

HETEROCYCLES, Vol. 85, No. 8, 2012, pp. 1949 - 1959. © 2012 The Japan Institute of Heterocyclic Chemistry
 Received, 18th May, 2012, Accepted, 25th June, 2012, Published online, 29th June, 2012
 DOI: 10.3987/COM-12-12511

NEW INDOLE ALKALOIDS FROM *MELODINUS HENRYI*

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Abstract – Two new indole alkaloids, melodinoxanine (**1**) and *N*_b-methylnortetraphyllicine (**2**), were isolated from the stems and leaves of *Melodinus henryi* growing in Yunnan, China. Melodinoxanine (**1**) is a unique oxindole alkaloid with an extra oxygen atom in the C-ring of a heteroyohimbine skeleton.

INTRODUCTION

Melodinus plants belonging to Apocynaceae are rich sources of monoterpene indole alkaloids. To date, more than one hundred alkaloids have been isolated.¹ Some species have been used in Chinese folk medicine to treat meningitis in children and fracture, etc. As part of our investigations of novel and bioactive alkaloids from various plant sources,² phytochemical research on *Melodinus henryi* growing in

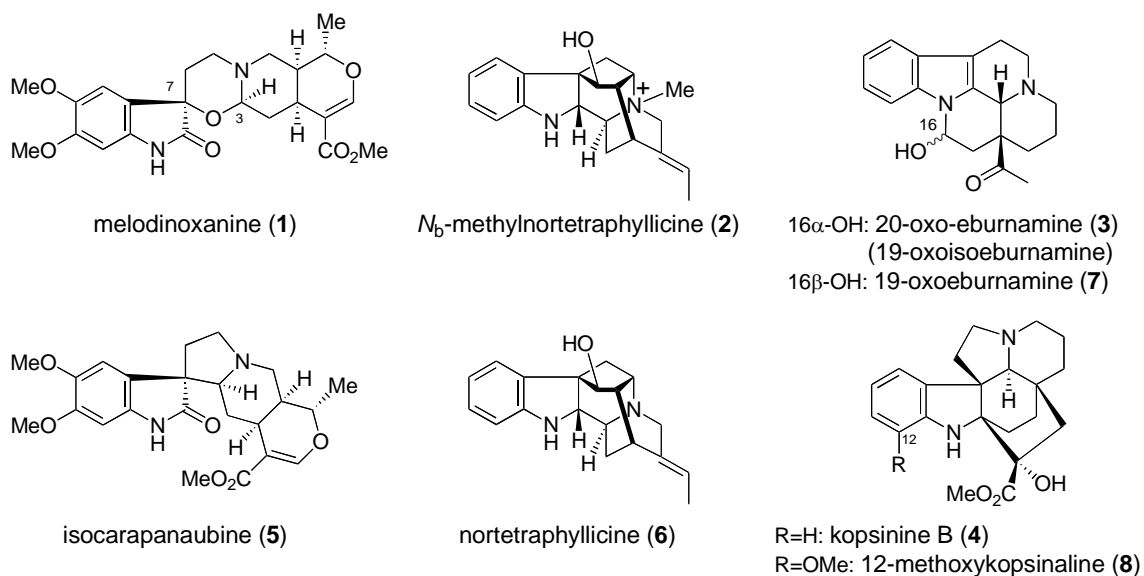


Figure 1. Structures of new (**1**, **2**) and known (**3-8**) alkaloids.

Yunnan, China, was carried out. We herein describe the isolation and structure elucidation of two new alkaloids, melodinoxanine (**1**) and *N*_b-methylnortetraphyllicine (**2**), and two known alkaloids, 20-oxo-eburnamine (19-oxoisoburnamine) (**3**) and kopsinine B (**4**) (Figure 1).

RESULTS AND DISCUSSION

From the MeOH extract of the dried stems and leaves of *M. henryi*, two new alkaloids **1** and **2** were isolated together with thirty-eight known indole alkaloids.

New alkaloid **1**, named melodinoxanine, was found to have the molecular formula C₂₃H₂₈N₂O₇ from HREIMS [*m/z* 444.1883 (M⁺)], indicating that it has one extra oxygen compared to isocarapanaubine (**5**),³ which was found to co-exist in this plant (Figure 2). Its UV spectrum was similar to that of **5**, a heteroyohimbine-type oxindole alkaloid having two methoxy groups at C-10 and C-11 positions. ¹H and ¹³C NMR spectral data (Table 1) showed the existence of two aromatic protons [δ_{H} 6.94 (s, H-9), 6.43 (s, H-12)] and one carbonyl carbon [δ_{C} 178.3 (C-2)] of the oxindole system, two aromatic methoxy groups (δ 3.86, 6H), one methyl β -alkoxy acrylic ester residue [δ_{H} 7.54 (s, H-17), 3.65 (3H, s, CO₂Me); δ_{C} 167.6 (CO₂Me), 155.3 (C-17), 109.7 (C-16), 51.0 (CO₂Me)], one oxygenated methine proton (δ_{H} 4.57, dq, H-19), and one methyl group (δ_{H} 1.41, 3H, d, H₃-18). These spectral data were similar to those of isocarapanaubine (**5**) except for the signals assigned to H-3 (δ_{H} 4.77), C-3 (δ 86.5), and C-7 (δ 75.0), which were observed in the low field compared to those of **5** (H-3, δ_{H} 3.30-3.20; C-3, δ_{C} 72.2; C-7, δ_{C} 57.2). HMBC correlations from the protons at δ_{H} 2.92 (H-21) and 1.45 (H-14) to the carbon at δ_{C} 86.5 (C-3), and from the protons at δ_{H} 6.94 (H-9) and 2.75-2.69 (H-5) to the carbon at δ_{C} 75.0 (C-7) suggested that **1** has a hemiaminal ether function with an ether linkage between C-3 and C-7 positions, and is an oxygenated derivative of isocarapanaubine (**5**). The relative stereochemistry was deduced as follows. NOE correlations from H-3 to H-5 α (δ_{H} 3.08), H-15 (δ_{H} 2.75-2.69), and H-21 α (δ_{H} 2.65) indicated a *trans* C/D ring junction and an α -axial H-3 in a chair-chair conformation of the C/D ring. Furthermore, NOE correlations from H-21 α to H-20 and from H-9 to H-6 and a large coupling constant (10.1 Hz) between H-19 and H-20 in the ¹H NMR spectrum suggested that the relative stereochemistry of **1** is the same as

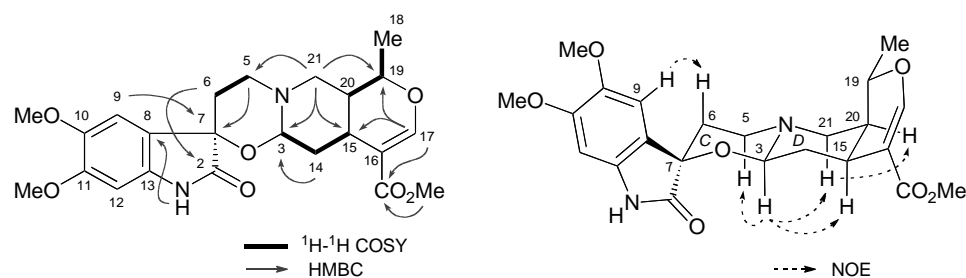


Figure 2. Selected 2D NMR and NOE data of **1**.

that of isocarapanaubine (**5**). The absolute configuration at C-15 position was deduced to be *S* based on the biogenesis of common monoterpene indole alkaloids generally derived from secologanin. Therefore, the structure of melodinoxanine was deduced to be that shown as formula **1**. This is the first example of a heteroyohimbine-type alkaloid with an ether linkage between C-3 and C-7 positions.

Table 1. ^1H and ^{13}C NMR Data for **1** in CDCl_3 .

Position	δ_{H}^a	δ_{C}^b	Position	δ_{H}^a	δ_{C}^b
2		178.3	15	2.75-2.69 (overlapped)	30.2
3	4.77 (dd, 10.1, 3.1)	86.5	16		109.7
5 α	3.08 (br-dd, 12.7, 12.7)	48.1	17	7.54 (s)	155.3
β	2.75-2.69 (overlapped)		18	1.41 (3H, d, 6.1)	18.6
6 α	1.81 (br-ddd, 12.7, 2.4, 2.4)	31.7	19	4.57 (dq, 10.1, 6.1)	72.0
β	2.36 (ddd, 12.7, 12.7, 4.6)		20	1.63 (m)	37.8
7		75.0	21 α	2.65 (dd, 12.7, 3.7)	53.7
8		121.2	β	2.92 (dd, 12.7, 1.4)	
9	6.94 (s)	108.7	CO ₂ Me		167.6
10		145.5 ^c	CO ₂ Me	3.65 (3H, s)	51.0
11		150.5 ^c	OMe	3.86 (3H, s)	56.6
12	6.43 (s)	95.3	OMe	3.86 (3H, s)	56.3
13		133.5	N _a H	7.13 (s)	
14 α	2.17 (ddd, 12.1, 3.4, 3.4)	35.6			
β	1.45 (ddd, 12.1, 12.1, 12.1)				

^a 500 MHz, ^b 125 MHz, ^c Interchangeable

Melodinoxanine (**1**) was biogenetically considered to be derived from isoreserpiline (**9**)⁴ via the pathway shown in Figure 3: (i) formation of a dioxetane ring by oxidation of the C-2 and C-7 positions of indole; and (ii) simultaneous bond cleavage between O-O and C-2–C-3 in a radical manner, followed by ring closure between C-3 and the oxygen at C-7 to construct a spiro ring.

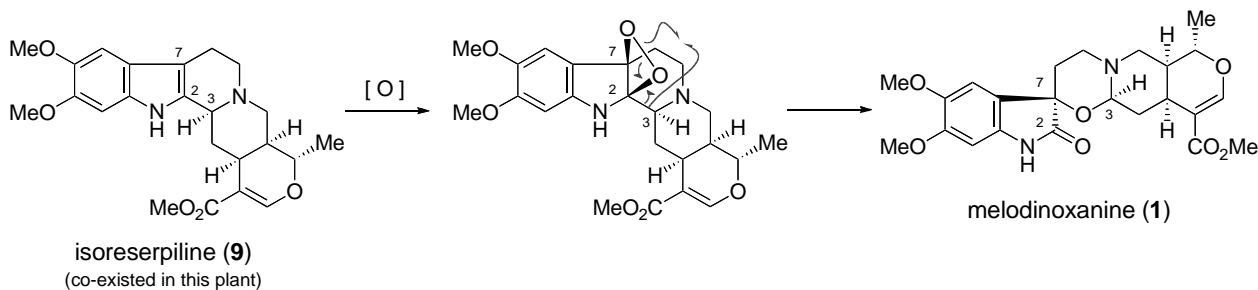


Figure 3. Plausible biosynthetic pathway of **1**.

The HREIMS of new alkaloid **2** gave a molecular ion peak at m/z 309.1953 (M^+) that corresponded to the molecular formula $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}$ (Figure 4). The UV spectrum exhibited a characteristic indoline chromophore. The ^1H and ^{13}C NMR spectra (Table 2) were very similar to those of nortetraphyllicine (**6**),⁵

an ajmaline-type alkaloid that co-existed in this plant. However, in the ^1H NMR spectrum (in CD_3OD), an additional N_b -methyl signal appeared at δ 3.25 and signals of protons around the N_b nitrogen atom (H-3, δ_{H} 3.87; H-5, δ_{H} 3.68; H₂-21, δ_{H} 4.23 and 3.76) were observed in the low field relative to those of **6** (in CDCl_3 , H-3, δ_{H} 3.02; H-5 and H₂-21, δ_{H} 3.40-3.32). In addition, the downfield shift of the signals due to carbons around the N_b nitrogen atom (C-3, C-5, and C-21) was observed in the ^{13}C NMR spectrum. These data suggested that **2** is an N_b -methyl derivative of nortetraphyllicine (**6**). HMBC correlations from the methyl protons at δ 3.25 to the carbons at δ_{C} 68.4 (C-5), 66.5 (C-21), and 63.8 (C-3) supported the existence of a methyl group on the N_b nitrogen atom. The *E* configuration of the ethylidene group was confirmed from the NOE correlation of H-19 (δ_{H} 5.41) to H-21 (δ_{H} 3.76). The CD spectrum showed a similar curve to that of nortetraphyllicine (**6**) with negative and positive Cotton effects at 290 and 241 nm, respectively, revealing a 7*R* configuration. As a result of the rigid character of the skeleton, the configurations at C-2, C-3, C-5, C-15, and C-16 were restricted, i.e., 2*R*, 3*S*, 5*S*, 15*R*, and 16*S*, respectively. The configuration at C-17 was deduced to be *R* because H-17 was observed as a broad singlet; the dihedral angle between H-17 and H-16 was ca. 90 degrees. From these data, compound **2** was deduced to be N_b -methylnortetraphyllicine.

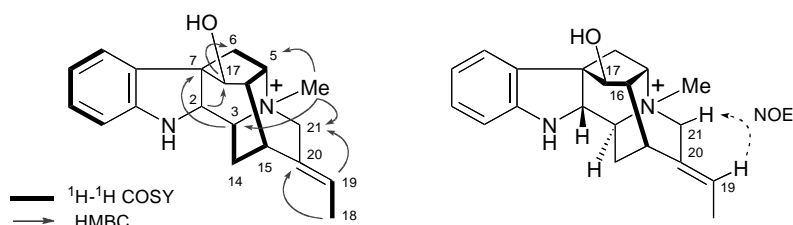


Figure 4. Selected 2D NMR and NOE data of **2**.

Table 2. ^1H and ^{13}C NMR Data for **2** in CD_3OD .

Position	δ_{H}^a	δ_{C}^b	Position	δ_{H}^a	δ_{C}^b
2	3.41 (br-s)	71.4	14	2.17-2.10 (overlapped)	29.7
3	3.87 (d, 9.8)	63.8	15	2.00 (dd, 14.3, 5.8)	28.2
5	3.68 (br-dd, 5.8, 5.8)	68.4	16	3.34 (dd, 5.8, 5.8)	54.0
6	2.28 (d, 14.3)	31.2	17	2.47 (br-dd, 5.8, 5.8)	75.9
	2.17-2.10 (overlapped)		18	4.34 (br-s)	12.7
7		56.4	19	1.67 (3H, dd, 6.8, 1.8)	120.7
8		132.3	20	5.41 (br-q, 6.8)	131.5
9	7.40 (ddd, 7.5, 1.2, 1.2)	125.0	21	4.23 (br-ddd, 14.4, 1.8, 1.8)	66.5
10	6.68 (dd, 7.5, 7.5)	121.3		3.76 (d, 14.4)	
11	6.98 (ddd, 7.5, 7.5, 1.2)	129.0	N_b -Me	3.25 (3H, s)	50.1
12	6.67 (d, 7.5)	112.3			
13		152.2			

^a 500 MHz, ^b 125 MHz

Alkaloid **3** was found to be 20-oxo-eburnamine, a compound that was reported in 1984.⁶ As its detailed structure elucidation, including stereochemical analysis, has not been described, we discuss them here. Alkaloid **3** was found to have the same molecular formula $C_{19}H_{22}N_2O_2$ as 19-oxoeburnamine (**7**)⁷ from HRESIMS (m/z 311.1744 $[M+H]^+$) (Figure 5). Its UV spectrum indicated the presence of a characteristic indole chromophore. The ^{13}C NMR spectrum showed the existence of carbonyl (δ_C 210.8) and hemiaminal (δ_C 74.4) carbons. HMBC correlations from the protons at δ_H 4.76 (H-21), 2.39 (H₃-18), 2.24 (H-17), and 1.83 (H-15) to the carbonyl carbon as well as from the hemiaminal proton to the carbons at δ_C 130.5 (C-2) and 49.7 (C-20) supported the existence of a C-19 carbonyl group and a hydroxy group at the C-16 position of the eburnan skeleton. The 1H NMR spectrum was similar to that of 19-oxoeburnamine (**7**) except for the hemiaminal proton at C-16; H-16 was observed at δ_H 6.11 as a doublet with the coupling constant of 4.1 Hz in **3**, whereas it was observed at δ_H 5.67 (dd, $J = 9.1, 5.5$ Hz) in **7**. This suggested that **3** is a C-16 epimer of **7**. The coupling constants between H-16 and H₂-17 ($J = 4.1, 0$ Hz) indicated that the C-16 hydroxy group is α -oriented. This was supported by the lower-field-shifted H-15 signal interpreted from the anisotropy effect of the 16α -hydroxy group. The relative stereochemistry was deduced from the NOE correlations shown in Figure 5. The absolute configuration at C-21 position was deduced to be *R*, which was identical with that of 19-oxoeburnamine (**7**), based on the positive Cotton effect at 288 nm in the CD spectrum. From these data, compound **3** was assigned to 20-oxo-eburnamine reported in 1984.⁶

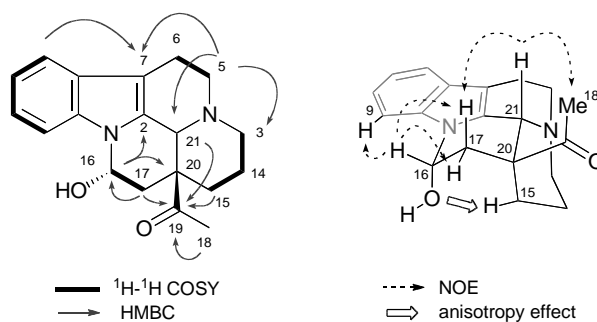


Figure 5. Selected 2D NMR and NOE data and NMR analysis of **3**.

Alkaloid **4** was found to be kopsinine B.⁸ As its detailed spectroscopic data as well as structure elucidation have not been described in the original paper, we discuss them here. The HREIMS of **4** gave a molecular ion peak at m/z 354.1938 (M^+) that corresponded to the molecular formula $C_{21}H_{26}N_2O_3$ (Figure 6). The UV spectrum exhibited a characteristic indoline chromophore. The 1H and ^{13}C NMR spectra showed the existence of an indoline system with a non-substituted A ring [δ_H 7.18 (br-d, H-9), 7.00 (ddd, H-11), 6.79 (ddd, H-10), 6.68 (br-d, H-12); δ_C 149.0 (C-13), 137.0 (C-8), 126.7 (C-11), 121.6 (C-9),

120.3 (C-10), 111.4 (C-12), 70.8 (C-2), 58.4 (C-7)], a carboxymethyl group [δ_{H} 3.85 (3H, s); δ_{C} 174.8, 52.9], an aminomethine group [δ_{H} 3.02 (d, H-21); δ_{C} 67.6 (C-21)], an oxygenated quaternary carbon [δ_{C} 77.9 (C-16)], and two aminomethylene groups [δ_{C} 50.5 (C-5), 47.7 (C-3)]. The NMR data were similar to those of 12-methoxykopsinaline (**8**)⁹ except for the absence of a signal due to a methoxy group in the aromatic region, suggesting that this compound is a 12-demethoxy derivative of 12-methoxykopsinaline (**8**). From the above data as well as 2D NMR data, compound **4** was deduced to be kopsinine B.

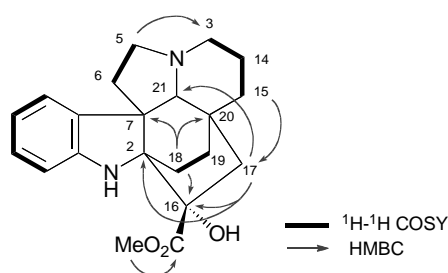


Figure 6. Selected 2D NMR data of **4**.

EXPERIMENTAL

General ^1H and ^{13}C NMR spectra: JEOL JNM ECP-400 at 400 MHz (^1H), JEOL JNM A-500 at 500 MHz (^1H) or 125 MHz (^{13}C), and JEOL JNM ECP-600 at 600 MHz (^1H) or 150 MHz (^{13}C). UV: JASCO V-560. EIMS and HREIMS: JEOL GC mate. FABMS: JEOL JMS-AX500. HRESIMS: Thermo Fisher Exactive. CD: JASCO J-720WI. TLC: precoated silica gel 60 F₂₅₄ plates (Merck, 0.25 mm thick), precoated amino-silica gel plates (Fuji Silysia Chemical). Column chromatography: silica gel 60 [Merck, 70-230 mesh (for open column chromatography)], silica gel 60N [Kanto Chemical, 40-50 μm (for flash column chromatography)], Chromatorex NH [Fuji Silysia Chemical, 100-200 mesh (for amino-silica gel column chromatography)], Sephadex LH-20 (GE Healthcare). Medium pressure liquid chromatography (MPLC): C. I. G. prepacked column CPS-HS-221-05 (Kusano Kagakukikai, SiO_2).

Plant Material *Melodinus henryi* was collected from Xishuangbanna, Yunnan Province, China and identified by one of the authors, Professor Dr. Rongping Zhang.

Extraction and Isolation The dried stems and leaves of *M. henryi* (2.0 kg) were extracted with MeOH (total 27.9 L, two times at room temperature and two times under reflux) to give a MeOH extract (102.1 g). The MeOH extract was dissolved in 1 N HCl (4.6 L). After extraction with ethyl acetate (6.1 L), the acidic layer was basified with Na_2CO_3 at 0 °C (pH 9) and extracted with 5% MeOH/ CHCl_3 (8.2 L) and *n*-BuOH (8.4 L) to give a crude alkaloidal fraction (7.91 g) and an *n*-BuOH extract (58.90 g), respectively. The crude alkaloidal fraction (7.91 g) was separated by silica gel open column chromatography with a MeOH/ CHCl_3 gradient to give seven fractions: fr. CA 0-30% MeOH/ CHCl_3 (800

mL, 76 mg); fr. CB 30-40% MeOH/CHCl₃ (200 mL, 5,238 mg); fr. CC 40% MeOH/CHCl₃ (100 mL, 596 mg); fr. CD 40-50% MeOH/CHCl₃ (200 mL, 490 mg); fr. CE 50% MeOH/CHCl₃ (300 mL, 412 mg); fr. CF MeOH (300 mL, 266 mg); fr. CG 5% AcOH-MeOH (700 mL, 51 mg). Fraction CB was separated by silica gel flash column chromatography with a MeOH/CHCl₃ gradient to give seven fractions (frs CB1-CB7). Fraction CB2 that was eluted with 10% MeOH/CHCl₃ was successively purified by a combination of column chromatographies [amino-silica gel open column chromatography with an AcOEt/*n*-hexane gradient, silica gel flash column chromatography with AcOEt/*n*-hexane and MeOH/AcOEt gradients] to afford melodinoxanine (**1**, 1.3 mg). Fraction CB4 was separated by silica gel flash column chromatography with 20% MeOH/CHCl₃ and amino-silica gel open column chromatography with 70% AcOEt/*n*-hexane to afford 20-oxo-eburnamine (**3**, 0.8 mg). Fractions CB3 and CB4 that were eluted with 30% MeOH/CHCl₃ were purified by repeated chromatography [silica gel flash column chromatography or MPLC with a MeOH/CHCl₃ gradient, amino-silica gel open column chromatography with an AcOEt/*n*-hexane gradient, and then 70% CHCl₃/*n*-hexane] to give kopsinine B (**4**, 0.6 mg). A portion of the *n*-BuOH extract (2.99 g) was separated by Sephadex LH-20 column chromatography with MeOH to give seven fractions (frs BA-BG). Fraction BC (185.3 mg) was purified by repeated column chromatographies using amino-silica gel with 10% NH₃ aq. in MeOH/CHCl₃ and MeOH/AcOEt gradients to give *N*₆-methylnortetraphyllicine (**2**, 2.3 mg). From the crude alkaloidal fraction, thirty-six known indole alkaloids were isolated: methyl chanofrucosinate,¹⁰ methyl demethoxycarbonylchanofrucosinate,¹⁰ methyl 11,12-methylenedioxychanofrucosinate,¹¹ methyl 11,12-methylenedioxy-*N*₁-demethoxycarbonylchanofrucosinate,¹¹ methyl 12-methoxychanofrucosinate,¹² kopsinine,^{9,13} kopsinilam,^{13b,14} kopsinic acid,¹⁵ kopsinoline,¹⁶ kopsilongine,⁹ 12-methoxykopsinaline,⁹ kopsamine,⁹ 11,12-methylenedioxykopsinaline,⁹ 11,12-dimethoxy-*N*-methoxycarbonylkopsinaline,^{9,17} aspidofractinine,¹⁸ (2β,5β)-aspidofractinin-16-ol,¹⁹ kopsifine,²⁰ 19*R*-hydroxyeburnamine,²⁰ 19-oxoeburnamine,⁷ norpleiomutine,²⁰ kopsoffinol,²¹ β-yohimbine,²² tetrahydroalstonine,²³ isoreserpiline,⁴ 3*R*,4*S*-reserpiline *N*-oxide,²⁴ isocarapanaubine,³ rhazinilam,²⁵ leuconolam,²⁶ rhazinaline,²⁷ rhazimol,²⁸ burnamine,²⁹ mitoridine,³⁰ raucaffricine,³¹ nortetraphyllicine,⁵ 17-*O*-acetylnortetraphyllicine,³² 10-hydroxy-16-*epi*-affinine.³³

Melodinoxanine (1): $[\alpha]_{\text{D}}^{18}$ -35.4 (*c* 0.07, CHCl₃). UV (MeOH) λ_{max} nm (log ϵ): 306 (sh, 3.33), 281 (3.58), 242 (sh, 4.00), 223 (4.28). ¹H and ¹³C NMR, see Table 1. EIMS *m/z* (%): 444 (M⁺, 34), 221 (38), 207 (100). HREIMS *m/z*: 444.1883 (M⁺, calcd for C₂₃H₂₈N₂O₇ 444.1896). CD (MeOH, 19 °C, *c* = 0.90 mmol/L) $\Delta\epsilon$ (λ nm): 0 (348), -0.54 (315), 0 (297), +1.23 (279), 0 (269), -11.45 (241), 0 (231), +10.99 (218).

***N*₆-Methylnortetraphyllicine (2):** $[\alpha]_{\text{D}}^{21}$ +90.6 (*c* 0.12, MeOH). UV (MeOH) λ_{max} nm (log ϵ): 288 (3.07), 238 (3.48), 205 (4.11). ¹H and ¹³C NMR, see Table 2. FABMS (NBA) *m/z*: 309 (M⁺). HRESIMS *m/z*: 309.1953 (M⁺, calcd for C₂₀H₂₅N₂O 309.1961). CD (MeOH, 12 °C, *c* = 0.43 mmol/L) $\Delta\epsilon$ (λ nm): 0 (305),

-0.42 (290), -0.08 (sh, 270), 0 (263), +0.12 (sh, 259), +2.17 (241), +0.92 (224), +1.34 (214), +1.12 (210).

20-Oxo-eburnamine (3): $[\alpha]_D^{20}$ -109.4 (*c* 0.06, CHCl₃). UV (MeOH) λ_{\max} nm (log ϵ): 289 (sh, 3.26), 282 (4.01), 276 (sh, 3.59), 227 (4.20). ¹H NMR (400 MHz, CDCl₃) δ : 7.52 (1H, d, *J* = 7.4 Hz, H-9), 7.39 (1H, d, *J* = 7.4 Hz, H-12), 7.22 (1H, dd, *J* = 7.4, 7.4 Hz, H-11), 7.17 (1H, dd, *J* = 7.4, 7.4 Hz, H-10), 6.11 (1H, d, *J* = 4.1 Hz, H-16), 4.76 (1H, br-s, H-21), 3.36-3.30 (2H, m, H₂-5), 3.02 (1H, dddd, *J* = 15.9, 10.3, 7.8, 2.4 Hz, H-6), 2.68-2.52 (3H, overlapped, H₂-3, H-6), 2.39 (3H, s, H₃-18), 2.24 (1H, br-d, *J* = 14.7 Hz, H-17), 2.21 (1H, m, H-15), 2.13 (1H, dd, *J* = 14.7, 4.1 Hz, H-17), 1.83 (1H, ddd, *J* = 13.5, 13.5, 3.5 Hz, H-15), 1.56 (1H, m, H-14), 1.43 (1H, br-dd, *J* = 13.5, 13.5 Hz, H-14). ¹³C NMR (150 MHz, CDCl₃) δ : 210.8 (C-19), 134.7 (C-13), 130.5 (C-2), 129.1 (C-8), 121.5 (C-11), 120.4 (C-10), 118.6 (C-9), 109.6 (C-12), 106.6 (C-7), 74.4 (C-16), 54.7 (C-21), 51.1 (C-5), 49.7 (C-20), 44.6 (C-3), 38.6 (C-17), 26.5 (C-15), 25.6 (C-18), 23.3 (C-14), 16.9 (C-6). IR ν cm⁻¹: 3039, 2921, 1703, 1054, 751. EIMS *m/z* (%): 310 (M⁺, 11), 249 (100). HRESIMS *m/z*: 311.1744 ([M+H]⁺, calcd for C₁₉H₂₃N₂O₂ 311.1754). CD (MeOH, 12 °C, *c* = 0.07 mmol/L) $\Delta\epsilon$ (λ nm): 0 (316), +0.23 (310), +0.27 (306), +0.63 (300), +0.66 (294), +1.31 (288), 0 (248), -15.0 (229), -0.32 (205).

Kopsinine B (4): UV (MeOH) λ_{\max} nm (log ϵ): 292 (3.29), 244 (sh, 3.66), 228 (sh, 3.74), 206 (4.24). ¹H NMR (400 MHz, CDCl₃) δ : 7.18 (1H, br-d, *J* = 7.6 Hz, H-9), 7.00 (1H, ddd, *J* = 7.6, 7.6, 1.5 Hz, H-11), 6.79 (1H, ddd, *J* = 7.6, 7.6, 1.0 Hz, H-10), 6.68 (1H, br-d, *J* = 7.6 Hz, H-12), 3.85 (3H, s, CO₂Me), 3.30-3.21 (2H, overlapped, H-5, H-17), 3.13 (1H, br-d, *J* = 13.3 Hz, H-3), 3.02 (1H, d, *J* = 1.4 Hz, H-21), 2.96 (1H, ddd, *J* = 13.3, 13.3, 3.2 Hz, H-3), 2.90 (1H, ddd, *J* = 8.0, 8.0, 3.0 Hz, H-5), 2.36 (1H, ddd, *J* = 14.0, 8.0, 3.0 Hz, H-6), 1.93-1.83 (2H, overlapped, H-14, H-18), 1.72 (1H, ddd, *J* = 12.8, 10.8, 7.7 Hz, H-18), 1.65 (1H, overlapped, H-15), 1.57 (1H, overlapped, H-6), 1.50 (1H, overlapped, H-19), 1.36-1.25 (2H, overlapped, H-14, H-15), 1.18 (1H, dd, *J* = 16.0, 1.4 Hz, H-17), 1.16 (1H, overlapped, H-19). ¹³C NMR (125 MHz, CDCl₃) δ : 174.8 (CO₂Me), 149.0 (C-13), 137.0 (C-8), 126.7 (C-11), 121.6 (C-9), 120.3 (C-10), 111.4 (C-12), 77.9 (C-16), 70.8 (C-2), 67.6 (C-21), 58.4 (C-7), 52.9 (CO₂Me), 50.5 (C-5), 47.7 (C-3), 40.9 (C-17), 36.3 (C-15), 35.2 (C-6), 33.4 (C-19), 32.8 (C-20), 26.5 (C-18), 17.3 (C-14). EIMS *m/z* (%): 354 (M⁺, 11), 83 (100). HREIMS *m/z*: 354.1938 (M⁺, calcd for C₂₁H₂₆N₂O₃ 354.1943). CD (MeOH, 12 °C, *c* = 0.24 mmol/L) $\Delta\epsilon$ (λ nm): 0 (324), +0.78 (293), +0.02 (263), +0.08 (259), +0.04 (256), +1.34 (232), +0.09 (210), +0.40 (204).

Some detailed spectroscopic data of nortetraphyllicine, 12-methoxykopsinaline, and 3*R*,4*S*-reserpiline *N*-oxide have not been reported so far and thus, we present them here.

Nortetraphyllicine (6): $[\alpha]_D^{21}$ -120.6 (*c* 0.03, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ : 7.45 (1H, d, *J* = 6.8 Hz, H-9), 7.07 (1H, ddd, *J* = 7.9, 7.9, 1.3 Hz, H-11), 6.79 (1H, dd, *J* = 7.3, 7.3 Hz, H-10), 6.76 (1H, d, *J* = 8.1 Hz, H-12), 5.23 (1H, q, *J* = 6.0 Hz, H-19), 4.46 (1H, d, *J* = 3.3 Hz, H-17), 4.08 (1H, br-s, *N*_aH or OH), 3.40-3.32 (4H, overlapped, H-2, H-5, H₂-21), 3.10 (1H, dd, *J* = 5.3, 5.3 Hz, H-15), 3.02 (1H, dd, *J* = 6.4, 6.4 Hz, H-3), 2.15 (1H, br-dd, *J* = 5.3, 5.3 Hz, H-16), 2.11 (1H, d, *J* = 12.3 Hz, H-6), 1.88 (1H, dd, *J* =

11.9, 5.7 Hz, H-6), 1.79 (1H, m, H-14), 1.65 (3H, ddd, $J = 6.8, 1.6, 1.6$ Hz, H₃-18), 1.58 (1H, m, H-14). ¹³C NMR (125 MHz, CDCl₃) δ 151.5 (C-13), 140.2 (C-20), 133.5 (C-8), 127.2 (C-11), 123.3 (C-9), 119.6 (C-10), 114.2 (C-19), 110.9 (C-12), 72.5 (C-2), 56.3 (C-7), 55.8 (C-3), 55.5 (C-21), 52.7 (C-16), 52.3 (C-5), 34.5 (C-6), 29.7 (C-14), 28.2 (C-15), 12.9 (C-18), C-17: under CDCl₃ signal. CD (MeOH, 12 °C, $c = 0.23$ mmol/L) $\Delta\epsilon$ (λ nm): 0 (306), -0.35 (289), 0 (274), +0.03 (269), 0 (265), +0.28 (259), +0.33 (257), +1.94 (242), +0.56 (226), +0.60 (223), +0.59 (220), +0.79 (216), +0.62 (212), +3.37 (202).

12-Methoxykopsinaline (8): CD (MeOH, 24 °C, $c = 0.26$ mmol/L) $\Delta\epsilon$ (λ nm): 0 (320), +5.14 (291), +1.98 (267), +7.20 (248), 0 (219), -4.12 (209), -0.13 (203).

3R,4S-Reserpiline N-oxide: $[\alpha]_D^{18}$ -33.3 (c 0.14, CHCl₃). UV (MeOH) λ_{\max} nm (log ϵ): 308 (sh, 3.81), 302 (3.87), 297 (3.87), 223 (4.40). ¹H NMR (400 MHz, CDCl₃) δ : 8.28 (1H, s, N_aH), 7.61 (1H, s, H-17), 6.99 (1H, s, H-12), 6.88 (1H, s, H-9), 5.12 (1H, dq, $J = 9.6, 6.0$ Hz, H-19), 4.71 (1H, br-s, H-3), 3.934 and 3.927 (each 3H, s, 10-OMe, 11-OMe), 3.81 (1H, ddd, $J = 12.1, 12.1, 7.4$ Hz, H-5), 3.76 (3H, s, CO₂Me), 3.76-3.70 (2H, overlapped, H-5, H-21), 3.43 (1H, d, $J = 12.7$ Hz, H-21), 3.07 (2H, m, H₂-6), 2.87 (1H, br-ddd, $J = 15.2, 15.2, 4.3$ Hz, H-14), 2.53-2.47 (2H, overlapped, H-14, H-15), 1.60 (1H, br-ddd, $J = 9.6, 4.8, 4.8$ Hz, H-20), 1.56 (3H, d, $J = 6.0$ Hz, H₃-18). ¹³C NMR (125 MHz, CDCl₃) δ : 167.9 (CO₂Me), 156.5 (C-17), 147.6 and 145.4 (C-10, C-11), 131.3 (C-13), 127.3 (C-2), 118.9 (C-8), 107.8 (C-16), 106.2 (C-7), 99.9 (C-9), 95.1 (C-12), 73.2 (C-19), 69.8 (C-3), 68.3 (C-5), 56.7 (C-21), 56.4 and 56.2 (10-OMe, 11-OMe), 51.3 (CO₂Me), 37.4 (C-20), 26.0 (C-14), 25.7 (C-15), 20.5 (C-6), 18.6 (C-18). FABMS (NBA) m/z : 429 [M+H]⁺, 451 [M+Na]⁺. HREIMS m/z : 428.1943 (M⁺, calcd for C₂₃H₂₈N₂O₆ 428.1947). CD (MeOH, 12 °C, $c = 0.29$ mmol/L) $\Delta\epsilon$ (λ nm): 0 (314), -0.45 (307), 0 (287), +2.41 (265), +1.66 (255), +3.83 (242), 0 (235), -8.15 (224), 0 (209), +1.43 (205).

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