Jerantinines A−G, Cytotoxic *Aspidosperma* Alkaloids from *Tabernaemontana corymbosa*

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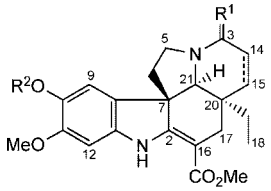
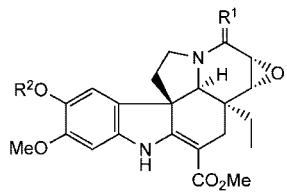
Seven new indole alkaloids of the *Aspidosperma* type, jerantinines A−G (**1**−**7**), were isolated from a leaf extract of the Malayan *Tabernaemontana corymbosa*. The structures were established using NMR and MS analysis. Five of the alkaloids isolated and two derivatives (**1**−**5**, **8**, **9**) displayed pronounced in vitro cytotoxicity against human KB cells (IC_{50} < 1 μg/mL).

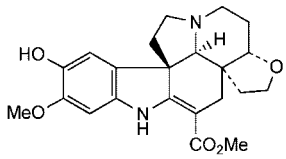
Plants of the genus *Tabernaemontana* comprising about 110 species have a widespread distribution in the pantropical regions and are rich in alkaloids.[1−4] In our systematic study of the Malaysian representatives of this genus, we have reported many examples of new alkaloids, which are distinguished by their structural novelty as well as useful bioactivity.[4−20] The Malayan *T. corymbosa* Roxb. ex Wall, for instance, provided several new alkaloids characterized by novel molecular skeletons such as the hexacyclic alkaloid tronoharine,[5] the pentacyclic indole tronocarpine,[6] and the quinolinic alkaloid voastrictine.[7] The same plant also yielded a number of new indole and bisindole alkaloids,[4,7−13,18,21,22] including several vobasinyl-iboga bisindoles, which reverse multidrug resistance in vincristine-resistant KB cells.[8] In continuation of our studies of biologically active alkaloids from Malaysian *Tabernaemontana*,[4−20] we now report the isolation of seven new indole alkaloids (**1**−**7**) of the *Aspidosperma* type from an investigation of the leaf extract of the same species, but involving plant material collected from a different location.



1 $R^1 = H_2$, R^2 = H, $\Delta^{14,15}$
3 R^1 = O, R^2 = H, $\Delta^{14,15}$
5 $R^1 = H_2$, R^2 = H
8 $R^1 = H_2$, R^2 = OAc, $\Delta^{14,15}$
10 $R^1 = H_2$, R^2 = OMe, $\Delta^{14,15}$



2 $R^1 = H_2$, R^2 = H
4 R^1 = O, R^2 = H
9 $R^1 = H_2$, R^2 = OAc
11 $R^1 = H_2$, R^2 = OMe



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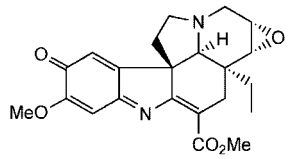

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Results and Discussion

Jerantinine A (**1**), constituting the major alkaloid from the leaf extract, was obtained as light yellowish crystals, mp 190−192 °C, with $[\alpha]_D$ −294 ($CHCl_3$, *c* 0.65). The EIMS of **1** showed a molecular ion at *m*/*z* 382, which analyzed for $C_{22}H_{26}N_2O_4$, with a fragment ion observed at *m*/*z* 351 due to loss of a methoxy group. The UV (246, 320, and 340 nm) and IR (3373, 1669, and 1606 cm^{-1}) data indicated the presence of a β-anilinoacrylate chromophore,[23] which was also in agreement with the presence of two quaternary carbons seen at δ 167.7 and 91.6, due to the acrylate double-bond carbons, C-2 and C-16, respectively, in the ^{13}C NMR spectrum. The large number of carbon resonances that resonated above 130 ppm suggested the presence of a highly oxygenated indole aromatic ring. The presence of only two aromatic hydrogen signals, which were observed as singlets in the ^1H NMR spectrum, suggested substitution at C-10 and C-11. Detailed analysis of the ^1H and ^{13}C NMR (Tables 1 and 2) and COSY data revealed that the nonindolic portion of jerantinine A (**1**) was identical to that of tabersonine.[24] Since there are a total of four oxygen atoms in **1**, and two are due to the acrylic ester function, the remaining two must be due to OMe and OH groups, by comparison of the molecular formula of **1** with that of tabersonine. The presence of the OH group was also indicated by a broad singlet observed at δ 5.36 in the ^1H NMR spectrum, as well as from the absorption band at 3538 cm^{-1} in the IR spectrum. Placement of the OH and OMe substituents on the aromatic ring was from NOE difference experiments. Thus, the observed enhancement of the OMe and NH signals on irradiation of H-12 allowed the OH and OMe groups to be placed at C-10 and C-11, respectively. Furthermore, such an arrangement is consistent with the facile transformation of **1** into its unstable iminoquinone form. This was indicated by the gradual development of a dark yellow coloration on exposure of a chloroform or dichloromethane solution of **1** to air. Jerantinine A (**1**) is thus the 10-hydroxy-11-methoxy-substituted derivative of tabersonine. An alkaloid purportedly identical to 10-hydroxy-11-methoxytabersonine was previously reported from *Hazunta modesta* but without any accompanying spectroscopic data.[25]

Jerantinine B (**2**) was obtained as light yellowish crystals, mp 235−237 °C, with $[\alpha]_D$ −386 ($CHCl_3$, *c* 0.65). The IR and UV spectra were similar to those of **1**. The mass spectrum of **2** showed a molecular ion at *m*/*z* 398 (base peak), in addition to a significant fragment ion at *m*/*z* 381, which can be attributed to loss of OH. HREIMS measurements gave the formula $C_{22}H_{26}N_2O_5$ (*m*/*z* 398.1842, calcd 398.1842), differing from jerantinine A (**1**) by 16 mass units and suggesting the presence of an additional oxygen atom compared to **1**. The ^1H and ^{13}C NMR spectra of **2** (Tables 1 and 2) were similar to those of **1**, except for the absence of signals due to the 14,15-double bond, which were replaced instead by signals due to an epoxide function (δ_H 3.50, δ_C 50.0; δ_H 3.10, δ_C 57.1). The orientation of the epoxide function was readily determined to be α from the observed upfield shift of the aminomethine C-21, and the methylene carbon of the ethyl side chain, C-19, from ca. δ 71 and 27 to δ 67 and 24, respectively, a shielding effect caused by the proximate epoxide oxygen and a feature characteristic of the

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Table 1. ^{1}H NMR Data (δ) for **1**−**7** (400 MHz, $CDCl_3$)[a]

H	1	2	3	4	5	6	7
3	3.16 br d (16)	2.86 m			2.38 td (10.8, 3.2)	2.70 m	2.80 m
	3.45 ddd (16, 4.6, 1.3)	3.51 m			3.10 m	2.93 m	3.50 m
5	2.68 ddd (11.5, 7, 4.3)	2.43 m	3.35 td (12, 5)	3.19 td (12, 5.8)	2.52 ddd (11.5, 8, 4.5)	2.63 ddd (11.5, 8, 4.5)	2.31 ddd (11.8, 8.8, 4.5)
	3.02 t (7)	2.86 m	4.29 dd (12, 7)	4.40 dd (12, 7)	2.89 dd (8, 6.7)	2.93 m	2.95 dd (8.8, 6.2)
6	1.76 dd (11.5, 4.3)	1.67 dd (11.5, 4.3)	1.86 dd (12, 5)	1.73 m	1.66 dd (11.5, 4.5)	1.74 dd (11.5, 4.5)	1.77 dd (11.8, 4.5)
	2.06 td (11.5, 7)	1.93 td (11.5, 6.2)	1.94 td (12, 7)	1.73 m	2.03 td (11.5, 6.7)	2.02 td (11.5, 6)	2.03 td (11.8, 6.2)
9	6.89 s	6.79 s	6.87 s	6.80 s	6.84 s	6.88 s	6.22 s
12	6.45 s	6.45 s	6.52 s	6.48 s	6.43 s	6.45 s	6.69 s
14	5.78 ddd (10.0, 4.6, 1.5)	3.50 m	5.95 d (10.0)	3.57 m	1.53 m	1.95 m	3.50 m
					1.81 m	1.95 m	
15	5.70 dt (10.0, 1.3)	3.10 d (3.5)	6.44 d (10.0)	3.43 d (3.6)	1.25 m	3.68 m	3.09 d (3.4)
					1.81 m		
17	2.42 d (15)	2.47 d (15)	2.04 dd (15.5, 1.5)	1.82 d (15.4)	2.27 dd (15.1, 1.5)	2.28 dd (14.5, 1.7)	2.79 m
	2.53 dd (15, 1.5)	2.57 d (15)	2.59 d (15.5)	2.63 d (15.4)	2.70 d (15.1)	2.73 d (14.5)	2.79 m
18	0.64 t (7.3)	0.74 t (7.2)	0.71 t (7)	0.77 t (7.4)	0.57 t (7)	3.69 m	0.88 t (7)
						3.78 m	
19	0.86 dq (14, 7.3)	0.89 dq (14, 7.2)	1.00 dq (14, 7)	1.02 dq (14, 7.4)	0.63 dq (14, 7)	1.30 ddd (12.5, 8, 4.5)	0.73 dq (14, 7)
	1.00 dq (14, 7.3)	1.10 dq (14, 7.2)	1.08 dq (14, 7)	1.23 dq (14, 7.4)	0.98 dq (14, 7)	1.44 ddd (12.5, 10, 7.5)	1.25 dq (14, 7)
21	2.60 s	2.38 s	3.92 s	3.57 s	2.36 d (1.5)	2.74 s	2.25 s
NH	8.87 brs	8.82 brs	8.91 brs	8.83 brs	8.77 brs	8.76 brs	
10-OH	5.36 brs	5.50 brs	5.59 brs	5.49 brs	5.37 brs	5.38 brs	
11-OMe	3.87 s	3.85 s	3.89 s	3.86 s	3.86 s	3.87 s	3.89 s
CO_2Me	3.76 s	3.78 s	3.77 s	3.76 s	3.75 s	3.77 s	3.91 s

[a] Assignments are based on COSY, HMQC, and HMBC.

Table 2. ^{13}C NMR Data (δ) of **1**−**7** (100 MHz, $CDCl_3$)[a]

C	1	2	3	4	5	6	7
2	167.7	168.6	166.4	166.9	168.6	168.3	169.2
3	50.6	53.9	161.4	164.8	50.5	46.0	50.0
5	50.8	50.5	43.2	43.4	51.7	51.4	50.9
6	44.3	44.5	43.4	41.7	44.9	45.1	43.0
7	55.2	55.0	56.8	57.6	55.6	55.2	54.5
8	130.1	129.4	127.2	127.0	129.7	129.8	156.7
9	108.8	108.7	108.7	108.6	108.6	108.7	118.8
10	139.9	140.0	140.6	140.6	140.0	140.0	180.8
11	145.8	146.0	146.7	146.7	145.8	146.0	158.1
12	94.4	94.6	94.8	94.8	94.6	94.5	104.1
13	135.9	135.7	135.8	135.6	136.1	136.0	166.3
14	124.8	50.0	122.7	51.1	21.9	26.9	53.7
15	133.0	57.1	145.2	57.1	32.7	80.0	56.5
16	91.6	90.0	89.6	88.1	92.1	93.5	118.4
17	28.3	23.1	25.9	22.2	25.6	27.5	27.3
18	7.4	7.1	7.3	7.2	7.1	64.9	7.4
19	26.8	24.2	27.0	26.2	29.3	34.8	25.1
20	41.4	41.0	40.5	40.7	38.1	46.7	44.0
21	70.1	67.6	66.5	63.2	72.5	68.8	68.1
11-OMe	56.3	56.2	56.3	56.3	56.3	56.3	52.5
CO_2Me	50.9	50.9	51.0	51.1	50.9	51.0	56.6
CO_2Me	169.2	168.8	168.4	168.3	169.2	168.3	167.1

[a] Assignments are based on COSY, HMQC, and HMBC.

lochnericine (tabersonine α-epoxide) series of alkaloids.[26] This was further supported by the NOESY/NOE data, which showed reciprocal NOEs between H-15 and H-17α, which is possible only if the orientation of H-15 is β. Jerantinine B (**2**) is therefore 10-hydroxy-11-methoxytabersonine α-epoxide.

Jerantinine C (**3**) was obtained as a light yellowish oil, with $[\alpha]_D$ −110 ($CHCl_3$, *c* 0.20). The UV and IR spectra of **3** were similar to those of **1**, indicating the presence of a β-anilinoacrylate chromophore. The mass spectrum showed a molecular ion at *m/z* 396, with the fragment ion due to loss of OMe observed at *m/z* 365. HREIMS measurements established the molecular formula as $C_{22}H_{24}N_2O_5$. The NMR data of **3** (Tables 1 and 2) were generally similar to those of **1**, except for the absence of the aminomethylene group and the presence instead of an additional lactam carbonyl carbon. The lactam carbonyl was readily deduced to be at position 3 since the usual $CH_2CH{=}CH$ fragment corresponding to C(3)−C(14)−C(15) was replaced by a $COCH{=}CH$ fragment. The downfield shift of the carbon and hydrogen resonances at position 15 (β-position of an α,β-unsaturated carbonyl system) from δ_C 133.0 and δ_H 5.70 in **1** to δ_C 145.2 and δ_H 6.44 in **3**, respectively, provided further support for the presence of a conjugated lactam function in the piperidine ring D. This was also in accord with the observed anisotropic effect of the carbonyl function on the C-5 hydrogens, which were shifted downfield from δ 2.68 and 3.02 in **1** to δ 3.19 and 4.40 in **3**. Jerantinine C (**3**) is therefore the 3-oxo derivative of **1**.

Jerantinine D (**4**), which was isolated as a light yellowish oil, with $[\alpha]_D$ −199 ($CHCl_3$, *c* 0.35), showed a molecular ion at *m/z* 412 in the mass spectrum, which analyzed for $C_{22}H_{24}N_2O_6$, differing from **3** by an additional oxygen atom. As in the previous compounds (**1**−**3**), the UV and IR data showed the presence of a β-anilinoacrylate chromophore. The ^{1}H and ^{13}C NMR spectroscopic data (Tables 1 and 2) were generally similar to those of **3**, except for the resonances associated with ring D, which indicated the presence of two oxymethines (δ_C 51.1, 57.1) due to an epoxide function, in place of the two 14,15-double bond carbons present in **3**. The corresponding H-14 and H-15 resonances were observed at δ 3.57 and 3.43, respectively, in the ^{1}H NMR spectrum. The orientation of H-15 was determined to be β from the NOE data, which showed reciprocal NOEs between H-15 and H-17α, thus confirming the orientation of the 14,15-epoxide function as α. The downfield shift of both the H-5, which was observed in **3** due to the anisotropic effect from the lactam carbonyl, was also observed in **4**, with the H-5 resonances shifted to δ 3.19 and 4.40. Jerantinine D (**4**) is therefore the 14,15-epoxide derivative of **3**.

Jerantinine E (**5**) was isolated as a light yellowish oil, with $[\alpha]_D$ −357 ($CHCl_3$, *c* 0.10). The EIMS showed an M^+ peak at *m/z* 384, which analyzed for $C_{22}H_{28}N_2O_4$, two mass units higher than that of **1**, while the UV and IR spectra of **5** were similar to those of **1**. Comparison of the ^{1}H and ^{13}C NMR data of **5** with those of **1** (Tables 1 and 2) indicated that the main difference was the absence of the 14,15-double bond in **5**. Jerantinine E (**5**) is therefore the 14,15-dihydro derivative of **1**. In accordance with this, the endocyclic homoallylic effect,[27] which caused the deshielding of C-21 in **1**, was absent in **5**, with the C-21 resonance of **5** observed at lower field compared to that of **1** (δ_C 72.5 vs 70.1). Apart from these differences, the NMR data of **5** were essentially similar to those of **1**.

Jerantinine F (**6**) was obtained in minute amounts as a light yellowish oil, with $[\alpha]_D$ −451 ($CHCl_3$, *c* 0.08). The UV and IR spectra were similar to those of the previous compounds, while the EIMS showed a molecular ion at *m/z* 398, indicating that **6** is isomeric with **2**. However, examination of the ^{1}H NMR spectrum of **6** showed the absence of the distinctive signals due to the ethyl side chain (a three-H triplet and two one-H doublets of quartets)

Table 3. Cytotoxic Effects of Compounds **1**−**6** and **8**−**11**

compound	IC_{50}, μg/mL (μM)	
	KB/S[a]	KB/VJ300[a]
jerantinine A (**1**)	0.76 (1.99)	0.66 (1.73)
jerantinine B (**2**)	0.44 (1.11)	0.38 (0.95)
jerantinine C (**3**)	0.32 (0.81)	0.61 (1.54)
jerantinine D (**4**)	0.28 (0.68)	0.39 (0.95)
jerantinine E (**5**)	0.98 (2.55)	0.78 (2.03)
jerantinine F (**6**)	5.1 (12.8)	4.9 (12.3)
jerantinine A acetate (**8**)	0.44 (1.04)	0.35 (0.83)
jerantinine B acetate (**9**)	0.30 (0.70)	0.33 (0.75)
10-*O*-methyljerantinine A (**10**)	4.77 (12.0)	5.40 (13.6)
10-*O*-methyljerantinine B (**11**)	2.93 (7.36)	4.25 (10.7)
vincristine	0.0044 (0.0054)	1.0 (1.2)

[a] KB/S and KB/VJ300 are vincristine-sensitive and -resistant human oral epidermoid carcinoma cell lines, respectively.

observed in all the previous compounds (**1**−**5**). The ^{13}C NMR data of **6** showed a striking resemblance to those of vandrikine,[24] except for the aromatic region, which were similar to those of compounds **1**−**5**. Jerantinine F (**6**) is therefore the 10-hydroxy derivative of vandrikine, in which a tetrahydrofuran ring fused to C-15 and C-20 has been incorporated, with the ether oxygen linking C-15 to C-18.

Jerantinine G (**7**) was also obtained in minute amounts as a yellow oil, with $[\alpha]_D$ −762 ($CHCl_3$, *c* 0.24). The UV spectrum (245, 285, 363, and 417 nm) showed a departure from those of the previous jerantinines (**1**−**6**), while the IR spectrum showed strong bands at 1697, 1651, and 1583 cm^{-1}. Conspicuously absent from the IR as well as ^1H NMR spectra were signals due to both NH and OH. The EIMS of **7** showed a molecular ion at *m/z* 396 ($C_{22}H_{24}N_2O_5$), which is two mass units less than that of jerantinine B (**2**). Examination of the ^1H NMR spectrum (Table 1) indicated that the chemical shifts of the nonindolic portion of **7** were generally similar to those of **2**. However, this was not the case for the ^{13}C NMR shifts of **7**, which were all shifted downfield when compared to those of **2**, with C-10 and C-13 experiencing the most pronounced shift from δ 140.0 and 135.7 in **2**, to δ 180.8 and 166.3, respectively, in **7**. These observations suggested the presence of an iminoquinone chromophore in **7**, which was readily confirmed when addition of ascorbic acid to the dichloromethane solution of **7** yielded a reduced product identical to **2**. Conversely, **2** was readily oxidized to **7** on exposure of a dichloromethane solution of **2** to air, or on treatment of a solution of **2** with activated MnO_2.[28,29] In light of this facile transformation, jerantinine G (**7**), which is the iminoquinone derivative of **2**, is in all probability an artifact, formed during the isolation of the jerantinines.

Jerantinines A−E (**1**−**5**) were found to display pronounced in vitro cytotoxicity toward drug-sensitive as well as vincristine-resistant (VJ300) KB cells (IC_{50} 0.3−0.8 μg/mL, Table 3). Jerantinine F (**6**) showed only moderate cytotoxicity, while the activity of jerantinine G (**7**) was not evaluated due to its instability, which leads to decomposition. Evaluation of simple derivatives revealed that acetylation (**8** and **9**) resulted in an enhancement of the cytotoxic activity, while *O*-methylation (**10** and **11**) resulted in a reduction of the biological activity.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a JASCO P-1020 digital polarimeter. IR spectra were recorded on a Perkin-Elmer RX1 FT-IR spectrophotometer. UV spectra were obtained on a Shimadzu UV-3101PC spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JNM-LA 400 spectrometer at 400 and 100 MHz, respectively. EIMS and HREIMS were obtained at Organic Mass Spectrometry, Central Science Laboratory, University of Tasmania, Tasmania, Australia.

Plant Material. Plant material was collected in Pahang, Malaysia, and identification was confirmed by Dr. K. M. Wong, Institute of Biological Sciences, University of Malaya, Kuala Lumpur, Malaysia. Herbarium voucher specimens (K 667) are deposited at the Herbarium, University of Malaya.

Extraction and Isolation. Extraction of the ground leaf material was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid as has been described in detail elsewhere.[30] The alkaloids were isolated by initial column chromatography on silica gel using CH_2Cl_2 with increasing proportions of MeOH followed by rechromatography of the appropriate partially resolved fractions using centrifugal TLC. Solvent systems used for centrifugal TLC were Et_2O−hexane (2:1), Et_2O−MeOH (50:1), EtOAc−hexane (1:6), EtOAc−hexane (1:3), EtOAc−hexane (1:2), EtOAc−hexane (1:1), CH_2Cl_2−hexane (2:1), CH_2Cl_2−hexane (5:1), CH_2Cl_2−hexane (6:1), CH_2Cl_2, CH_2Cl_2−MeOH (100:1), and $CHCl_3$−MeOH (50:1). The yields (g kg^{-1}) of the alkaloids were as follows: **1** (0.184), **2** (0.041), **3** (0.011), **4** (0.002), **5** (0.002), **6** (0.001), and **7** (0.0005).

Jerantinine A (1): light yellowish crystals (EtOAc−CH_2Cl_2); mp 190−192 °C; $[\alpha]_D$ −294 (*c* 0.65, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 246 (4.05), 320 (4.23), 340 (4.17) nm; IR (dry film) ν_{max} 3538, 3373, 1669, 1606 cm^{-1}; ^1H NMR and ^{13}C NMR data, Tables 1 and 2, respectively; EIMS *m/z* 382 $[M]^+$ (87), 351 $[M - OMe]^+$ (5), 275 (79), 260 (16), 243 (46), 216 (20), 200 (13), 161 (14), 135 (100), 122 (22), 107 (37), 93 (16), 71 (9), 57 (12), 40 (17); HREIMS *m/z* 382.1892 (calcd for $C_{22}H_{26}N_2O_4$, 382.1893).

Jerantinine B (2): light yellowish crystals (EtOAc−CH_2Cl_2); mp 235−237 °C; $[\alpha]_D$ −386 (*c* 0.65, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 245 (3.80), 319 (3.97), 343 (3.90) nm; IR (dry film) ν_{max} 3538, 3372, 1671, 1606 cm^{-1}; ^1H NMR and ^{13}C NMR data, Tables 1 and 2, respectively; EIMS *m/z* 398 $[M]^+$ (100), 381 $[M - OH]^+$ (12), 311 (7), 275 (59), 260 (26), 243 (19), 199 (11), 169 (4), 151 (24), 138 (31), 123 (17), 108 (15), 49 (10); HREIMS *m/z* 398.1842 (calcd for $C_{22}H_{26}N_2O_5$, 398.1842).

Jerantinine C (3): light yellowish oil; $[\alpha]_D$ −110 (*c* 0.20, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 245 (4.22), 316 (4.31), 342 (4.21) nm; IR (dry film) ν_{max} 3538, 3371, 1661, 1606 cm^{-1}; ^1H NMR and ^{13}C NMR data, Tables 1 and 2, respectively; EIMS *m/z* 396 $[M]^+$ (12), 365 $[M - OMe]^+$ (1), 312 (2), 373 (43), 258 (3), 241 (100), 226 (7), 198 (13), 170 (5), 85 (5), 57 (8), 40 (10); HREIMS *m/z* 396.1690 (calcd for $C_{22}H_{24}N_2O_5$, 396.1685).

Jerantinine D (4): light yellowish oil; $[\alpha]_D$ −199 (*c* 0.35, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 246 (4.00), 317 (4.14), 341 (4.05) nm; IR (dry film) ν_{max} 3534, 3371, 1651, 1606 cm^{-1}; ^1H NMR and ^{13}C NMR data, Tables 1 and 2, respectively; EIMS m/z 412 $[M]^+$ (36), 380 $[M - OMe]^+$ (10), 273 (19), 260 (11), 241 (100), 228 (10), 200 (12), 167 (7), 149 (16), 129 (11), 83 (14), 71 (19), 57 (25), 40 (35); HREIMS *m/z* 412.1635 (calcd for $C_{22}H_{24}N_2O_6$, 412.1634).

Jerantinine E (5): light yellowish oil; $[\alpha]_D$ −357 (*c* 0.10, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 242 (4.00), 318 (4.05), 340 (3.98) nm; IR (dry film) ν_{max} 3535, 3368, 1671, 1606 cm^{-1}; ^1H NMR and ^{13}C NMR data, Tables 1 and 2, respectively; EIMS *m/z* 384 $[M]^+$ (28), 297 (5), 124 (100), 40 (15); HREIMS *m/z* 384.2048 (calcd for $C_{22}H_{28}N_2O_4$, 384.2049).

Jerantinine F (6): light yellowish oil; $[\alpha]_D$ −451 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 246 (3.95), 319 (4.08), 342 (4.01) nm; IR (dry film) ν_{max} 3538, 3372, 1671, 1606 cm^{-1}; ^1H NMR and ^{13}C NMR data, Tables 1 and 2, respectively; EIMS *m/z* 398 $[M]^+$ (17), 297 (8), 138 (100), 110 (15), 95 (11), 69 (12), 57 (19), 43 (36); HREIMS *m/z* 398.1847 (calcd for $C_{22}H_{26}N_2O_5$, 398.1842).

Jerantinine G (7): yellow oil; $[\alpha]_D$ −762 (*c* 0.24, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 245 (3.80), 285 (3.86), 363 (3.81), 417 (3.91) nm; IR (dry film) ν_{max} 1697, 1651, 1583 cm^{-1}; ^1H NMR and ^{13}C NMR data, Tables 1 and 2, respectively; EIMS *m/z* 396 $[M]^+$ (71), 365 $[M - OMe]^+$ (12), 337 (14), 311 (13), 293 (8), 275 (62), 260 (49), 239 (47), 224 (23), 200 (26), 182 (15), 151 (38), 138 (93), 123 (40), 108 (100), 97 (27), 71 (33), 57 (42), 43 (33); HREIMS *m/z* 396.1686 (calcd for $C_{22}H_{24}N_2O_5$, 396.1685).

Jerantinine A Acetate (8). Jerantinine A (**1**) (30 mg, 0.079 mmol) was dissolved in a mixture of acetic anhydride (1 mL) and pyridine (1 mL), and the mixture was stirred for 20 min. Water (10 mL) was then added, after which the mixture was basified to pH 9.0 with 10% Na_2CO_3 solution. Extraction with CH_2Cl_2, followed by removal of the solvent and chromatography (silica gel, Et_2O−hexane, 1:1), afforded **8** (29 mg, 87%): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.64 (t, *J* = 7.3 Hz, 3H), (Me-18), 0.87 (dq, *J* = 15, 7.3 Hz, 1H) (H-19a), 1.00 (dq, *J* = 15, 7.3 Hz, 1H) (H-19b), 1.84 (dd, *J* = 11.5, 4.9 Hz, 1H) (H-6a), 2.06 (td, *J* = 11.5, 7 Hz, 1H) (H-6b), 2.30 (s, 3H) (COMe), 2.39 (d, *J* = 15.1 Hz,

1H) (H-17a), 2.54 (dd, $J = 15.1$, 1.5 Hz, 1H) (H-17b), 2.63 (brs, 1H) (H-21), 2.67 (m, 1H) (H-5a), 3.03 (t, $J = 7$ Hz, 1H) (H-5b), 3.17 (d, $J = 15.9$ Hz, 1H) (H-3a), 3.43 (dd, $J = 15.9$, 4.6 Hz, 1H) (H-3b), 3.77 (s, 3H) (CO_2Me), 3.81 (s, 3H) (MeO-11), 5.70 (d, $J = 10$ Hz, 1H) (H-15), 5.78 (ddd, $J = 10$, 4.6, 1.5 Hz, 1H) (H-14), 6.51 (s, 1H) (H-12), 6.93 (s, 1H) (H-9), 8.97 (brs, 1H) (NH); EIMS *m/z* 424 $[M]^+$ (49), 393 $[M - OMe]^+$ (5), 317 (19), 275 (55), 260 (7), 242 (21), 216 (14), 200 (13), 135 (100), 122 (34), 107 (57), 93 (25), 81 (7).

Jerantinine B Acetate (9). In the same manner as above, treatment of **2** (20 mg, 0.050 mmol) with acetic anhydride and pyridine gave the acetate **9** (19 mg, 86%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.74 (t, $J = 7.3$ Hz, 3H), (Me-18), 0.90 (dq, $J = 14.5$, 7.3 Hz, 1H) (H-19a), 1.14 (dq, $J = 14.5$, 7.3 Hz, 1H) (H-19b), 1.74 (dd, $J = 11.5$, 4.4 Hz, 1H) (H-6a), 1.91 (td, $J = 11.5$, 6.1 Hz, 1H) (H-6b), 2.29 (s, 3H) (COMe), 2.37 (brs, 1H) (H-21), 2.41 (ddd, $J = 11.9$, 4.1, 3.9 Hz, 1H) (H-5a), 2.46 (d, $J = 15$ Hz, 1H) (H-17a), 2.57 (dd, $J = 15$, 1.4, 1H) (H-17b), 2.85 (m, 2H) (H-3a, H-5b), 3.10 (d, $J = 3.4$ Hz, 1H) (H-15), 3.48 (m, 1H) (H-14), 3.50 (m, 1H) (H-3b), 3.79 (s, 3H) (CO_2Me), 3.80 (s, 3H) (MeO-11), 6.49 (s, 1H) (H-12), 6.82 (s, 1H) (H-9), 8.91 (brs, 1H) (NH); EIMS *m/z* 440 $[M]^+$ (98), 410 $[M - OMe + H]^+$ (20), 397 $[M - CO_2Me]^+$ (14), 353 (19), 316 (19), 302 (62), 275 (39), 260 (46), 241 (15), 200 (14), 138 (100), 123 (13), 108 (61), 93 (10).

10-*O*-Methyljerantinine A (10). $TMSCHN_2$ (2 M hexane solution, 0.395 mL, 0.79 mmol) was added to a stirred solution of **1** (30 mg, 0.079 mmol) and *N*,*N*-diisopropylethylamine (0.135 mL, 0.79 mmol) in methanol−acetonitrile (1:9, 2 mL). The mixture was kept in the dark at −10 °C for 86 h. Removal of the solvent under reduced pressure, followed subsequently by chromatography of the residue (silica gel, acetone−hexane, 1:4), gave **10** (24 mg, 77%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65 (t, $J = 7.3$ Hz, 3H) (Me-18), 0.88 (dq, $J = 14$, 7.3 Hz, 1H) (H-19a), 1.02 (dq, $J = 14$, 7.3 Hz, 1H) (H-19b), 1.79 (dd, $J = 11$, 3 Hz, 1H) (H-6a), 2.08 (td, $J = 11$, 7 Hz, 1H) (H-6b), 2.40 (d, $J = 15$ Hz, 1H) (H-17a), 2.55 (d, $J = 15$ Hz, 1H) (H-17b), 2.63 (s, 1H) (H-21), 2.70 (m, 1H) (H-5a), 3.05 (t, $J = 6.7$ Hz, 1H) (H-5b), 3.21 (d, $J = 16$ Hz, 1H) (H-3a), 3.47 (dd, $J = 16$, 4 Hz, 1H) (H-3b), 3.77 (s, 3H) (CO_2Me), 3.87 (s, 6H) (MeO-10, MeO-11), 5.73 (d, $J = 10.0$ Hz, 1H) (H-15), 5.79 (ddd, $J = 10.0$, 4, 1 Hz, 1H) (H-14), 6.49 (s, 1H) (H-12), 6.85 (s, 1H) (H-9), 8.88 (brs, 1H) (NH); EIMS *m/z* 396 $[M]^+$ (76), 381 $[M - Me]^+$ (9), 365 $[M - OMe]^+$ (17), 326 (9), 289 (100), 274 (29), 257 (50), 242 (40), 230 (53), 214 (33), 184 (29), 168 (16), 135 (97), 122 (33), 107 (84), 92 (43), 79 (12), 65 (16).

10-*O*-Methyljerantinine B (11). In the same manner as above, **2** (30 mg, 0.075 mmol) was treated with $TMSNCH_2$ (0.75 mmol) in the presence of *N*,*N*-diisopropylethylamine (0.79 mmol) to yield **11** (22 mg, 74%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.75 (t, $J = 7.3$ Hz, 3H) (Me-18), 0.91 (dq, $J = 14.5$, 7.3 Hz, 1H) (H-19a), 1.15 (dq, $J = 14.5$, 7.3 Hz, 1H) (H-19b), 1.69 (dd, $J = 11.7$, 4.4 Hz, 1H) (H-6a), 1.95 (td, $J = 11.7$, 6.3 Hz, 1H) (H-6b), 2.42 (d, $J = 1.2$ Hz, 1H) (H-21), 2.44 (m, 1H) (H-5a), 2.48 (d, $J = 14.9$ Hz, 1H) (H-17a), 2.58 (dd, $J = 14.9$, 2.0, 1H) (H-17b), 2.90 (m, 2H) (H-3a, H-5b), 3.13 (d, $J = 3.7$ Hz, 1H) (H-15), 3.51 (m, 1H) (H-14), 3.52 (m, 1H) (H-3b), 3.79 (s, 3H) (CO_2Me), 3.85 (s, 6H) (MeO-10, MeO-11), 6.48 (s, 1H) (H-12), 6.74 (s, 1H) (H-9), 8.81 (brs, 1H) (NH); EIMS *m/z* 442 $[M]^+$ (8), 412 $[M - OMe + H]^+$ (100), 381 $[M - OMe - OMe + H]^+$ (11), 353 $[M - OMe - CO_2Me]^+$ (12), 313 (26), 289 (30), 274 (89), 255 (17), 242 (26), 228 (14), 214 (25), 138 (77), 123 (17), 108 (85), 93 (11).

Cytotoxicity Assays. Cytotoxicity assays were carried out following the procedure that has been described in detail previously.[31,32]

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