

Rupestrines A-D, alkaloids from the aerial parts of *Corydalis rupestris*Maryam Naseri^a, Seyyed Ahmad Emami^a, Javad Asili^a, Zahra Tayarani-Najaran^a, Gholamreza Dehghan^b, Bernd Schneider^c, Mehrdad Iranshahi^{d,*}^a Department of Pharmacognosy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran^b Department of Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran^c Max-Planck-Institute for Chemical Ecology, Beutenberg Campus, Hans-Knöll-Str. 8, D-07745 Jena, Germany^d Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Phytochemical investigation of the dichloromethane extract of the dried aerial parts of *Corydalis rupestris* (Papaveraceae) resulted in the identification of four new isoquinoline alkaloids rupestrines A-D and one known isoquinoline alkaloid, namely, stylophine. The structures of these compounds were characterized by extensive spectroscopic methods including 1D- (¹H and ¹³C) and 2D NMR experiments (COSY, HSQC, HMBC, and NOESY) as well as HRESIMS analyses. In addition, the absolute configurations of rupestrines A-D were determined using modified Mosher's method. Cytotoxic effects of alkaloids and their interaction with albumin were also investigated in this study.

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1. Introduction

The genus *Corydalis* (Papaveraceae) is mainly distributed in the North Temperate Zone with highest diversity in the Sino-Himalayan area. About 280 out of 400 species of *Corydalis* are restricted to this region [1]. The genus *Corydalis* has at least 357 species in China. In Chinese traditional medicine, these species are used mainly for the treatment of dysmenorrhea, hernia, chest pains, lumbago cardiovascular and abdominal problems, headache/migraine, pain, and insomnia [2–4].

The chemical constituents of plants in the genus *Corydalis* have been studied by many groups [5]. The components typically found in this genus are alkaloids [6] of which there are mainly isoquinoline skeleton alkaloids [7]. Up to now, different types of isoquinoline alkaloids have been found in *Corydalis* species including aporphine [8–11], protoberberine [12,13], tetrahydroberberine [14,15], benzophenanthridine and phthalideisoquinoline alkaloids [16]. Currently, researches have been focused on anti-cancer, acetylcholinesterase and butyrylcholinesterase inhibitory [17], anti-platelet aggregation [18], anti-inflammatory [19], and antiviral properties of alkaloids from *Corydalis* spp. [20], together with their applications in cardiovascular diseases [21].

In an attempt to discover the chemical constituents of an endemic Iranian species of *Corydalis*, we studied the chemical constituents of *Corydalis rupestris*. This study resulted in the isolation and structural elucidation of four new isoquinoline alkaloids (rupestrines A-D) along with the known alkaloid stylophine [22]. Cytotoxic effects of alkaloids and their interaction with albumin have also been investigated in this study.

2. Results and discussion

2.1. Phytochemistry

The molecular formula (C₂₀H₁₈O₆N) of compound **1** was established by HRESIMS ([M+H]⁺, *m/z* 368.1119, calcd. 368.1134). The ¹H NMR spectrum of compound **1** showed signals of a *N*-methyl group at δ 2.53 (3H, s) and two methylenedioxy groups at δ 5.84 (2H, s) and 6.10 (2H, s). The aromatic region also exhibited four proton resonances. In the ¹H NMR spectrum, signals of two protons in *para* position, H-1 and H-4 at δ 6.40 (1H, s) and 6.67 (1H, s) and signals of two protons in *ortho* position of H-11 and H-12 at δ 6.92 (1H, d, *J* = 7.9 Hz), δ 7.12 (1H, d, *J* = 7.9 Hz) appeared. A resonance signal also appeared at δ 5.61 (1H, d, *J* = 4.0 Hz) that was attributed to H-13. Spin-spin coupling systems include aliphatic protons at δ 4.02 (H-14) and 5.61 (each 1H, d, *J* = 4.0 Hz). In the APT spectrum of compound **1**, seven resonances (CH₃ and CH, positive signals) and

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13 resonances (CH₂ and C, negative signals) totally attributable to 20 carbon atoms were observed.

In the HMBC spectrum of **1** (Fig. 2), the correlations of δ_{H} 6.40 (H-1) with δ_{C} 29.1 (C-5), 125.0 (C-14a), and 145.8 (C-2), and δ_{H} 6.67 (H-4) with δ_{C} 66.3 (C-14), 130.0 (C-4a) and 146.3 (C-3), suggested that C-1 is in *para* position to C-4. The correlations of δ_{H} 5.61 (H-13) with δ_{C} 66.3 (C-14), 125.0 (C-14a), 115.9 (C-12), 140.8 (C-12a), 110.0 (C-8a) and 167.7 (carbonyl group, C-8) indicated the position of C-13. In addition, other HMBC correlations including δ_{H} 6.92 (H-11) with δ_{C} 115.9 (C-12), 140.8 (C-12a), 144.1 (C-10), 148.9 (C-9), and δ_{H} 7.12 (H-12) with δ_{C} 82.9 (C-13), 110.0 (C-8a), 112.9 (C-11), 144.1 (C-10) and 148.9 (C-9) confirmed the structure of compound **1**. There are also correlations of δ_{H} 5.84 (H-15, O-CH₂-O) with δ_{C} 145.8 (C-2), 146.3 (C-3) and δ_{H} 6.10 (H-16, O-CH₂-O) with 144.1 (C-10) and 148.9 (C-9), that suggests the position of H-15 and H-16 in the structure of compound **1**.

The optical rotation of this compound was determined to be $[\alpha]_{\text{D}}^{25} = -120$. Thus, the structure of compound **1** was assigned as a new compound, namely, rupestrine A (Fig. 1).

The exact molecular weight of compound **2**, m/z 368.1122 was very close to that of compound **1**, m/z 368.1119. Compound **2** was also obtained as yellowish crystals, and its molecular formula C₂₀H₁₈O₆N was established by HRESIMS ($[\text{M}+\text{H}]^+$, m/z 368.1122, calcd. 368.1134). The ¹H and ¹³C NMR data of **2** were similar to those of **1** (Tables 1 and 2). The only significant difference was the chemical shift of H-12 (δ 6.16) in compound **2** as compared with that of H-12 (δ 7.12) in rupestrine A. The optical rotation of compound **2** was determined to be $[\alpha]_{\text{D}}^{25} = +150$. Therefore, we figured out that compounds **1** and **2** should be epimers with different configuration at quaternary nitrogen. The compound **2** was named rupestrine B.

The molecular formula (C₂₁H₂₂O₆N) of compound **3** was established by HRESIMS ($[\text{M}+\text{H}]^+$, m/z 384.1436, calcd. 384.1447). In contrast to rupestrines A and B, compound **3** had only one

methylenedioxy group as shown in its ¹H NMR spectrum [two resonances at δ 5.88 and 5.89 (d, $J = 1.3$ Hz)]. Different from the ¹H NMR spectrum of rupestrines A and B, the spectrum of compound **3** displayed signals of two methoxy groups at δ 3.87 and 4.04 (each 3H, s), suggesting an open ring instead of a methylenedioxy group. The aromatic region of the ¹H NMR spectrum showed four resonances, H-1 and H-4 of protons in *para* position at δ 6.36 and 6.56 (both 1H, s) and two signals, H-11 and H-12 at δ 7.07 (1H, d, $J = 8.2$ Hz) and 6.49 (1H, d, $J = 8.2$ Hz) of protons in *ortho* position. The doublet of H-13 appeared at δ 5.46 (1H, $J = 4.0$ Hz) and showed spin-spin coupling with the doublet of H-14 at δ 3.97 ($J = 4.0$ Hz). The APT spectrum showed twelve negative signals including three methylene, one carbonyl and eight quaternary carbon atoms, and nine positive resonances including three methyl and six methene groups (totally 21 carbon signals). In the HMBC spectrum of **3** (Fig. 2), the correlations of δ_{H} 6.36 (H-4) with δ_{C} 66.0 (C-14), 130.4 (C-4a), and 146.6 (C-2), and δ_{H} 6.56 (H-1) with δ_{C} 26.6 (C-5), 124.6 (C-14a) and 145.7 (C-3), suggested that C-1 is in *para* position to C-4. There are also correlations of δ_{H} 7.07 (H-11) with δ_{C} 140.6 (C-12a) and 147.8 (C-10), and δ_{H} 6.49 (H-12) with δ_{C} 83.0 (C-13), 119.6 (C-8a) and δ_{C} 152.5 (C-9), confirmed the structure. The proton resonating at δ_{H} 5.46 (H-13) is the only signal which has a correlation with δ_{C} 167.9 (carbonyl group, C-8). Thus, the structure of compound rupestrine C was determined as shown, and named rupestrine C.

The molecular formula (C₂₀H₂₀O₆N) of compound **4** was established by HRESIMS ($[\text{M}+\text{H}]^+$, m/z 370.1279, calc. for, 370.1291). Compound **4** was obtained as an optically active yellow powder. The ¹H NMR data of this compound suggested the presence of two methine groups at δ_{H} 6.26 (H-8, s, 1H) and δ_{H} 5.30 (H-13, s, 1H), the aromatic protons appeared at δ_{H} 6.83 (H-11, d, $J = 7.9$ Hz), δ_{H} 6.84 (H-12, d, $J = 7.9$ Hz), δ_{H} 6.72 (H-1, s) and δ_{H} 6.62 (H-4, s). The remaining ¹H and ¹³C NMR data of **4**, were, in part, similar to those of compounds **1–3** except for N-methyl group which

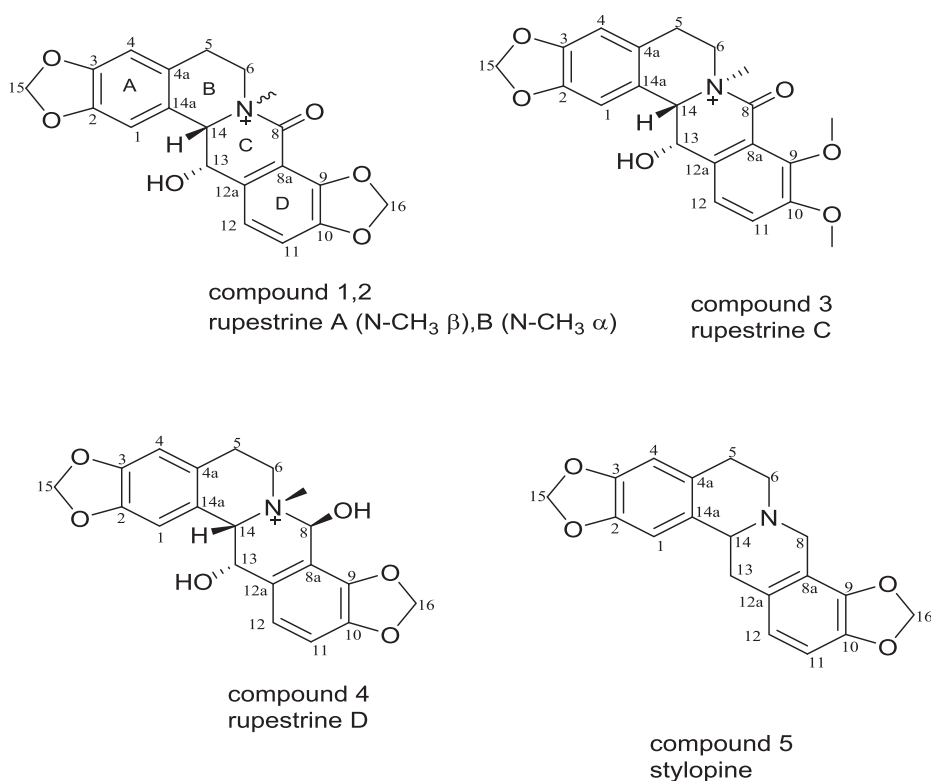


Fig. 1. The chemical structures of alkaloids from *Corydalis rupestris*.

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