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Novel monoterpenoid indole alkaloids from *Melodinus yunnanensis*

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ABSTRACT

Five monoterpenoid indole alkaloids, namely meloyines A-B (**1**–**2**), meloyines II-III (**3**–**4**), and 10-*O*-glucosyl-scandine (**5**) together with thirty-four known alkaloids were isolated from leaves and twigs of *Melodinus yunnanensis*. Alkaloid **1** was characterized as an unprecedented skeleton with a 6/5/5/6/6/4 ring system, and alkaloids **3**–**4** were dimeric monoterpenoid quinolone alkaloids. Their structures were elucidated based on 1D and 2D- NMR, FTIR, UV, and MS spectroscopic data. The cytotoxic activity of new alkaloids were evaluated against three human cancer cell lines.

1. Introduction

Monoterpenoid quinolone alkaloids (MQAs) were a special kind of natural products, which were proposed to arise by rearrangement of monoterpenoid indole alkaloids (MIAs). A possible route for MQAs biosynthesis was that the N_1–C_2 or C_2–C_7 bond cleaved in the indole heterocyclic ring and then generated new amine and/or keto functions. Then a new quinolone heterocycle would be formed by this nucleophilic reaction. Natural MQAs mainly were distributed in plants of *Alstonia* (corialstonine[1] and scholarisine I-II[2]), *Melodinus* (meloscandonine and scandine derivatives,[3] rhazimine,[4] meloyunine C[5]) and *Gardneria* (gardquinolone[6]), *Tabernaemontana* (voastrictine[7] and voaharine[8]) genera among family Apocynaceae. Pharmacological investigations on MQAs have demonstrated their significant bioactivities. Additionally, famous drugs, camptothecin from plants of both *Camptotheca* and *Nothapodytes* genera, and quinine from *Cinchona* genus were belonged to MQAs. Previous research indicated MQAs derived from Aspidosperma-type MIAs are mainly alkaloids in plants of *Melodinus* genus.[5,9,10] Likewise, another small subtype in Aspidosperma types, with C–C new bond such as C_2–$C_{18/19}$ (vindolinine and venalstonine)[11] and C_{17}–C_{21} (pandine),[12] were widely distributed in *Alstonia* and *Tabernaemontana* genera. To discover novel and bioactive alkaloids, the first studied on *M. yunnanensis* distributed in south of Yunnan Province, China, led to ten new alkaloids.[13] Since the production of plant secondary metabolites were influenced by variable environments,[14] phytochemical research on same plant from different place was undertaken again. Herein, this paper described the isolation, structural determination, and cytotoxic activities of new alkaloids (**1**–**5**) together with the thirty four known ones, namely 15α-hydroxy-meloscandonine (**6**),[15] 10-hydroxyscandine (**7**),[16] scandine (**8**),[9] epimeloscine (**9**),[17] meloscandonine (**10**),[18] 19-epimeloscandonine (**11**),[19] tubotaiwine (**12**),[20] 19*R*-hydroxytabersonine (**13**),[21] 11-methoxytabersonine (**14**),[22] tabersonine (**15**),[23] 11-methoxy-19-hydroxytabersonine (**16**),[24] 11-hydroxytabersonine (**17**),[25] pachysiphine (**18**),[25] lochnericine (**19**),[26] 11-hydroxylochnericine (**20**),[27] venalstonine (**21**),[11] 17α-hydroxyvenalstonine (**22**),[28] venalstonidine (**23**),[29] 19β-hydroxyvenalstonidine (**24**),[30] kopsinine (**25**),[31] kopsiloscine G (**26**),[32] 19*R*-vindolinine (**27**),[11] 16β-hydroxy-19*R*-vindolinine (**28**),[19] 19*S*-vindolinine (**29**),[11] 19,20-dihydroakuammicine (**30**),[33] strictcine (**31**),[34] rhazimol (**32**),[35] scholarisin VII (**33**),[36] picrinine (**34**),[37] 14-hydroxymeloyunine (**35**),[13] 14,15-dehydrovincamine (**36**),[38] 16-hydroxymethylpleiocarpamine (**37**),[39] akuammidine (**38**),[40] voaphylline (**39**).[41]

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2. Results and discussion

The MeOH extract of leaves and twigs of *M. yunnanensis* was partitioned between H_2O and EtOAc and column chromatography was used to separate the alkaloidal fraction into 39 alkaloids.

Alkaloid (**1**) was isolated as a white powder. Its molecular formula was determined as $C_{21}H_{24}N_2O_3$ by the HRESIMS (*m/z* 353.1859 $[M+H]^+$, calcd. 353.1865) in association with the ^1H and ^{13}C NMR spectroscopic data, indicating 11° of unsaturation. Its UV spectrum showed the characteristic absorptions of the indoline chromophore at 210, 248 and 289 nm,[42] and IR absorption bands at 3423, 3356, 1710 and 1640 cm^{-1} suggested the presence of NH, OH, aromatic ring and ester carbonyl functionalities. The ^{13}C NMR and DEPT data suggested that alkaloid **1** possessed 21 carbons including seven quaternary carbons, eight methines, four methylenes, one methoxycarbonyl and one methyl (Table 1), close to tabersonine skeleton. The ^1H NMR spectrum of **1** displayed proton signals for an unsubstituted indole A ring [δ_H 7.10 (d, J = 7.8 Hz, H-9), 6.58 (t, J = 7.8 Hz, H-10), 6.92 (t, J = 7.8 Hz, H-11), 6.63 (d, J = 7.8 Hz, H-12)], two olefin protons [δ_H 5.80 (dd, J = 11.9, 4.3 Hz, H-14), 5.66 (d, J = 11.9 Hz, H-15)], one methoxyl (δ_H 3.49, s) and one methyl (δ_H 0.63, d, J = 7.4 Hz, H-18) (Table 1). In the ^{13}C NMR spectrum, the downfield shifts at δ_C 50.0 (t), 53.5 (t) and 75.4 (d) were easy to assigned as CH_2-3/5 and CH-21, respectively. The characteristic quaternary carbon at δ_C 52.0 was assigned as C-7 according to its correlations from H-9 and H-5 in the HMBC spectrum (Fig. 2). In addition, the HMBC correlations also indicated the connections of C_7–C_6–C_5, C_3–C_{14}–C_{15} and C_{15}–C_{20}–C_{21}. The doublets methyl at δ_H 0.63 was assigned as C-18 on the basis of the cross peaks from H-18 to C-19 and C-20. The methylene signals (δ_H 2.36, 1.98) were assigned as H_2-6, which was supported by the correlations from δ_H 2.36 to C-8 and C-21. And the correlations from δ_H 2.32 to C-19 and C-21 suggested the signals (δ_H 2.32, 2.09) were belonged to H_2-17. Furthermore, the correlations from H_2-17 (δ_H 2.32, 2.09), H-18 (δ_H 0.63), and OH (δ_H 4.35) to signal of δ_C 89.0 and the correlations from H-15 (δ_H 5.66), H_2-17, OH (δ_H 4.35) to C-19 revealed the connection of C_{16}–C_{19}. The chemical formula and the HMBC correlations from N–H (δ_H 5.61), H_2-6, H_2-17 and H-21 (δ_H 2.13) to the signal at δ_C 60.5 (s) suggested that the quaternary carbon was C-2 which was substituted by the methoxycarbonyl.

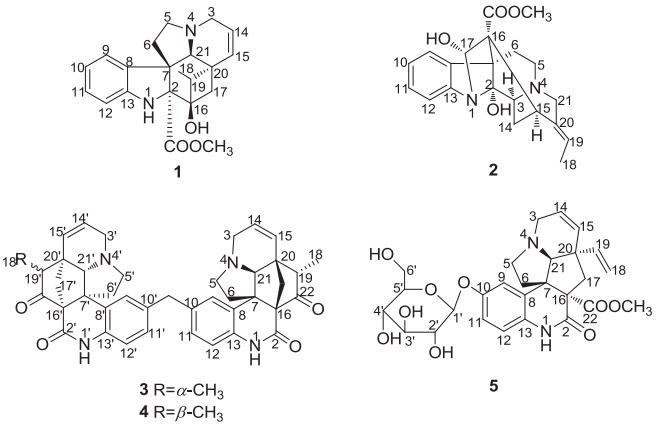

Fig. 1. Structures of alkaloids **1**–**5** from *M. yunnanensis*.

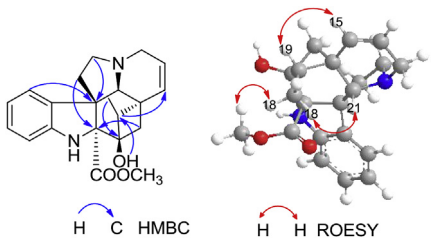

Fig. 2. The key HMBC and NOE correlations of alkaloid **1**.

The configuration of alkaloid **1** was determined by NOE correlations (Fig. 2). The absolute configurations at C-7, C-20, C-21 were determined as *R*, *R*, *S*, for compound **1** was originated from tabersonine-type alkaloid.[23] The absolute configurations were then determined as 2*S*, 7*R*, 16*R*, 19*S*, 20*R*, 21*S*, by the correlations between H-18/H-21, H-18/carbomethoxy and H-19/H-15, which was further confirmed by ECD calculation method. The geometry was optimized at B3LYP/6–31 + g(d,p) level in methanol using the continuum polarizable continuum model (CPCM). Harmonic vibration frequencies were then calculated to confirm the stability of these conformers. The theoretical ECD spectrum of (2*S*, 7*R*, 16*R*, 19*S*, 20*R*, 21*S*)-**1** (**1a**) and (2*R*, 7*R*, 16*R*, 19*S*, 20*R*, 21*S*)-**1** (**1b**) was calculated in methanol using Time-dependent Density functional theory (TD-DFT) at the B3LYP/6–311 + g(d,p) level of the Gaussian 09 program package.[43] The experimental ECD spectrum of alkaloid **1** and that the calculated ECD spectrum for the molecular having 2*S*, 7*R*, 16*R*, 19*S*, 20*R*, 21*S* (**1a**) were in good agreement, which validated the absolute configurations of **1** (Fig. 3). Thus, the structure of alkaloid **1** was elucidated and alkaloid **1** was named subsequently meloyine A (Fig. 1).

Alkaloid **2** possessed molecular formula of $C_{21}H_{24}N_2O_4$ as established by HRESIMS ($[M+H]^+$ at *m/z* 369.1816) as well as the NMR data. In the ^1H-NMR spectrum (Table 1) of **2**, an unsubstituted indole ring [δ_H 7.26 (d, J = 8.0 Hz), 6.95 (t, J = 8.0 Hz), 6.68 (t, J = 8.0 Hz) and 6.51 (d, J = 8.0 Hz)], one methyl ester group

Table 1
^1H and ^{13}C NMR spectroscopic data from alkaloids **1**–**2** in acetone-d_6 (δ in ppm, J in Hz).

No	**1**[a]		**2**[b]	
	δ_H	δ_C	δ_H	δ_C
NH	5.61, s			
2		60.5 s		112.0 s
3	3.36, dd (16.4, 4.3) 3.11, d (16.4)	50.0 t	3.35, overlap	59.4 d
5	3.20, t (7.2) 2.96, overlap	53.5 t	3.52, m 2.64, m	49.2 t
6	2.36, m 1.98, m	37.4 t	2.82, m 2.20, m	24.2 t
7		52.0 s		50.7 s
8		125.9 s		127.8 s
9	7.10, d (7.8)	126.7 d	7.26, d (8.0)	128.5 d
10	6.58, t (7.8)	117.4 d	6.68, t (8.0)	118.9 d
11	6.92, t (7.8)	127.3 d	6.95, t (8.0)	128.4 d
12	6.63, d (7.8)	113.8 d	6.51, d (8.0)	115.6 d
13		143.4 s		144.5 s
14	5.80, dd (11.9, 4.3)	130.6 d	2.29, m 1.93, m	28.3 t
15	5.66, d (11.9)	129.1 d	3.57, m	37.8 d
16		89.0 s		58.1 s
17	2.32, d (10.1) 2.09, overlap	42.6 t	4.88, s	85.0 d
18	0.63, d (3H, 7.4)	9.3 q	1.45, d (3H, 7.0)	12.9 q
19	2.27, q (7.4)	53.4 d	5.32, q (7.0)	117.6 d
20		47.8 s		143.8 s
21	2.13, s	75.4 d	3.86, d (16.8) 2.88, d (16.8)	55.0 t
$COOCH_3$	3.49, s (3H)	51.4 q	3.52, s (3H)	51.6 q
$COOCH_3$		171.9 s		171.2 s
OH	4.35, s			

[a] ^1H NMR recorded at 600 MHz, ^{13}C NMR recorded at 150 MHz.
[b] ^1H NMR recorded at 400 MHz, ^{13}C NMR recorded at 100 MHz.