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

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**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 detoxic 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.
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 antiplatelet activities. 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 (hendersonine, corydalinone, propolone and β-alloaristolochine) fifteen years ago (Fan et al., 2002). Therefore, in order to further explore 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 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 C20H13NO7 by HRESIMS (m/z 380.0769 [M + H]+ (calcd for 380.0770)), demonstrating 14 degrees of unsaturation. The NMR data of Table 1 indicated that the presence of an extra methoxy signals (δC 34.4, 3H, s; δC 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 δH 3.44 to δC 166.8 in the HMBC spectrum. Therefore, the structure of 1 was determined and named as hendersonine B methyl ester.

Compound 2 was a colorless acicular crystal from MeOH with [α]D20 − 28.92 (MeOH). Its molecular formula was established as C21H17NO6 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 [δH 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-tetrasubstituted phenyl group [δH 6.58 (1H, d, J = 7.9 Hz, H-2'), 6.90 (1H, d, J = 7.9 Hz, H-3')] and showed signals of methyl [δC 91.9, C-9]. In the 2D NMR spectra, the key correlations between δH 6.38 (1H, s) and δC 104.3, and δH 3.50 (3H, s, OCH3) were also observed in the 1H NMR spectrum. The 13C NMR spectrum demonstrated twenty carbon signals, including fifteen aromatic carbons, two carbonyl carbons at δC 195.3 and δC 166.8, two methylenedioxy carbons at δC 104.1 and 104.7, and one methoxy at δC 53.4, respectively. Detailed analysis on the NMR data of Table 1 determined that 2 had a similar structure to that of hendersonine B (Yin et al., 2016). However, the presence of an extra methoxy signals in 1H NMR spectrum implied the methyl substitution on carboxyl group, which could be confirmed by the crosspeak from δH 3.44 to δC 166.8 in the HMBC spectrum. Therefore, the structure of 1 was determined and named as hendersonine B methyl ester.
