SHORT REPORT

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Anti-inflammatory Diterpenoid Alkaloids from *Aconitum taipeicum*

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Abstract: Aconitaimine A, a new hetidine-type C_{20}-diterpenoid alkaloid (**1**), and three known aconitine-type C_{19}-diterpenoid alkaloids (**2-4**) were isolated from the roots of *Aconitum taipeicum*. The structures of all isolates were identified by spectroscopic methods and comparison with literature data. Compounds **1** and **2** showed inhibition of nitric oxide production in RAW 264.7 macrophages stimulated by lipopolysaccharide with IC_{50} values of 30.5 and 4.7 μM compared to positive control (dexamethasone, IC_{50} = 12.9 μM).

Keywords: *Aconitum taipeicum*; Ranunculaceae; diterpenoid alkaloids; NO inhibitory activity.

1. Plant Source

Fresh roots of *Aconitum taipeicum* Hand.-Mazz. (Ranunculaceae) were collected in the Taibai Mountains of Shaanxi Province in China (107°89′ E, 34°12′ N) in October 2018 and identified by senior experimentalist Jitao Wang, Shaanxi University of Chinese Medicine, Xianyang, P. R. China. A voucher specimen (No. 20181015) was deposited at room temperature in the Herbarium of the Natural Product Research Centre of Shaanxi University of Chinese Medicine.

2. Previous Studies

Aconitum taipeicum, commonly known as "Jin-Niu-Qi", is a perennial herb around an altitude of 2600−3400 meters in the Southern Shaanxi Province and in Western Henan Province in China, and its roots have long been used as an anti-inflammatory and analgesic drug in Chinese folk medicine [1]. This species is well known to be a rich source of diterpenoid alkaloids (DAs) with a diverse range of

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pharmacological activities [1–5], mainly focusing on analgesic, anticancer, anti-inflammatory, and cardiac effects [6].

In our previous research on this plant, aconicumines A–D, an advanced class of norditerpenoid alkaloids were isolated [5]. Further investigation on the constituents of *A. taipeicum* resulted in the isolation of one unprecedented hetidine-type C_{20}-DA (**1**) along with three previously identified aconitine-type C_{19}-DAs (**2**-**4**). Herein, the isolation, structure elucidation and nitric oxide (NO) inhibiton of these alkaloids are described.

3. Present Study

The fresh roots of *A. taipeicum* (4.0 kg) were cut and soaked with a 2% H_2SO_4 solution (3 × 25 L, 24 h each) under ambient temperature, and the H_2SO_4 aqueous solution was concentrated and extracted with EtOAc (2.0 L x 4). The acidic water-soluble materials were adjusted to pH 9–10 with NH_4OH solution and extracted with $CHCl_3$ (2.0 L x 4). The $CHCl_3$ extract (14.7 g) was fractionated by MCI gel medium pressure liquid chromatography with MeOH–H_2O (0, 50%, 100%) to afford fractions A–C. Fr.C was separated by an ODS column and eluted with MeOH–H_2O (1:1–1:0) to give six subfractions (Fr.C.1–Fr.C.6). Fr.C.6 was subjected to silica gel CC eluted with $CHCl_3$–MeOH (40:1–1:1) to give six subfractions (Fr.C.6.1–Fr.C.6.6). Fr.C.6.3 was subjected to silica gel CC eluted with petroleum ether/acetone (40:1–0:1) to give compounds **2** (8.0 mg), **3** (5.0 mg) and subfractions (Fr.C.6.3.1–Fr.C.6.3.4). Fr.C.6.3.2 was purified using preparative HPLC (ACN/H_2O, 76:24; flow rate, 7.0 mL/min) to give **1** (1.3 mg, t_R = 22.7 min). Fr.C.6.3.3 was separated by silica gel CC eluted with petroleum ether/EtOAc (40:1–1:1) to afford **4** (2.8 mg).

*Aconitaimine A (**1**)*: White powder; IR (ν_{max}): 3405, 2921, 2853, 1724, 1659, 1582, 1457, 1387, 1183, 1025 cm^{-1}; HRESIMS *m/z* 344.2587 $[M + H]^+$ (calcd for $C_{22}H_{34}NO_2$, 344.2590). ^1H (400 MHz) and ^{13}C NMR (100 MHz) data, see Table 1.

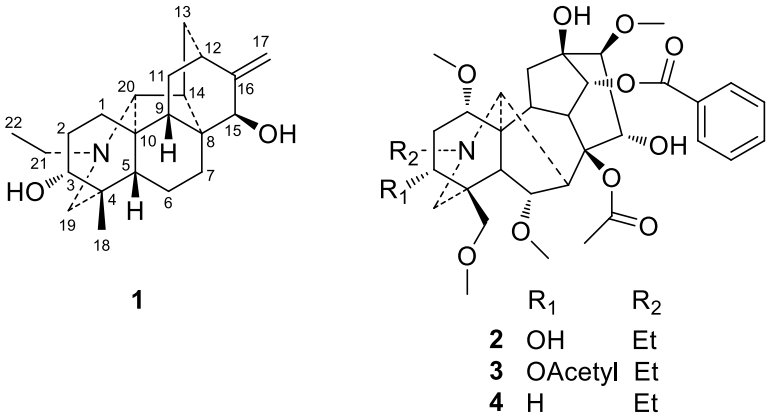

Figure 1. Chemical structures of compounds **1**−**4**

Compound **1**, a white powder, displayed a molecular formula of $C_{22}H_{33}NO_2$ as determined by positive HR-ESI-MS (*m/z* 344.2587 $[M + H]^+$, calcd. 344.2590), requiring 7 indices of hydrogen deficiency. The absorption band at 3405 cm^{-1} in the IR spectrum indicated the presence of hydroxyl group. The ^1H NMR spectrum (Table 1) exhibited signals for an *N*-ethyl side chain [δ_H 1.03 (3H, t, *J* = 7.2 Hz, H-22), 2.38 (1H, m, H-21a) and 2.62 (1H, m, H-21b)], a methyl group at δ_H 1.05 (3H, s, H-18), an isolated methylene attached to the *N*-atom [δ_H 2.45, 2.46 (2H, ABq, *J* = 12.1 Hz, H-19)], an *N*-containing methine at δ_H 2.33 (1H, br s, H-20), two *O*-containing methines [δ_H 3.21 (1H, dd, *J* = 11.3, 4.9 Hz, H-3) and 4.01 (1H, t, *J* = 2.0 Hz, H-15)], and an exocyclic double bond [δ_H 4.83, 4.93 (each 1H, br s, H-17)]. The ^{13}C NMR, DEPT, and HSQC spectroscopic data displayed 22 carbon signals (Table 1), including two methyls [δ_C 23.1 (C-18) and 12.4 (C-22)], eight methylenes [two nitrogen-

bearing at δ_C 50.6 (C-19) and 50.0 (C-21)], seven methines [two oxygenated at δ_C 77.7 (C-3) and 72.4 (C-15), one nitrogen-containing at δ_C 76.3 (C-20)], three quaternary carbons [δ_C 39.4 (C-4), 44.3 (C-8) and 44.4 (C-10)] and an exocyclic double bond [δ_C 158.3 (C-16) and 104.2 (C-17)]. The above NMR features suggested that **1** possessed a hetidine-type C_{20}-diterpenoid alkaloid carbon skeleton, similar to trabzonine, which has been previously observed from *Aconitum nasutum* (Ranunculaceae) [7]. Comparison of the ^{13}C NMR data of **1** with those of trabzonine suggested that the hydroxymethyl at C-22 (δ_C 58.9, t) in trabzonine was reduced to methyl group (δ_C 12.4, q) in **1**, which was verified by the HMBC (Figure 2) correlation from H-22 [δ_H 1.03 (3H, t, J = 7.2)] to C-21 (δ_C 50.0) and a spin system (H_2-22/H-21/N) deduced from analysis of the ^1H–^1H COSY spectrum. Another difference was that the hydroxyl group located at C-7 in trabzonine was connected to C-3 in **1**, which was confirmed by the HMBC cross-peaks of H-1, H-18 and H-19 to C-3. Thus, the planar structure of **1** was determined as shown (Figure 1).

The relative configuration of **1** was assigned on the basis of the NOESY analysis (Figure 2). The NOESY correlations of H-5 with H-1β, H-3, H-7β, H-9 and H-18 indicated that these protons were β-oriented. The cross-peaks from H-7α to H-15 and H-14 suggested these hydrogens were on the sameface. Furthermore, the correlation between H-1α and H-20 in the NOESY spectrum indicated that H-1α and H-20 possessed identical orientations. The calculated ECD curve of 3*R*,4*R*,5*S*,8*S*,9*S*,10*R*,12*R*,14*R*,15*R*,20*S*-**1** was consistent with the experimental curve (Figure 3). Therefore, the absolute configuration of **1** was assigned, and named as aconitaimine A.

Table 1. ^1H (400 MHz) and ^{13}C (100MHz) NMR data for **1** (δ in ppm, J in Hz) in $CDCl_3$

No.	δ_H	δ_C
1a	1.18 (1H, m)	31.2 (t)
1b	1.87 (1H, m)	—
2a	1.43 (1H, m)	29.1 (t)
2b	1.75 (1H, m)	—
3	3.21 (1H, dd, J = 11.3, 4.9)	77.7 (d)
4	—	39.4 (s)
5	1.02 (1H, m)	44.2 (d)
6a	1.66 (1H, m)	22.2 (t)
6b	2.21 (1H, m)	—
7a	1.43 (1H, m)	31.0 (t)
7b	1.98 (1H, m)	—
8	—	44.3 (s)
9	1.44 (1H, m)	45.2 (d)
10	—	44.4 (s)
11a	1.56 (1H, m)	29.3 (t)
11b	1.85 (1H, m)	—
12	2.20 (1H, m)	34.7 (d)
13a	1.57 (1H, m)	36.6 (t)
13b	1.78 (1H, m)	—
14	1.65 (1H, m)	50.1 (d)
15	4.01 (1H, t, J = 2.0)	72.4 (d)
16	—	158.3 (s)
17a	4.83 (1H, br s)	104.2 (t)
17b	4.93 (1H, br s)	—
18	1.05 (3H, s)	23.1 (q)
19	2.45, 2.46 (2H, ABq, J = 12.1)	50.6 (t)
20	2.33 (1H, br, s)	76.3 (d)
21a	2.38 (1H, m)	50.0 (t)
21b	2.62 (1H, m)	—
22	1.03 (3H, t, J = 7.2)	12.4 (q)

Recorded in $CDCl_3$. Assignments were based on DEPT, ^1H–^1H COSY, HSQC, and HMBC experiments.

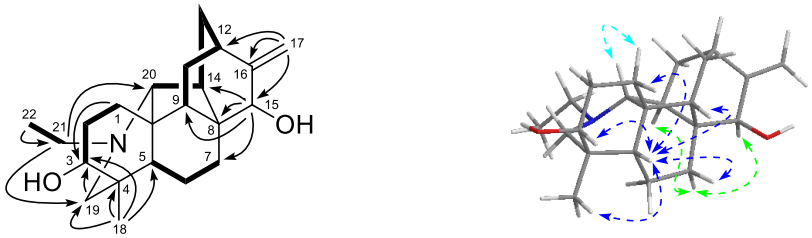

Figure 2. Key ^{1}H–^{1}H COSY (—), HMBC (⟶), and NOESY (⇢) correlations of **1**

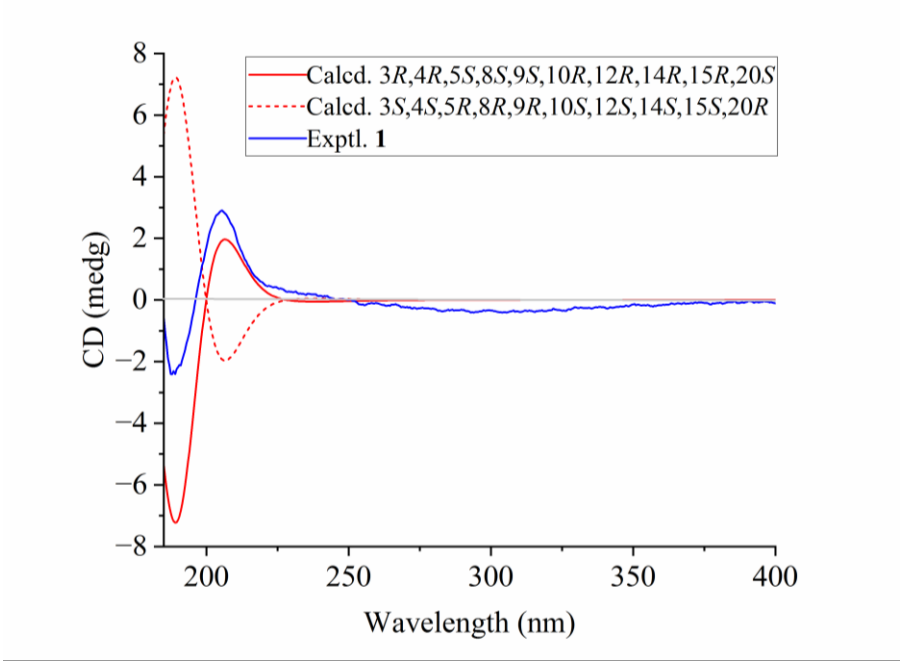

Figure 3. Experimental and calculated ECD spectra of **1**

Three known aconitine-type C_{19}-DAs (**2**-**4**) (Figure 1) were also isolated and identified as aconitine (**2**) [8], 3-acetylaconitine (**3**) [8] and 3-deoxyaconitine (**4**) [9] by comparison of their physical and spectroscopic data with those reported in the literature.

Considering the folkloric uses of *A. taipeicum*, the primary anti-inflammatory activities of compounds **1**-**4** were evaluated by inhibition of NO production in RAW 264.7 macrophages induced by LPS. Cell culture, Griess and MTT procedures, and data analysis for the inhibition of NO production were the same as in the previous protocol [5]. The results showed that compounds **1** and **2** potentially inhibited NO production with IC_{50} values of 30.5 and 4.7 μM compared to positive control (dexamethasone, IC_{50} = 12.9 μM), while others showed no obvious activities (IC_{50} > 50.0 μM). All isolates were non-cytotoxic to RAW 264.7 macrophages at the tested concentrations.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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