

Notes

Alkaloids from *Gelsemium elegans*You-Kai Xu,[‡] Sheng-Ping Yang,[†] Shang-Gao Liao,[†] Hua Zhang,[†] Li-Ping Lin,[†] Jian Ding,[†] and Jian-Min Yue^{*†}

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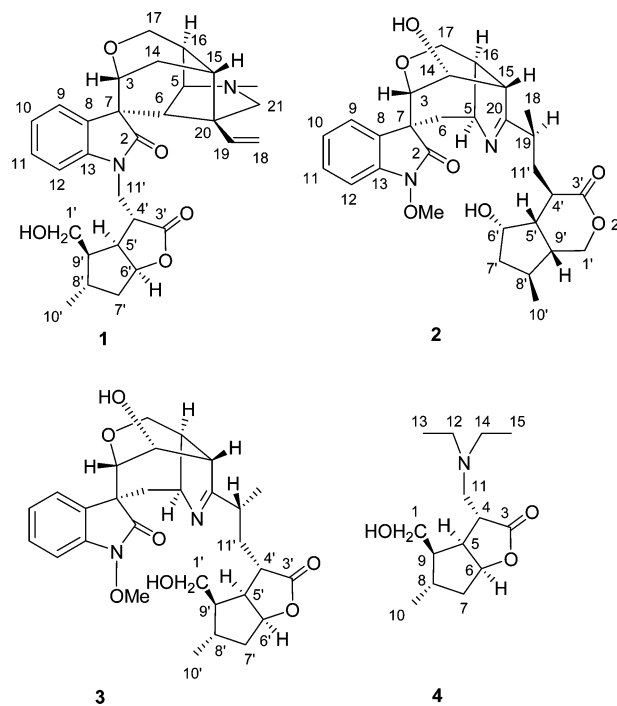
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Three new alkaloids, gelsebanine (**1**), 14 α -hydroxyelegansamine (**2**), and 14 α -hydroxygelsamydine (**3**), and a new extraction artifact, gelsebamine (**4**), together with 12 known alkaloids, were isolated from the stems and leaves of *Gelsemium elegans*. The structures of **1–4** were determined by spectroscopic methods, especially 2D NMR techniques. Compounds **1–4** were evaluated for cytotoxic activity against four tumor cell lines, and gelsebamine (**4**) selectively inhibited the A-549 human lung adenocarcinoma cell line.

Gelsemium (Loganiaceae) is a small genus of three species, *G. elegans* (Gardn. & Champ.) Benth., *G. sempervirens* (L.) Jaume St.-Hilaire, and *G. rankinii* Small. Of these, *G. elegans* is distributed in Southeast Asia and the two other species are native to North America.¹ The genus *Gelsemium* is a rich source of indole alkaloids. *G. elegans*, which is known as “Gou-Wen” (Lethal Kiss) or “Duan-Chang-Cao” (Intestinal-Damaging Herb) in mainland China, is very toxic and has been used traditionally for the treatment of pain, spasticity, and skin ulcers in Chinese folkloric medicine.² A number of indole alkaloids based on six different structural skeletons were reported from *G. elegans*. Pharmacological investigations on the crude and purified alkaloids of this plant have demonstrated promising antitumor,³ analgesic and anti-inflammatory,⁴ immunomodulating,⁵ and antiarrhythmic⁶ activities. An injection of the crude alkaloids of *G. elegans* has been used clinically to treat terminal esophageal⁷ and liver cancer.⁸ One alkaloid, sempervirine, obtained previously from *G. sempervirens* with strong DNA affinity and antitumor activity,⁹ was currently isolated from *G. elegans* for the first time.

The interesting chemical, pharmacological, and clinical significance of *G. elegans* prompted us to conduct the current project, which has led to the isolation of three new alkaloids, namely, gelsebanine (**1**), 14 α -hydroxyelegansamine (**2**), and 14 α -hydroxygelsamydine (**3**), and an extraction artifact, gelsebamine (**4**), together with 12 known compounds, anhydrovobasindiol,¹⁰ 14-hydroxygelsenine (humantenidine),¹¹ 19-(Z)-akuammidine,^{11b} gelsenine,^{11b,12} gelsemine,^{11b,13} 19R-hydroxydihydrogelsevirine,¹³ gelsevirine,^{11b,14} 16-*epi*-voacarpine,^{11b,15} N-methoxyanhydrovobasindiol,¹⁶ humantenine,¹⁷ koumine,^{14a,18} and sempervirine.¹⁹ Compounds **1–3** bear a rare iridoid monoterpenoid moiety. The structures of **1–4** were determined by spectroscopic methods, especially 2D NMR techniques, and they were evaluated for antitumor activity against four tumor cell lines (P388, HL-60, A-549, and BEL-7402). We report herein the isolation and structural elucidation of these new alkaloids and their cytotoxic evaluation.

Gelsebanine (**1**) was obtained as a white, amorphous powder and was assigned the molecular formula C₃₀H₃₆N₂O₅, as determined by HREIMS at *m/z* 504.2633 [M]⁺. The IR spectrum showed



absorptions at 3423 cm⁻¹ (hydroxyl group), 1709 cm⁻¹ (amide), and 1759 cm⁻¹ (five-membered lactone ring). The ¹H (Table 1) and ¹³C NMR (Table 2) data showed the presence of two carbonyls at δ 177.4 and 177.2, four double bonds (two trisubstituted, one disubstituted, and one terminal), and 20 sp³ carbons (two methyls, six methylenes, 10 methines, and two quaternary carbons). The coupling pattern of four aromatic proton signals at δ 7.43, 7.04, 7.25, and 6.98 in the ¹H NMR spectrum indicated the presence of an *ortho*-substituted benzene ring. The UV absorptions at 255, 287 (shoulder) and 317 nm showed the characteristic bands of an oxindole nucleus.^{11b} A direct comparison of the ¹H and ¹³C NMR data of **1** with those of a known alkaloid, gelsemine,^{11b,13} which was also isolated in this study, suggested that alkaloid **1** is a derivative of gelsemine with an iridoid monoterpenoid moiety (C-1' to C-11') at the N atom of the amido group. The ¹H and ¹³C NMR patterns of the iridoid monoterpenoid moiety of **1** were similar to that of a coexisting known compound, gelsamydine,^{12c} except for the chemi-

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Table 1. ^1H NMR Spectroscopic Data for Compounds **1–4** (in CDCl_3)

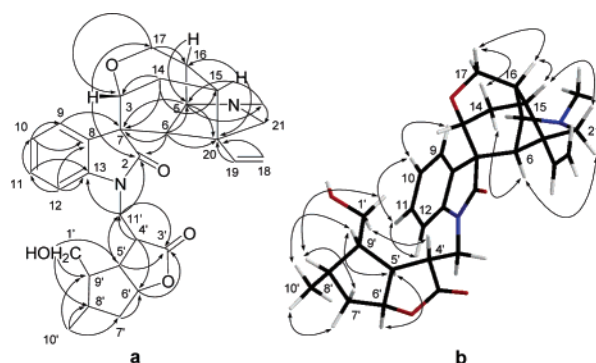
position	1	2	3	position	4
3	3.80 (br s)	3.63 (br s)	3.62 (br s)	1a	3.72 (dd, 12.1, 4.8)
5	3.49 (br s)	4.31 (m)	4.45 (m)	1b	3.37 (dd, 12.1, 11.4)
6 α	2.03 (br s)	2.22 (dd, 15.6, 1.9)	2.35 (br d, 16.4)	4	2.67 (ddd, 11.4, 6.6, 2.4)
6 β		2.39 (dd, 15.6, 4.8)	2.49 (dd, 16.4, 5.1)	5	2.93 (dd, 7.6, 6.6)
9	7.43 (d, 7.4)	7.48 (d, 7.4)	7.49 (d, 7.4)	6	5.01(dd, 7.6, 7.4)
10	7.04 (dd, 7.8, 7.4)	7.08 (dd, 7.7, 7.4)	7.10 (dd, 7.7, 7.4)	7 α	1.51 (ddd, 14.0, 12.1, 7.4)
11	7.25 (dd, 7.8, 7.7)	7.26 (dd, 7.7, 7.7)	7.29 (dd, 7.7, 7.6)	7 β	2.12 (dd, 14.0, 6.1)
12	6.98 (d, 7.7)	6.89 (d, 7.7)	6.90 (d, 7.6)	8	1.62 (m)
14 α	2.84 (dd, 14.3, 3.0)			9	1.89 (m)
14 β	1.99 (ddd, 14.3, 5.5, 2.5)	4.49 (br s)	4.50 (d, 1.7)	10	0.97 (d, 6.0)
15	2.31 (m)	2.87 (d, 8.4)	3.21 (d, 8.1)	11a	2.92 (dd, 13.0, 2.4)
16	2.46 (br d, 8.2)	2.55 (m)	2.59 (m)	11b	2.55 (br d, 13.0)
17 α	3.90 (dd, 11.1, 1.5)	4.25 (d, 11.0)	4.33 (d, 11.0)	12a	2.77 (dq, 14.4, 7.2)
17 β	4.11 (dd, 11.1, 2.1)	4.42 (dd, 11.0, 3.5)	4.45 (dd, 11.0, 3.8)	12b	2.48 (dq, 14.4, 7.2)
18a	5.10 (d, 11.0)	1.53 (d, 7.4)	1.29 (d, 7.3)	13	1.10 (t, 7.2)
18b	4.95 (d, 17.8)			14a	2.77 (dq, 14.4, 7.4)
19	6.20 (dd, 17.8, 11.0)	2.68 (m)	3.62 (m)	14b	2.48 (dq, 14.4, 7.2)
21 α	2.24 (d, 10.8)			15	1.10 (t, 7.2)
21 β	2.82 (d, 10.8)				
N-OMe		3.94 (s)	3.90 (s)		
N-Me	2.25 (s)				
1'a	3.70 (dd, 10.9, 3.6)	α 3.91 (dd, 10.8, 11.0)	a 3.68 (dd, 11.6, 4.8)		
1'b	3.43 (dd, 10.9, 9.1)	β 4.26 (br d, 10.8)	b 3.52 (dd, 11.6, 11.0)		
4'	3.09 (m)	3.07 (br t, 11.2)	3.50 (m)		
5'	2.94 (m)	2.08 (m)	2.86 (dd, 13.8, 7.8)		
6'	4.99 (dd, 6.4, 5.0)	4.33 (m)	4.94 (br t, 7.1)		
7' α	1.39 (m)	1.98 (dd, 12.9, 6.0)	1.44 (m)		
7' β	2.15 (dd, 14.3, 5.4)	1.38 (dt, 12.9, 3.6)	2.13 (dd, 14.1, 6.0)		
8'	1.67 (m)	2.08 (m)	1.77 (m)		
9'	1.72 (m)	1.93 (m)	1.87 (m)		
10'	0.97 (d, 5.9)	1.05 (d, 6.3)	0.90 (d, 6.3)		
11'a	3.84 (dd, 14.2, 6.2)	2.32 (dd, 13.4, 10.4)	1.77 (m)		
11'b	4.06 (dd, 14.2, 7.6)	1.86 (dd, 13.4, 10.7)	2.12 (m)		

Table 2. ^{13}C NMR Spectroscopic Data of Compounds **1–4**

position	1 ^a	2 ^a	3 ^a	3 ^b	position	4 ^a
2	177.4	171.0	171.0	171.1	1	60.4
3	69.1	79.2	79.6	79.4	3	178.0
5	71.6	70.4	70.8	71.1	4	38.8
6	50.4	37.0	36.9	36.0	5	47.9
7	53.4	53.7	53.6	53.6	6	82.1
8	130.6	131.2	131.1	131.2	7	42.3
9	127.6	124.5	124.9	124.9	8	32.4
10	122.0	123.5	123.7	123.6	9	52.8
11	127.9	128.3	128.5	128.3	10	16.9
12	107.8	106.6	107.0	106.8	11	57.4
13	141.5	137.6	138.1	137.8	12	47.4
14	22.4	66.0	65.6	64.8	13	10.7
15	35.6	52.0	50.5	50.3	14	47.4
16	36.8	38.3	37.7	37.7	15	10.7
17	61.1	61.3	61.3	61.1		
18	112.0	18.3	20.1	19.7		
19	138.0	37.8	33.6	32.9		
20	53.3	183.4	ND ^c	185.0		
21	65.4					
N-OMe		63.2	63.3	63.0		
N-Me	39.6					
1'	60.3	70.3	60.2	60.0		
3'	177.2	178.0	181.8	182.5		
4'	39.2	37.5	35.8	35.9		
5'	44.4	48.3	48.4	48.2		
6'	82.8	72.5	82.1	82.4		
7'	41.3	43.4	42.3	42.0		
8'	32.5	34.9	33.0	29.5		
9'	50.8	44.8	52.2	52.0		
10'	16.9	19.2	17.1	16.9		
11'	40.9	32.9	37.2	36.7		

^a Measured in CDCl_3 . ^b Measured in CDCl_3 (80%) + CD_3OD (20%).
^c Not detected.

cal shift changes of $\text{CH-4}'$ and $\text{CH}_2\text{-11}'$ caused by the different locations of the iridoid monoterpene moiety in the two compounds, implying that they have the same iridoid substituent, and this was confirmed from the HMBC and ROESY NMR spectra

**Figure 1.** Selected HMBC (\rightarrow) and key ROESY (\leftrightarrow) correlations of gelsebanine (**1**).

(Figure 1). The key HMBC correlations from $\text{H}_2\text{-11}'$ to C-2 and C-13 clearly demonstrated the linkages of C-2, C-13, and C-11' to the N-1 nitrogen atom in **1**. All proton signals were assigned to their bonded carbons from the HMQC spectrum. Analysis of the HMBC spectrum (Figure 1a) and ROESY spectrum (Figure 1b) confirmed these assignments. Therefore, the structure of gelsebanine was established as **1**.

14 α -Hydroxyelegansamine (**2**) was assigned the molecular formula $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_7$ as deduced from HREIMS at m/z 524.2527 $[\text{M}]^+$ (calcd for 524.2523), showing 16 mass units more than that of a coexisting known alkaloid, elegansamine.²⁰ The IR spectrum showed absorptions at 3423 cm^{-1} (hydroxyl group) and 1720 cm^{-1} (amide and six-membered lactone ring). By comparing the ^{13}C NMR data of **2** with those of elegansamine, it was observed that the structures of these two compounds are closely related, with the only difference being a hydroxyl in place of a hydrogen at C-14 of elegansamine, which caused a downfield shift for the C-14 signal to δ 66.0 in compound **2**. In the HMBC spectrum (Figure S1, Supporting Information), the correlations from H-3, H-15, and H-16

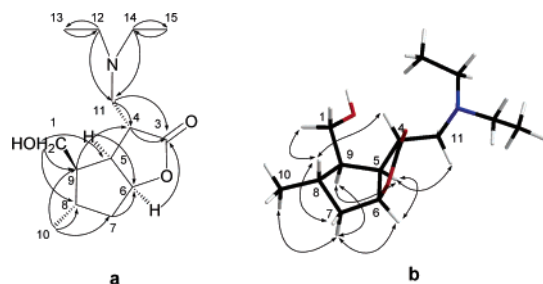


Figure 2. Selected HMBC (→) and key ROESY (↔) correlations of gelsebamine (**4**).

to C-14 and from H-14 to C-16 and C-20 verified the above deduction. The relative stereochemistry of C-14 was then fixed by a ROESY experiment (Figure S1, Supporting Information). The strong ROESY correlation between H-14 and H₃-18 indicated that H-14 was in a β -orientation. A 3D structure of **2** generated by computer modeling (using Chem3D Ultra 9.0 and MM2 force field calculations for energy minimization) was consistent with the X-ray structure of elegansamine, supporting the above structural assignment for compound **2**. The full assignments of ¹H and ¹³C NMR data of **2** were carried out using 2D NMR techniques (HSQC, HMBC, and ROESY).

14 α -Hydroxygelsamydine (**3**) was obtained as colorless needles. The HREIMS at m/z 524.2509 [M]⁺ gave a molecular formula of C₂₉H₃₆N₂O₇ (calcd 524.2523) for alkaloid **3**. The IR spectrum showed absorptions at 3462 cm⁻¹ (hydroxyl group), 1711 cm⁻¹ (amide), and 1749 cm⁻¹ (five-membered lactone ring). The ¹³C NMR spectrum recorded in CDCl₃ (Table 2) resolved only 28 carbon signals, while the HMBC spectrum showed a correlation between H₃-18 and a downfield carbon signal around δ_c 185–186. After addition of 20% CD₃OD (v/v) to the NMR tube, the carbon signal (Table 2) was observed at δ_c 185.0. Comparison of the ¹³C NMR data of **3** with those of gelsamydine,^{12c} also isolated from this plant, suggested that **3** is 14-hydroxygelsamydine, as judged by the downfield shifted carbon signals of C-14 (δ_c 65.6), C-3 (δ_c 79.6), and C-15 (δ_c 50.5). The HMBC correlations (Figure S2, Supporting Information) from H-3 and H-15 to C-14 and from H-14 to C-3, C-5, and C-16 confirmed the presence of HO-14. The key ROESY cross-peak between H-14 and H-19 (Figure S2, Supporting Information) was used to assign the β -configuration for H-14. Compound **3** was therefore identified as 14 α -hydroxygelsamydine.

Gelsebamine (**4**) gave a molecular formula of C₁₄H₂₅NO₃, as determined by HREIMS at m/z 255.1835 [M]⁺ (calcd 255.1834). The IR spectrum showed a broad peak at 3182 cm⁻¹ (for a hydroxyl) and a typical absorption at 1749 cm⁻¹ (for a five-membered lactone ring). The ¹³C NMR and HSQC spectra indicated the presence of 14 carbon signals composed of five methines, five methylenes, three methyls, and one carbonyl, suggesting that **4** has an iridoid monoterpene scaffold. The ¹H and ¹³C NMR data of gelsebamine (**4**) showed two N-Et groups (Tables 1 and 2). Comparison of the ¹³C NMR data of **4** with those of **1** and gelsemine^{11b,13} indicated the iridoid monoterpene moieties to be identical. Key HMBC correlations linked two ethyl groups and the iridoid monoterpene part via C-11 to the N atom and also confirmed the iridoid monoterpene scaffold (part a in Figure 2). The relative configuration of **4** was assigned from the ROESY spectrum (part b in Figure 2), in which the correlated pairs H-5/H-6, H-5/H-9, H-7 α /H-9, and H-6/H-7 α indicated that they were coplanar (*syn*-position) and were assigned as α -oriented. In consequence, the ROESY correlation between H-4 and H-8 revealed that H-4 and H-8 are β -oriented. Therefore, the structure and relative stereochemistry of gelsebamine were assigned as **4**. As a result of the use of diethylamine in the process of purification, compound **4** is an artifact and does not exist among the crude alkaloids as checked by TLC (Supporting Information).

The twelve known compounds were identified as anhydrobasindiol,¹⁰ 14-hydroxygelsenicine (humantenidine),¹¹ 19-(*Z*)-akuammidine,^{11b} gelsemine,^{11b,12} gelsemine,^{11b,13} 19R-hydroxydihydrogelsevirine,¹³ gelsevirine,^{11b,14} 16-*epi*-voacarpine,^{11b,15} *N*-methoxyanhydrobasindiol,¹⁶ humantenine,¹⁷ koumine,^{14a,18} and sempervirine,¹⁹ by measurement of their NMR and EIMS data and comparison with literature values.

Compounds **1–4** were evaluated for cytotoxic activity against four tumor cell lines with the MTT method for P388 murine leukemia and HL-60 human leukemia and the SRB method for A-549 human lung adenocarcinoma and BEL-7402 human hepatocellular carcinoma according to the standard protocols,²¹ and pseudolaric acid B²² was used as a positive control. In this test, gelsebamine (**4**) selectively inhibited the A-549 human lung adenocarcinoma cell line with an IC₅₀ value of 6.34 \times 10⁻⁷ M, while compounds **1–3** were inactive against the four tested tumor cell lines (IC₅₀ > 1.0 \times 10⁻⁵ M).

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. UV spectra were measured on a Shimadzu UV-210A spectrometer. IR spectra were obtained on a Perkin-Elmer 577 spectrometer with KBr disks. NMR spectra were measured on a Bruker AM-400 spectrometer with TMS as internal standard. EIMS (70 eV) were carried out on a Finnigan-MAT 95 mass spectrometer. All solvents used were of analytical grade (Shanghai Chemical Plant, Shanghai, People's Republic of China). Silica gel (200–300 mesh) was used for column chromatography, and precoated silica gel GF 254 plates (Qingdao Haiyang Chemical Plant, Qingdao, People's Republic of China) were used for TLC. C₁₈ reversed-phase silica gel (150–200 mesh, Merck) was also used for column chromatography.

Plant Material. The leaves and stems of *G. elegans* were collected from Xishuangbanna Tropical Botanical Garden (XTBG), Chinese Academy of Sciences, Mengla County, Yunnan Province, People's Republic of China, in April 2005. The plant was identified by one of the authors (Y.K.X.) of Xishuangbanna Tropical Botanical Garden, where a voucher specimen (accession number: 033769) was deposited.

Extraction and Isolation. The air-dried leaves and stems of *G. elegans* (2 kg) were percolated with EtOH (20 L) three times at room temperature. The ethanolic extract was dissolved in 1.5 L of water to form a suspension and was acidified with 20% H₂SO₄ to ca. pH 4. The acidic suspension was first partitioned with EtOAc to remove neutral components, and the aqueous phase was then basified with Na₂CO₃ to ca. pH 10 and was extracted with CHCl₃ to give a crude alkaloid extract (18 g). The crude alkaloid was subjected to silica gel column chromatography, eluted with CHCl₃–MeOH (30:1 to 1:1), to give two major fractions (1 and 2). Fraction 1 (5 g) was subjected to silica gel column chromatography using gradient solvent systems of cyclohexane–EtOAc–Et₂NH (30:1:0.15 to 5:1:0.1) and then cyclohexane–*i*-PrOH–Et₂NH (40:3:0.2 to 5:1:0.1) to obtain gelsebamine (**4**) (50 mg), 14-hydroxygelsenicine (50 mg), gelsenicine (1500 mg), gelsevirine (40 mg), anhydrobasindiol (25 mg), humantenine (80 mg), and an alkaloid mixture. The mixture was separated on a silica gel column eluted with cyclohexane–EtOAc–Et₂NH (5:1:0.1 to 3:1:0.1) to yield 14 α -hydroxygelsamydine (**3**) (10 mg), *N*-methoxyanhydrobasindiol (5 mg), koumine (8 mg), and a further alkaloid mixture, which was separated by preparative HPLC (C₁₈ reversed-phase silica gel column) using a gradient solvent system of CH₃CN–H₂O (60:40 to 80:20) to afford 14 α -hydroxyelegansamine (**2**) (50 mg), 14 α -hydroxygelsamydine (**3**) (20 mg), 19-(*Z*)-akuammidine (50 mg), and 16-*epi*-voacarpine (15 mg). Fraction 2 (3 g) was subjected to passage over a silica gel column, eluted with cyclohexane–EtOAc–Et₂NH (15:1:0.1 to 3:1:0.1), to give four major fractions. Each of these was purified on a C₁₈ reversed-phase silica gel column, eluted with aqueous methanol (50%–80%), to yield gelsebanine (**1**) (40 mg), gelsemine (1400 mg), 19R-hydroxydihydrogelsevirine (3 mg), and sempervirine (150 mg), respectively.

Gelsebanine (1): white, amorphous powder; [α]_D²⁰ –8 (c 0.076, CHCl₃); UV (MeOH) λ_{max} (log ϵ) 317 (3.08), 287 (shoulder), 255 (4.06) nm; IR (KBr) ν_{max} 3423, 3076, 2924, 2870, 1759, 1709, 1608, 1487, 1466, 1363, 1190, 1094, 1009, 758 cm⁻¹; ¹H and ¹³C NMR (measured in CDCl₃), see Tables 1 and 2; EIMS m/z 504 [M]⁺ (78), 461 (64),

433 (48), 378 (9), 341 (8), 328 (35), 315 (16), 279 (6), 261 (9), 236 (8), 190 (7), 180 (12), 158 (12), 146 (11), 120 (12), 108 (100), 91(8), 70 (6); HREIMS m/z 504.2633 (calcd for $C_{30}H_{36}N_2O_5$, 504.2624).

14 α -Hydroxyelegansamine (2): white, amorphous powder; $[\alpha]^{20}_D$ -90 (c 0.12, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 258 (3.87), 209 (4.49) nm; IR (KBr) ν_{max} 3423, 2922, 1720, 1618, 1466, 1329, 1234, 1136, 1018, 876, 750 cm^{-1} ; 1H and ^{13}C NMR (measured in $CDCl_3$), see Tables 1 and 2; EIMS m/z $[M]^+$ 524 (56), 493 (52), 465 (8), 445 (4), 395 (5), 365 (8), 355 (48), 342 (100), 312 (30), 290 (22), 256 (8), 238 (4), 210 (6), 180 (8), 166 (9), 146 (12), 108 (17), 94 (14), 81 (9), 55 (5); HREIMS m/z 524.2527 (calcd for $C_{29}H_{36}N_2O_7$, 524.2523).

14 α -Hydroxygelsamyne (3): colorless needles; $[\alpha]^{20}_D$ -71.5 (c 0.069, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 258 (4.66) nm; IR (KBr) ν_{max} 3462, 2960, 2928, 1749, 1711, 1633, 1614, 1464, 1329, 1186, 1140, 1041, 876, 756 cm^{-1} ; 1H and ^{13}C NMR (measured in $CDCl_3$), see Tables 1 and 2; EIMS m/z $[M + H]^+$ 525 (13), 524 (37), 493 (45), 465 (5), 356 (13), 355 (44), 342 (100), 311 (28), 290 (17), 256 (6), 180 (8), 150 (10), 146 (16), 120 (16), 108 (23), 83 (21), 81 (12), 55 (9); HREIMS m/z 524.2509 (calcd for $C_{29}H_{36}N_2O_7$, 524.2523).

Gelsebamine (4): white, amorphous powder; $[\alpha]^{20}_D$ +69.2 (c 0.19, $CHCl_3$); IR (KBr) ν_{max} 3162, 2958, 2818, 1749, 1471, 1448, 1390, 1367, 1311, 1225, 1186, 1078, 1043, 991, 779, 650 cm^{-1} ; 1H and ^{13}C NMR (measured in $CDCl_3$), see Tables 1 and 2; EIMS m/z $[M]^+$ 255 (1), 240 (4), 226 (1), 210 (1), 182 (1), 164 (1), 140 (2), 123 (1), 107 (1), 93 (1), 86 (100), 73 (5), 67 (1), 58 (10), 53 (1); HREIMS m/z 255.1835 (calcd for $C_{14}H_{25}NO_3$, 255.1834).

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Supporting Information Available: Figures of selected HMBC and key ROESY correlations of compounds **2** and **3**, 1H , ^{13}C NMR, HSQC, HMBC, ROESY, EIMS, IR, and UV spectra of compounds **1–4**, and TLC check of the crude alkaloids for gelsebamine (**4**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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