. The absence of signal protons at C-7 and C-7′ indicated a linkage through this bond. The aromatic protons of rings A and A′ exhibited as a singlet signal at δ 7.06 (H-3, H-3′), while the three protons in rings D and D′ showed a spin pattern of methoxy substitution on C-10 and C-10′ at δ 7.08 (d, J = 9.0 Hz, H-8, H-8′), 6.95 (dd, J = 9.0, 2.6 Hz, H-9, H-9′), and 8.62 (d, J = 2.6 Hz, H-11, H-11′). The methylenedioxy protons and aliphatic methylene groups (H-4, H-4′ and H-5, H-5′) appeared as a singlet and complex multiplet signal, respectively. The methoxy group at C-10 or C-10′ showed a resonance signal (δ 3.94) at lower field than those of **3**, suggesting no effect of ring current. The ^{13}C NMR and DEPT spectra (Table 2) contained 18 carbon signals of monomeric resonances accountable for 10 aromatic quarternary carbons, four aromatic methine carbons (δ 108.5, 110.1, 117.2, 125.2), three methylene carbons (δ 31.3, 41.7, 101.4), and one methoxy carbon (δ 55.9). The COSY spectrum showed correlations between H-4↔H-5 and H-8↔H-9↔H-11, whereas the correlation between protons and carbons was indicated by the HMQC spectrum. In addition, the HMBC spectral data of **4** demonstrated the correlations of H-3 to C-1, C-1a, C-1b, C-2, and C-4; H-4 to C-3, C-3a, C-1b, and C-5; H-5 to C-3a, C-4, and C-6a; H-8 to C-7, C-10, and C-11a; H-9 to C-7a, C-10, and C-11; H-11 to C-9, C-7a, and C-10; methoxy hydrogens to C-10; and methylenedioxy to C-1. On the basis of these spectral data, the structure of bidebiline D (**4**) was determined as a bis-7,7′-dehydro-10,10′-dimethoxyanonaine.

Bidebilines A−D (**1**−**4**) are a rare group of bis-7,7′-dehydroaporphine alkaloid from *Polyalthia* species, the only other examples being the urabaine, 7,7′-bisdehydro-*O*-methylisopiline, and 7-dehydronornuciferinyl-7′-dehydro-*O*-methylisopiline alkaloids from *P. bullata*.[15]

Bidebiline C (**3**) and bidebiline D (**4**) exhibited moderate antimalarial activity with IC_{50} values of 5.4 and 4.1 μg/mL, respectively.

Experimental Section

General Experimental Procedures. CC and preparative TLC were carried out on silica gel 60 (230−400 mesh) and silica gel 60 PF_{254}, respectively. NMR spectra ($CDCl_3$) were recorded on Bruker DRX300 or Bruker DRX400 spectrometers, using residual $CHCl_3$ (δ 7.26) as an internal standard. IR spectra were obtained from a FTIR-8601PC Shimadzu spectrophotometer. EIMS and ESI-TOF MS were measured on Finningan Mat INCOS 50 and Micromass LCT mass spectrometers, respectively. UV spectra were measured on a Hitachi 330 spectrophotometer. Melting points were uncorrected.

Plant Material. Roots of *Polyalthia debilis* (Piere) Finet & Gagnep were collected on the campus of Khon Kaen University in March 1999 and identified by Dr. Pranom Chantaranothai, Department of Biology, Khon Kaen University. A plant specimen (voucher number S.Kanokmedhakul-1) was deposited at the herbarium of the Department of Biology, Faculty of Science, Khon Kaen University, Thailand.

Extraction and Isolation. Air-dried roots of *P. debilis* (2.2 kg) were ground and extracted successively with hexane (4 L × 3) and CH_2Cl_2 (4 L × 3) at room temperature. Filtrates were combined and the solvents were removed in vacuo to yield a hexane extract (38.2 g) and a CH_2Cl_2 extract (44.7 g). The CH_2Cl_2 extract (44 g) was subjected to silica gel (300 g) flash column chromatography and eluted with increasing concentrations of EtOAc in hexane followed by MeOH in EtOAc. Each fraction was monitored by TLC; fractions with similar TLC patterns were combined to yield 10 major fractions, F_1−F_{10}. Fraction F_5 (6.4 g) eluted with EtOAc−hexane (50:50, 3 L) was precipitated in CH_2Cl_2−hexane to give a yellow-green solid (0.696 g). The solid was further purified by preparative TLC developed with CH_2Cl_2−hexane (80:20) to give compound **1** (12.3 mg, CH_2Cl_2−hexane, 80:20, R_f 0.86), compound **2** (71 mg, CH_2Cl_2−hexane, 80:20, R_f 0.77), compound **3** (66.6 mg, CH_2Cl_2−hexane, 80:20, R_f 0.71), and compound **4** (74 mg, CH_2Cl_2−hexane, 80:20, R_f 0.67). The filtrate was evaporated to dryness and further purified by preparative TLC using the method described above to give an additional amount of compound **2** (0.911 g), compound **3** (1.035 g), and compound **4** (1.151 g).

Antimalarial Bioassays. The malarial parasite, *Plasmodium falciparum* (K1, multidrug resistant strain), was cultured according to the method of Trager and Jensen.[22] Quantitative assessment of malarial activity in vitro was determined by means of the microculture radioisotope technique based upon the method described by Desjardin et al.[23] The inhibitory concentration (IC_{50}) represents the concentration that causes 50% reduction in parasite growth as indicated by the in vitro uptake of $[^3H]$-hypoxanthine by *P. falciparum*. The standard compound, artemisinin, exhibited an IC_{50} value of 1 ng/mL.

Bidebiline A (1): yellowish amorphous powder; mp 240 °C (dec); UV ($CHCl_3$) λ_{max} (log ϵ) 261 (4.65), 335 (4.10), 384 (3.89) nm; IR (KBr) ν_{max} 3380, 2929, 2830, 1624, 1597, 1582, 1533, 1051, 949 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 524 $[M]^+$ (100), 494 (2), 465 (1), 436 (0.7), 264 (7), 263 (43), 262 (7), 232 (5), 204 (5), 178 (1); ESI-TOF MS *m/z* 525.1813 $[M + H]^+$ (calcd for $C_{34}H_{24}N_2O_4$ + H, 525.1814).

Bidebiline B (2): yellow-green amorphous powder; mp 245 °C (dec); UV ($CHCl_3$) λ_{max} (log ϵ) 260 (4.69), 335 (4.22), 384 (4.08) nm; IR (KBr) ν_{max} 3381, 2893, 2833, 1626, 1597, 1577, 1537, 1211, 1051, 949 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 554 $[M]^+$ (100), 522 (23), 521 (4), 495 (4), 293 (5), 263 (1), 262(7), 232(2), 195 (1); ESI-TOF MS *m/z* 555.1924 $[M + H]^+$ (calcd for $C_{35}H_{26}N_2O_5$ + H, 555.1920).

Bidebiline C (3): yellow-green amorphous powder; mp 210 °C (dec); UV ($CHCl_3$) λ_{max} (log ϵ) 266 (4.72), 334 (4.29), 384 (4.16) nm; IR (KBr) ν_{max} 3383, 2929, 2833, 1624, 1597, 1582, 1533, 1211, 1051, 950 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 584 $[M]^+$ (100), 569 (3), 552 (14), 538 (12), 508 (10), 293 (10), 292 (3), 276 (5), 260 (7), 231 (2), 194 (1); *anal.* C 73.87%, H 4.78%, N 4.78%, calcd for $C_{36}H_{28}N_2O_6$, C 73.96%, H 4.83%, N 4.79%.

Bidebiline D (4): yellow-green amorphous powder; mp 205 °C (dec); UV ($CHCl_3$) λ_{max} (log ϵ) 256 (4.92), 333 (4.48), 384 (4.36) nm; IR (KBr) ν_{max} 3370, 2926, 2828, 1624, 1597, 1458, 1208, 1044, 950 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 584 $[M]^+$ (100), 552 (11), 538 (19), 508 (23), 292 (45), 276 (33), 260 (55), 232 (44), 195 (25), 32 (13); *anal.* C 73.57%, H 4.81%, N 4.75%, calcd for $C_{36}H_{28}N_2O_6$, C 73.96%, H 4.83%, N 4.79%.

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References and Notes

(1) Pharmaceutical Sciences, Mahidol University. *Saim-Phi-Chacha-Ya-Prug*; Amarin Printing and Publishing: Bangkok, 1996; p 190.
(2) Ma, X.; Lee, I. S.; Chai, H. B.; Zaw, K.; Farnsworth, N. R.; Soejarto, D. D.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. *Phytochemistry* **1994**, *37*, 1659−1662.
(3) Hara, N.; Asaki, H.; Fujimoto, Y.; Gupta, Y. K.; Singh, A. K.; Sahai, M. *Phytochemistry* **1995**, *38*, 189−194.
(4) Chen, C. Y.; Chang, F. R.; Shih, Y. C.; Hsieh, T. J.; Chia, Y. C.; Tseng, H. Y.; Chen, H. C.; Chen, S. J.; Hsu, M. C.; Wu, Y. C. *J. Nat. Prod.* **2000**, *63*, 1475−1478.
(5) Li, H. Y.; Sun, N. J.; Kashiwada, Y.; Sun, L.; Snider, J. V.; Cosentino, L. M.; Lee, K, H. *J. Nat. Prod.* **1993**, *56*, 1130−1133.
(6) Lue, Y. P.; Mu, Q.; Zheng, H. L.; Li, C. M. *Phytochemistry* **1998**, *49*, 2053−2056.
(7) González, M. C.; Sentandreu, M. A.; Rao, K. S.; Zafra-Polo, M. C.; Cortes, D. *Phytochemistry* **1996**, *43*, 1361−1364.
(8) Kanokmedhakul, S.; Kanokmedhakul, K.; Ohtani, I. I.; Isobe, M. *Phytochemistry* **1998**, *47*, 131−133.
(9) Tuchinda, P.; Pohmakotr, M.; Reutrakul, V.; Thanyachareon, W.; Sophasan, S.; Yoosook, C.; Santisuk, T.; Pezzuto, J. M. *Planta Med.* **2001**, *67*, 572−575.
(10) Tuchinda, P.; Pohmakotr, M.; Munyoo, B.; Reutrakul, V.; Santisuk, T. *Phytochemistry* **2000**, *53*, 1079−1082.
(11) Hasan, C. M.; Healey, T. M.; Waterman, P. G.; Schwalbe, C. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, *12*, 2807−2812.
(12) Musa, H.; Zarga A.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 471−475.
(13) Jossang, A.; Leboeuf, M.; Cavé, A. *Tetrahedron Lett.* **1982**, *23*, 5147−5150.
(14) Jossang, A.; Leboeuf, M.; Cavé, A.; Sévenet, T.; Padmawinata, K. *J. Nat. Prod.* **1984**, *47*, 504−513.
(15) Connolly, J. D.; Haque, Md. E.; Kadir, A. A. *Phytochemistry* **1996**, *43*, 295−297.
(16) Hocquemiller, R.; Dubois, G.; Leboeuf, M.; Cavé, A.; Kunesch, N.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.* **1981**, *22*, 5057−5060.
(17) Lee, K. H.; Chuah, C. H.; Goh, S. H. *Tetrahedron Lett.* **1997**, *38*, 1253−1256.
(18) González, M. C.; Zafra-Polo, M. C.; Blázquez, M. A.; Serrano, A.; Cortes, D. *J. Nat. Prod.* **1997**, *60*, 108−110.
(19) Cavé, A.; Leboeuf, M.; Waterman, P. G. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, W., Ed.; John Wiley & Sons: New York, 1987; Vol. 5, p 133.
(20) Lenz, G. R.; Koszyk, F. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1273−1277.
(21) Arango, G.; Cortes, D.; Cavé, A. *Phytochemistry* **1987**, *26*, 1227−1229.
(22) Trager, W.; Jensen, J. B. *Science* **1967**, *193*, 673−675.
(23) Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. *Antimicrob. Agents. Chemother.* **1979**, *16*, 710−718.

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