Cytotoxic Amide Alkaloids from *Piper boehmeriaefolium*

Gui-Hua Tang,[†,‡] Dong-Mei Chen,[§] Bei-Ying Qiu,[§] Li Sheng,[§] Yue-Hu Wang,[†] Guang-Wan Hu,[†] Fu-Wei Zhao,[†,‡] Li-Juan Ma,[⊥] Huan Wang,[∥] Qiao-Qin Huang,[∥] Jin-Jin Xu,[∥] Chun-Lin Long,*[,†,⊥] and Jia Li*[,§]

Key Laboratory of Economic Plants and Biotechnology, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, People's Republic of China, Graduate University of Chinese Academy of Sciences, Beijing 100049, People's Republic of China, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, People's Republic of China, College of Life and Environmental Sciences, Minzu University of China, Beijing 100081, People's Republic of China, and Yunnan Agricultural University, Kunming 650201, People's Republic of China

Eight new amide alkaloids (**1**–**8**) and 19 known ones were isolated from the whole plant of *Piper boehmeriaefolium*. Their structures were determined through spectroscopic data analyses. Cytotoxic activity of these amides against human cervical carcinoma HeLa cells was evaluated, and 1-[(9*E*)-10-(3,4-methylenedioxyphenyl)-9-decenoyl]pyrrolidine (**9**) exhibited significant inhibitory activity with an IC_{50} value of 2.7 μg/mL.

Phytochemical investigations of *Piper* species have revealed the occurrence of amides, propenylphenols, lignans, neolignans, terpenes, steroids, kawapyrones, piperolides, and flavonoids.[1] The amides are reported to possess various ACAT inhibitory,[2] cytotoxic,[3−5] antimycobacterial,[6−8] insecticidal,[9−11] antiprotozoan,[12] analgesic,[13] anxiolytic,[14] and antidepressant[14,15] activities.

Piper boehmeriaefolium (Miq.) C. DC. (Piperaceae) is a subshrub distributed mainly in eastern India, Bhutan, Myanmar, Thailand, northern Vietnam, Malaysia, and Yunnan Province of China.[16] In China, the whole plant (luziteng, Chinese name) is used in Traditional Chinese Medicine and ethnomedicine to alleviate pain and for the treatment of rheumatism and arthritic conditions.[17] Previous phytochemical investigations of Indian *P. boehmeriaefolium* resulted in the isolation of amides such as piperine,[18] aristolactams,[19,20] and 4,5-dioxoaporphines.[19] However, there has been no report about chemical constituents of Chinese *P. boehmeriaefolium*. In our research, methanolic extracts of *P. boehmeriaefolium* were separated by a series of chromatographic steps to afford eight new amide alkaloids (**1**–**8**), along with 19 known ones. The cytotoxic activity of these compounds against HeLa (human cervical carcinoma) cells was evaluated.
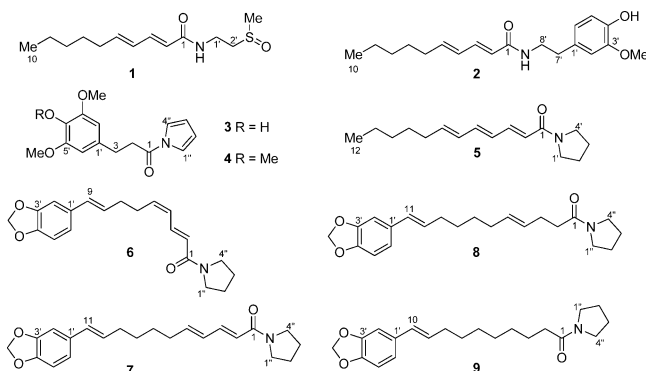
Results and Discussion

The molecular formula of compound **1**, $C_{13}H_{23}NO_2S$, was determined by HRESIMS [*m/z* 280.1315 [M + Na]+ (calcd

* Corresponding authors. Tel/Fax: +86-10-68930381. E-mail: long@mail.kib.ac.cn (C.-L.L.). Tel/Fax: +86-21-50801552/50800721. E-mail: jli@mail.shcnc.ac.cn (J.L.).
† Kunming Institute of Botany.
‡ Graduate University of Chinese Academy of Sciences.
§ Shanghai Institute of Materia Medica.
⊥ Minzu University of China.
∥ Yunnan Agricultural University.

280.1313)]. Its IR spectrum showed a strong absorption at 1014 cm^{-1}, indicating the existence of a sulfoxide group.[21] Absorptions at 3259, 1660, 1634, 1618, and 1557 cm^{-1} in the IR spectrum, combined with the occurrence of four olefin proton resonances [δ_H 5.80 (d, *J* = 15.2 Hz, H-2), 7.19 (dd, *J* = 15.2 and 10.0 Hz, H-3), 6.14 (dd, *J* = 15.1 and 10.0 Hz, H-4), and 6.07 (ddd, *J* = 15.1, 6.5, and 6.5 Hz, H-5)] in the ^{1}H NMR spectrum of **1**, suggested the presence of an α,β,γ,δ-unsaturated secondary amide.[22] Thirteen signals consistent with an amide carbonyl, four methine, six methylene, and two methyl groups were observed in the ^{13}C NMR spectrum of **1** (Table 1). The ^{1}H−^{1}H COSY spectrum (Figure 1) exhibited four partial structures (**a**−**d**). On the basis of the HMBC correlations (Figure 1) from H-3 to C-1 and C-5, H-4 to C-6, H_2-6 to C-4, H_2-8 to C-10, and H_3-10 to C-8, a decadienoyl group was confirmed. Fragment **d** showed HMBC correlations from H-1′ to C-1, and *N*H to C-1 and C-1′. The methyl sulfoxide group was located at C-2′ by the HMBC correlations to *S*Me/C-2′ and H_2-2′/*S*Me. Therefore, the structure of compound **1** was elucidated as (2*E*,4*E*)-*N*-[2-(methylsulfinyl)ethyl]-2,4-decadienamide.

The molecular formula of compound **2** was confirmed as $C_{19}H_{27}NO_3$ by the HREIMS. Its IR spectrum showed absorptions for OH, amine, carbonyl, phenyl, and double-bond functionalities. The ^{1}H NMR spectrum of **2** (Table 2) clearly showed an aromatic ABX coupling system [δ_H 6.84 (1H, d, *J* = 8.0 Hz, H-5′), 6.69 (1H, s, H-2′), and 6.67 (1H, d, *J* = 8.0 Hz, H-6′)], two *trans* double bonds (*J*$_{2,3}$ = 14.8 Hz, *J*$_{4,5}$ = 14.7 Hz), and two methyl groups [δ_H 3.86 (3H, s, OMe), 0.88 (3H, t, *J* = 6.6 Hz, H-10)]. Comparison of the NMR data of **2** with those of **1** (Table 1) was indicative of the same amide chain but with a different *N*-substituent. The *N*-substituent of **2** was determined to be *N*-(4-hydroxy-3-methoxyphenyl)ethyl, which was verified by correlations observed in the ^{1}H−^{1}H COSY and HMBC spectra (Figure 1). Consequently, compound **2** was deduced as (2*E*,4*E*)-*N*-[(4-hydroxy-3-methoxyphenyl)ethyl]-2,4-decadienamide.

Compound **3** was obtained as a white crystalline solid having the molecular formula $C_{15}H_{17}NO_4$ based on the [M + H]+ at *m/z* 276.1231 (HRESIMS). The IR spectrum indicated the presence of OH (3463 cm^{-1}), carbonyl (1710 cm^{-1}), pyrrole (1460 cm^{-1}), and aromatic (1615 and 1519 cm^{-1}) groups. The ^{1}H and ^{13}C NMR spectra of **3** (Table 2) displayed signals indicating a 1,3,4,5-symmetrically tetrasubstituted phenyl [δ_H 6.42 (2H, s, H-2′, H-6′); δ_C 130.9 (C-1′), 104.7 (C-2′, C-6′), 146.7 (C-3′, C-5′), and 132.9 (C-4′)], a pyrrole [δ_H 7.26 (2H, br s, H-1″, H-4″) and 6.22 (2H, t, *J* = 2.3 Hz, H-2″, H-3″); δ_C 118.6 (C-1″, C-4″) and 112.8 (C-2″, C-3″)], two methylene [δ_H 3.06 (2H, t, *J* = 7.6 Hz, H-2) and 2.96 (2H, t, *J* = 7.6 Hz, H-3); δ_C 36.6 (C-2) and 30.3 (C-3)], an amide

Table 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR Data of **1** and **2** in CDCl$_3$

	1			**2**	
position	δ_C	δ_H (*J* in Hz)	position	δ_C	δ_H (*J* in Hz)
1	167.0 C		1	166.5 C	
2	121.1 CH	5.80, d (15.2)	2	121.3 CH	5.68, d (14.8)
3	141.8 CH	7.19, dd (15.2, 10.0)	3	141.6 CH	7.18, dd (14.8, 9.0)
4	128.1 CH	6.14, dd (15.1, 10.0)	4	128.1 CH	6.10, dd (14.7, 9.0)
5	143.8 CH	6.07, ddd (15.1, 6.5, 6.5)	5	143.6 CH	6.05, ddd (14.7, 6.8, 6.8)
6	32.9 CH$_2$	2.15, 2H, ddd (6.8, 6.8, 6.5)	6	32.9 CH$_2$	2.13, 2H, ddd (6.8, 6.0, 6.0)
7	28.4 CH$_2$	1.41, 2H, m	7	28.4 CH$_2$	1.41, 2H, m
8	31.3 CH$_2$	1.28, 2H, m	8	31.3 CH$_2$	1.28, 2H, m
9	22.4 CH$_2$	1.30, 2H, m	9	22.4 CH$_2$	1.29, 2H, m
10	14.0 CH$_3$	0.89, 3H, t (6.7)	10	14.0 CH$_3$	0.88, 3H, t (6.6)
			1′	130.6 C	
			2′	111.2 CH	6.69, s
			3′	146.6 C	
			4′	144.2 C	
			5′	114.4 CH	6.84, d (8.0)
			6′	121.3 CH	6.67, d (8.0)
1′	34.2 CH$_2$	3.90, m	7′	35.2 CH$_2$	2.76, 2H, t (6.8)
		3.79, m			
2′	53.2 CH$_2$	3.13, m	8′	40.9 CH$_2$	3.55, 2H, m
		2.85, m			
SMe	38.5 CH$_3$	2.64, 3H, s	OMe	55.9 CH$_3$	3.86, 3H, s
NH		6.94, br. s	NH		5.59, t (5.1)

Table 2. NMR Spectroscopic Data for Compounds **3** and **4**

	3[a]		**4**[b]	
position	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	169.6 C		169.7 C	
2	36.3 CH$_2$	3.06, 2H, t (7.6)	36.6 CH$_2$	3.13, 2H, m
3	30.3 CH$_2$	2.96, 2H, t (7.6)	30.8 CH$_2$	3.04, 2H, m
1′	130.9 C		136.0 C	
2′, 6′	104.7 CH	6.42, 2H, s	105.3 CH	6.45, 2H, s
3′, 5′	146.7 C		153.3 C	
4′	132.9 C		136.0 C	
1″, 4″	118.6 CH	7.26, 2H, br s	118.9 CH	7.30, 2H, br s
2″, 3″	112.8 CH	6.22, 2H, t (2.3)	113.2 CH	6.28, 2H, t (2.3)
3′,5′-OMe	55.9 CH$_3$	3.79, 6H, s	55.1 CH$_3$	3.84, 6H, s
4′-OH or OMe		5.63 (OH, s)	60.8 CH$_3$	3.82, 3H, s

[a] Measured in CDCl$_3$ at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. [b] Measured in CDCl$_3$ at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR.

carbonyl [δ_C 169.6 (C-1)], and two methoxy [δ_H 3.79 (6H, s), δ_C 55.9 (2 C)] groups. According to the HMBC correlations from H-2 to C-1′, H-3 to C-1 and C-2′, and H-2′ to C-3, compound **3** was determined to be 3-(4-hydroxy-3,5-dimethoxyphenyl)propanoylpyrrole.

Compound **4** exhibited a molecular ion peak at *m/z* 289.1313 [M]$^+$ (calcd, 289.1314), consistent with the molecular formula C$_{16}$H$_{19}$NO$_4$. Comparison of the NMR data (Table 2) and MS of **4** with those of **3** demonstrated that **4** had an additional OCH$_3$ group, which was located at C-4′ from analysis of the HMBC spectrum. Thus, compound **4** was identified as 3-(3,4,5-timethoxyphenyl)pro-panoylpyrrole.

The HREIMS of **5** exhibited a molecular ion peak at *m/z* 247.1935 (calcd 247.1936), corresponding to the molecular formula C$_{16}$H$_{25}$NO. Comparing the NMR data (Tables 3 and 4) and MS of

Figure 1. Key 2D NMR correlations of **1** and **2**.

5 and of the known 1-[(2*E*,4*E*)-2,4-dodecadienoyl]pyrrolidine (**10**),[23] it appeared that the former had an additional *trans* double bond (*J*$_{6,7}$ = 14.8 Hz). In the ^{1}H–^{1}H COSY spectrum, six mutually coupled olefin protons indicated that the three *trans* double bonds of **5** were conjugated. Therefore, compound **5** was determined to be 1-[(2*E*,4*E*,6*E*)-2,4,6-dodecatrienoyl]pyrrolidine.

The molecular formula of compound **6** was defined as C$_{20}$H$_{23}$NO$_3$. Its NMR spectra (Tables 3 and 4) were very similar to those of 1-[(2*E*,4*E*,8*E*)-9-(3,4-methylenedioxyphenyl)-2,4,8-non-atrienoyl]pyrrolidine.[7] However, the coupling constant of the olefin protons (*J*$_{2,3}$ = 14.5 Hz, *J*$_{4,5}$ = 11.0 Hz, *J*$_{8,9}$ = 16.0 Hz) in the ^{1}H NMR spectrum of **6** (Table 3) indicated the presence of two *trans* double bonds and one *cis* double bond, rather than three *trans* double bonds as in the known compound. The double bonds were deduced to be 2*E*, 4*Z*, 8*E* by interpretation of the 2D NMR data. Hence, compound **6** was 1-[(2*E*,4*Z*,8*E*)-9-(3,4-methylenedioxyphe-nyl)-2,4,8-nonatrienoyl]pyrrolidine.

Compound **7** was assigned the molecular formula C$_{22}$H$_{27}$NO$_3$ by HREIMS. Similar to the known 1-[(2*E*,4*E*,8*E*)-9-(3,4-methyl-enedioxyphenyl)-2,4,8-nonatrienoyl]pyrrolidine,[23] its ^{1}H and ^{13}C NMR spectra (Tables 3 and 4) showed a 3,4-methylenedioxyphenyl group, three *trans* double bonds, and a pyrrolidine-amide. The difference between **7** and the above-mentioned known compound was that there were two additional methylene groups in **7**, which was confirmed by the MS analysis. On the basis of the observed HMBC correlations, compound **7** was determined to be 1-[(2*E*,4*E*,9*E*)-10-(3,4-methylenedioxyphenyl)-2,4,9-undecatrienoyl]pyrrolidine.
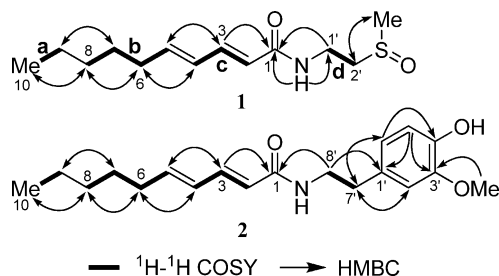
Table 3. ^{1}H NMR Spectroscopic Data for Compounds **5−8** (δ in ppm, J in Hz)

position	5[a]	6[b]	7[b]	8[b]
2	6.15, d (14.8)	6.20, d (14.5)	6.08, d (15.0)	2.31, 2H, m
3	7.32, dd (14.8, 11.3)	7.65, dd (14.5, 11.0)	7.29, dd (15.0, 10.5)	2.33, 2H, m
4	6.24, dd (14.8, 11.3)	6.19, t (11.0)	6.18, dd (15.5, 10.5)	5.46, m
5	6.51, dd (14.8, 10.4)	5.83, ddd (11.0, 7.5, 7.5)	6.09, ddd (15.5, 6.5, 6.5)	5.46, m
6	6.12, dd (14.8, 10.4)	2.51, 2H, ddd (7.5, 7.0, 7.0)	2.18, 2H, m	2.00, 2H, m
7	5.90, ddd (14.8, 7.0, 7.0)	2.32, 2H, ddd (7.0, 7.0, 7.0)	1.47, 2H, m	1.40, 2H, m
8	2.13, 2H, ddd (7.0, 7.0, 7.0)	6.05, ddd (16.0, 7.0, 7.0)	1.47, 2H, m	1.44, 2H, m
9	1.41, 2H, m	6.34, d (16.0)	2.18, 2H, ddd (7.1, 6.6, 6.6)	2.17, ddd (7.0, 6.5, 6.5)
10	1.29, 2H, m		6.02, ddd (16.0, 7.1, 7.1),	6.02, ddd (15.5, 7.0, 7.0)
11	1.30, 2H, m		6.28, d (16.0)	6.28, d (15.5)
12	0.89, 3H, t (6.8)			
1′	3.52, 2H, m			
2′	1.97, 2H, m	6.91, s	6.89, s	6.89, s
3′	1.87, 2H, m			
4′	3.55, 2H, m			
5′		6.77, overlapped	6.75, d (8.2)	6.73, d (8.1)
6′		6.77, overlapped	6.72, d (8.2)	6.75, d (8.1)
1″		3.55, 2H, m	3.53, 2H, m	3.39, 2H, m
2″		1.99, 2H, m	1.91, 2H, br s	1.93, 2H, m
3″		1.90, 2H, m	1.91, 2H, br s	1.84, 2H, m
4″		3.57, 2H, m	3.53, 2H, m	3.46, 2H, m
OCH$_2$O		5.96, 2H, s	5.93, 2H, s	5.93, s

^{a} Measured in CDCl$_3$ at 400 MHz for ^{1}H NMR. ^{b} Measured in CDCl$_3$ at 500 MHz for ^{1}H NMR.

Table 4. ^{13}C NMR (100 MHz) Spectroscopic Data for Compounds **5−8** in CDCl$_3$ (δ in ppm)

position	5	6	7	8
1	165.1 C	165.1 C	165.2 C	171.3 C
2	120.8 CH	122.2 CH	119.7 CH	34.8 CH$_2$
3	141.9 CH	136.5 CH	142.3 CH	28.0 CH$_2$
4	128.3 CH	127.3 CH	128.8 CH	128.9 CH
5	139.9 CH	138.8 CH	143.0 CH	131.2 CH
6	129.9 CH	27.9 CH$_2$	32.8 CH$_2$	32.4 CH$_2$
7	139.6 CH	32.7 CH$_2$	28.2 CH$_2$	28.9 CH$_2$
8	32.9 CH$_2$	127.7 CH	28.9 CH$_2$	29.0 CH$_2$
9	28.7 CH$_2$	130.2 CH	32.8 CH$_2$	32.7 CH$_2$
10	31.4 CH$_2$		128.9 CH	129.3 CH
11	22.5 CH$_2$		129.5 CH	129.3 CH
12	14.0 CH$_3$			
1′	46.4 CH$_2$	132.1 C	132.3 C	132.6 C
2′	26.1 CH$_2$	105.4 CH	105.3 CH	105.3 CH
3′	24.3 CH$_2$	147.8 C	147.9 C	147.9 C
4′	45.9 CH$_2$	146.6 C	145.5 C	146.5 C
5′		108.2 CH	108.2 CH	108.2 CH
6′		120.4 CH	120.2 CH	120.2 CH
1″		46.5 CH$_2$	46.2 CH$_2$	46.6 CH$_2$
2″		26.1 CH$_2$	24.5 CH$_2$	26.1 CH$_2$
3″		24.3 CH$_2$	24.3 CH$_2$	24.4 CH$_2$
4″		45.9 CH$_2$	46.2 CH$_2$	45.7 CH$_2$
OCH$_2$O		100.9 CH$_2$	100.9 CH$_2$	100.8 CH$_2$

Compound **8** had the molecular formula $C_{22}H_{29}NO_3$ with nine degrees of unsaturation based on HREIMS analysis. Comparison of the MS and NMR data of **8** and **7** (Tables 3 and 4) suggested that a double bond conjugated with the pyrrolidine-amide had disappeared in **8**, which was also supported by the ^{1}H−^{1}H COSY and HMBC correlations. The double bond conjugated to the aromatic ring had a *trans* configuration ($J_{10,11}$ = 16.0 Hz), but the geometry of the 4,5-double bond could not be determined by the ^{1}H NMR spectrum of **8** owing to overlapped proton signals [δ_H 5.46 (2H, m, H-4, H-5)]. However, measurement by 2D NMR confirmed the assignment of two allylic methylene carbons (C-3 and C-6) adjacent to the isolated double bond to be at δ 28.0 and 32.4. The non-upfield chemical shift of these signals indicated the geometry of this double bond to be *E*.[24] Accordingly, the structure of **8** was deduced as 1-[(4E,9E)-10-(3,4-methylenedioxyphenyl)-4,9-nonadienoyl]pyrrolidine.

The known alkaloids, 1-[(9E)-10-(3,4-methylenedioxyphenyl)-9-decenoyl]pyrrolidine (**9**),[25] 1-[(2E,4E)-2,4-decadienoyl]pyrrolidine (**10**),[26] 1-[(2E,4E)-2,4-dodecadienoyl]pyrrolidine (**11**),[23] 1-[(2E)-7-(3,4-methylenedioxyphenyl)-2-heptenoyl]pyrrolidine (**12**),[27] 1-[(2E,4E)-7-(3,4-methylenedioxyphenyl)-2,4-heptadienoyl]pyrrolidine (**13**),[28] 1-[(2E,8E)-9-(3,4-methylenedioxyphenyl)-2,8-nonadienoyl]pyrrolidine (**14**),[23] 1-[(8E)-9-(3,4-methylenedioxyphenyl)-8-nonenoyl]pyrrolidine (**15**),[23] 1-[(2E,4E,8E)-9-(3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl]pyrrolidine (**16**),[23] 1-[(2E,4E)-11-(3,4-methylenedioxyphenyl)-2,4-undecenoyl]pyrrolidine (**17**),[27] 1-[(2E,10E)-11-(3,4-methylenedioxyphenyl)-2,10-undecenoyl]pyrrolidine (**18**),[27] (2E,4E)-N-isobutyl-2,4-decadienamide (**19**),[24b] (2E,4E)-N-isobutyl-2,4-dodecadienamide (**20**),[29] (2E,4E)-N-isobutyl-7-(3,4-methylenedioxyphenyl)-hepta-2,4-dienamide (**21**),[30] (2E)-N-isobutyl-7-(3,4-methylenedioxyphenyl)hepta-2-enamide (**22**),[31] (2E,8E)-N-isobutyl-9-(3,4-methylenedioxyphenyl)nona-2,4-dienamide (**23**),[32] (8E)-N-isobutyl-9-(3,4-methylenedioxyphenyl)nona-8-enamide (**24**),[2] (2E,4E,8E)-N-isobutyl-11-(3,4-methylenedioxyphenyl)undeca-2,4,8-trienamide (**25**),[10] N-trans-feruloyltyramine (**26**),[33,34] and N-trans-sinapoyltyramine (**27**),[35] were identified by comparison of their spectroscopic data with data in the literature. All of these known alkaloids were isolated for the first time from *P. boehmeriaefolium*. Among them, **12**, **17**, and **18** are reported here for the first time as natural products. Moreover, the ^{13}C NMR assignments of **11**, **12**, **17**, **18**, **20**, and **22**, which were not reported previously, are shown in the Supporting Information.

All of the amides from *P. boehmeriaefolium* were evaluated for their inhibitory activities against human cervical carcinoma (HeLa cells) using doxorubicin as the positive control (IC$_{50}$ = 0.163 ± 0.019 μg/mL). Compound **9** exhibited cytotoxic activity with an IC$_{50}$ value of 2.67 ± 0.68 μg/mL, whereas compounds **6−8** and **14−16** showed weak inhibitory activities (IC$_{50}$ = 7.42 ± 1.61, 11.61 ± 3.71, 12.19 ± 4.21, 14.96 ± 1.14, 17.95 ± 1.69, and 13.74 ± 2.37 μg/mL, respectively), and the remaining compounds were inactive against HeLa cells.

Experimental Section

General Experimental Procedures. Melting points were determined using an X-4 melting point apparatus (Yingyu Yuhua Apparatus Factory, Gongyi, People's Republic of China) and were not corrected. UV spectra were measured on a Shimadzu double-beam 210A spectrometer. IR spectra were determined on a Bio-Rad FTS-135 infrared spectrophotometer with KBr disks. 1D and 2D NMR spectra were recorded on Bruker AM-400 and DRX-500 spectrometers with TMS as internal standard. ESIMS and HRESIMS analyses were carried out on an API Qstar Pulsar 1 instrument. EIMS and HREIMS were carried out on a Waters Autospec Premier P776 mass spectrometer. Semipreparative HPLC was performed on an Agilent 1200 series pump

equipped with a diode array detector and a Zorbax SB-C$_{18}$ column (5.0 μm, 9.4 × 250 mm). Silica gel G (80−100 and 300−400 mesh, Qingdao Makall Group Co., Ltd.), MCI gel CHP 20P (75−150 μm, Mitsubishi Chemical Corporation, Tokyo), C$_{18}$ silica gel (40−75 μm, Fuji Silysia Chemical Ltd.), silica gel H (10−40 μm), and Sephadex LH-20 (GE Healthcare Bio-Xciences AB) were used for column chromatography (CC), and silica gel GF$_{254}$ (Qingdao), for preparative TLC as procoated plates. TLC spots were visualized under UV light and by dipping into 5% H$_2$SO$_4$ in alcohol followed by heating.

Plant Material. The whole plant, *P. boehmeriaefolium* (Miq.) C. DC., was collected from Luxi County, Yunnan Province, People's Republic of China, in October 2008. The plant was identified by one of the authors (G.-W.H.), and a voucher specimen (LX002) was deposited at the Key Laboratory of Economic Plants and Biotechnology, Kunming Institute of Botany.

Extraction and Isolation. The air-dried, powdered *P. boehmeriaefolium* plant (4.2 kg) was extracted with MeOH (4, 3, and 3 h, respectively) under reflux. The combined MeOH extracts were evaporated under reduced pressure to yield a residue, which was suspended in H$_2$O and then partitioned successively with petroleum ether and CHCl$_3$ to give two corresponding portions. After TLC testing, the two portions were combined because both contained alkaloids. The combined extract (176.0 g) was subjected to CC over silica gel G (80−100 mesh) using petroleum ether−Me$_2$CO (20:1, 10:1, 5:1, and 0:1) and CHCl$_3$−MeOH (1:1) to yield six fractions (A−F).

Each fraction was subjected to CC over MCI gel CHP 20P, C$_{18}$ silica gel, and Sephadex LH-20 and then further purified by repeated CC over silica gel, preparative TLC, and semipreparative HPLC to obtain pure compounds. Compounds **19** (33.2 mg) and **20** (20.0 mg) were obtained from fraction A. Fraction B gave compounds **4** (19.9 mg) and **11** (80.8 mg). Fraction C afforded compounds **3** (296.4 mg), **5** (6.3 mg), **6** (13.2 mg), **7** (26.1 mg), **8** (4.8 mg), **9** (36.9 mg), **10** (21.8 mg), **12** (243.5 mg), **14** (376.7 mg), **15** (557.0 mg), **17** (40.3 mg), **18** (173.1 mg), **21** (127.7 mg), **22** (119.2 mg), **23** (41.2 mg), **24** (13.1 mg), and **25** (50.3 mg). Fraction D yielded compounds **2** (12.0 mg), **13** (15.2 mg), and **16** (30.7 mg). Compounds **26** (70.7 mg), and **27** (12.4 mg) were obtained from fraction E, and compound **1** (9.7 mg) was obtained from fraction F. The details on isolation of these compounds are provided in the Supporting Information.

(2E,4E)-N-[2-(Methylsulfinyl)ethyl]-2,4-decadienamide (1): yellow solid (CHCl$_3$); mp 86−87 °C; UV (CHCl$_3$) λ_{max} (log ε) 263 (4.06), 233 (3.90) nm; IR (KBr) ν_{max} 3295, 1660, 1634, 1618, 1557, 1439, 1340, 1264, 1253, 1050, 1014, 990, 668 cm^{-1}; ^{1}H and ^{13}C NMR, (see Table 2); ESIMS *m/z* 280 [M + Na]$^+$, 537 [2 M + Na]$^+$; EIMS *m/z* 257 [M]$^+$ (3), 242 (41), 194 (91), 151 (100), 136 (12), 122 (14), 95 (15), 91 (6), 81 (76), 69 (19), 55 (7); HRESIMS *m/z* 280.1315 [M + Na]$^+$ (calcd for C$_{13}$H$_{23}$NO$_2$SNa, 280.1313); HRESIMS *m/z* 258.1508 [M + H]$^+$ (calcd for C$_{13}$H$_{24}$NO$_2$S, 258.1494).

(2E,4E)-N-[4-Hydroxy-3-methoxyphenyl)ethyl]-2,4-decadienamide (2): yellow oil (CHCl$_3$); UV (CHCl$_3$) λ_{max} (log ε) 263 (3.81), 234 (3.64) 210 (3.54) nm; IR (KBr) ν_{max} 3395, 3295, 1656, 1627, 1611, 1542, 1522, 1457, 1271, 1030, 996 cm^{-1}; ^{1}H and ^{13}C NMR (see Table 2); EIMS *m/z* 317 [M]$^+$ (10), 168 (11), 150 (100), 81 (7); HRESIMS *m/z* 317.1991 [M]$^+$ (calcd for C$_{19}$H$_{27}$NO$_3$, 317.1991).

3-(4-Hydroxy-3,5-dimethoxyphenyl)propanoylpyrrole (3): white, crystalline solid (CHCl$_3$); mp 89−90 °C; UV (CHCl$_3$) λ_{max} (log ε) 242 (3.64), 229 (3.20), 220 (3.22), 215 (3.21) nm; IR (KBr) ν_{max} 3463, 3124, 1710, 1615, 1519, 1460, 1318, 1302, 1249, 1106, 923, 762 cm^{-1}; ^{1}H and ^{13}C NMR (see Table 1); ESIMS *m/z* 276 [M + H]$^+$; HRESIMS *m/z* 276.1231 [M + H]$^+$ (calcd for C$_{15}$H$_{18}$NO$_4$, 276.1235).

3-(3,4,5-Trimethoxyphenyl)propanoylpyrrole (4): white, crystalline solid (CHCl$_3$); mp 52−53 °C; UV (CHCl$_3$) λ_{max} (log ε) 242 (3.80), 231 (3.36), 225 (3.38), 218 (3.39), 200 (3.38) nm; IR (KBr) ν_{max} 3151, 1724, 1590, 1509, 1468, 1375, 1299, 1243, 1128, 1115, 1001, 923, 753 cm^{-1}; ^{1}H and ^{13}C NMR (see Table 1); EIMS *m/z* 289 [M]$^+$ (87), 222 (13), 194 (16), 181 (100), 165 (6), 148 (11), 136 (5), 91 (3), 77 (3), 67 (3); HREIMS *m/z* 289.1313 [M]$^+$ (calcd for C$_{16}$H$_{19}$NO$_4$, 289.1314).

1-[(2E,4E,6E)-2,4,6-Dodecatrienoyl]pyrrolidine (5): yellow oil (CHCl$_3$); UV (CHCl$_3$) λ_{max} (log ε) 263 (3.43), 235 (3.31), 221 (3.29), 203 (3.23) nm; IR (KBr) ν_{max} 1627, 1002 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 3 and 4); EIMS *m/z* 247 [M]$^+$ (3), 179 (31), 150 (94), 98 (65), 81 (29), 70 (100), 55 (31); HREIMS *m/z* 247.1935 [M]$^+$ (calcd for C$_{16}$H$_{25}$NO, 247.1936).

1-[(2E,4Z,8E)-9-(3,4-Methylenedioxyphenyl)-2,4,8-nonatrienoyl]pyrrolidine (6): yellow oil (CHCl$_3$); UV (CHCl$_3$) λ_{max} (log ε) 270 (4.04), 233 (3.91), 223 (3.90), 216 (3.90) nm; IR (KBr) ν_{max} 1648, 1613, 1598, 1503, 1490, 1442, 1249, 1038 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 3 and 4); EIMS *m/z* 325 [M]$^+$ (6), 161 (74), 149 (8), 131 (100), 113 (10), 103 (37), 77 (12); HREIMS *m/z* 325.1679 [M]$^+$ (calcd for C$_{20}$H$_{23}$NO$_3$, 325.1678).

1-[(2E,4E,9E)-10-(3,4-Methylenedioxyphenyl)-2,4,9-undecatrienoyl]pyrrolidine (7): white solid (CHCl$_3$); mp 46−47 °C; UV (CHCl$_3$) λ_{max} (log ε) 381 (1.68), 363 (1.87), 265 (2.87), 234 (2.82), 228 (2.84), 225 (2.85), 220 (2.88), 215 (2.90) nm; IR (KBr) ν_{max} 1647, 1626, 1503, 1490, 1446, 1249, 1038 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 3 and 4); EIMS *m/z* 353 [M]$^+$ (23), 254 (10), 240 (21), 218 (51), 150 (96), 135 (100), 113 (36), 103 (48), 98 (79), 77 (29), 70 (21); HREIMS *m/z* 353.1992 [M]$^+$ (calcd for C$_{22}$H$_{27}$NO$_3$, 353.1991).

1-[(4E,9E)-10-(3,4-Methylenedioxyphenyl)-4,9-nonadienoyl]pyrrolidine (8): yellow oil (CHCl$_3$); UV (CHCl$_3$) λ_{max} (log ε) 305 (2.35), 264 (2.67), 234 (2.51), 221 (2.48), 214 (2.45), 209 (2.44) nm; IR (KBr) ν_{max} 1641, 1503, 1490, 1443, 1249, 1038 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 3 and 4); EIMS *m/z* 355 [M]$^+$ (21), 220 (31), 148 (21), 135 (36), 131 (28), 126 (20), 113 (100), 103 (23), 98 (43), 77 (6), 70 (13); HREIMS *m/z* 355.2156 [M]$^+$ (calcd for C$_{22}$H$_{29}$NO$_3$, 355.2147).

Cytotoxicity Evaluation. The isolated amide alkaloids were tested in vitro for their cytotoxicity against proliferation of HeLa cells using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay.[36] In brief, HeLa cells in the log phase of their growth cycle were harvested with 0.01% trypsin and then seeded in 96-well plates at a density of 3.0 × 10^3 cells per well in a 100 μL volume. The cells were grown in a humidified 5% CO$_2$ atmosphere at 37 °C overnight. Six concentrations (100.00, 33.33, 11.11, 3.70, 1.23, and 0.41 μg/mL) of each compound were diluted, respectively, in 300 μL of culture medium and then distributed to the cell cultures on 96-well plates in triplicate to achieve a total culture medium in a volume of 200 μL. After incubation for 72 h at 37 °C, a 20 μL aliquot of MTT solution (5 mg/mL) was added to each well. Incubation was continued for another 3 h, the supernatant was removed, and 100 μL of dimethyl sulfoxide (DMSO) was added. The absorbance was measured at the detection wavelength of 550 nm (L_1) and the reference wavelength of 690 nm (L_2) on a Molecular Devices SpectraMax 340 PC microplate reader. The 50% inhibitory concentration (IC$_{50}$) was obtained by nonlinear regression analysis of logistic curves (the value of $L_1 - L_2$ of different concentrations of inhibitors).

Supporting Information Available: 1D and 2D NMR, HRMS, and IR spectra for all of the new compounds (**1**−**8**); key 2D NMR correlations of compounds **3**−**8**; structures of all compounds; ^{13}C NMR data for six known compounds (**11**, **12**, **17**, **18**, **20**, and **22**); a flowchart for the isolation of chemical constituents from *P. boehmeriaefolium*. This material is available free of charge via the Internet at http://pubs.acs.org.

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