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NEW MONOTERPENOID INDOLE ALKALOIDS FROM *GELSEMIUM ELEGANS*

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Abstract – Three new monoterpenoid indole alkaloids, 18, 19-dihydro-21-oxo-koumine (**1**), 14-hydroxygelselegine (**2**) and N_b-methyl-19, 20-dihydrorankinidine (**3**), together with five known alkaloids (**4**-**8**) were isolated from the roots of *Gelsemium elegans*. The structures with absolute configurations of the new compounds were elucidated on the basis of HR-ESI-MS, NMR, CD spectra analysis and single crystal X-ray diffraction.

Gelsemium elegans Benth. (Loganiaceae) is known as a highly toxic plant grown in Southeast Asia. The roots of this plant have been used as a Chinese folk medicine for the treatment of cancer, nervous pain, skin ulcer and spasticity.[1] The monoterpenoid indole alkaloids typically existed in genus Gelsemium were named as gelsemium alkaloids. Up to now, more than 120 Gelsemium alkaloids have been reported,[2] some of which demonstrated anti-inflammatory, antitumor and analgesic activities.[1,3] The diversified structures and various biological activities of Gelsemium alkaloids have attracted much attention of chemists and pharmacologist.[4,5] In our previous studies, six new monoterpenoid indole alkaloids had been reported from the aerial part of *G. elegans*.[6] Our further investigation on the roots of *G. elegans* growing in Guangdong province of China led to the isolation of three new alkaloids (**1**-**3**), together with five known ones (**4**-**8**) (Figure 1). In the present paper, we describe the isolation and structure elucidation of

the new alkaloids by means of NMR, HR-ESI-MS, circular dichroism spectroscopy and single crystal X-ray diffraction.

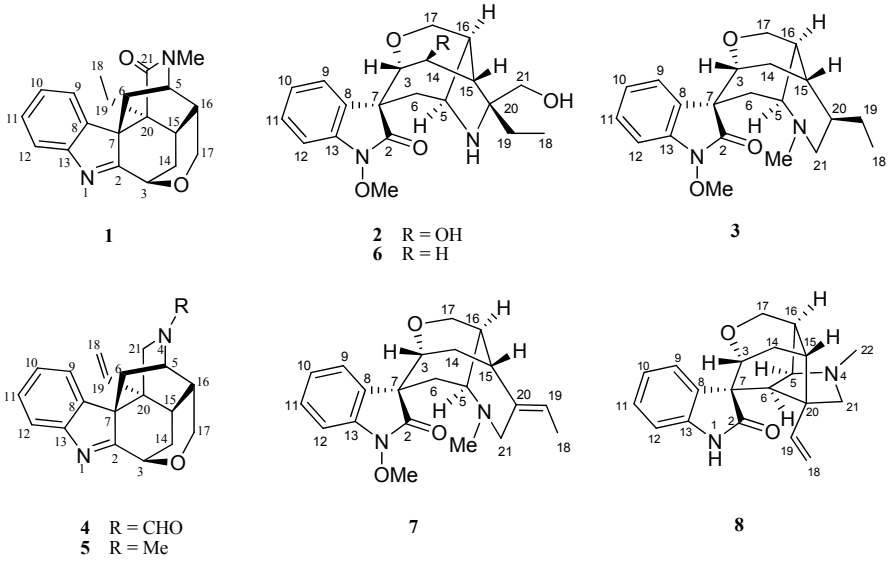

Figure 1. Chemical structures of **1**-**8**

Compound **1** was obtained as colorless needles. The molecular formula of **1** was deduced as $C_{20}H_{22}N_2O_2$ by HR-ESI-MS (*m/z* 323.1734 $[M+H]^+$; calcd for $C_{20}H_{23}N_2O_2$, 323.1754). The UV absorption maxima at 217 and 263 nm and the IR bands at 3410, 1711, 1623, 1593 and 1495 cm^{-1} indicated that **1** was an indole alkaloid.[7] In the ^{1}H-NMR spectrum, signals for four aromatic protons [δ_H 7.56 (1H, d, *J* = 7.6 Hz, H-12), 7.30 (1H, dd, *J* = 7.6, 7.6 Hz, H-11), 7.19 (1H, dd, *J* = 7.6, 7.6 Hz, H-10), 7.09 (1H, d, *J* = 7.6 Hz, H-9)] assignable to the indole moiety, three oxygenated protons [δ_H 5.03 (1H, m, H-3), 4.22 (1H, dd, *J* = 12.3, 4.4 Hz, H-17), 3.66 (1H, d, *J* = 12.3 Hz, H-17)], and a *N*-methyl group [δ_H 3.14 (3H, s)] were observed. The ^{13}C NMR spectrum of **1** exhibited twenty carbon signals including six aromatic carbon signals [δ_C 154.6 (C-13), 142.4 (C-8), 128.5 (C-11), 126.7 (C-10), 122.9 (C-9), 121.3 (C-12)] and an imine carbon signal [δ_C 180.4 (C-2)]. With the aid of 1D and 2D NMR experiments, all the ^{1}H- and ^{13}C-NMR signals of **1** were assigned as shown in Table 1. Comparison of the NMR data of **1** with those of koumine (**5**)[7] revealed that most signals were similar except for the presence of a carbonyl signal (δ_C 172.9) and an ethyl carbon signals [δ_C 18.8 (C-19), 8.0 (C-18)] in **1**, instead of a methylene signal [δ_C 57.2 (C-21)] and two terminal vinyl carbon signals [δ_C 136.8 (C-19), 115.3 (C-18)] in koumine (**5**). The carbonyl group was located at C-21 position based on the HMBC correlations between H-5 (δ_H 3.58) and C-21 (δ_C 172.9), and between *N*-Me (δ_H 3.14) and C-21 (δ_C 172.9) (Figure 2). In addition, the ^{1}H-^{1}H COSY cross peak between H-18 (δ_H 0.69) and H-19 (δ_H 1.40, 0.14), as well as the HMBC correlation between H-18 and C-20 confirmed an ethyl was connected to C-20 (Figure 2). Thus, the planar structure of **1** could be

deduced as shown in Figure 1. Fortunately, a single crystal of **1** was obtained from MeOH and an X-ray diffraction experiment was performed with Cu Kα radiation, which unambiguously determined the absolute stereochemistry of **1** with a small Flack parameter of 0.0 (2) (Figure 3). Furthermore, the CD spectra of **1** showed similar Cotton effects as the known koumine-type alkaloids, such as furanokoumine [8] indicating that the absolute configuration of C-7 was *R* (Figure 4). Base on the above evidences, the structure of **1** was established as 18, 19-dihydro-21-oxo-koumine (Figure 1).

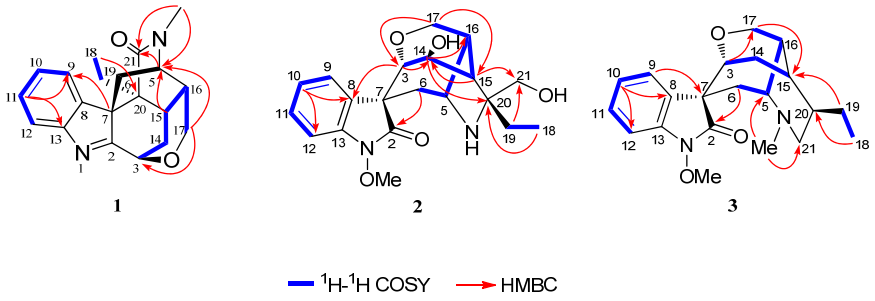

Figure 2. Key ^{1}H-^{1}H COSY and HMBC correlations of **1-3**

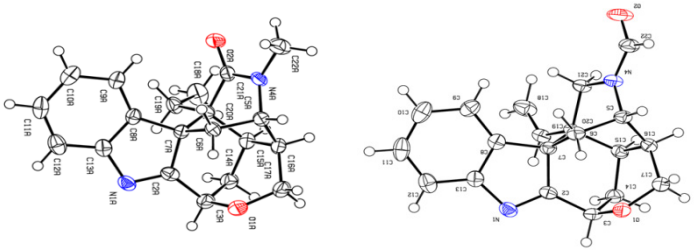

Figure 3. X-Ray crystal structures of **1** and **4**

Compound **2** was shown to have the molecular formula $C_{20}H_{26}N_2O_5$ by its HR-ESI-MS data (*m/z* 375.1919 $[M+H]^+$; calcd for $C_{20}H_{27}N_2O_5$, 375.1915), which indicated that **2** has an extra oxygen atom compared to the known alkaloid gelselegine (**6**).[9] The UV and IR spectra revealed the characteristic absorptions for an indolin-2-one chromophore. The ^{1}H NMR spectrum displayed some readily assignable signals due to the known gelselegine (**6**) portion, such as four aromatic protons [δ_H 7.36 (1H, d, J = 7.6 Hz, H-9), 7.28 (1H, dd, J = 7.6, 7.6 Hz, H-11), 7.11 (1H, dd, J = 7.6, 7.6 Hz, H-10), 6.94 (1H, d, J = 7.6 Hz, H-12)], three oxygenated protons [δ_H 4.37 (1H, dd, J = 11.2, 4.3 Hz, H-17), 4.29 (1H, d, J = 11.2 Hz, H-17), 3.44 (1H, d, J = 1.8 Hz, H-3)], a *N*-methoxy group [δ_H 3.99 (3H, s)], and an ethyl group [δ_H 2.03 (1H, m, H-19), 1.93 (1H, dq, J = 14.5, 7.5 Hz, H-19), 1.01 (1H, t, J = 7.5 Hz, H-18)]. In addition, signals for an oxygenated methine [δ_H 4.46 (1H, d, J = 1.8 Hz, H-14)] were observed. The ^{13}C NMR spectrum of **2** also demonstrated signals similar to those of gelselegine (**6**).[9] The main difference was that **2** was substituted by a hydroxyl group instead of a hydrogen atom at the C-14 position, which was further

confirmed by the HMBC correlations between H-3 (δ_H 3.44)/H-15 (δ_H 1.85) and C-14 (δ_C 65.8), between H-14 (δ_H 4.46) and C-16 (δ_C 38.4)/C-20 (δ_C 68.6), as well as the ^{1}H-^{1}H COSY cross peak between H-3 (δ_H 3.44) and H-14 (δ_H 4.46) (Figure 2). The relative configuration of the hydroxyl group at C-14 was deduced to be β on the basis of the coupling constant between H-14 and H-3/H-15 ($J < 2$ Hz).[3, 10] To determine the absolute configuration of **2**, a circular dichroism measurement was applied. The CD spectrum of **2** showed negative Cotton effect at 215 nm ($\Delta\varepsilon$ −10.32) and positive one at 237 nm ($\Delta\varepsilon$ +4.51), which was accordance with the known gelsedine-type alkaloids with 7*S* configurations (Figure 4).[3,9] Thus, the structure of **2** was determined and named as 14-hydroxygelselegine (Figure 1).

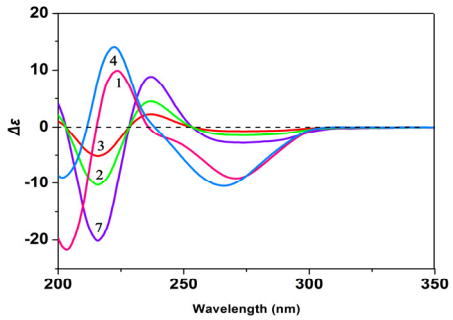

Figure 4. CD spectra for **1**-**4** and **7** (in MeCN)

Compound **3** was isolated as amorphous powder. The molecular formula of **3** was established as $C_{21}H_{28}N_2O_3$ by a quasi-molecular ion at *m/z* 357.2196 $[M+H]^+$ (calcd for $C_{21}H_{29}N_2O_3$, *m/z* 357.2173) in its HRESIMS. The IR spectrum showed absorptions due to carbonyl (1719 cm^{-1}) and aromatic ring (1617, 1464 cm^{-1}). The UV spectrum of **3** displayed absorption maxima at 208 and 256 nm, characteristic for an indolin-2-one chromophore. The ^{1}H NMR spectrum of **3** showed signals for an ortho-disubstituted benzene ring [δ_H 7.34 (1H, d, J = 7.6 Hz, H-9), 7.28 (1H, dd, J = 7.6, 7.6 Hz, H-11), 7.09 (1H, dd, J = 7.6, 7.6 Hz, H-10), 6.97 (1H, d, J = 7.6 Hz, H-12)], a methoxyl [δ_H 3.97 (3H, s)], a *N*-methyl [δ_H 2.37 (3H, s)], and an ethyl group [δ_H 1.69 (1H, dq, J = 13.6, 7.0 Hz, H-19), 1.53 (1H, dq, J = 13.6, 7.0 Hz, H-19), 0.95 (1H, t, J = 7.0 Hz, H-18)]. The ^{13}C NMR spectrum of **3** displayed twenty-one signals. The signals for a carbonyl at δ_C 174.5, a spiro quaternary carbon at δ_C 55.4 and a methylene at δ_C 48.3 were characteristic for humantenine-type alkaloid. Comparison of the NMR data of **3** with those of the known compound 19, 20-dihydrorankinidine revealed that their NMR signals were similar,[11] except for the resonances for CH-5 (δ_H 3.49; δ_C 62.1) and CH_2-21 (δ_H 2.47, 3.22; δ_C 48.3) were changed and an additional methyl group (δ_H 2.37; δ_C 42.8) was existed in **3**. Thus, **3** was proposed as a N_b-methyl substituted derivative of 19, 20-dihydrorankinidine, which was confirmed by the HMBC correlations between methyl protons and C-5/C-21. The relative stereochemistry of **3** was deduced by analysis of its NOESY spectrum. The

absolute configuration of the spiro-center at C-7 was determined to be *S* by comparison of its CD spectrum with that of humantenine (**7**) (Figure 4).[12] Based on the above evidences, the structure of **3** was established as N_b-methyl-19, 20-dihydrorankinidine.

Table 1. ^{1}H and ^{13}C NMR Data of Compounds **1-3** ($CDCl_3$, δ in ppm, *J* in Hz) [a)]

No.	**1**		**2**		**3**	
	δ_H [b)]	δ_C [c)]	δ_H [d)]	δ_C [e)]	δ_H [d)]	δ_C [e)]
2	-	180.4	-	174.3	-	174.5
3	5.03 (m)	70.9	3.44 (d, 1.8)	81.4	3.61 (d, 6.1)	72.6
5	3.58 (m)	58.5	3.56 (dt, 9.0, 3.1)	58.6	3.49 (m)	62.1
6	α 2.69 (dd, 13.7, 3.1)	36.5	α 2.17 (dd, 16.1, 3.7)	34.9	α 2.43 (dd, 15.7, 7.6)	26.3
	β 1.98 (d, 13.7)		β 1.98 (d, 16.1)		β 1.75 (dd, 15.7, 9.5)	
7	-	58.9	-	55.1	-	55.4
8	-	142.4	-	131.5	-	129.4
9	7.09 (d, 7.6)	122.9	7.36 (d, 7.6)	125.5	7.34 (d, 7.6)	125.8
10	7.19 (dd, 7.6, 7.6)	126.7	7.11 (dd, 7.6, 7.6)	124.1	7.09 (dd, 7.6, 7.6)	123.3
11	7.30 (dd, 7.6, 7.6)	128.5	7.28 (dd, 7.6, 7.6)	128.8	7.28 (dd, 7.6, 7.6)	128.3
12	7.56 (d, 7.6)	121.3	6.94 (d, 7.6)	107.6	6.97 (d, 7.6)	107.5
13	-	154.6	-	138.1	-	138.8
14	α 2.63 (dd, 15.0, 3.6)	25.2	4.46 (d, 1.8)	65.8	α 2.24	28.1
	β 1.68 (d, 15.0)		-		β 2.23	
15	2.75 (m)	37.8	1.85 (d, 6.0)	48.1	1.87 (m)	29.5
16	2.41 (br d, 13.6)	26.9	2.71 (m)	38.4	2.48 (m)	33.4
17	α 4.22 (dd, 12.3, 4.4)	60.8	α 4.37 (dd, 11.2, 4.3)	63.5	α 4.16 (d, 11.1)	67.2
	β 3.66 (d, 12.3)		β 4.29 (d, 11.2)		β 3.99 (dd, 11.1, 5.4)	
18	0.69 (t, 7.2)	8.0	1.01 (t, 7.5)	9.3	0.95 (t, 7.0)	12.6
19	1.40 (dq, 14.6, 7.2)	18.8	2.03 (m)	23.4	1.69 (dq, 13.6, 7.0)	26.5
	0.14 (dq, 14.6, 7.2)		1.93 (dq, 14.5, 7.5)		1.53 (dq, 13.6, 7.0)	
20	-	51.0	-	68.6	1.58 (m)	41.5
21	-	172.9	α 3.14 (d, 10.2)	63.2	α 2.47 (m)	48.3
			β 3.43 (d, 10.2)		β 3.22 (dd, 12.7, 3.4)	
N_b-Me	3.14 (s)	32.2	-	-	2.37 (s)	42.8
N_a-OMe	-	-	3.99 (s)	63.8	3.97 (s)	63.5

[a)] Overlapped signals were reported without designating multiplicity.

[b)] Measured at 400 MHz. [c)] Measured at 100MHz. [d)] Measured at 500 MHz. [e)] Measured at 125 MHz.

The structure of **4** was elucidated as 1, 2, 18, 19-tetradehydro-4-demethyl-4-formaldehyde-3, 17-epoxy-7, 20 (2H, 19H)-cyclovobasan by comprehensive analysis of its spectroscopic data including UV, IR, HRESIMS, and NMR. This compound was recently obtained as a metabolite of koumine incubated with phenobarbital-treated rat liver microsomes.[13] However, the absolute configuration of **4** was not clearly defined in the previous work. In present study, the absolute configuration of **4** was determined through CD experiment (Figure 4) and single crystal X-ray diffraction with Cu Kα radiation [Flack parameter of 0.0 (2), Figure 3].

The structures of the known alkaloids koumine (**5**),[7] gelselegine (**6**)[9] humantenine (**7**)[12] and gelsemine (**8**)[14] were also isolated and determined by comparing their spectroscopic data with those reported in literatures.

EXPERIMENTAL

General:

All melting points were obtained on an X-5 micro melting point apparatus without correction. Optical rotations were measured on a Jasco P-1020 polarimeter with a 1 cm cell at room temperature. UV spectra were recorded on a Jasco V-550 UV/VIS spectrophotometer. IR spectra were determined on a Jasco FT/IR-480 plus Fourier transform infrared spectrometer using KBr pellets. HR-ESI-MS were carried out on Agilent 6210 LC/MSD TOF mass spectrometer. NMR spectra were measured on Bruker AV-400 and AV-500 spectrometers in $CDCl_3$. TLC analyses were carried out using precoated silica gel GF_{254} plates (Qingdao Marine Chemical Plant, Qingdao, P. R. China). Column chromatography was performed on silica gel (200-300 mesh, Qingdao Marine Chemical Plant, Qingdao, P. R. China) and Sephadex LH-20 (Pharmacia Biotec AB, Sweden). HPLC was performed on an Agilent 1260 Chromatograph equipped with a G1311C pump and a G1315D photodiode array detector with a C_{18} reversed-phase column (Cosmosil, 10×250 mm, 5 μm). All solvents used in column chromatography and HPLC were of analytical grade (Shanghai Chemical Plant, Shanghai, P. R. China) and chromatographic grade (Fisher Scientific, New Jersey, U. S. A), respectively.

Plant material:

The roots of *Gelsemium elegans* were collected from Conghua, Guangdong Province, P. R. China, in September of 2012, and authenticated by Prof. Guang-Xiong Zhou (Jinan University). A voucher specimen (No. 2012092801) was deposited in the Institute of Traditional Chinese Medicine & Natural Products, Jinan University, Guangzhou, P. R. China.

Extraction and isolation:

The powder of the air-dried roots (20 kg) of *G. elegans* was extracted with 95% EtOH under reflux to afford a crude extract (1.9 kg), which was suspended in H_2O and acidified with 5% HCl to pH 3. The acidic suspension was partitioned with $CHCl_3$ to remove the neutral components. The aqueous layer was then basified with $NH_3 \cdot H_2O$ to pH 9 and re-extracted with $CHCl_3$ to obtain a total alkaloid fraction (250 g). The alkaloid fraction was subjected to silica gel column chromatography (CC) eluting with $CHCl_3$-MeOH (100:0→0:100) to afford eleven major fractions (Fr. A-K). Fraction A (35 g) was re-subjected to silica gel column chromatography (*n*-hexane-EtOAc-Et_2NH, 100:0:1→0:100:1) to afford seven sub-fractions (Fr. A1-A7). Fr. A1 was then chromatographed on Sephadex LH-20 ($CHCl_3$-MeOH,

1:1) and was further fractionated by HPLC using MeOH-H_2O (1:1) as mobile phase to obtain compounds **1** (6.5 mg) and **4** (5.3 mg). Fr. A6 was purified by silica gel CC eluting with $CHCl_3$-MeOH with increasing polarity to yield compounds **3** (6.0 mg) and **7** (8.3 mg). Fr. A3 was purified by Sephadex LH-20 to obtain compounds **5** (18.6 mg) and **8** (10.2 mg). Fr. B was purified by Sephadex LH-20 ($CHCl_3$-MeOH, 1:1) to give eight sub-fractions (B1 to B8). Fr. B5 was purified by preparative HPLC (MeOH-H_2O-Et_2NH, 62:38:0.01) to yield compound **2** (5.6 mg). Fr. B8 was separated by Sephadex LH-20 ($CHCl_3$-MeOH, 1:1) and HPLC (MeOH-H_2O-Et_2NH, 60:40:0.01) to obtain compound **6** (7.9 mg).

Compound 1:

Colorless needles; mp 169 ~ 170 °C; $[\alpha]_D^{25}$ - 17.85 (*c* 0.25, MeOH); UV (MeOH) λ_{max} (log ε) 217 (3.27), 263 (2.71) nm; CD (MeCN, $\Delta\varepsilon$) λ_{max} 223 (+ 9.86), 271 (− 9.16) nm; IR (KBr) ν_{max} 3410, 2938, 2857, 1711, 1623, 1593, 1495, 1214, 1109, 939, 826 cm^{-1}; ^1H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) NMR data, see Table 1. HR-ESI-MS *m/z* 323.1734 $[M+H]^+$ (calcd for $C_{20}H_{23}N_2O_2$, 323.1754).

Compound 2:

Yellow oil; $[\alpha]_D^{25}$ - 13.50 (*c* 0.25, MeOH); UV (MeOH) λ_{max} (log ε) 210 (3.09), 260 (2.54) nm; CD (MeCN, $\Delta\varepsilon$) λ_{max} 215 (− 10.32), 237 (+ 4.51) nm; IR (KBr) ν_{max} 3403, 2917, 1724, 1617, 1588, 1462, 1318, 1042, 751 cm^{-1}; ^1H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR data, see Table 1. HR-ESI-MS *m/z* 375.1919 $[M+H]^+$ (calcd for $C_{20}H_{27}N_2O_5$, 375.1915).

Compound 3:

Amorphous powder; $[\alpha]_D^{25}$ - 30.45 (*c* 1.00, MeOH); UV (MeOH) λ_{max} (log ε) 208 (3.43), 256 (2.35) nm; CD (MeCN, $\Delta\varepsilon$) λ_{max} 216 (− 5.16), 237 (+ 2.26) nm; IR (KBr) ν_{max} 3413, 2924, 1719, 1617, 1464, 1325, 1208, 1117, 1075, 956, 749 cm^{-1}; ^1H (500 MHz, $CDCl_3$) and ^{13}C (125 MHz, $CDCl_3$) NMR data, see Table 1. HR-ESI-MS *m/z* 357.2196 $[M+H]^+$ (calcd for $C_{21}H_{29}N_2O_3$, 357.2173).

Compound 4:

Colorless needles; mp 174 ~ 175 °C; CD (MeCN, $\Delta\varepsilon$) λ_{max} 222 (+ 13.99), 266 (− 10.51) nm.

Compound 7:

Amorphous powder; CD (MeCN, $\Delta\varepsilon$) λ_{max} 216 (− 20.14), 237 (+ 8.81) nm.

Single-crystal X-ray crystallography of 1

Suitable colorless needles of **1** were obtained from a solution of methanol. The crystal belongs to the triclinic system, space group *P*1 (#1), with *a* = 7.5745(3) Å, *b* = 8.1556(3) Å, *c* = 14.9064(5) Å, β = 84.522(3)°, *V* = 842.51(5) $Å^3$, *Z* = 2, D_{calcd} = 1.271 g/cm^3, *F*(000) = 344. Data collection was performed on a SMART CCD using graphite monochromated radiation (λ = 1.54184 Å) under low temperature (nitrogen gas); 4814 unique reflections were collected to θ_{max} = 62.97°, in which 5068 reflections were observed [$F_2 > 4\sigma(F^2)$]. The structure was solved by direct methods (SHELX97) and refined with

full-matrix least-squares on F^2 procedure. In the structure refinements, non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms bonded to oxygen were located by the difference Fourier method and were included in the calculation of structure factors with isotropic temperature factors. Hydrogen atoms were located by different Fourier techniques and refined anisotropically. The refined structural model converged to a final $R_1 = 0.0368$, $wR_2 = 0.0840$ and $S = 1.044$. Crystallographic data of **1** have been deposited with the Cambridge Crystallographic Data Centre (deposit No. CCDC 989048). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK (Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

Single-crystal X-ray crystallography of 4

Colorless needles, $C_{20}H_{20}N_2O_2$, monoclinic, $P2_1$, $a = 7.6859(2)$, $b = 7.71266(16)$, $c = 13.5130(3)$Å, $\beta = 105.195(3)$, $V = 773.03(3)$ Å^3, $Z = 2$, $d_x = 1.376$ Mg/m^3, $F(000) = 340$. Data collection was performed on a SMART CCD using graphite monochromated radiation (λ = 1.54184 Å) under low temperature (nitrogen gas); 2363 unique reflections were collected to $\theta_{max} = 62.77°$, in which 2466 reflections were observed [$F_2 > 4\sigma(F^2)$]. The structures were solved by direct methods (SHELXTL) and refined by full-matrix least-squares on F^2. Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were located by different Fourier techniques and refined with isotropic thermal parameters. The final $R_1 = 0.0267$, $wR_2 = 0.0658$ and $S = 1.045$. Crystallographic data of **2** have been deposited with the Cambridge Crystallographic Data Centre (deposit No. CCDC 989049). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK (Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

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REFERENCES

1. M. Kitajima, *J. Nat. Med.*, 2007, **61**, 14.
2. G. L. Jin, Y. P. Su, M. Liu, Y. Xu, J. Yang, K. J. Liao, and C. X. Yu, *J. Ethnopharmacol.*, 2014, **152**, 33.
3. M. Kitajima, T. Nakamura, N. Kogure, M. Ogawa, Y. Mitsuno, K. Ono, S. Yano, N. Aimi, and H. Takayama, *J. Nat. Prod.*, 2006, **69**, 715.
4. S. Diethelm and E. M. Carreira, *J. Am. Chem. Soc.*, 2013, **135**, 8500.

5. M. Liu, H. H. Huang, J. Yang, Y. P, Su, H. W. Lin, L. Q. Lin, W. J. Liao, and C. X. Yu, *Psychopharmacology*, 2013, **225**, 839.
6. S. Ouyang, L. Wang, Q. W. Zhang, G. C. Wang, Y. Wang, X. J. Huang, X. Q. Zhang, R. W. Jiang, X. S. Yao, C. T. Che, and W. C. Ye, *Tetrahedron*, 2011, **67**, 4807.
7. L. Z. Lin, G. A. Cordell, C. Z. Ni, and J. Clardy, *Phytochemistry*, 1990, **29**, 965.
8. M. X. Sun, X. L. Hou, H. H. Gao, J. S. Guo, and K. Xiao, *Molecules*, 2013, **18**, 1819.
9. Y. K. Xu, S. G. Liao, Z. Na, H. B. Hu, L. Yan, and H. R. Luo, *Fitoterapia*, 2012, **83**, 1120.
10. M. Kitajima, A. Urano, N. Kogure, H. Takayama, and N. Aimi, *Chem. Pharm, Bull.*, 2003, **51**, 1211.
11. M. Kitajima, H. Kobayashi, N. Kogure, and H. Takayama, *Tetrahedron*, 2010, **66**, 5987.
12. L. Z. Lin and G. A. Cordell, *J. Nat. Prod.*, 1989, **52**, 588.
13. L. Zhang, L. Du, W. W. Lv, Q. C. Zhao, W. Hua, Y. An, T. Guo, and L. J. Wu, *J. Asian Nat. Prod. Res.*, 2013, **15**, 46.
14. Y. Schun and G. A. Cordell, *J. Nat. Prod.*, 1986, **49**, 483.