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Hendersine A, a novel isoquinoline alkaloid from *Corydalis hendersonii*

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ABSTRACT

A pair of enantiomeric alkaloids, (±) hendersine A (**1a** and **1b**), featuring an unprecedented couple pattern of an isoquinoline and a succinic acid derivative, a new isoquinoline hendersine B (**2**), and a known (+)-magnoflorine (**3**) were isolated from the EtOH extract of *Corydalis hendersonii*. Their structures were elucidated on the basis of spectroscopic data including HRESIMS, NMR, and experimental and calculated electronic circular dichroism (ECD). Compound **3** exhibited strong inhibitory effects against Ca^{2+} overload in glutamate-induced PC12 cells. Compounds **1**–**3** exhibited a protective effect against H9c2 myocyte injuries induced by LPS-stimulation conditioned medium.

Chronic pain seriously affects quality of life and results in severe health and economic burdens for patients. It is estimated that around $600 billion per annum has been used for the treatment of chronic pain in America, and this amount exceeds the combined annual cost of heart diseases, cancer, and diabetes mellitus.[1] In China, at least 100 million people suffer from chronic pain.[2] Current available drugs, however, such as nonsteroidal anti-inflammatory drugs and opiate drugs, are limited due to various side effects.[3–6] Natural products have been a rich source of lead molecules in drug discovery due to their high chemical diversities and unique biological activities.[7] Therefore, the discovery of analgesic leads from natural resources is urgently needed. Some attractive discoveries have been reported in recent years, such as furanocoumarin imperatorin,[8] peptide μ-SLPTX-Ssm6a,[9] and isoquinoline alkaloid dehydrocorybulbine.[10]

Corydalis hendersonii Hemsl. (Papaveraceae) is commonly grown at the overflow lands and alpine screes in the high altitude area (4200–5200 m) in Tibet.[11] It has been used as a Tibetan folk medicine for the treatment of angitis, hypertension, and chronic pain.[11,12]

The whole plant of *C. hendersonii* was extracted by 85% EtOH. The EtOH extract was acidified with 3% HCl, followed by a positive ion-exchange resin column chromatography to give the total alkaloid (TA) and non-alkaloid residue. A bioassay-guided fractionation through various chromatographic techniques led to the isolation of compounds **1**–**3** (Fig. 1).

Compound **1** was obtained as light yellow amorphous powder. Its molecular formula, $C_{22}H_{15}NO_7$, was deduced from the HRESIMS (*m*/*z* 406.0922 $[M+H]^+$, calcd for $C_{22}H_{16}NO_7$, 406.0921) and ^{13}C NMR spectroscopic data, indicating 16 degrees of unsaturation. The ^1H NMR data (Table 1) revealed the presence of two pairs of *ortho* aromatic protons [δ_H 8.06 (H-3, J = 5.5 Hz), 7.44 (H-4, J = 5.5 Hz), and δ_H 6.45 (H-2′, J = 8.0 Hz), 6.90 (H-3′, J = 8.0 Hz)], two aromatic singlet protons (H-5 and H-8), two methylenedioxy signals [δ_H 6.11, 6.07, and δ_H 6.21, 6.24], two methine protons [δ_H 5.63 (H-1a) and 2.75 (m, H-9′)], and methylene protons [δ_H 2.20 (2H, m, H-8′)]. The ^{13}C NMR data (Table 1) indicated the presence of 22 carbon resonances, which were assigned to 15 aromatic carbons, two carbonyl carbons, and five sp^3 carbons including two methines, two methylenedioxys, and one methylene.

The HMBC spectrum of **1** displayed correlations from H-8 to C-1, C-4a, and C-6, H-5 to C-7 and C-8a, H-4 to C-8a and C-5, H-3 to C-4a and C-1, and from methylenedioxy protons (δ_H 6.11, 6.07) to C-6 and C-7. These HMBC correlations along with the spin system (CH═CH, H-3/H-4) determined by the coupling constant

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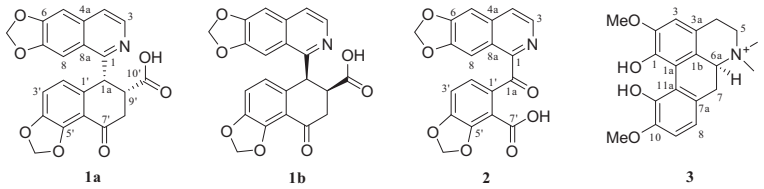

Figure 1. Structures of compounds **1**, **2**, and **3**.

Table 1
NMR spectroscopic data of **1**–**2** (500/125 MHz, in DMSO-d_6), δ in ppm and J in Hz

Position	**1**		**2**	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1		161.7, C		155.1, C
1a	5.63 (1H, d, 3.0)	45.7, CH		197.5, C
3	8.06 (1H, d, 5.5)	140.4, CH	8.08 (1H, d, 5.5)	139.2, CH
4	7.44 (1H, d, 5.5)	118.5, CH	7.63 (1H, d, 5.5)	121.9, CH
4a		134.4, C		134.8, C
5	7.34 (1H, s)	103.0, CH	7.33 (1H, s)	102.0, CH
6		150.0, C		150.0, C
7		148.4, C		148.3, C
8	7.93 (1H, s)	101.0, CH	8.05 (1H, s)	104.0, CH
8a		122.8, C		123.1, C
1′		137.1, C		136.6, C
2′	6.45 (1H, d, 8.0)	122.0, CH	6.79 (1H, d, 8.0)	121.7, CH
3′	6.91 (1H, d, 8.0)	111.8, CH	6.84 (1H, d, 8.0)	106.7, CH
4′		146.0, C		148.7, C
5′		146.4, C		144.7, C
6′		118.8, C		124.8, C
7′		195.8, C		165.7, C
8′	2.20, 2.60 (2H, m)	37,7, CH_2		
9′	2.75 (1H, m)[a]	47.4, CH		
10′		163.1, C		
OCH_2O (6, 7)	6.11 (1H, br s) 6.07 (1H, br s)	101.9, CH_2	6.21 (2H, br s)	101.8, CH_2
OCH_2O (4′, 5′)	6.21 (1H, br s) 6.24 (1H, br s)	101.7, CH_2	5.99 (2H, br s)	101.0, CH_2

[a] Confirmed by COSY data.

(J = 5.5 Hz) and COSY data established the partial structure A (Fig. 2), which accounted for eight of 16 degrees of unsaturation. The remaining part consists of six aromatic carbons, two carbonyls, two methines, one methylene, and one methylenedioxy. HMBC correlations from H-2′ to C-4′ and C-6′, H-3′ to C-1′ and C-5′, H-1a to C-1′, C-2′, and C-6′, and from methylenedioxy protons to C-4′ and C-5′ suggested the presence of a 1,2,3,4-tetrasubstituted phenyl unit with methylenedioxyl substitution. Calculation of degrees of unsaturation implied the existence of an alicyclic ring, containing a spin system among H-1a, H-9′, and H-8′ (CH–CH–CH_2) based on COSY correlations (Fig. 2), which was attached to C-1′ and C-7′ via C-1a and C-8′, respectively, by HMBC correlations from H-8′ and H-9′ to C-7′, and from H-1a and H-9′ to C-1′. A carboxyl group was linked to C-9′ supported by HMBC correlations from H-1a and H-8′ to C-10′. Therefore, substructure B was constructed. Finally, HMBC correlations from H-1a to C-8a and C-1 established the linkage of substructures A and B.

The obvious NOESY correlations between H-1a and H-9′, both H-1a and H-9′ with H-8 (Fig. S7, Supplementary data) combined with a small coupling constant of $J_{1a,9'}$ (3.0 Hz) implied their *erythro* configuration. Notably, the specific rotation value of zero (*c* 0.1, MeOH) and absence of ECD signal suggested **1** to be a racemate. Then, an online HPLC using an AD-H chiral column coupled with the ECD method was employed for separation and determination of its absolute configuration. The result showed that **1** contains equal amounts of two enantiomers which exhibited near mirror image ECD spectra over the 220–420 nm range (Fig. 3). Enantiomer **1a** (t_R = 27.7 min) exhibited a strong positive Cotton

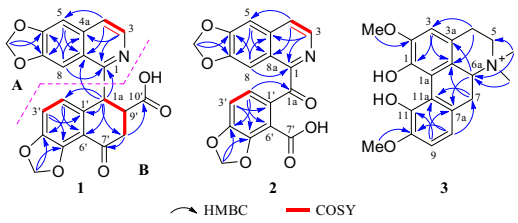

Figure 2. Key HMBC and COSY correlations of **1**, **2**, and **3**.

effect at 244 nm and a weak positive Cotton effect at 334 nm, while enantiomer **1b** (t_R = 39.8 min) exhibited a negative Cotton effect at the same wavelength. Quantum chemical calculations of the theoretical ECD spectrum were performed to determine its absolute configuration (Computation details, Supplementary data). The calculated spectra of the (1a*R*,9′*R*)-isomer and (1a*S*,9′*S*)-isomer were in agreement with the experimental ECD spectra of **1a** and **1b**, respectively, confirming their absolute configurations (Fig. 3). Therefore, the enantiomers of **1a** and **1b** were elucidated as depicted and named (+) hendersine A (**1a**) and (−) hendersine A (**1b**), respectively.

Compound **2**, obtained as a light brown amorphous powder with high polarity, had a molecular formula of $C_{19}H_{11}NO_7$ determined by HRESIMS (m/z 366.0598 $[M+H]^+$, calcd for $C_{19}H_{12}NO_7$, 366.0608; m/z 364.0445 $[M-H]^+$, calcd for $C_{19}H_{10}NO_7$, 364.0463) and ^{13}C NMR spectroscopic data, indicating 15 degrees of unsaturation. The ^1H and ^{13}C NMR data (Table 1) indicated that