นิพนธ์ต้นฉบับ

อินโดลแอลคาลอยด์จากผลของพญาสัตบรรณ

สัมพันธ์ วงศ์เสรีพิพัฒนา, ลักขณา ฉายศรี, บุญชู ศรีตุลารักษ์ และ กิตติศักดิ์ ลิขิตวิทยาวุฒิ *

ภาควิชาเภสัชเวท คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย พญาไท กรุงเทพ 10330
* *ผู้เขียนที่สามารถติดต่อได้ ที่อยู่อิเลคโทรนิค: lkittisa@chula.ac.th*

บทคัดย่อ

สิ่งสกัดเมธานอลซึ่งเตรียมได้จากผลของพญาสัตบรรณ หลังจากที่นำมาสกัดแยกโดยใช้กรด-ด่างแล้ว ได้สิ่งสกัดหยาบแอลคาลอยด์ซึ่งเมื่อนำมาแยกต่อโดยวิธีโครมาโทกราฟีได้อินโดลแอลคาลอยด์ 4 ชนิดคือ 19-*E*-picrinine (**1**) 19-*E*-akuammidine (**2**) 19-*E*-vallesamine (**3**) และ 19*S*-scholaricine (**4**) การพิสูจน์โครงสร้างสารเหล่านี้ทำโดยการวิเคราะห์คุณสมบัติสเปกโตรสโคปี (MS, โปรตอนและคาร์บอน-13 NMR, DEPT, COSY, NOESY, HETCOR, COLOC, HMQC และ HMBC) นับเป็นครั้งแรกที่แอลคาลอยด์ **1**, **3** และ **4** ถูกสกัดแยกได้จากผลของพืชนี้

กุญแจคำ

พญาสัตบรรณ, วงศ์ Apocynaceae, อินโดลแอลคาลอยด์, ผล

Original Article

Indole Alkaloids from the Fruits of *Alstonia scholaris*

Sumphan Wongseripipatana, Lakhana Chaisri, Boonchoo Sritularak and Kittisak Likhitwitayawuid*

Department of Pharmacognosy, Faculty of Pharmaceutical Science, Chulalongkorn University, Bangkok 10330, Thailand
* *Corresponding author. E-mail address: lkittisa@chula.ac.th*

Abstract

A MeOH extract prepared from the fruits of *Alstonia scholaris*, after acid-base treatment, gave a crude alkaloid extract which was then subjected to chromatographic separation to afford four indole alkaloids, namely 19-*E*-picrinine (**1**),19-*E*-akuammidine (**2**), 19-*E*-vallesamine (**3**) and 19*S*-scholaricine (**4**). The structure identifications of these compounds were done by analysis of their spectroscopic properties (MS, ^{1}H and ^{13}NMR, DEPT, COSY, NOESY, HETCOR, COLOC, HMQC and HMBC). Alkaloids **1**, **3**, and **4** were isolated from the fruits of this plant for the first time.

Key words

Alstonia scholaris, Apocynaceae, Indole alkaloid, Fruit

Introduction

Alstonia scholaris (Apocynaceae) is a large tree known in Thai as Phayaa-sattaban. In Thai traditional medicine, its stem bark and root bark have been used as remedies for the treatment of malaria and some other ailments including chronic diarrhoea, dysentery, menstrual disorders, acute arthritis and fever (1). Several biological activities, such as anticancer, antimalarial, antileishmanial and antibacterial activities, have been reported for *A. scholaris* (2-6). Furthermore, the plant has been subjected to extensive chemical studies, and to date about 38 indole alkaloids have been isolated from the leaves, flowers, stem bark and root bark, with majority possessing corynanthean and strychnan skeleta (7-21). However, for the fruits, only one chemical report has appeared, describing the presence of an alkaloid named akuammidine (22). Our re-investigation of the chemical composition of the fruits of this plant led to the isolation of four indole alkaloids namely 19-*E*-picrinine (**1**),19-*E*-akuam-midine (**2**), 19-*E*-vallesamine (**3**) and 19*S*-scholaricine (**4**).

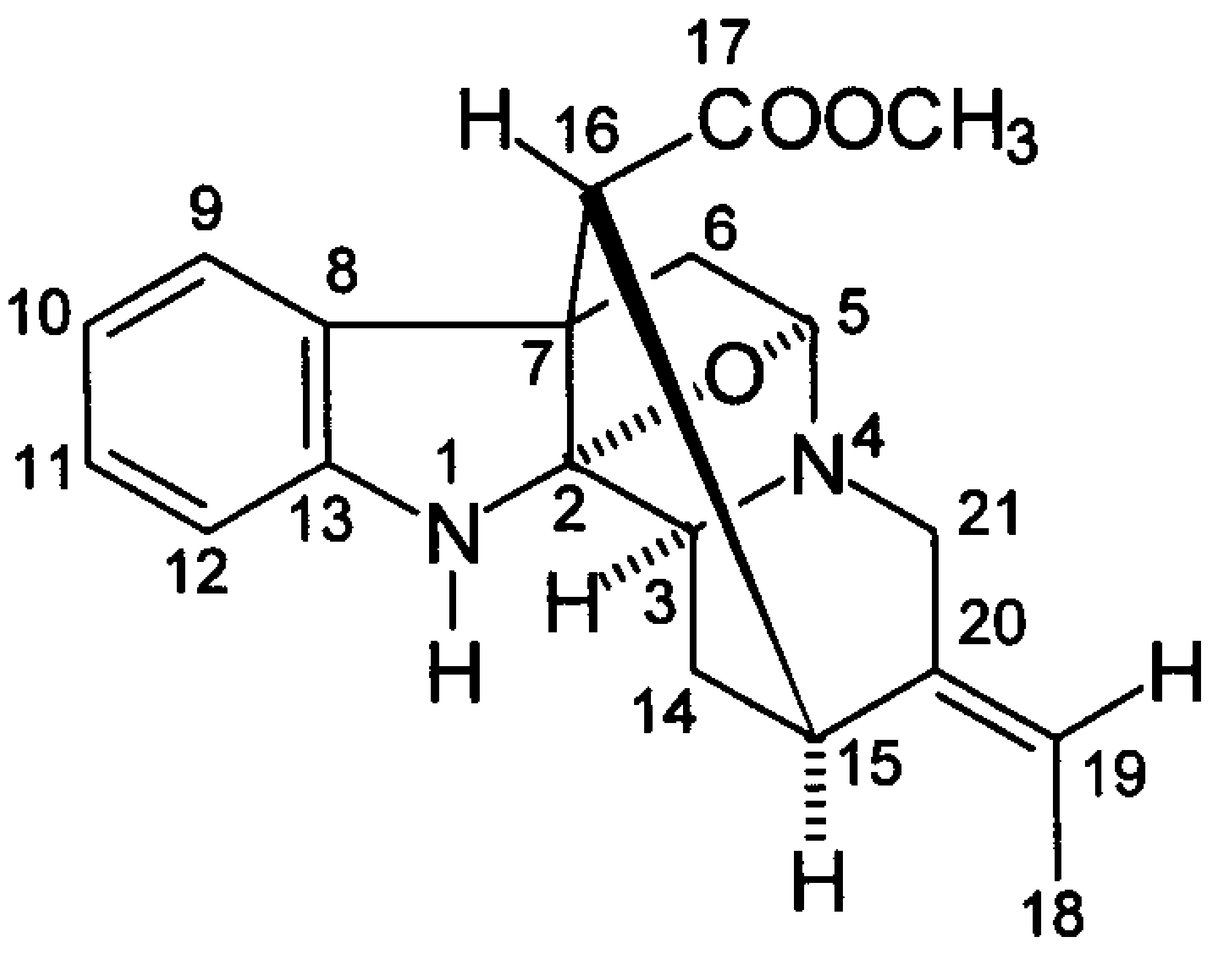
Materials and Methods

General procedures

Melting points were recorded with a Fisher/Johns melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. UV spectra were obtained with a JASCO V-560 instrument, and IR were recorded with a Perkin-Elmer FT-IR 1760X spectrometer. EIMS were measured with a JEOL JMS-AM 20 mass spectrometer. ^{1}H NMR (500 MHz) and ^{13}C (125 MHz) were taken on a JEOL JNM-A 500 NMR spectrometer.

Plant material

Fruits of *A. scholaris* (L.) R. Br. were collected from Phukae Botanical Garden, Saraburi province, in February 2000. Authentification of the plant material was performed by Dr. Dhavadee Ponglux of the Pharmacognosy Department,



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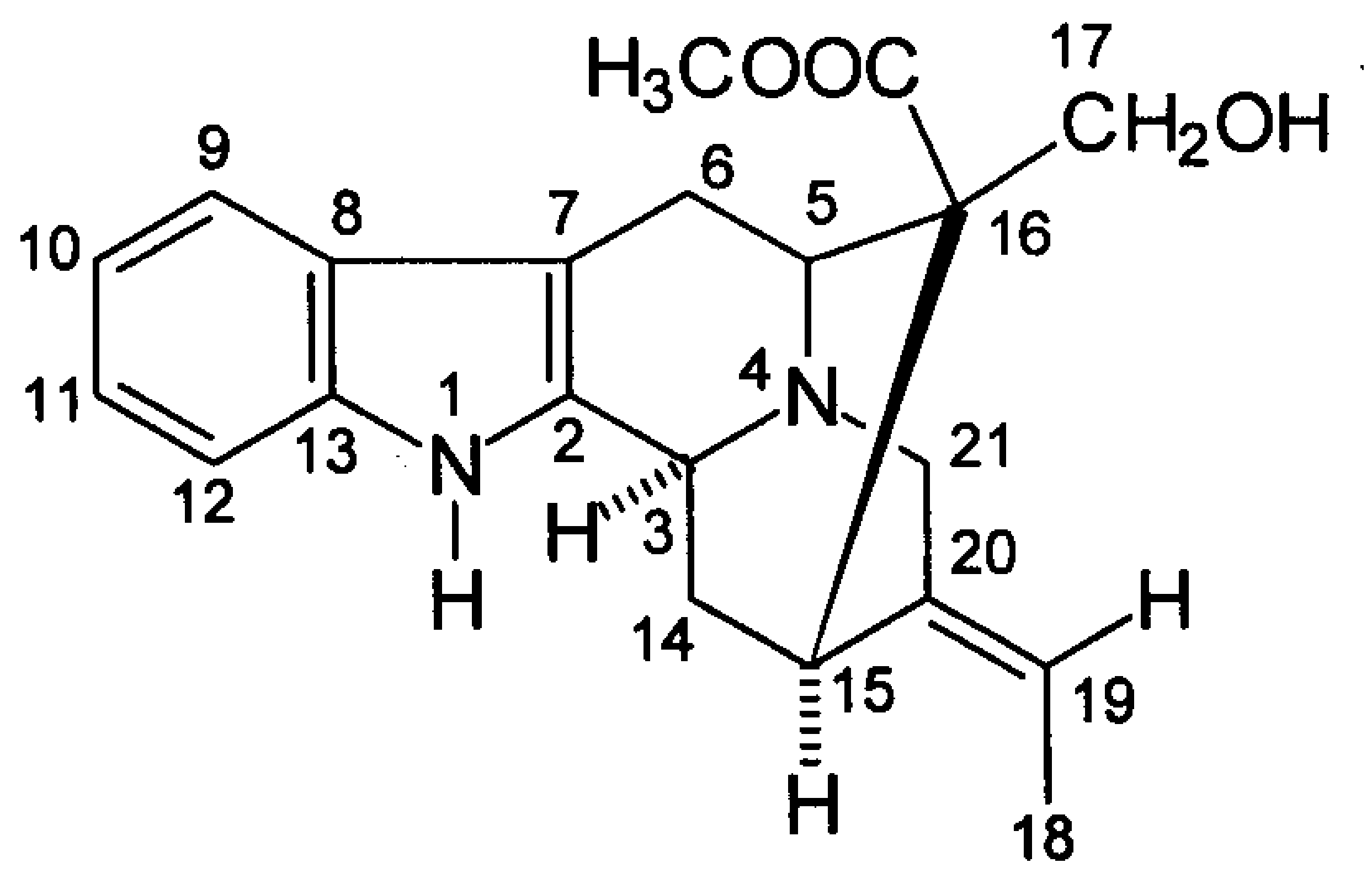

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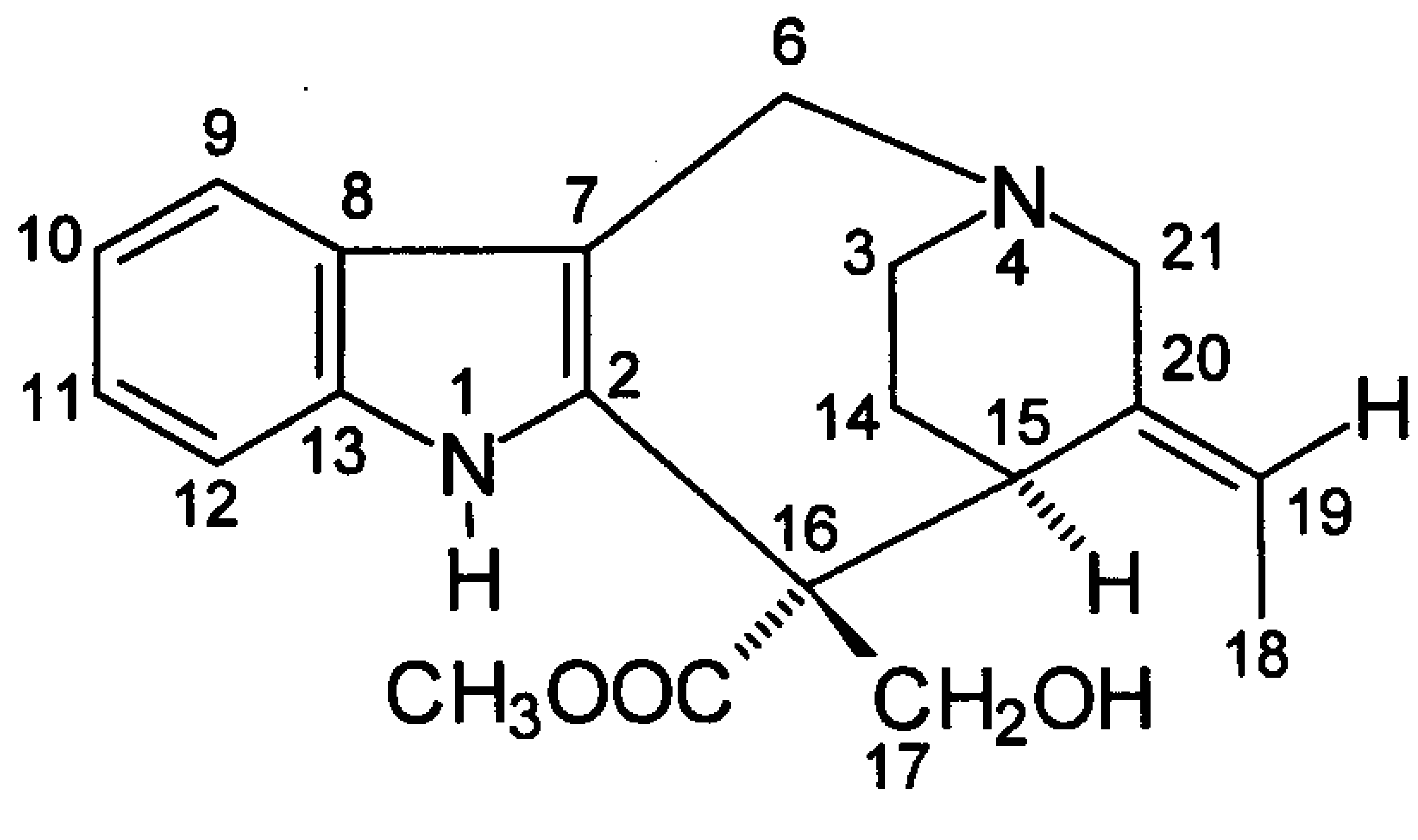

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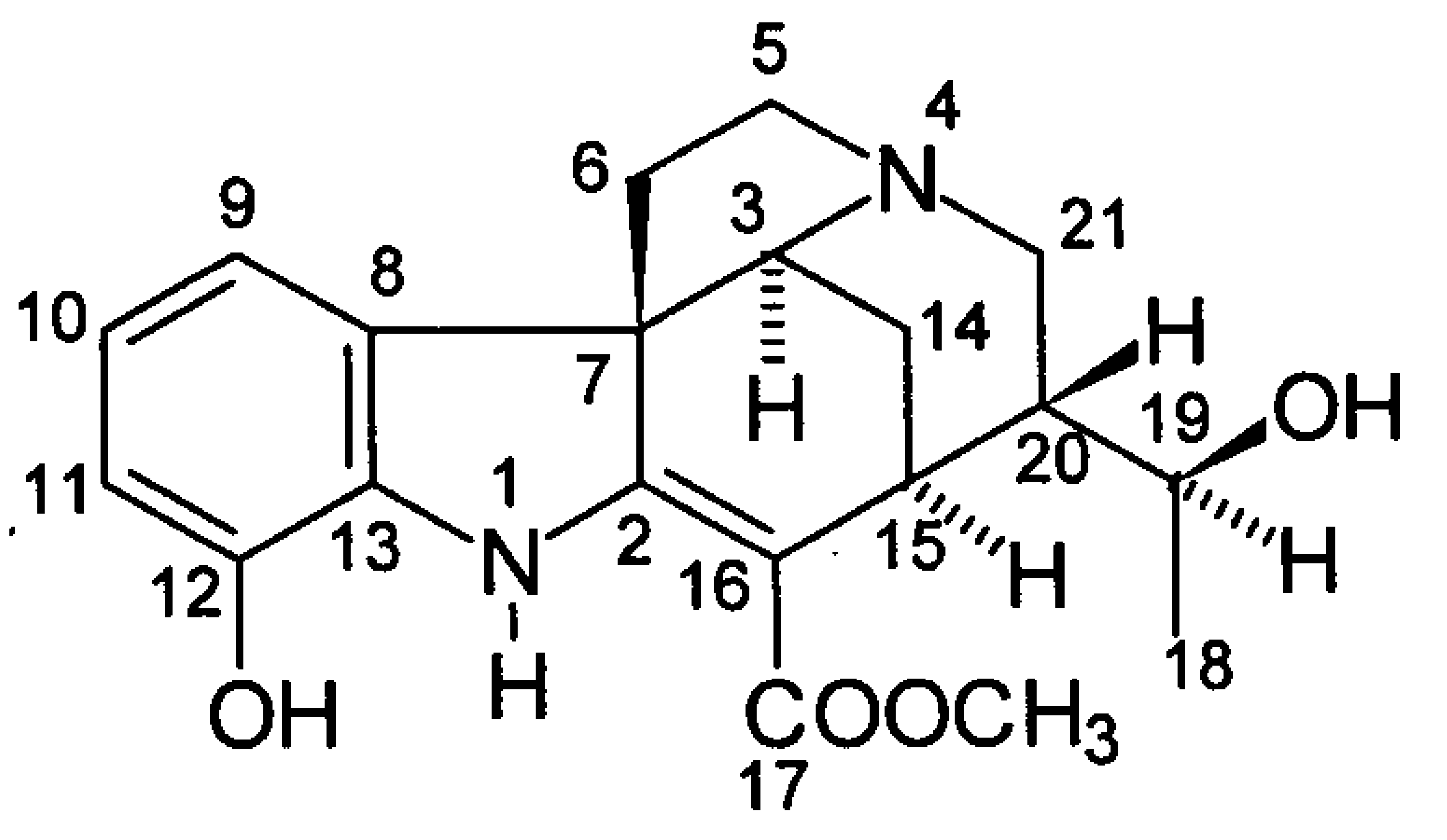

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Faculty of Pharmaceutical Sciences, Chulalongkorn University.

Extraction

Fresh fruits (60 kg) were chopped and blended into small pieces, and then extracted with methanol 4 times (4 x 40 L) and filtered. The combined filtrate was concentrated to syrupy mass under reduced pressure, mixed with glacial acetic acid (500 ml) and then poured into a large volume of water to give about 5% acetic acid solution (10 L). The suspension obtained was well shaken and left to stand overnight. The acidic filtrate was washed with portions of petroleum ether, and then made alkaline (pH 10) with NH_4OH and extracted with $CHCl_3$ (3 × 300 ml). The combined $CHCl_3$ fraction was washed with water and dried over anhydrous Na_2SO_4. Removal of the organic solvent gave a crude alkaloid extract (15 g).

Isolation

A portion of the crude alkaloid extract (7 g) was initially separated by SiO_2 column chromatography with $CHCl_3$-MeOH gradient (9:1 to 2:8) system to give 7 major fractions (fractions A – G). Fraction A (3 g) was further separated on a SiO_2 column ($CHCl_3$-MeOH gradient; 19:1 to 13:3) to yield 13 subfractions (subfractions A-1 – A-13). Separation of subfraction A-12 (400 mg) on SiO_2 using a mixture of EtOAc-MeOH (9:1) gave alkaloid 1 (15 mg). Subfraction A-13 was fractionated on a SiO_2 column ($CHCl_3$-acetone 1:1) and then separated on Sephadex LH-20 (MeOH) to afford 2 (9 mg). Fraction B (1.2 g) was separated on SiO_2. Elution was performed in a polarity gradient manner, eluted with $CHCl_3$, acetone and MeOH, respectively. Forty-five fractions (50 ml each) were collected. Fractions 19-24 were pooled, dried and further separated by flash column chromatography (SiO_2, $CHCl_3$-acetone-MeOH 1:9:9) to give 3 (10 mg). Fractions 29-34 were combined, dried, and then separated on a flash column (SiO_2, $CHCl_3$-MeOH 9:1) to furnish 4 (6 mg).

Physical and spectral properties

19-*E*-picrinine (1): Mp 220-222 °C; $[\alpha]^{20}_{D}$ −52° (*c* 0.129 g/100 ml, MeOH); UV (MeOH) λ_{max} nm (log ε): 288 (0.25), 235 (0.64), 206 (2.22); IR (KBr) ν_{max} cm^{-1}: 3391, 1724, 1611, 1464, 1168; EIMS *m/z* (% relative intensity): 338 (M$^+$, 27), 279 (2), 239 (89), 206 (16), 180 (58), 156 (23), 130 (64), 108 (74), 77 (100), 59 (62); ^{1}H NMR (500 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$): see Table 2.

19-*E*-akuammidine (**2**): Mp 235-237 °C; $[\alpha]^{20}_D$ +22° (*c* 0.313 g/100 ml, MeOH); UV (MeOH) λ_{max} nm (log ε): 282 (0.31), 227 (1.64); IR (KBr) ν_{max} cm^{-1}: 3419, 3265, 1715, 1622, 1456; EIMS *m/z* (% relative intensity): 352 (M$^+$, 81), 321 (45), 293 (17), 281 (6), 249 (80), 221 (16), 182 (23), 169 (100); ^{1}H NMR (500 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$): see Table 2.

19-*E*-vallesamine (**3**): Mp 160-162 °C; $[\alpha]^{20}_D$ +119° (*c* 0.573 g/100 ml, MeOH); UV (EtOH) λ_{max} nm (log ε): 284 (0.27), 221 (1.35); IR (KBr) ν_{max} cm^{-1}: 3431, 1725; EIMS *m/z* (% relative intensity): 340 (M$^+$, 6), 339 (3), 310 (11), 309 (4), 208 (7), 201 (9), 199 (11), 194 (11), 180 (7), 170 (11), 169 (12), 167 (11), 154 (13), 143 (6), 130 (9), 122 (25), 108 (9), 58 (100); ^{1}H NMR (500 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$): see Table 2.

19*S*-scholaricine (4): Mp 177-180 °C; $[\alpha]^{20}_D$ -339° (*c* 0.978 g/100 ml, MeOH); UV (EtOH) λ_{max} nm (log ε): 340 (1.04), 286 (0.33), 236 (1.09), 211 (1.65); IR (KBr) ν_{max} cm^{-1}: 3432, 1597; EIMS *m/z* (% relative intensity): 356 (M$^+$, 28), 257 (83), 139 (23), 94 (62), 44 (100); ^{1}H NMR (500 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$): see Table 2.

Results and Discussion

Compound **1** was obtained as a white powder. The UV spectrum of 1 demonstrated maximal absorptions at 206, 235 and 288 nm, suggesting the presence of an indoline chromophore. The IR spectrum showed bands for NH, carbonyl, aromatic and ether functionalities at 3391, 1724, 1611 and 1168 cm^{-1}, respectively. The EIMS showed a molecular ion [M$^+$] at *m/z* 338, consistent with the molecular formula $C_{20}H_{22}N_2O_3$. In the ^{1}H NMR spectrum, the signals at δ 2.45 (1H, d, *J* = 3.7 Hz, H-16), 1.48 (3H, dd, *J* =7.0, 2.4 Hz, H_3-18), 5.40 (1H, br q, *J* = 7.0 Hz, H-19) were characteristics of indole alkaloids belonging to the akuammiline group of the corynanthean type. A lack of substitution on the aromatic ring of the indole nucleus was indicated by the resonances at δ 7.14 (1H, dd, *J* = 7.6, 1.3 Hz, H-9), 6.78 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz, H-10), 7.08 (1H, ddd, *J* = 7.6, 7.6, 1.3 Hz, H-11) and 6.75 (1H, br d, *J* = 7.8 Hz, H-12) in the COSY spectrum. The ^{13}C NMR, DEPT and HETCOR spectra revealed the existence of a methoxyl and a methyl group, together with three methylene and nine methine carbons. The intense peak at *m/z* 279, [M-59]$^+$, in the EIMS was attributed to the loss of a carbomethoxyl group ($COOCH_3$), which was confirmed by the ^{13}C NMR signals at δ 172.4 and 51.1 ppm. This carbomethoxyl group was placed at C-16 by the COLOC correlation between the carbonyl carbon ($COOCH_3$) and H-16, and their orientations were determined by the NOESY cross-peak between H-16 and one of the C-14 methylene protons at δ 1.85. Compound **1** should have 19*E* configuration, as indicated by the NOESY correlation of H-19 (δ 5.40) with H-21 at δ 3.09. The ^{13}C NMR resonances at δ 106.3 (C-2) and 87.3 (C-5) indicated an ether bridge between the two carbons. By comparing the MS and NMR data of **1** with literature values (23, 24), the compound was identified as 19-*E*-picrinine.

Compound **2**, a white powder, displayed a molecular ion at *m/z* 352, suggesting the molecular formula $C_{21}H_{24}N_2O_3$. The UV absorptions at 227 and 289 nm were indicative of indole chromophore. The IR spectrum showed bands for OH, NH and C=O functionalities at 3419, 3265 and 1715 cm^{-1}, respectively. The ^{13}C NMR, DEPT and HMQC spectra revealed the presence of 14 protonated carbons which included a methoxyl and a methyl carbon, in addition to four methylenes and eight methines. In the ^{1}H NMR spectrum of **2**, characteristic signals for a sarpagine structure of the corynanthean type were observed at δ 4.22 (1H, br d, *J* = 11.0, 2.0 Hz, H-3), 3.10 (1H, m, H-5), 2.91 (dd, *J* = 16.0, 5.0 Hz, H-6a), 3.29 (dd, *J* = 16.0, 1.5 Hz, H-6b), 5.41 (1H, br q, *J* = 7.0 Hz, H-

Table 1. ^{1}H NMR (500 MHz) data of alkaloids **1** – **4**

Position	1	2	3	4
1	4.84 (br s)	7.70 (br s)	9.55 (br s)	8.58 (s)
3	3.60 (d, 4.7)	4.22 (br d, 11.0, 2.0)	2.94 – 2.85 (m)	3.91 (m)
5	4.82 (d, 2.2)	3.1 (m)	-	3.10 (m) 2.92 (m)
6	3.41 (d, 13.8) 2.26 (dd, 13.8, 2.8)	3.29 (dd, 16.0, 1.5) 2.91 (dd, 16.0, 5.0)	4.82 (d, 17.0) 4.08 (d, 17.0)	2.85 (m) 1.90 (m)
9	7.14 (dd, 7.6, 1.3)	7.43 (d, 7.3)	7.48 (br d, 7.9)	6.77 (d, 8.0)
10	6.78 (ddd, 7.6, 7.6, 1.2)	7.05 (dd, 7.3, 7.3)	7.07 (dd, 7.9)	6.82 (dd, 8.0, 8.0)
11	7.08 (ddd, 7.6, 7.6, 1.3)	7.11 (dd, 10.3, 7.3)	7.18 (dd, 7.9)	6.68 (d, 8.0)
12	6.75 (br d, 7.8)	7.28 (10.3)	7.30 (br d, 7.9)	-
14	2.14 (ddd, 14.2, 4.7, 2.8) 1.85 (dd, 14.5, 3.4)	2.66 (ddd, 12.5, 3.0, 2.0) 1.86 (ddd, 12.5, 11.0, 2.0)	2.33 (m) 1.90 (m)	2.02 (br d, 13.0) 1.42 (dd, 13.0, 3.0, 3.0)
15	3.28 (br d, 2.8)	3.1 (m)	3.63 (m)	3.35 (br s)
16	2.45 (d, 3.7)	-	-	-
17	-	3.84 (d, 11.0) 3.68 (d, 11.0)	4.19 (d, 10.8) 3.81 (d, 10.8)	-
18	1.48 (dd, 7.0, 2.4)	1.65 (ddd, 7.0, 2.0, 2.0)	1.74 (d, 7.0)	1.17 (d, 6.0)
19	5.40 (br q, 7.0)	5.41 (br q, 7.0)	5.55 (q, 7.0)	3.28 (m)
20	-	-	-	1.78 (m)
21	3.77 (br d, 17.8) 3.09 (d, 17.8)	3.60 (br d, 16.0) 3.58 (br d, 16.0)	3.61 (m)	2.95 (dd, 13.0, 6.0) 1.98 (dd, 13.0, 11.0)
17-CO_2CH_3	3.65 (s)	-	-	3.88 (s)
CO_2CH_3	-	2.94 (s)	3.75 (s)	

Table 2. ^{13}C NMR (125 MHz) data of alkaloids **1** – **4**

Position	1	2	3	4
2	106.3	136.6	133.6	172.2
3	52.0	51.4	47.5	61.0
5	87.3	58.0	-	54.0
6	40.6	24.8	51.0	43.4
7	51.8	106.2	109.2	57.9
8	135.2	127.0	128.1	137.1
9	125.1	118.1	118.3	111.5
10	120.7	119.4	119.2	122.4
11	127.9	121.5	122.4	115.6
12	110.5	110.9	110.7	141.5
13	147.5	137.2	135.4	131.9
14	26.0	29.2	23.9	31.0
15	31.0	29.4	36.2	28.9

Table 2. (Continued)

Position	1	2	3	4
16	51.4	51.4	58.5	96.8
17	172.4	68.7	70.4	169.2
18	12.7	13.0	14.1	19.8
19	120.3	116.7	124.4	68.5
20	136.3	137.4	132.5	45.9
21	46.3	55.5	53.9	48.1
17-CO_2CH_3	51.1	-	-	52.1
$CO_2\underline{C}H_3$	-	50.6	53.0	-
$\underline{C}O_2CH_3$	-	174.1	175.2	-

19) and 1.65 (3H, ddd, $J = 7.0, 2.0, 2.0$ Hz, H_3-18). The presence of a methylenehydroxyl (CH_2OH) group was suggested by the fragment ion at *m/z* 321, $[M-31]^+$ in the EIMS, and a carbomethoxyl ($COOCH_3$) group by the carbon resonances at δ 174.1 and 50.6. These two functionalities were placed at C-16 by the HMBC connectivies from H_2-17 to C-16 and $COOCH_3$, and their orientations were established by nOe's observed for the methylene protons (CH_2OH) and H-5 in nOe difference experiments. Further-more, nOe interactions between H-19 and H_2-21 indicated 19-*E* configuration. Based on all of the above spectral data, **2** was identified as 19-*E*-akuammidine. All of the MS and NMR data of **2** were in excellent agreement with those earlier reported for 19-*E*-akuammidine (25).

A molecular formula of $C_{20}H_{24}N_2O_3$ was deduced for compound **3** from its molecular ion $[M^+]$ at *m/z* 340. Typical UV absorptions for indole chromophore (221 and 284 nm) and IR bands for NH (3431 cm^{-1}) and C=O (1725 cm^{-1}) were observed for **3**. The COSY spectrum displayed a coupling system consisting of two pairs of methylene protons at δ 2.85 – 2.94 (2H, m, H_2-3) and at δ 1.90 (1H, m, H-14a) and 2.33 (1H, m, H-14b), which correlated to the carbons at δ 47.5 (C-3) and 23.9 (C-14), respectively in the HMQC spectrum. In addition, three separate methylene groups were observed at δH 4.82 and 4.08 (1H each, d, $J = 17.0$ Hz)/δ_C 51.0 (C-6); δ_H 4.19 and 3.81 (1H each, d, $J = 10.8$ Hz)/δ_C 70.4 (C-17); δ_H 3.61 (2H, m)/δ_C 53.9 (C-21). These spectral features suggested that **3** possessed a skeleton of the vallesamine type. The fragment ion at *m/z* 281 $[M-59]^+$ and the carbon resonances at δ175.2 and 53.0 suggested a carbomethoxyl group, which was then placed at C-16 because of the HMBC correlation of the carbonyl carbon ($COOCH_3$) to H_2-17. A trisubstituted olefinic partial structure was also present, as evident from the carbon resonances at δ 124.4 (C-19) and 132.5 (C-20), which was connected to C-15 and C-21 through the HMBC coupling of H-19 to C-15 and C-21. The nOe interaction of H-19 to H_2-21 of **3** in an nOe differnce experiment indicated 19-*E* configuration. These spectral data suggested the structure of 19-*E*-vallesamine for **3**. Careful analysis of the MS and NMR spectral properties of **3** revealed that they were superimposable with previously reported values for 19-*E*-vallesamine (10, 12).

The EIMS of compound **4** gave a molecular ion $[M^+]$ at *m/z* 356, suggesting the molecular formula $C_{20}H_{24}N_2O_4$. An anilino-acrylate chromophore was indicated by the UV absorptions at 211, 236, 286 and 340 nm, and this was supported by the IR bands at 3432 and 1597 cm^{-1} (NH and C=O, respectively). The ^1H NMR spectrum of **4** exhibited signals for NH at δ 8.58 (1H, s) and $COOCH_3$ at 3.88 (3H, s). From the COSY and HMQC spectra, a coupling system consisting of two pairs of methylene protons was present. The first pair appeared at δ 2.92 and 3.10 (1H each, m), being attached to C-5 (δ 54.0), while the second resonated at δ 1.90 and 2.85 (1H each, m) belonging to C-6 (δ 43.4). The above spectral data and additional information obtained from the COSY and HMQC spectra suggested a strychnan skeleton for compound **4**. In the aromatic region of the COSY spectrum, an ABC three-proton coupling pattern was observed, indicating the presence of a phenolic group on the aromatic ring. The HMBC correlation of H-9 (δ 6.77, d, $J = 8.0$ Hz) to C-7 (δ 57.9) placed the phenolic subtituent at C-12. Compound **4** also showed an OH-bearing methine aliphatic carbon at δ 68.5 (C-19). This carbon (C-19) carried a methyl group (δ_H 1.17, 3H, d, $J = 6.0$ Hz, H_3-18; δ_C 19.8.), and was attached to C-20, as evidenced by the HMBC connectivity from H-20 to C-19 and H_3-18 to C-20. Compound **4** was identified as 19*S*-scholaricine by comparison of its specific rotation, ^{1}H and ^{13}C NMR data with literature values (10, 12, 13)

In this chemical investigation, four indole alkaloids (**1**–**4**) belonging to the corynanthean, strychnan and vallesamine types were isolated from the fruits of *A. scholaris*. Alkaloid **2** has been previously isolated from the fruits of this plant (22), whereas alkaloids **1**, **3** and **4** have been obtained for the first time in this study.

Acknowledgement

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