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Terpenoid indole alkaloids from *Mappianthus iodoides* Hand.-Mazz.

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ABSTRACT

Ten terpenoid indole alkaloids, mappiodines A–C and mappiodosides A–G, together with eight known compounds, were isolated from stems of *Mappianthus iodoides* Hand.-Mazz. Their structures were elucidated by spectroscopic analyses including 1D, 2D NMR, MS and CD methods. The ten compounds were evaluated for their cytotoxic activity, but were inactive.

Introduction

The genus *Mappianthus* (Icacinaceae family) consists of three species which are distributed in subtropical and tropical zones. *Mappianthus iodoides* Hand.-Mazz., one species occurring in China, is used by local people for treatment of conditions including traumatic injury, rheumatalgia and arthralgia (Fang and Qin, 2002). Phytochemical studies have led to isolation of monoterpenoid indole alkaloids, sesquiterpenes, iridoid glycosides, lignans and phenolic glycosides (Chen et al., 2000; Xiao et al., 2011). These monoterpenoid indole alkaloids originate from condensation of tryptophan with secologanin to give strictosidine, which then elaborates to an impressive array of structural variants (Hutchinson, 1981). Many of them, such as yohimbine (Bader et al., 1954), reserpine (Muller et al., 1952), and camptothecin (Mattern et al., 1987; Jain et al., 1998), are well known for their pharmacological significance. This study of *M. iodoides* focused on indole alkaloids, and led to the isolation of ten previously unreported monoterpenoid indole alkaloids, namely, mappiodines A–C (**1**–**3**), mappiodosides A–G (**4**–**10**), and eight known alkaloids. The structures of the ten alkaloids were elucidated by spectroscopic methods, while the known alkaloids were identified as tryptophan (Bak et al., 1968), 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (Kicha et al., 2003), 5-carboxystrictosidine (Aimi et al., 1992), strictosidinic acid (Subhadhirasakul et al., 1994), 3α, 5α-tetrahydrodeoxycordifoline lactam (Lamidi et al., 2005), 3α, 5α-tetrahydrodeoxycordifolic acid (De Silva et al., 1971), lyaloside (Valverde et al., 1999), and desoxycordifoline (Brandt et al., 1999) by comparison with data in the literature. A biogenetic pathway for the indole alkaloids is proposed.

Results and discussion

Mappiodine A (**1**) was obtained as a yellow amorphous powder and had a molecular formula of $C_{22}H_{28}N_2O_6$ by HRESIMS. Its IR spectrum showed bands at 1724 and 1628 cm^{-1} due to the presence of carbonyl groups, while the UV spectrum had absorption maxima at 206, 274 and 311 nm, suggesting the presence of an indole chromophore group. The ^1H NMR and ^{13}C NMR spectroscopic data of **1** indicated presence of a 1,2,4-trisubstituted phenyl ring [δ_H 7.50 (d, J = 2.1 Hz), 7.42 (d, J = 8.5 Hz) and 7.24 (dd, J = 8.5, 2.1 Hz)] (Table 2), one tetrasubstituted double bond (δ_C 136.7 and 105.9), two carbonyl groups (δ_C 176.4 and 175.6), two methyls, five methylenes and five methines, respectively (Table 1). In the ^1H–^1H COSY spectrum, correlations between H-3/H-14/H-15/H-16/H-17, H-18/H-19/H-20/H-21, H-15/H-20, H-5/H-6 and H-11/H-12 were apparent. The ^{13}C and ^1H NMR spectroscopic data of **1** were very similar to those of dihydrositsirikine (Clivio et al., 1991), except for additional signals for one carboxyl group and one hydroxyl group. The carboxyl group was located at C-5 as deduced from the HMBC correlation between H-5 (δ_H 3.73) and C-23 (δ_C 176.4). The methoxyl group was considered to be bound to C-22 by a HMBC correlation between the OMe (δ_H 3.50) and C-22 (δ_C 175.6) functionalities. The H-15 is almost invariably α-oriented in the skeleton of these alkaloids (Brown et al., 1972), according to the biogenetic pathway (Fig. 5). The coupling constants ($J_{3,\ 14\beta}$ = 10.6 Hz, $J_{14\beta,\ 15}$ = 12.0 Hz) suggested a trans-diaxial relationship for H-3/H-14β/H-15. ROESY correlations of H-3/H-5, H-3/H-15, H-3/H-20 and H-15/H-20 indicated an α-orientation of

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Table 1
^{13}C NMR Spectroscopic Data (125 MHz) for Compounds **1–10**.[a]

No.	**1**[b]	**2**[c]	**3**[d]	**4**[b]	**5**[c]	**6**[d]	**7**[d]	**8**[e]	**9**[e]	**10**[c]
2	136.7, s	134.9, s	130.1, s	137.0, s	135.5, s	130.7, s	178.2, s	177.4, s	135.2, s	131.4, s
3	61.2, d	140.9, s	61.9, d	61.1, d	141.9, s	61.8, d	65.5, d	62.6, d	53.4, d	53.0, d
5	67.3, d	132.8, d	68.5, d	67.1, d	133.4, d	68.4, d	59.3, d	57.6, d	63.0, d	59.3, d
6	27.9, t	116.6, d	26.1, t	27.8, t	116.9, d	26.1, t	39.1, t	38.5, t	26.6, t	23.8, t
7	105.9, s	131.9, s	105.9, s	106.5, s	132.8, s	106.8, s	58.7, s	56.6, s	108.1, s	108.1, s
8	129.1, s	121.5, s	128.0, s	128.5, s	121.6, s	127.6, s	130.8, s	129.8, s	127.2, s	127.7, s
9	103.7, d	106.6, d	103.3, d	106.5, d	109.4, d	106.0, d	124.6, d	125.9, d	104.6, d	106.4, d
10	152.8, s	152.4, s	152.0, s	153.2, s	154.4, s	153.5, s	123.8, d	121.5, d	151.3, s	153.2, s
11	112.3, d	123.2, d	113.3, d	113.6, d	125.3, d	114.9, d	130.8, d	128.3, d	112.6, d	114.8, d
12	112.6, d	114.7, d	113.1, d	112.3, d	114.7, d	113.0, d	111.7, d	109.9, d	111.6, d	112.8, d
13	132.7, s	139.6, s	133.1, s	134.2, s	141.4, s	134.5, s	142.6, s	141.6, s	132.1, s	134.6, s
14	33.3, t	29.8, t	32.5, t	33.3, t	30.1, t	32.6, t	26.9, t	25.0, t	27.0, t	34.4, t
15	41.7, d	27.6, d	31.4, d	41.7, d	28.0, d	31.5, d	27.9, d	23.1, d	29.6, d	32.5, d
16	49.7, d	112.7, s	109.8, s	49.6, d	111.2, s	109.8, s	108.4, s	108.4, s	95.8, s	108.5, s
17	59.3, t	154.3, d	157.3, d	59.2, t	155.7, d	157.3, d	149.2, d	146.1, d	146.5, d	157.4, d
18	10.9, q	18.5, q	18.6, q	10.9, q	18.6, q	18.6, q	120.5, t	120.1, t	118.6, t	120.1, t
19	23.9, t	71.8, d	71.9, d	23.9, t	72.1, d	72.0, d	133.3, d	132.5, d	134.5, d	135.0, d
20	39.9, d	36.8, d	38.7, d	39.9, d	37.1, d	38.7, d	44.5, d	43.3, d	40.0, d	45.2, d
21	58.1, t	55.6, t	53.3, t	58.0, t	55.8, t	53.4, t	97.6, d	94.6, d	71.5, t	97.5, d
22	175.6, s	174.0, s	170.4, s	175.5, s	172.5, s	170.4, s	165.9, s	166.0, s	165.0, s	171.9, s
OMe	51.7, q			51.7, q						53.1, q
23	176.4, s		174.1, s	176.6, s		174.1, s	174.8, s	172.8, s	172.5, s	175.5, s
1′				104.9, d	103.3, d	103.7, d	99.8, d	97.7, d	102.1, d	100.4, d
2′				75.6, d	74.9, d	75.1, d	74.6, d	73.1, d	75.4, d	74.5, d
3′				78.9, d	77.8, d	77.9, d	77.8, d	76.4, d	78.7, d	77.8, d
4′				71.7, d	71.4, d	71.6, d	71.5, d	70.0, d	71.7, d	71.4, d
5′				79. 1, d	78.2, d	78.0, d	78.3, d	77.4, d	79.4, d	78.8, d
6′				62.7, t	62.6, t	62.6, t	62.6, t	61.0, t	61.0, t	62.5, t
1″										103.7, d
2″										75.0, d
3″										77.9, d
4″										71.6, d
5″										78.5, d
6″										62.9, t

[a] Values in δ (ppm).
[b] Spectra obtained in pyridine-d_5.
[c] Spectra obtained in $CD_3OD + D_2O$.
[d] Spectra obtained in CD_3OD.
[e] Spectra obtained in DMSO-d_6.

Table 2
^{1}H NMR Spectroscopic Data (500 MHz) for Compounds **1–5**.[a]

No.	**1**[b]	**2**[c]	**3**[d]	**4**[b]	**5**[c]
1	11.69, s			11.89, s	
3	3.60, d (10.6)		4.17, d (10.9)	3.58, d (10.7)	
5	3.73, dd (10.4, 2.9)	8.24, d (6.6)	3.69, m	4.01, dd (10.6, 3.9)	8.39, d (5.6)
6	3.34, m; 3.63, m	8.22, d(6.6)	3.08, m; 3.27, m	3.30, m; 3.53, m	8.47, d (5.6)
9	7.50, d (2.1)	7.50, d (2.1)	6.79, d (2.0)	7.75, d (2.1)	7.96, s
11	7.24, dd (8.5, 2.1)	7.28, dd (8.9, 2.1)	6.71, dd (8.7, 2.0)	7.41, dd (8.6, 2.1)	7.57, m
12	7.42, d (8.5)	7.53, d (8.9)	7.18, d (8.7)	7.37, d (8.6)	7.65, m
14α	2.74, d (12.2)	3.96, dd (17.5, 6.2)	2.93, d (14.2)	2.73, d (12.0)	4.08, m
14β	2.01, ddd (12.2, 12.0, 10.6)	3.25, dd (17.5, 8.6)	1.71, ddd (14.2, 11.4, 10.9)	2.00, ddd (12.0, 11.5, 10.7)	3.25, m
15	2.11, m	3.13, dd (14.6, 6.5)	2.87, d (11.4)	2.11, m	3.09, m
16	3.28, m			3.27, m	
17	4.02, dd (10.6, 3.8) 4.33, m	7.52, s	7.62, s	4.01, dd (10.6, 3.9) 4.33, m	7.63, s
18	0.81, t (7.3)	1.44, d (6.2)	1.49, d (5.6)	0.79, t (7.4)	1.47, d (6.0)
19	1.25, m; 1.60, m	3.88, dq (9.1, 6.2)	4.45, dq (10.1, 5.6)	1.23, m; 1.59, m	3.95, m
20	2.05, m	2.54, m	1.93, m	2.04, m	2.54, m
21α	3.80, dd (10.2, 2.1)	4.92, dd (14.4, 5.1)	4.09, d (12.5)	3.78, dd (10.5, 2.1)	5.01, m
21β	2.25, t (10.2)	4.57, dd (14.4, 4.3)	3.10, m	2.24, t (10.5)	4.61, m
OMe	3.50, s			3.48, s	
1′				5.72, d (6.9)	5.11, d (6.9)
2′				4.40, m	3.55, m
3′				4.13, m	3.55, m
4′				4.42, m	3.44, m
5′				4.44, m	3.59, m
6′				4.46, m	4.00, d (12.0)
				4.56, dd (11.8, 1.9)	3.76, dd (12.0, 6.2)

[a] Values in δ (ppm); coupling constants (Hz) in parentheses.
[b] Spectra obtained in pyridine-d_5.
[c] Spectra obtained in $CD_3OD + D_2O$.
[d] Spectra obtained in CD_3OD.

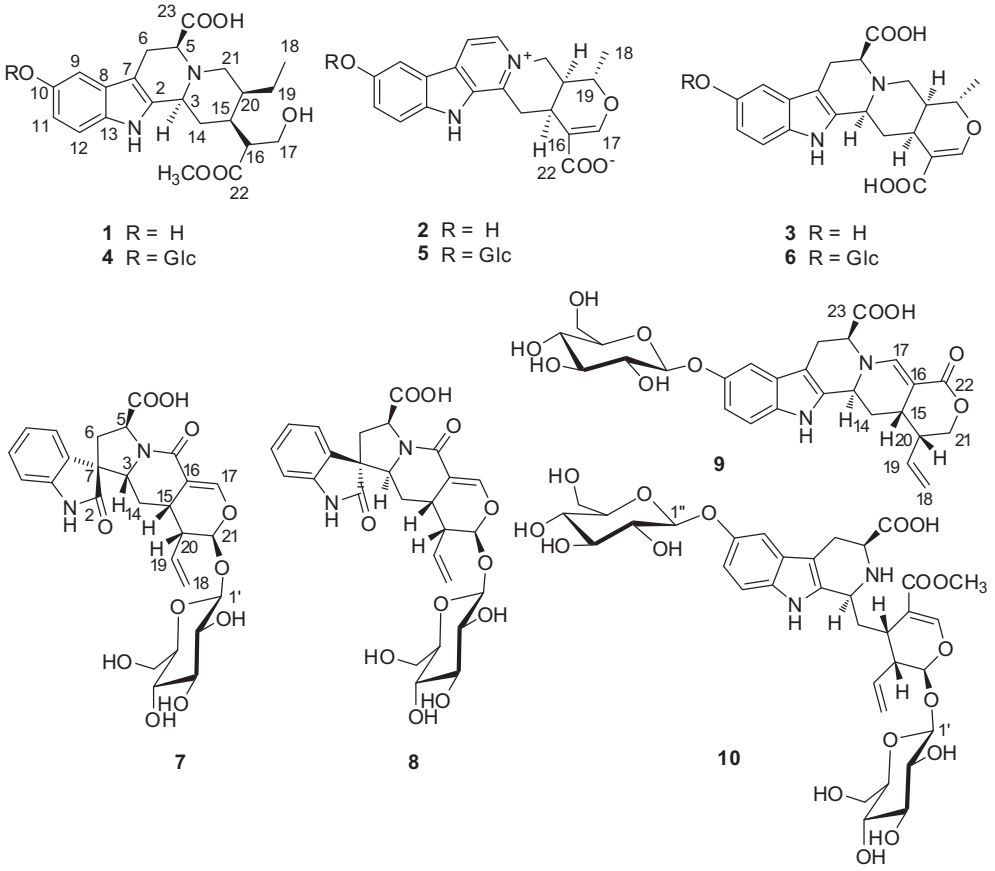

Fig. 1. Chemical structures of compounds **1**–**10**.

H-3, H-5, and H-20 (Fig. 3). Thus, mappiodine A (**1**) was established as shown (Fig. 1).

Mappiodine B (**2**), isolated as a yellow amorphous powder, had to a molecular formula of $C_{20}H_{18}N_2O_4$ by HRESIMS. Its IR spectrum showed bands at 1675 and 1637 cm^{-1} due to the presence of an α, β-unsaturated carbonyl group, and its UV spectrum had absorption maxima at 210, 233, 273 and 314 nm, indicating the presence of an indole chromophore and an α, β-unsaturated carbonyl moiety. In the ^1H NMR spectrum, compound **2** had signals corresponding to a 1,2,4-trisubstituted phenyl ring at δ_H 7.53 (d, J = 8.9 Hz), 7.50 (d, J = 2.1 Hz) and 7.28 (dd, J = 8.9, 2.1 Hz), a tetrasubstituted pyridine ring at δ_H 8.24 (d, J = 6.6 Hz) and 8.22 (d, J = 6.6 Hz), and an olefinic proton at δ_H 7.52 (s, 1H), respectively (Table 2). The ^{13}C NMR and DEPT spectra also indicated the existence of one carbonyl group (δ_C 174.0), six aromatic carbons (δ_C 152.4, 139.6, 123.2, 121.5, 114.7, 106.6), five pyridine carbons (δ_C 140.9, 134.9, 132.8, 131.9, 116.6) and one trisubstituted double bond (δ_C 154.3, 112.7) (Table 1). Analysis of the 1D and 2D NMR spectra showed that **2** was similar to rauvotetraphylline E (Gao et al., 2012), a known monoterpenoid indole alkaloid isolated from *Rauwolfia tetraphylla*, except for the existence of a hydroxyl group in **2**. The stereochemistry of **2** was determined through analysis of all proton coupling constants and from ROESY correlations. The coupling constants ($J_{14\alpha,\ 15}$ = 6.2 Hz, $J_{14\beta,\ 15}$ = 8.6 Hz, $J_{19,\ 20}$ = 9.1 Hz) strongly suggested a trans-diaxial relationship of H-14β/H-15 and H-19/H-20. Combined with the ROESY correlations of H-14β/H-21β, H-14β/H-19, H-14α/H-15, H-15/H-20 and H-19/H-21β, its relative configuration could be determined (Fig. 3). Accordingly, **2** was assigned an inner salt form (Xiao et al., 2011) and named mappiodine B.

Mappiodine C (**3**) was obtained as a yellow amorphous powder and its molecular formula was determined to be $C_{21}H_{22}N_2O_6$ by HRESIMS. Its IR spectrum had an absorption band at 1630 cm^{-1} due to presence of an α, β-unsaturated carbonyl group, and its UV spectrum had absorption maxima at 224 and 275 nm, consistent with an indole chromophore. Analysis of the ^1H NMR and ^{13}C NMR spectra of **3** established a 1,2,4-trisubstituted phenyl ring [δ_H 7.18 (d, J = 8.7 Hz), 6.79 (d, J = 2.0 Hz) and 6.71 (dd, J = 8.7, 2.0 Hz)], a trisubstituted double bond [(δ_H 7.62, δ_C 157.3) and δ_C 109.8)], a tetrasubstituted double bond, one methyl group, three methylene groups, five methine groups and two carboxyl groups, respectively (Tables 1 and 2). In the ^1H–^1H COSY spectrum, correlations between H-18/H-19/H-20/H-21, H-3/H-14/H-15/H-20, H-5/H-6 and H-11/H-12 were apparent. These characteristics suggested that **3** possessed a carbon skeleton similar to that of aricine (Iacobucci and Deulofeu, 1957). However, a key difference between these two compounds was that **3** possessed one more carboxyl group. The carboxyl group (δ_C 174.1) was deduced to be bound to C-5 by the HMBC correlation between H-5 (δ_H 3.69) and C-23 (δ_C 174.1). The coupling constants ($J_{3,\ 14\beta}$ = 10.9 Hz, $J_{14\beta,\ 15}$ = 11.4 Hz and $J_{19,\ 20}$ = 10.1 Hz) suggested a trans relationship of H-3/H-14β/H-15, H-19/H-20, and ROESY correlations of H-3/H-5, H-3/H-15 and H-15/H-20 indicated that H-3, H-5, H-15 and H-20 were α-oriented (Fig. 3). ROESY correlations of H-19/H-14β and H-3/H-14α established that H-19 was β-oriented. Thus, the relative configuration of **3** was determined.

Mappiodoside A (**4**), a yellow amorphous powder, was determined to have molecular formula of $C_{28}H_{38}N_2O_{11}$ by HRESIMS. Its IR spectrum had similar bands to those of **1**, and its UV spectrum (209, 270 and 311 nm) was also similar to **1**. By comparison of the ^1H and ^{13}C NMR spectroscopic data with those of **1**, compound **4** differed in resonances corresponding to one additional sugar unit. Cellulase hydrolysis of **4** produced compound **1** and D-glucose. Its sugar unit was identified as β-glucose from the proton

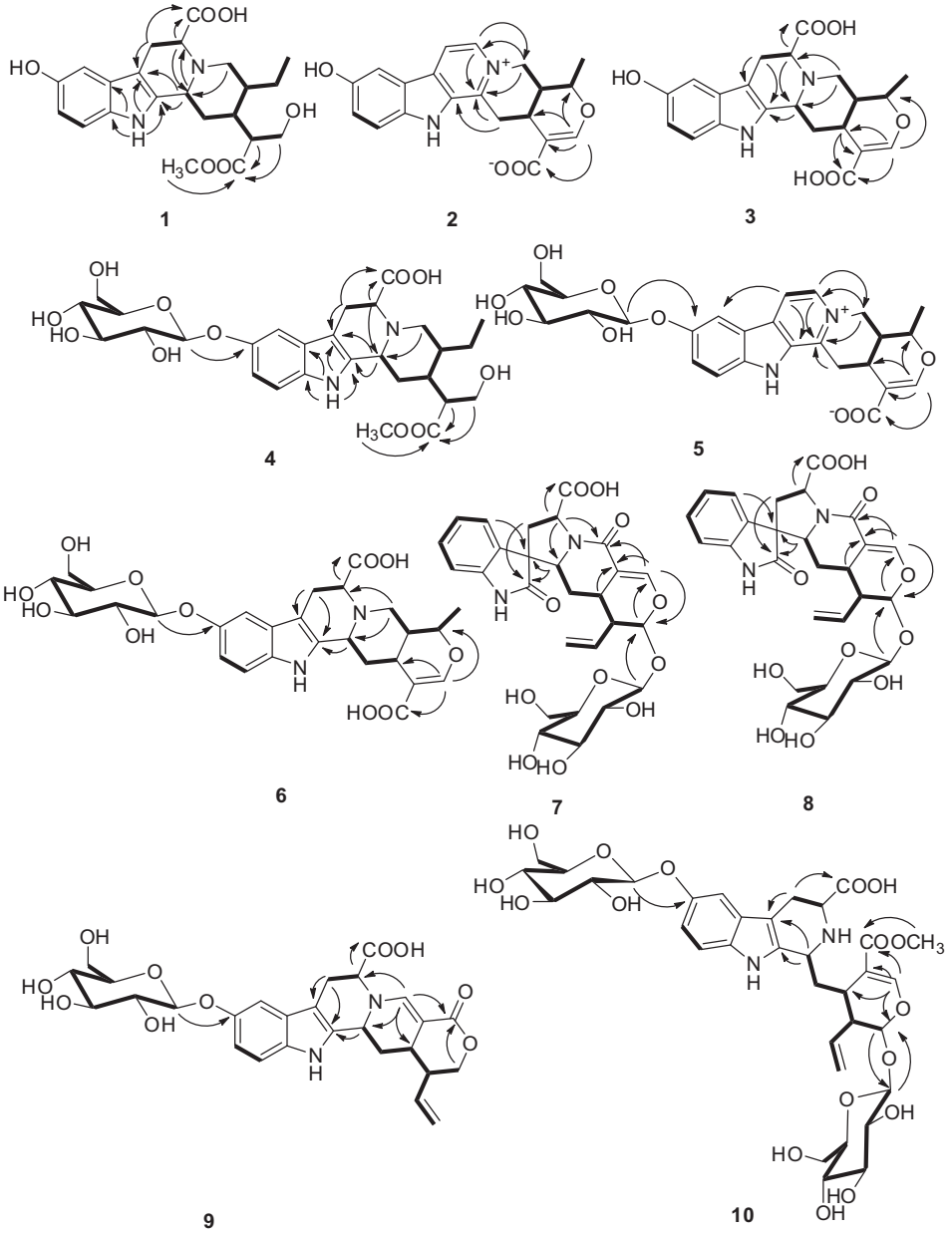

Fig. 2. Key HMBC (H → C) and ^{1}H-^{1}H COSY (-) correlations of **1**–**10**.

at δ_H 5.72 (d, J = 6.9 Hz) and the anomeric carbon at 104.9. The β-D-glucose unit was deduced to be located at C-10 due to the HMBC correlation between H-1′ (δ_H 5.72) and C-10 (δ_C 153.2). Thus, compound **4** had the same stereochemistry as compound **1**, which was also confirmed by the ROESY spectrum of **4**. Thus, compound **4** was named mappiodine A 10-*O*-β-D-glucoside.

Mappiodoside B (**5**), a yellow amorphous powder, had a molecular formula of $C_{26}H_{28}N_2O_9$ by HRESIMS. Its IR and UV spectra were similar to those of **2**. By comparison of the ^{1}H and ^{13}C NMR spectroscopic data with those of **2**, compound **5** was had the same moiety as **2**, except for resonances of one additional sugar unit. The latter was identified as β-glucose from the proton at δ_H 5.11 (d, J = 6.9 Hz) and the anomeric carbon at δ_C 103.3. This was confirmed by cellulase hydrolysis of **5**, which yielded D-glucose and compound **2**. The β-D-glucose moiety was located at C-10 is deduced from the HMBC correlation between H-1′ at δ_H 5.11 and C-10 at δ_C 154.4. Its relative configuration was further confirmed by analysis of the ROESY spectrum. Compound **5** was named mappiodine B 10-*O*-β-D-glucoside.

Mappiodoside C (**6**), a yellow amorphous powder, was determined to have the molecular formula of $C_{27}H_{32}N_2O_{11}$ by HRESIMS. By comparison of the ^{1}H and ^{13}C NMR spectroscopic data with those of **3**, compound **6** had the same moiety as **3**, except for resonances of one additional sugar unit. The sugar unit was identified as β-glucose from the proton at δ_H 4.83 (d, J = 7.3 Hz) and the anomeric carbon at δ_C 103.7. This was confirmed by cellulase hydrolysis of **6**, which yielded D-glucose and compound **3**. The β-D-glucose unit was located at C-10 due to the HMBC correlation between H-1′ (δ_H 4.83) and C-10 (δ_C 153.5). The relative configuration was further confirmed by the ROESY spectrum. Compound **6** was named mappiodine C 10-*O*-β-D-glucoside.

Mappiodoside D (**7**) was obtained as a colorless amorphous powder. It had a molecular formula of $C_{27}H_{30}N_2O_{11}$ as determined from the HRESIMS, ^{1}H NMR and ^{13}C NMR spectroscopic data. In its ^{1}H NMR spectrum, compound **7** displayed signals corresponding to a 1, 2-disubstituted phenyl ring at δ_H 7.26 (dd, J = 7.4, 7.4 Hz), 7.03 (dd, J = 7.4, 7.4 Hz), 6.96 (d, J = 7.4 Hz) and 6.90 (d, J = 7.4 Hz). Also present were resonances assigned to a terminal vinyl group at δ_H

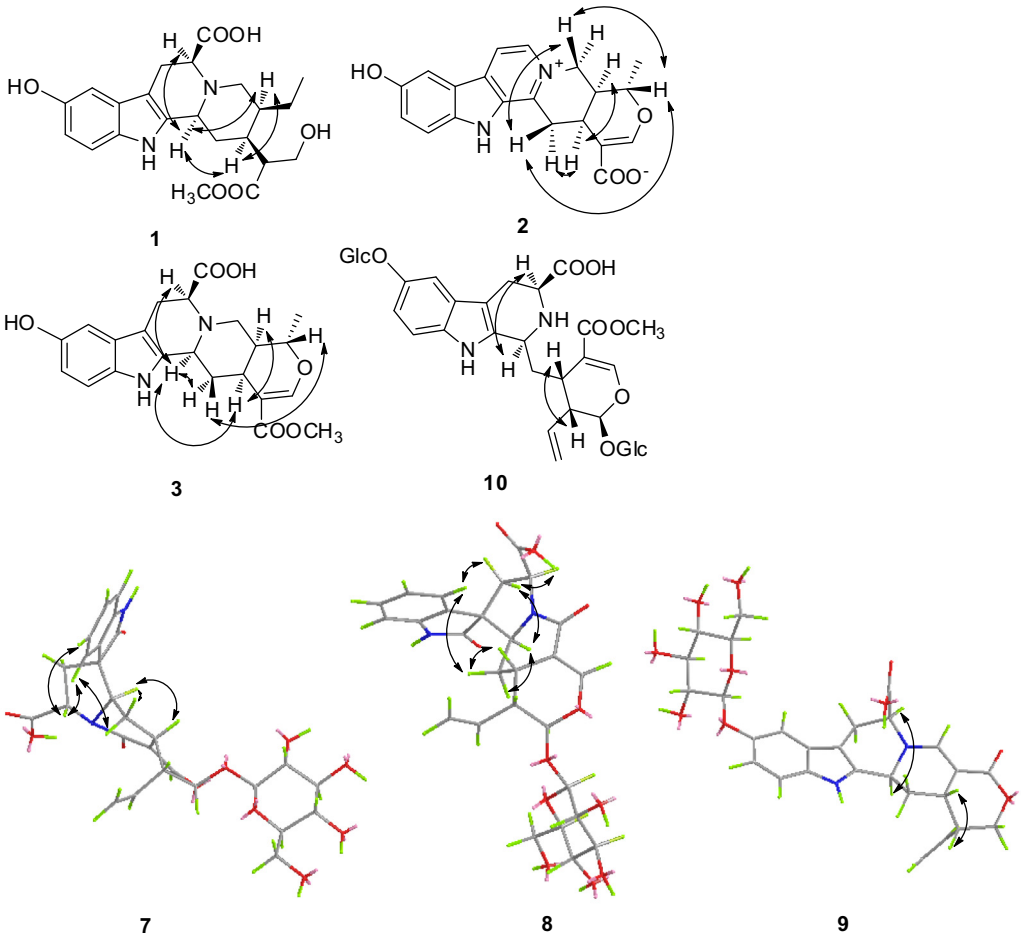

Fig. 3. Key ROESY correlations of **1–3** and **7–10**.

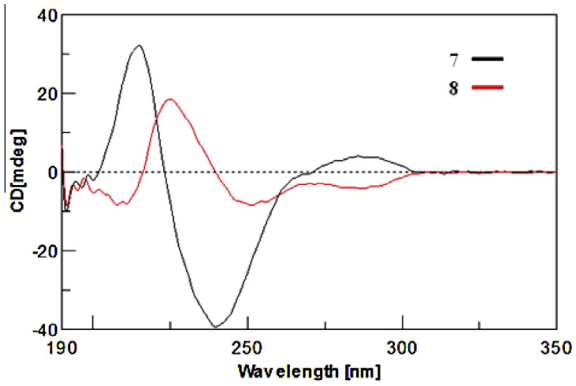

Fig. 4. CD spectra of compounds **7** and **8**.

5.27 (dt, J = 17.2, 10.1 Hz), 5.06 (dd, J = 17.2, 1.6 Hz) and 4.96 (dd, J = 10.1, 1.6 Hz), an olefinic proton at δ 7.40 (d, J = 2.1 Hz), and a hemi-acetal proton at δ_H 5.41 (d, J = 1.7 Hz) (Table 3). The ^{13}C and DEPT spectra established the presence of three carbonyl groups (δ_C 178.2, 174.8 and 165.9), six aromatic carbons (δ_C 142.6, 130.8, 130.8, 124.6, 123.8 and 111.7), two aliphatic terminal vinyl carbons (δ_C 133.3 and 120.5), and one trisubstituted double bond (δ_C 149.2 and 108.4) (Table 1). Additionally, signals corresponding to a glucopyranose moiety were also identified from ^{13}C NMR experiments. The assignment of carbon resonances corresponding to each proton signal was achieved by analysis of an HSQC experiment. Its ^1H–^1H COSY spectrum indicated four separate spin–spin coupling systems. In the ^{13}C NMR spectrum, a sp^3 quaternary carbon at δ_C 58.7 (C-7) and a carbonyl carbon at δ_C 178.2 (C-2) suggested the presence of an oxindole ring which was linked to a pyrrole ring via spiro-carbon C-7 (Pham et al., 2005). This was supported by analysis of the HMBC spectrum, in which long range correlations were observed from both H-3 (δ_H 4.24) and H_2-6 (δ_H 2.43) to C-2 (δ_C 178.2), from H-3 (δ_H 4.24), H_2-6 (δ_H 2.43) and H-9 (δ_H 6.90) to C-7 (δ_C 58.7), and from H_2-6 (δ_H 2.43) to C-3 (δ_C 65.5) (Fig. 2). The carboxyl group (δ_C 174.8) was indicated to be bound to C-5 by the HMBC correlation between the H-5 (δ_H 4.84) and C-23 (δ_C 174.8). These findings showed that **7** was closely related to javaniside, a known monoterpenoid 2-oxo-indole alkaloid previously isolated from an *Alangium* species (Pham et al., 2005), except for the existence of a carboxyl group at C-5.

The stereochemistry of **7** was determined through careful analysis of all proton coupling constants and ROESY correlations. The coupling constants between H-20/H-21 (J = 1.7 Hz) and H-20/H-15 (J = 5.6 Hz) strongly suggested the $\beta/\beta/\alpha$ orientation of H-15, H-20, H-21. The β configuration of H-3 was supported by coupling constants between H-3 and H-14 protons ($J_{3,14\alpha}$ = 11.4 Hz, $J_{3,14\beta}$ = 3.4 Hz). Combined with ROESY correlations of H-9/H-14α, H-9/H-5, the relative configuration could be determined (Fig. 3). Its CD spectrum exhibited a positive Cotton effect at 285 nm ($\Delta\varepsilon$ = +2.89, Fig. 4), indicating that the absolute configuration at C-7 was R (Ali et al., 1975; Aimi et al., 1997). Accordingly, 3R, 5S, 7R, 15S, 20R and 21S configurations were readily assigned based on the relative configurations.

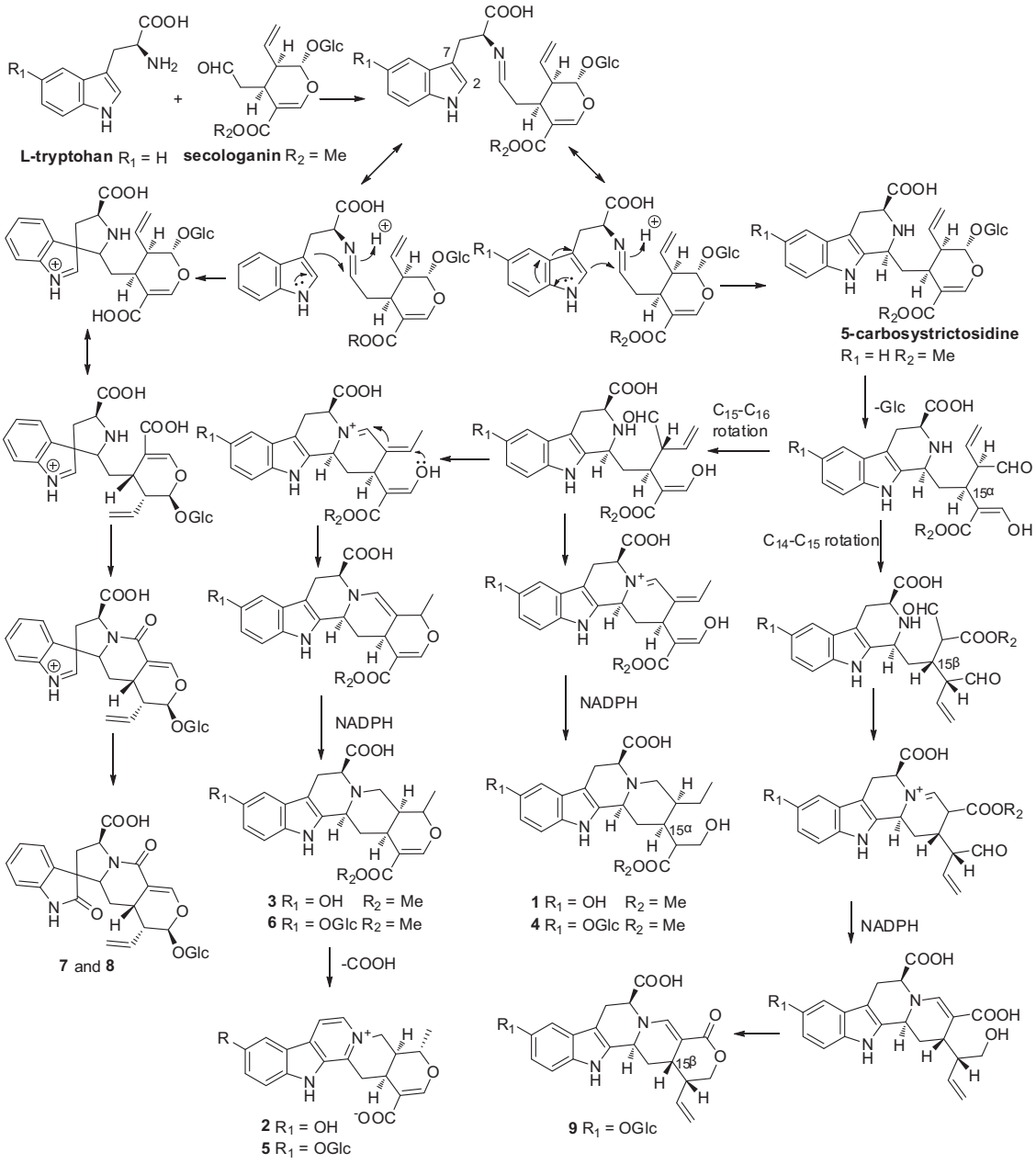

Fig. 5. Postulated biogenetic pathway for compounds **1**–**9**.

Mappiodoside E (**8**), a colorless amorphous powder, had the same molecular formula as **7** on the basis of HRESIMS and NMR spectra. The UV, IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data were similar to those of **7**. Thus, **8** was considered to possess the same skeletal structure as **7**, and 2D NMR (^{1}H–^{1}H COSY, HSQC and HMBC) confirmed this conclusion. The relative configuration of **8** was determined by the proton coupling constants and ROESY correlations. The coupling constants between H-20/H-21 (J = 1.1 Hz) and H-20/H-15 (J = 5.3 Hz) strongly suggested a $\beta/\beta/\alpha$ orientation for H-15, H-20, H-21. Combined with the ROESY correlations of H-9/H-14β, H-9/H-6β, H-5/H-6α, H-5/H-3, the relative configuration could be determined (Fig. 3). The CD spectrum exhibited a negative Cotton effect at 283 nm ($\Delta\varepsilon$ = −2.84, Fig. 4), suggesting that the absolute configuration at C-7 was S (Ali et al., 1975; Aimi et al., 1997). Accordingly, 3S, 5S, 7S, 15S, 20R and 21S configurations were readily assigned based on the relative configurations.

Mappiodoside F (**9**), a yellow amorphous powder, had a molecular formula of $C_{27}H_{30}N_2O_{10}$ by HRESIMS. Its ^{1}H NMR and ^{13}C NMR spectra indicated a 1,2,4-trisubstituted phenyl ring [δ_H 7.21 (d, J = 8.7 Hz), 7.05 (d, J = 2.0 Hz) and 6.81 (dd, J = 8.7, 2.0 Hz)], one trisubstituted double bond (δ_C 146.5 and 95.8), one tetrasubstituted double bond (δ_C 135.2 and 108.1), two carbonyl groups (δ_C 172.5 and 165.0), three methylenes, four methines and a sugar unit (δ_C 102.1, 79.4, 78.7, 75.4, 71.7, 61.0), respectively (Tables 1 and 3). Correlations between H-3/H-14/H-15/H-20/H-21, H-18/H-19/H-20, H-5/H-6 and H-11/H-12 were apparent in the ^{1}H–^{1}H COSY spectrum. Analysis of the 1D and 2D NMR spectra showed that compound **9** had a similar skeleton to that of 3α, 5α-tetrahydrodeoxycordifoline lactam (Lamidi et al., 2005), except for a different arrangement at the trisubstituted double bond and the carboxyl group. This was validated by HMBC correlations between H-17/C-5, H-17/C-3 and H-21/C-22. The D-glucose, the presence of which was confirmed by hydrolysis of **9**, was located at C-10 by the HMBC

Table 3
^{1}H NMR Spectroscopic Data (500 MHz) for Compounds **6**–**10**.[a]

No.	**6**[b]	**7**[b]	**8**[c]	**9**[c]	**10**[d]
3	4.04, d (11.5)	4.24, dd (11.4, 3.4)	3.69, m	4.86, m	4.47, m
5	3.63, m	4.84, m	4.56, d (10.3)	4.16, d (8.7)	3.78, m
6α	3.10, m	2.43, m	2.72, t (12.3)	2.97, d (14.3)	3.30, m
6β	3.28, m	2.43, m	2.08, d (12.6)	2.71, m	2.95, m
9	7.13, d (1.9)	6.90, d, (7.4)	7.56, d (7.5)	7.05, d (2.0)	7.13, d (1.9)
10		7.03, dd, (7.4, 7.4)	6.95, dd(7.5, 7.5)		
11	6.99, dd (8.7, 1.9)	7.26, dd, (7.4, 7.4)	7.21, dd (7.5, 7.5)	6.81, dd (8.7, 2.0)	6.96, dd (8.7, 1.9)
12	7.27, d (8.7)	6.96, d (7.4)	6.88, d (7.5)	7.21, d (8.7)	7.17, d (8.7)
14α	2.91, d (14.0)	0.88, td (12.7, 11.4)	1.17, d (11.8)	1.73, m	2.23, m
14β	1.70, ddd (14.0, 11.5, 9.6)	1.43, dd (12.7, 3.4)	1.58, td (11.8, 13.1)	2.53, m	2.38, m
15	2.85, m	3.12, m	3.10, m	2.45, m	3.05, m
17	7.62, s	7.40, d (2.1)	7.09, d (2.5)	7.70, s	7.85, s
18	1.50, d (6.1)	4.96, dd (10.1, 1.6)	5.13, dd (10.1, 1.7)	5.24, d (11.8)	5.27, d (10.6)
		5.06, dd (17.2, 1.6)	5.22, dd (17.2, 1.7)	5.28, d (18.4)	5.38, d (17.2)
19	4.46, dq (10.2, 6.1)	5.27, dt (17.2, 10.1)	5.56, dt (17.2, 10.1)	5.76, m	5.82, m
20	1.96, m	2.55, ddd (9.5, 5.6, 1.7)	2.39, ddd (9.5, 5.3, 1.1)	2.44, m	2.77, m
21	4.08, m	5.41, d (1.7)	5.29, d (1.1)	4.03, d (10.4)	5.89, d (9.1)
	3.08, m			4.26, d (10.4)	
OMe					3.81, s
1′	4.83, d (7.3)	4.63, d (7.9)	4.48, d (7.8)	4.75, d (7.4)	4.89, d (7.7)
2′	3.46, m	3.18, m	2.92, t (8.4)	3.20, m	3.26, m
3′	3.48, m	3.36, m	2.99, t (9.2)	3.26, m	3.46, m
4′	3.38, m	3.25, m	3.13, m	3.13, m	3.27, m
5′	3.40, m	3.27, m	3.13, m	3.14, m	3.53, m
6′	3.89, d (11.9)	3.63, dd (11.9, 5.6)	3.39, dd (11.6, 6.2)	3.45, dd (11.5, 5.8)	3.73, m
	3.69, dd (11.9, 5.0)	3.86, dd (11.9, 1.8)	3.65, m	3.67, d (11.5)	3.93, d (11.7)
1″					4.91, d (7.2)
2″					3.26, m
3″					3.52, m
4″					3.27, m
5″					3.53, m
6″					3.68, m;
					4.01, d (11.7)

[a] Values in δ (ppm); coupling constants (Hz) in parentheses.
[b] Spectra obtained in CD_3OD.
[c] Spectra obtained in DMSO-d_6.
[d] Spectra obtained in $CD_3OD + D_2O$.

correlation between H-1′ (δ_H 4.75) and C-10 (δ_C 151.3) (Fig. 2). The H-5 was α-oriented, as this compound was also derived from L-tryptophan. The H-15 was β-oriented in the rearranged skeleton according to the biogenetic pathway (Fig. 5), in 3α, 5α-tetrahydro-deoxycordifoline lactam. Combined with the ROESY correlations of H-3/H-5 and H-15/H-20 (Fig. 3), the relative configuration was determined.

Mappiodoside G (**10**), a yellow amorphous powder, was determined to have a molecular formula of $C_{34}H_{44}N_2O_{17}$ by HRESIMS. Its UV and IR spectroscopic data were similar to those of 5-carboxystrictosidine. By comparison of the ^{1}H and ^{13}C NMR spectroscopic data, it differed from 5-carboxystrictosidine through one additional sugar unit. The sugar was determined as D-glucose by hydrolysis of **10**. The D-glucose unit was located at C-10 as deduced from the HMBC correlation between the proton at δ_H 4.91 and C-10 at δ_C 153.2. The methoxyl group was concluded to be bound to C-22 as reasoned from the HMBC correlation between OMe (δ_H 3.81) and C-22 (δ_C 171.9). The ROESY correlation of H-3/H-5 indicated that H-3 and H-5 were α-oriented. The proton coupling constant ($J_{20,21}$ = 9.1) and the presence of the ROESY correlation H-15/H-20 suggested that H-15 and H-20 were β-oriented, and H-21 was α-oriented. Thus, the relative configuration of **10** was determined.

A biogenetic pathway of the compounds is postulated in Fig. 5. L-tryptohan combines with secologanin giving a Schiff base. Attack of the indole C-2 nucleophile on the iminium carbon could then yield 5-carboxystrictosidine. Hydrolysis of the glycoside function allows opening of the hemiacetal, and following exposure of the aldehydic moiety, it can react with the secondary amine function thereby giving a quaternary Schiff base. The Schiff base can then potentially be reduced to compound **1** in the presence of NADPH. Allylic isomerization, moving the vinyl double bond into conjugation with the iminium, and attack of the oxygen nucleophile on α, β-unsaturated iminium ion is then hypothesized to generate **3**. Compound **2** could be produced from **3** after decarboxylation and dehydrogenation. Attack of the C-7 nucleophile on the iminium intermediate could form the spiro system and eventually yield compounds **7** and **8**. Also, compound **9** could be biosynthesized by a series of reactions from 5-carboxystrictosidine.

The stereochemistry at C-15 is invariably the same as that of secologanin, as no reaction has happened at C-15. Therefore, H-15 is α-oriented in the skeleton of compounds **1–6** and β-oriented in skeleton of compounds **7–9** after rearrangement.

Table 4
Growth inhibition% @ 100 μM for four cell lines.

Compound	HT29	BEL-7402	MDA-MB-231	K562
1	5.8 ± 0.5	3.3 ± 0.2	5.7 ± 0.2	4.5 ± 1.9
2	1.5 ± 2.5	5.1 ± 4.6	0.6 ± 1.2	4.9 ± 4.8
3	2.5 ± 2.9	4.6 ± 1.2	1.5 ± 1.4	3.1 ± 0.9
4	−1.5 ± 5.1	−1.6 ± 3.5	−3.3 ± 2.6	−0.4 ± 1.7
5	7.8 ± 4.8	2.1 ± 0.5	6.1 ± 2.4	4.8 ± 4.3
6	6.2 ± 3.4	11.1 ± 5.3	5.0 ± 1.7	6.8 ± 0.8
7	5.7 ± 8.6	5.7 ± 5.5	2.7 ± 4.3	3.8 ± 2.8
8	6.9 ± 2.9	13.1 ± 0.2	5.9 ± 1.5	9.9 ± 4.2
9	11.6 ± 4.3	15.8 ± 3.2	10.1 ± 2.1	14.9 ± 4.6
10	1.3 ± 3.1	2.8 ± 5.0	−0.5 ± 0.6	−0.4 ± 0.5

Vinorelbin was used as positive control with IC_{50} of 2.6 nM for HT29, 1.2 nM for BEL-7402, 2.0 nM for MDA-MB-231and 3.4 nM for K562.

Compounds **1–10** were evaluated for cytotoxicity against four human cancer cell lines. However, these compounds did not exhibit significant cytotoxicity (IC_{50} > 10 μM), compared to vinorelbin (IC_{50} < 10 nM, Table 4).

Conclusions

Ten terpenoid indole alkaloids, mappiodines A-C (**1**–**3**) and mappiodosides A-G (**4**–**10**), together with eight known compounds, were isolated from stems of *M. iodoides*. Their structures were elucidated by intensive spectroscopic analyses. In previous phytochemical investigations, five monoterpenoid indole alkaloids were isolated from *M. iodoides* stems (Xiao et al., 2011). The findings herein thus complement previous reports of the occurrence of terpenoid indole alkaloids in the *Mappianthus* genus. It is concluded that the rich source of terpenoid indole alkaloids in *M. iodoides* might be a useful chemotaxonomic marker of the *Mappianthus* genus.

Experimental

General

Optical rotations were measured on a Perkin-Elmer 341 polarimeter, whereas UV and IR spectra were recorded on a Shimadzu UV-2450 and a Perkin-Elmer 577 spectrophotometer, respectively. NMR spectra were acquired on a Varian Mercury NMR spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C. HRESIMS was measured using an Agilent G6224A TOF spectrometer. Thin-layer chromatography (TLC) used precoated silicagel GF254 plates (Yantai, People's Republic of China). Column chromatography (CC) used Sephadex LH-20 (20–80 μm; Amersham Pharmacia Biotech AB), Chromatorex C_{18}-OPN (20–45 μm; Fuji Silysia Chemical Ltd.) and MCI gel CHP20P (75–150 μm, Mitsubishi Chemical Industries Co., Ltd.), respectively. β-Cellulase was manufactured by Sinopharm Chemical Reagent Co., Ltd., Shanghai, People's Republic of China.

Plant material

Stems of *Mappianthus iodoides* were collected from Nanning, in Guangxi Province, PR China, in September 2011, and authenticated by Prof. *Heming Yang*. A voucher specimen (No. SIMMMI78) is deposited at the Herbarium of Shanghai Institute of Materia Medica, Chinese Academy of Sciences, PR China.

Extraction and isolation

Air-dried, powdered stems (5.0 kg) of *M. iodoides* were extracted with acetone-H_2O (3 × 20 L, 7:3, v/v, 3 times) at room temperature for 48 h, respectively. The combined extracts were concentrated to give a crude extract (420 g), which was partitioned between $CHCl_3$ and H_2O to obtain a water-soluble fraction (300 g). The latter was applied to a MCI gel CHP20P column eluted with H_2O–MeOH (100:0; 80:20; 60:40; 40:60; 0:100, v/v). Fourteen major fractions (A–N) were obtained. Fraction F was applied to C_{18} CC, eluted with H_2O–MeOH (90:10 to 80:20, v/v) to give fractions (F_1, F_2 and F_3). Fraction F_1 was further subjected to MCI gel CHP20P CC with H_2O-MeOH (90:10 to 70:30, v/v) to afford **6** (30 mg). Fraction F_2 was further separated by RP-HPLC (YMC 5 μm, 250 × 10 mm, H_2O–MeOH, 75:25, v/v, 3.0 mL/min, eluting at 8.0–15.0 min, UV 254 nm) to yield compound **1** (52 mg) and **4** (40 mg). Fraction F_3 was further subjected to MCI gel CHP20P CC with H_2O–MeOH (90:10 to 70:30, v/v) to afford tryptophan (60 mg) and **10** (28 mg). Fraction H was subjected to a C_{18} CC eluted with H_2O-MeOH (80:20 to 60:40, v/v) to give compound 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (20 mg). Fraction I was subjected to LH-20 CC (MeOH) to give fractions (I_1 and I_2). Fraction I_2 was separated by RP-HPLC (YMC 5 μm, 250 × 10 mm, H_2O–CH_3CN, 87:13, v/v, 3.0 mL/min, eluting at 10–12 min, UV 254 nm) to yield compound **3** (60 mg). Fraction J was subjected to C_{18} CC eluted with H_2O–MeOH (80:20 to 60:40, v/v) to give compound 5-carboxystrictosidine (500 mg) and desoxycordifoline (9 mg). Fraction K was applied to a C_{18} column eluted with H_2O–MeOH (80:20 to 50:50, v/v) to give fractions (K_1, K_2 and K_3). Fraction K_1 was separated by RP-HPLC (YMC 5 μm, 250 × 10 mm, H_2O–CH_3CN, 85:15, v/v, 3.0 mL/min, eluting at 14–34 min, UV 254 nm) to yield compound **8** (40 mg) and **9** (25 mg). Fraction K_2 was separated by RP-HPLC (YMC 5 μm, 250 × 10 mm, H_2O–MeOH, 55:45, v/v, 3.0 mL/min, eluting at 6.5–12.5 min, UV 254 nm) to yield compound **7** (50 mg) and strictosidinic acid (35 mg). Fraction K_3 was separated by RP-HPLC (YMC 5 μm, 250 × 10 mm, H_2O–CH_3CN, 84:16, v/v, 3.0 mL/min, eluting at 8–17 min, UV 254 nm) to yield compound **5** (60 mg) and 3α, 5α-tetrahydrodeoxycordifolic acid (20 mg). Fraction L was subjected to a C_{18} CC eluted with H_2O–MeOH (80:20 to 45:55, v/v) to give compound **2** (71 mg) and 3α, 5α-tetrahydrodeoxycordifoline (55 mg). Fraction M was applied to a C_{18} CC eluted with H_2O–MeOH (80:20 to 40:60, v/v) to give lyaloside (45 mg).

*Mappiodine A (**1**)*
Yellow amorphous powder, $[\alpha]_D^{23}$ −4.0 (*c* 0.15, MeOH), UV (MeOH) (log ε) λ_{max} 206 (3.96), 274 (3.58), 311 (3.42); IR (KBr) ν_{max} 3407, 2924, 1724, 1628, 1460, 1383, 1201, 1073, 1041 cm^{-1}; for ^{13}C and ^1H NMR spectroscopic data, see Tables 1 and 2. HRESIMS: *m/z* 417.2016 $[M+H]^+$ (calcd for $C_{22}H_{29}N_2O_6^+$, 417.2020).

*Mappiodine B (**2**)*
Yellow amorphous powder, $[\alpha]_D^{24}$ +49.0 (*c* 0.13, MeOH), UV (MeOH) (log ε) λ_{max} 210 (4.06), 233 (4.07), 273 (3.92), 314 (3.94); IR (KBr) ν_{max} 3399, 3089, 1675, 1637, 1577, 1506, 1454, 1328, 1200, 1128, 821, 719 cm^{-1}; for ^{13}C and ^1H NMR spectroscopic data, see Tables 1 and 2. HRESIMS: *m/z* 351.1340 $[M+H]^+$ (calcd for $C_{20}H_{19}N_2O_4^+$, 351.1339).

*Mappiodine C (**3**)*
Yellow amorphous powder, $[\alpha]_D^{24}$ -68.1 (*c* 0.3, MeOH), UV (MeOH) (log ε) λ_{max} 224 (4.59), 275 (4.09); IR (KBr) ν_{max} 3420, 2922, 2872, 1630, 1460, 1392, 1209, 1075, 1039 cm^{-1}; for ^{13}C and ^1H NMR spectroscopic data, see Tables 1 and 2. HRESIMS: *m/z* 399.1559 $[M+H]^+$ (calcd for $C_{21}H_{23}N_2O_6^+$, 399.1551).

*Mappiodoside A (**4**)*
Yellow amorphous powder, $[\alpha]_D^{23}$ -12.2 (*c* 0.3, MeOH), UV (MeOH) (log ε) λ_{max} 209 (3.84), 270 (3.48), 311 (3.29); IR (KBr) ν_{max} 3408, 2923, 1724, 1627, 1459, 1382, 1201, 1074, 1041 cm^{-1}; for ^{13}C and ^1H NMR spectroscopic data, see Tables 1 and 2. HRESIMS: *m/z* 579.2542 $[M+H]^+$ (calcd for $C_{28}H_{39}N_2O_{11}^+$, 579.2548).

*Mappiodoside B (**5**)*
Yellow amorphous powder, $[\alpha]_D^{24}$ +11.7 (*c* 0.1, MeOH), UV (MeOH) (log ε) λ_{max} 210 (3.70), 234 (3.65), 262 (3.55), 312 (3.52); IR (KBr) ν_{max} 3400, 3089, 1676, 1637, 1577, 1506, 1454, 1329, 1199, 1128 cm^{-1}; for ^{13}C and ^1H NMR spectroscopic data, see Tables 1 and 2. HRESIMS: *m/z* 513.1875 $[M+H]^+$ (calcd for $C_{26}H_{29}N_2O_9^+$, 513.1868).

*Mappiodoside C (**6**)*
Yellow amorphous powder, $[\alpha]_D^{23}$ −18.7 (*c* 0.2, MeOH), UV (MeOH) (log ε) λ_{max} 225 (4.37), 272 (3.81); IR (KBr) ν_{max} 3419, 2921, 2871, 1629, 1460, 1392, 1209, 1076, 1039, 611 cm^{-1}; for ^{13}C and ^1H NMR spectroscopic data, see Tables 1 and 3. HRESIMS: *m/z* 561.2085 $[M+H]^+$ (calcd for $C_{27}H_{33}N_2O_{11}^+$, 561.2079).

*Mappiodoside D (**7**)*

Colorless amorphous powder, $[\alpha]_D^{20}$ −119.0 (*c* 0.3, MeOH); UV (MeOH) (log ε) λ_{max} 207 (4.37), 244 (4.26); CD (MeOH) λ_{max} nm ($\Delta\varepsilon$) 215 (+22.2), 240 (−26.9), 285 (+2.89); IR (KBr) ν_{max} 3421, 2923, 1714, 1656, 1619, 1594, 1471, 1338, 1214, 1174, 1068 cm^{-1}; for ^{13}C and ^{1}H NMR spectroscopic data, see Tables 1 and 3. HRESIMS: *m*/*z* 559.1929 $[M+H]^+$ (calcd for $C_{27}H_{31}N_2O_{11}^+$, 559.1922).

*Mappiodoside E (**8**)*

Colorless amorphous powder, $[\alpha]_D^{23}$ −97.5 (*c* 0.14, MeOH), UV (MeOH) (log ε) λ_{max} 208 (4.42), 244 (4.21); CD (MeOH) λ_{max} nm ($\Delta\varepsilon$) 207 (−12.51), 225 (+6.25), 251 (−5.70), 273 (−1.95), 287 (−2.84); IR (KBr) ν_{max} 3420, 2924, 1714, 1657, 1620, 1594, 1471, 1068 cm^{-1}; for ^{13}C and ^{1}H NMR spectroscopic data, see Tables 1 and 3. HRESIMS: *m*/*z* 559.1928 $[M+H]^+$ (calcd for $C_{27}H_{31}N_2O_{11}^+$, 559.1922).

*Mappiodoside F (**9**)*

Yellow amorphous powder, $[\alpha]_D^{24}$ +70.0 (*c* 0.1, MeOH), UV (MeOH) (log ε) λ_{max} 224 (4.27), 299 (4.10); IR (KBr) ν_{max} 3383, 2920, 1587, 1552, 1456, 1396, 1306, 1250, 1198, 1132, 1072, 1043, 534 m^{-1}; for ^{13}C and ^{1}H NMR spectroscopic data, see Tables 1 and 3. HRESIMS: *m*/*z* 543.1978 $[M+H]^+$ (calcd for $C_{27}H_{31}N_2O_{10}^+$, 543.1973).

*Mappiodoside G (**10**)*

Yellow amorphous powder, $[\alpha]_D^{21}$ −109.8 (*c* 0.3, MeOH), UV (H_2O) (log ε) λ_{max} 221 (4.96), 289 (4.21); IR (KBr) ν_{max} 3419, 2927, 1628, 1400, 1076, 748, 598 cm^{-1}; for ^{13}C and ^{1}H NMR spectroscopic data, see Tables 1 and 3. HRESIMS: *m*/*z* 753.2733 $[M+H]^+$ (calcd for $C_{34}H_{45}N_2O_{17}^+$, 753.2726).

*Enzymatic Hydrolysis of Compounds **4–10***

Compounds **4–10** (10 mg each) were dissolved in H_2O (5 mL), and β-cellulase (20 mg) was added to the solution and kept at 37 °C for 2 days, in each case. Reaction mixtures were extracted with EtOAc, and aqueous phases were compared with an authentic sugar sample by co-TLC (EtOAc–MeOH–H_2O–HOAc, 13:3:3:4, R_f 0.46 for glucose). Identification of D-glucose in each aqueous layer was carried out by comparing the optical rotation of the liberated glucose with that of an authentic sample of D-glucose $[\alpha]_D^{22}$+52). The EtOAc solubles from compounds **4–6** were purified on LH-20 column (MeOH) separately to afford compounds **1–3**.

Cytotoxicity assays

Cytotoxicity of the test compounds against the HT29 (Human colon carcinoma), MDA-MB-231 (Human breast carcinoma) and BEL-7402 (Human hepatocellular carcinoma) cell lines was measured using a sulforhodamine B (SRB) assay, K562 (Human chronic myelogenous leukemia) cell line was measured using a MTT assay, as described in the literature (Skehan et al., 1990). Vinorelbin was used as positive control. Briefly for SRB assay, cells were seeded in 96-well culture plates for 24 h and then treated with serial dilutions of the compounds, with a maximum concentration of 100 μM. After being incubated for 72 h under a humidified atmosphere of 5% CO_2 at 37 °C, cells were fixed with 10% CCl_3CO_2H and incubated at 4 °C for 1 h. After washing with distilled H_2O and air-drying, the plate was stained for 15 min with 100 μL of 0.4% SRB (Sigma) in 1% AcOH. The plates were washed with 1% AcOH and air-dried. For reading the plate, the protein-bound dye was dissolved in 10 mM Tris base (150 μL) with the absorbance measured at 510 nm on a microplate spectrophotometer. For MTT assay, cells were seeded in 96 wells plate, and incubated with solutions of compounds for 72 h. MTT (4 mg/mL) was added to each well and incubated at 37 °C for a further 4 h, DMSO was added and absorbance was measured at 570 nm on a microplate spectrophotometer (Molecular Devices Spectra Max 340, MWG-Biothech, Inc., Sunnyvale, CA, USA). All tests were performed in triplicate, and results are expressed as inhibition% @ 100 μM values.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phytochem.2014.01.004.

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