



Isoquinolines from *Corydalis tomentella* from Tibet, China, possess hepatoprotective activities



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PGIOBGCIEGZHJH-UHFFFAOYSA-O
 DTELHNAUJWFUDO-SFTDATJTSA-N
 FYTDXOGJMXIITH-UHFFFAOYSA-N
 MQKFSXLBPPCAGR-UHFFFAOYSA-N
 OYCDIRUGACCROL-UHFFFAOYSA-N
 FPJQGFLUORYYPE-UHFFFAOYSA-N
 MJWZHPKXEWLMFJ-BSHCFOPNSA-N
 DAVCKLBEJNRFJ-FCHUYIYVSA-N
 MGHLSZCJFTUMR-UHFFFAOYSA-N
 XNZFFRJWTVYMBF-UHFFFAOYSA-N
 VZXLAXXEQBLBP-UHFFFAOYSA-N
 FQMDLXCXOLPOLT-UHFFFAOYSA-N
 ZHIQBQMWWICIRQ-UHFFFAOYSA-N
 LVGXMHIJYFJCNA-UHFFFAOYSA-O
 WPKMGEXQTYQXGI-UHFFFAOYSA-N
 VVYKOOGBPZAPW-UHFFFAOYSA-N
 FZERPBZADBNRMF-UHFFFAOYSA-N
 PBBVMOBELJQARG-UHFFFAOYSA-N
 DTELHNAUJWFUDO-RTWAWAEBSA-N
 JTZZGWPIBBTYNE-MPBGBICISA-N
 IYGYMKDQCDDOMRE-QZTJIDSGSA-N
 CNXVDVMAYXLWPD-UHFFFAOYSA-N
 IYGYMKDQCDDOMRE-MSOLQXFVSA-N
 MJWZHPKXEWLMFJ-FMZIRWGMMSA-N
 WIUVXEAALLSQN-UHFFFAOYSA-N
 VMSDIGAKRLHGTG-UHFFFAOYSA-N
 ONEHMWWDDDSJBB-QGZVFWFLSA-N

ABSTRACT

The phytochemical study on *Corydalis tomentella* Franch, a traditional Chinese medicinal plant in Tibet, China, led to the isolation of six previously undescribed isoquinolines, including two rarely reported *N*-benzyl ones, and twenty-one known ones firstly obtained from this plant. Their planar structures were elucidated by 1D, 2D NMR experiments and high resolution mass spectrometry, and the absolute configurations were determined by NOE experiments, electronic circular dichroism, and specific rotation. Seven isoquinolines exhibited stronger hepatoprotective activities than that of positive control in D-galactosamine induced L02 cells damage model, which could be served as the leading compounds for further investigations. The primary structure-activity relationship was also summarized accordingly.

1. Introduction

The liver is of critical importance because of its irreplaceable detoxification function. However, with the aggravation of environmental pollution, the increasing work pressure, and various exposure to

xenobiotics, a variety of hepatic damages associated with distortion of many metabolic functions were induced (Prakash et al., 2008; Wolf, 1999). Moreover, the current hepatoprotective medicines are not satisfying because of poor effect or side-effect. As a consequence, searching new leading compounds to protect liver is always urgent.

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Corydalis tomentella Franch (Papaveraceae) is native to the southwest of China (Prakash et al., 2008). As a traditional medicinal plant, *Corydalis tomentella* has strongly biological activities, such as anti-inflammatory, antibiosis, analgesia, and antipsychotic activities, etc. Moreover, it is used as a hepatoprotective herb to treat hepatitis, liver cirrhosis and liver cancer. Although the plants from *Corydalis* contain abundant isoquinolines (Iranshahy et al., 2014), the phytochemical and biological studies on *Corydalis tomentella* were rarely reported except for the isolation of four isoquinolines (henderine, corynoline, protopine and β -alloycryptopine) fifteen years ago (Fan et al., 2002). Therefore, in order to find more hepatoprotective compounds from this plant and support its traditional applications on liver disease in China, a comprehensive study was carried out, in which twenty-seven isoquinolines, including simple, protoberberine, phthalide, phenylphenanthridine, and rarely reported *N*-benzyl type isoquinolines were isolated. Their hepatoprotective activities, as well as primary structure-activity relationship were also investigated through hepatoprotective evaluations employing D-galactosamine induced L02 cells damage model.

2. Results and discussion

2.1. Structural elucidations

Compound **1** was a yellow acicular crystal obtained from MeOH. Its molecular formula was determined to be $C_{20}H_{13}NO_7$ by HRESIMS (m/z 380.0769 [M + H]⁺ (calcd for 380.0770)), demonstrating 14 degrees of unsaturation. **1** displayed signals of a 1,6,7-trisubstituted isoquinoline moiety [δ_H 7.26 (1H, s, H-5), 7.98 (1H, s, H-8), 8.33 (1H, d, $J = 5.7$ Hz, H-3), 7.80 (1H, d, $J = 5.6$ Hz, H-4)] and a 1,2,3,4-tetra-substituted phenyl group [δ_H 7.22 (1H, d, $J = 8.0$ Hz, H-2'), 6.99 (1H, d, $J = 8.0$ Hz, H-3')]. Besides, two typical methylenedioxy at δ_H 6.17 and 6.19 (each 2H, s), and one methoxy signals at δ_H 3.44 (3H, s) were also observed in the ¹H NMR spectrum. The ¹³C NMR spectrum demonstrated twenty carbon signals, including fifteen aromatic carbons, two carbonyl carbons at δ_C 195.3 and δ_C 166.8, two methylenedioxy carbons at δ_C 104.1 and 104.7, and one methoxy at δ_C 53.4, respectively. Detailed analysis on the NMR data (Table 1) indicated that **1** had

a similar structure to that of hendersine B (Yin et al., 2016). However, the presence of an extra methoxy signals (δ_H 3.44, 3H, s; δ_C 53.4) in **1** (Table 1) instead of the active hydrogen in ¹H NMR spectrum implied the methyl substitution on carboxyl group, which could be confirmed by the crosspeak from δ_H 3.44 to δ_C 166.8 in the HMBC spectrum. Therefore, the structure of **1** was determined and named as hendersine B methyl ester.

Compound **2** was a colorless acicular crystal from MeOH with $[\alpha]_D^{20} - 28.92$ (MeOH). Its molecular formula was established as $C_{21}H_{17}NO_6$ by HRESIMS at m/z 380.1130 [M + H]⁺ (calcd for 380.1134), demonstrating 13 degrees of unsaturation. Similar to **1**, the ¹H and ¹³C NMR data (Table 1) of **2** also displayed signals of a 1,6,7-trisubstituted isoquinoline moiety [δ_H 7.34 (1H, s, H-5), 7.33 (1H, s, H-8), 8.30 (1H, d, $J = 5.4$ Hz, H-3), 7.63 (1H, d, $J = 5.5$ Hz, H-4)] and a 1,2,3,4-tetra-substituted phenyl group [δ_H 6.58 (1H, d, $J = 7.9$ Hz, H-2'), 6.90 (1H, d, $J = 7.9$ Hz, H-3')]. In addition, the ¹H and ¹³C NMR spectra (Table 1) of **2** displayed signals of methyl [δ_H 1.98 (3H, s, H-10)], methoxy [δ_H 3.50 (3H, s, OCH₃-7')], oxygenated methine [δ_H 6.38 (1H, s, H-7')], and oxygenated tertiary carbon (δ_C 91.9, C-9). In the 2D NMR spectra, the key correlations between δ_H 6.38 (1H, s) and δ_C 104.3, and δ_H 3.50 (3H, s) and δ_C 55.2 in the HSQC spectrum, as well as the cross peaks from δ_H 6.38 (H-7', 1H, s) to δ_C 55.2 (OCH₃), 91.9 (C-9), 142.7 (C-1') and 142.1 (C-5'), δ_H 3.50 (OCH₃, 3H, s) to 104.3 (C-7') in the HMBC spectrum (Fig. 2) indicated that the methyl and methoxy groups were attached to C-9 and C-7', respectively. Therefore, the presence of a five-membered acetal moiety in the structure could be confirmed and the planar structure of **2** was then determined as shown in Fig. 1. In the NOESY spectrum, the correlation (Fig. 2) between δ_H 1.98 (3H, s, H-10) and δ_H 3.50 (3H, s, OCH₃-7') indicated that the relative configuration of the chiral carbons was 9 α ,7' α . Their absolute configurations were proposed by comparing the experimental circular dichroism spectrum with the ECD spectrum predicted from quantum mechanical time-dependent density functional theory (TDDFT) calculations (Li et al., 2015). The results showed that the experimental CD spectrum of **2** was in agreement with that of the calculated ECD spectrum of 9S, 7'S-isomer (Fig. 3). Therefore, the structure was finally determined and **2** was given a trivial name, (9S, 7'S) tomentelline A.

Table 1
The NMR data of **1–4**^a.

position	1		2		3		4	
	δ_C , type	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	153.7, C		157.9		159.6		158.8	
3	139.9, CH	8.33, d (5.7)	139.9	8.30, d (5.4)	140.0	8.16, d (5.5)	139.4	8.19, d (5.4)
4	125.8, CH	7.80, d (5.6)	121.4	7.63, d (5.5)	120.8	7.55, d (5.4)	120.1	7.58, d (5.4)
4a	138.4, C		136.1		136.2		134.6	
5	104.2, CH	7.26, s	103.6	7.34, s	103.5	7.35, s	106.1	7.34, s
6	153.5, C		150.0		150.0		152.2	
7	152.2, C		147.9		147.7		149.2	
8	104.1, CH	7.98, s	102.3	7.33, s	103.4	8.24, s	106.1	8.15, s
8a	125.2, C		122.9		122.5		121.4	
9	195.3, C		91.9		91.6		91.6	
10			31.6, CH ₃	1.98, s	30.4, CH ₃	1.87, s	30.4, CH ₃	1.91, s
1'	134.3, C		142.7		141.5		141.8	
2'	128.4, CH	7.22, d (8.0)	115.8	6.58, d (7.9)	118.7	6.96, d (7.9)	118	6.86, d (7.9)
3'	111.2, CH	6.99, d (8.0)	110.1	6.90, d (7.9)	109.5	7.01, d (7.9)	109.6	6.99, d (7.9)
4'	153.5, C		148.0		148.0		147.7	
5'	149.2, C		142.1		141.3		141.6	
6'	115.6, C		118.7		119.0		119.1	
7'	166.8, C		104.3, CH	6.38, s	104.0, CH	6.30, s	104.2, CH	6.32, s
7'-OCH ₃	53.4, CH ₃	3.44, s	55.2	3.50, s	55.2	3.10, s	55.2	3.18, s
6,7-OCH ₂ O-	104.1, CH ₂	6.19, s	102.3	6.15, d (11.7)	102.3	6.21, d (3.4)		
4',5'-OCH ₂ O-	104.7, CH ₂	6.17, s	102.3	6.13, s	102.1	6.08, d (6.8)	102.1	6.08, d (2.1)
6-OCH ₃							55.9, CH ₃	3.92, s
7-OCH ₃							56.1, CH ₃	3.83, s

^a **1** in acetic acid-*d*₄ 600 MHz for ¹H and 150 MHz for ¹³C; **2** in DMSO-*d*₆ 400 MHz for ¹H and 100 MHz for ¹³C; **3** and **4** in DMSO-*d*₆ 600 MHz for ¹H and 150 MHz for ¹³C.

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