HETEROCYCLES, Vol. 106, No. 6, 2023, pp. -. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 9th March, 2023, Accepted, 17th April, 2023, Published online, 26th April, 2023
DOI: 10.3987/COM-23-14846

NEW C_{19}-DITERPENOID ALKALOIDS FROM *ACONITUM NOVOLURIDUM*

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Abstract – Four new C_{19}-diterpenoid alkaloids novolunines D–F (**1**–**3**) and 8-*O*-ethylbrevicanine C (**4**), were isolated from the root of *Aconitum novoluridum*. The structures of four new alkaloids were established on the basis of spectra data (HR-ESI-MS, 1D- and 2D-NMR). The anti-inflammatory activity of isolated alkaloids was also carried out.

The *Aconitum* genus plants are known to contain a number of norditerpenoid and diterpenoid alkaloids.[1] Pharmacological studies have shown that alkaloids in *Aconitum* not only have rich and diverse structures, but also have a wide range of biological activities, such as analgesic, anti-inflammatory, insecticidal, anti-arrhythmia.[1] *Aconitum novoluridum* (Ranunculaceae) is a perennial herb distributed in Tibet, India, Nepal, Sikkim, Bhutan and other regions.[2] In a previously published article, nineteen diterpenoid alkaloids were isolated from *Aconitum novoluridum*.[3] However, the diterpenoid alkaloids and their bioactivities have not been studied in detail yet, which prompted us to undertake a systematic study of this plant. Our continued studies on the roots of *A. novoluridum* have resulted in the isolation of four new diterpenoid alkaloids, which were identified as novolunines D–F (**1**–**3**), 8-*O*-ethylbrevicanine C (**4**) (Figure 1). In addition, three known ones were isolated and identified as scaconine (**5**),[4] 8-*O*-ethylscaconine (**6**)[5] and 14-*O*-acetyl-8-*O*-methyl-18-*O*-2-(2-metyl-4-oxo-4*H*-quinazolin-3-yl)benzoylcammaconine (**7**).[6] Herein, we report the isolation and structural elucidation of these compounds, as well as their cytotoxicity and inhibitory effect on NO production of RAW264.7 cells induced by LPS.

Compound **1** was obtained as a white amorphous powder and gave a positive reaction to Dragendorff's

reagent. Its molecular formula was determined as $C_{40}H_{51}N_3O_8$ by analysis of its HR-ESI-MS spectrum (*m/z* 702.3770 $[M+H]^+$, calcd for $C_{40}H_{51}N_3O_8$ 702.3754). The NMR spectra displayed signals of an *N*-ethyl group (δ_H 1.18, t, 3H, J = 7.2 Hz; δ_C 49.1 t, 11.4 q), and three methoxy groups (δ_H 3.25, 3.27, 3.32, each 3H; δ_C 55.8, 56.1, 57.5). Furthermore, the signals [δ_H 8.57 (1H, d, J = 8.0 Hz), 7.56 (1H, t, J = 8.0 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.97 (1H, d, J = 7.2 Hz), 7.13 (1H, t, J = 8.0 Hz), 7.44 (1H, t, J = 8.0 Hz), 7.76 (1H, d, J = 8.0 Hz), 8.69 (1H, d, J = 8.0 Hz); δ_C 140.9, 115.3, 130.7, 123.0, 134.7, 120.5, 120.2, 140.0, 121.3, 132.8, 123.3, 126.9], two amide groups [δ_H 11.87 (1H, s), 11.10 (1H, s); δ_C 167.5, 168.7], a methyl group [δ_H 2.15 (3H, s), δ_C 25.1], and a carbonyl group (δ_C 168.0), indicated the presence of a 2-(2'-acetamide-benzoylamide)benzoyloxy moiety. It was supported by the HMBC correlations between H-6′ (δ_H 8.69) and C-7′ (δ_C 168.0)/C-2′ (δ_C 115.3), H-3′ (δ_H 7.97) and C-7′ (δ_C 168.0)/C-2′ (δ_C 115.3), 1′-*N*H (δ_H 11.87) and C-2′ (δ_C 115.3)/C-6′ (δ_C 120.5), *N*H*CO*C_6H_4 (δ_C 167.5) and 1′-*N*H (δ_H 11.87)/H-6″ (δ_H 7.76), 2″-*N*H (δ_H 11.10) and C-3″ (δ_C 121.3)/*N*H*CO*Me (δ_C 168.7), H-8″ (2.15) and *N*H*CO*Me (δ_C 168.7). Further analysis of the ^{13}C NMR, DEPT and HMQC data of **1** revealed that the unassigned carbon signals could be attributed to three quaternary carbons, seven methylenes and nine methines, these features suggested that **1** consists of a C_{19} diterpenoid alkaloid.[8] Three methoxy groups were located at C-1, C-14 and C-16, respectively, on the basis of the HMBC correlations from 1-OMe (δ_H 3.32, s) to C-1 (δ_C 83.7), 14-OMe (δ_H 3.25, s) to C-14 (δ_C 82.1, d), 16-OMe (δ_H 3.27) to C-16 (δ_C 82.2). In HMBC spectrum, H-18 (δ_H 4.09, 3.95, each 1H, m) was correlated with C-7' (δ_C 168.0), so it was assumed that 2-(2'-acetamide-benzoylamide)benzoyloxy moiety was attached to C-18. In addition, five oxygen-bearing carbon signals were observed in ^{13}C NMR spectrum, apart from the above four ones, one hydroxyl group was considered to exist. In the HMBC spectrum, the correlations from H-7 (δ_H 2.08, m), H-14 (δ_H 3.11, m), H-15 (δ_H 2.00, m) to C-8 suggested that the hydroxyl group was installed at C-8. The stereochemistry of compound **1** was deduced from the NOESY experiment, the correlations between H-1 and H-10β, H-10β and H-14, H-16 and H-13α in the NOESY experiment (Figure 3), 16-OMe was β-oriented, 1-OMe and 14-OMe were α-oriented. Thus, the structure of **1** was determined as shown in Figure 1, and named novolunine D.

Compound **2** was obtained as a white amorphous powder, and its molecular formula was determined as $C_{37}H_{41}N_3O_8$ by analysis of its HR-ESI-MS spectrum (*m/z* 656.2956 $[M + H]^+$, calcd for $C_{37}H_{41}N_3O_8$ 656.2972). The NMR spectra displayed signals of two methoxy groups (δ_H 3.22, 3.37, each 3H; δ_C 56.1, 56.8), and one 2-(2-methyl-4-oxoquinazolin-3-yl)benzoate moiety[7] [δ_H 7.51 (1H, t, J = 6.8 Hz), 7.73 (1H, d, J = 8.0 Hz), 7.29 (1H, t, J = 6.4 Hz), 8.22 (1H, d, J = 8.0 Hz), 8.29 (1H, d, J = 8.0 Hz), 7.64 (1H, t, J = 8.0 Hz), 7.75 (1H, m), 7.79 (1H, d, J = 8.0 Hz), 2.25 (3H, s)]. The NMR data for **2** was similar to those for piepunensine A,[9] except that the methoxy group at C-18 of piepunensine A was replaced by a 2-(2-methyl-4-oxoquinazolin-3-yl)benzoate moiety in **2**, which was supported by the HMBC correlations between H-18 (δ_H 4.69, 4.40, d, J = 12.0 Hz) and C-7' (δ_C 164.5). Two methoxy groups were located at C-1, and C-16,

respectively, on the basis of the HMBC correlations from 1-OMe (δ_H 3.22) to C-1 (δ_C 83.9), 16-OMe (δ_H 3.37) to C-16 (δ_C 82.0). Thus, the structure of **2** was determined as novolunine E (Figure 1), and the full assignment of its spectroscopic data was achieved based on 1D- and 2D-NMR analyses.

Compound **3** was obtained as a white amorphous powder with a molecular formula of $C_{37}H_{41}N_3O_7$ based on its HR-ESI-MS data. The characteristic NMR data of **3** strongly suggested it to be a C_{19}-diterpenoid alkaloid[8] possessing two methoxy groups (δ_H 3.20, 3.37, each 3H; δ_C 56.2, 56.7) and a 2-(2-methyl-4-oxo-quinazolin-3-yl)benzoate moiety[7] [δ_H 7.51(1H, t, *J* = 8.0Hz), 7.73 (1H, m), 7.31 (1H, t, *J* = 8.0Hz), 8.23 (1H, d, *J* = 8.0Hz), 8.26 (1H, d, *J* = 8.0Hz), 7.65 (1H, t, *J* = 8.0Hz), 7.78 (1H, m), 7.81 (1H, m), 2.24 (3H, s)]. Distinctive allylic signals at δ_H 7.29 (1H, brs) and δ_C 163.2 confirmed the presence of an imino group. The NMR data for **3** was similar to those for novolunine C,[3] except that the *O*-acetamidobenzoate moiety at C-18 of novolunine C was replaced by a 2-(2-methyl-4-oxoquinazolin-3-yl)benzoate moiety in **3**, and the methoxy group at H-14 of novolunine C had been replaced by a hydroxyl group in **3**, which were further supported by the HMBC correlations. The correlations between H-1 and H-10, H-16 and H-17, H-10 and H-14 in the NOESY spectrum indicated that 1-OMe was α-oriented, 16-OMe was β-oriented, and 14-OH was α-oriented. Thus, the structure of **3** was determined and it was named novolunine E (Figure 2).

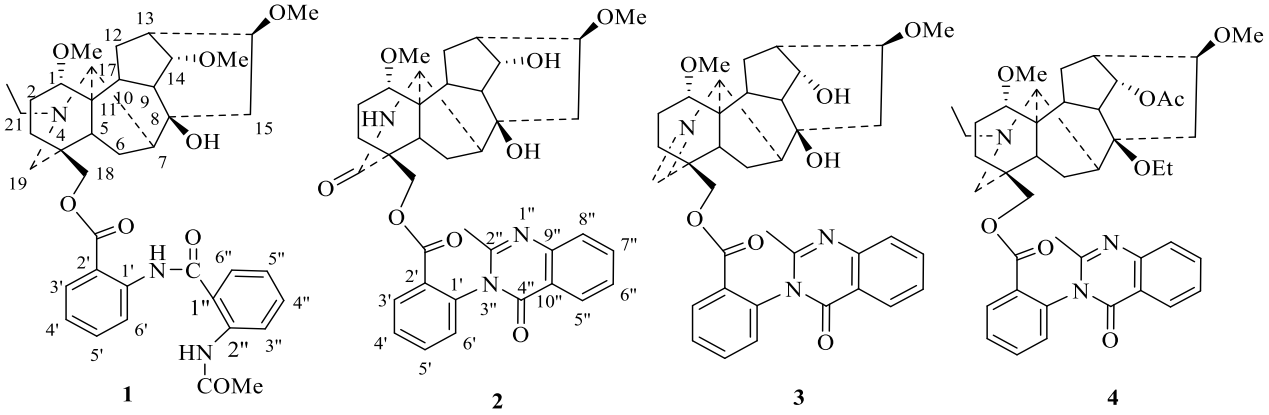

Figure 1. Structures of compounds **1-4**

Its molecular formula of **4** was determined as $C_{43}H_{53}N_3O_8$ by analysis of its HR-ESI-MS data (*m/z* 740.3933 $[M+H]^+$, calcd for $C_{43}H_{53}N_3O_8$ 740.3911). The characteristic NMR data of **4** suggested it to be a C_{19}-diterpenoid alkaloid[8] possessing to one *N*-ethyl group, an acetyl group, an ethoxy group, two methoxy groups and a 2-(2-methyl-4-oxoquinazolin-3-yl)benzoate moiety. Two methoxy groups were located at C-1, and C-16, respectively, on the basis of the HMBC correlations from 1-OMe (δ_H 3.24) to C-1 (δ_C 85.1), 16-OMe (δ_H 3.32) to C-16 (δ_C 83.4). Comparing compound **4** with the known compound brevicanine C,[7] the C-8 signal changed from δ_C 73.6 to δ_C 84.1, it was inferred that the hydroxyl group of brevicanine C had been replaced by the ethoxy group of compound **4**. The acetyl group should be located at C-14

according to the HMBC correlation between H-14 (δ_H 4.73) and the carbonyl of the acetyl group (δ_C 171.4). The correlations between H-1 and H-9, H-16 and H-17, H-10 and H-14 in the NOESY spectrum, indicated that 1-OMe was α-oriented, 16-OMe was β-oriented, 14-OAc was α-oriented. Thus, the structure of **4** was determined and it was named 8-*O*-ethylbrevicanine C (Figure 2).

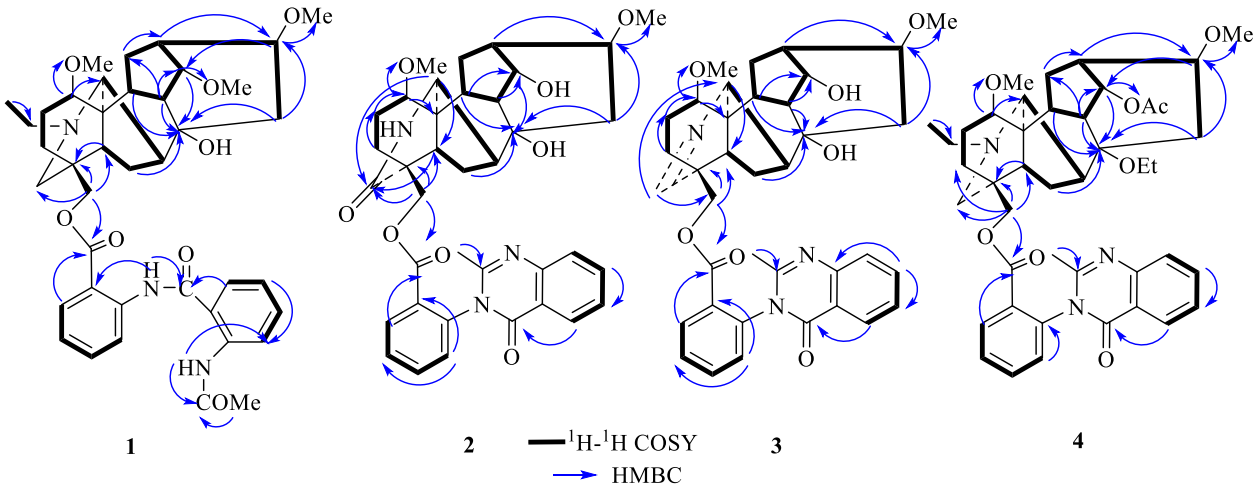

Figure 2. Key HMBC and ^{1}H-^{1}H COSY correlations for compounds **1**–**4**

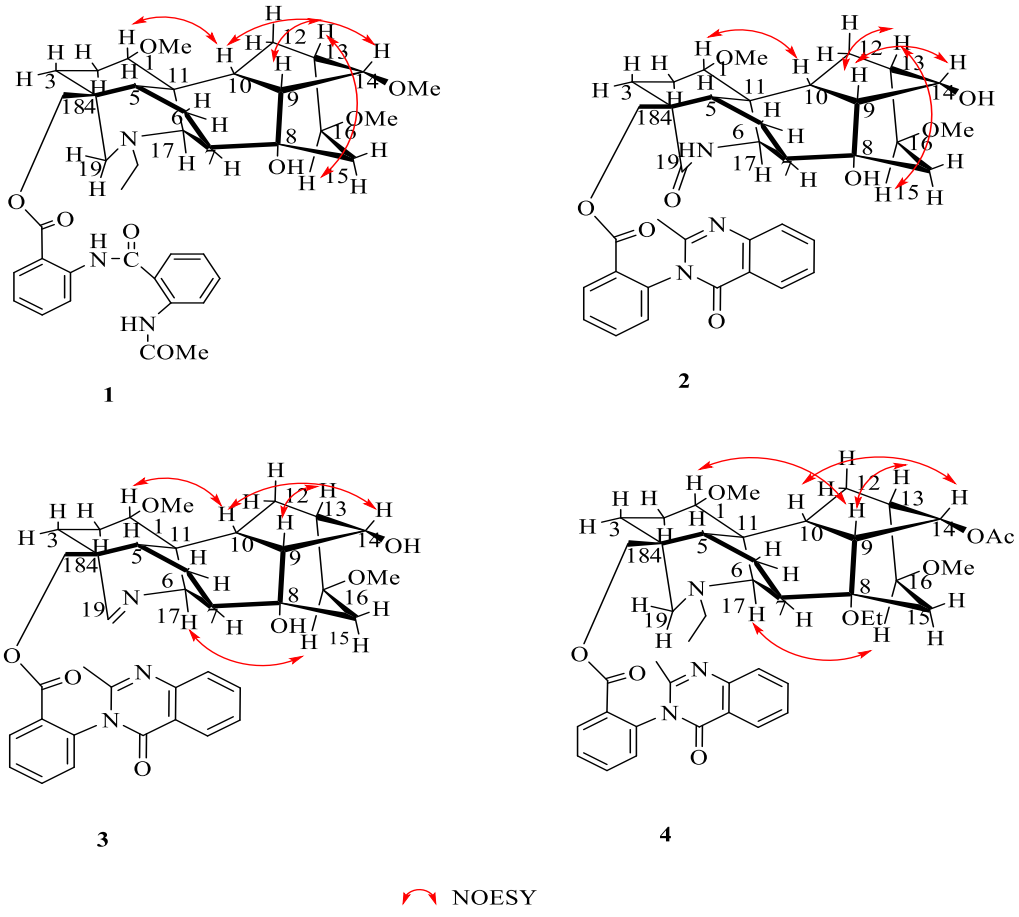

Figure 3. Key NOESY correlations of compounds **1-4**

Table 1. ^{1}H- and ^{13}C-NMR data (400 and 100 MHz) of compounds **1** - **4**

No.	**1** in $CDCl_3$		**2** in $CDCl_3$		**3** in $CDCl_3$		**4** in $CDCl_3$	
	δ_C	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	83.7 d	3.63 t (4.4)	83.9 d	3.02 m	84.4 d	3.00 m	85.1 d	2.96 m
2	24.9 t	2.19 m, 2.23 m	26.2 t	1.45 m, 1.95 m	25.4 t	1.56 m, 1.86 m	26.2 t	1.18 m, 1.74 m
3	27.7 t	1.57 m, 1.63 m	30.1 t	1.34 m, 1.78 m	27.2 t	1.60 m, 1.81 m	32.3 t	1.26 m, 1.57 m
4	37.3 s	-	50.8 s	-	47.6 s	-	37.5 s	-
5	42.4 d	1.74 m	37.1 d	2.45 m	42.5 d	1.49 m	45.5 d	1.41 m
6	23.3 t	1.66 m, 1.75 m	26.7 t	1.61 m, 1.80 m	25.8 t	1.35 m, 1.86 m	24.0 t	1.18 m, 1.74 m
7	45.2 d	2.08 m	54.9 d	2.02 m	52.4 d	2.10 m	40.9 d	2.27 m
8	73.8 s	-	71.5 s	-	72.3 s	-	84.9 s	-
9	44.2 d	1.90 m	45.5 d	2.15 m	46.2 d	2.00 m	44.8 d	1.71 m
10	36.6 d	2.36 m	45.3 d	1.76 m	46.2 d	1.62 m	38.2 d	2.34 m
11	49.1 s	-	47.2 s	-	49.8 s	-	48.9 s	-
12	29.2 t	1.90 m, 1.79 m	27.0 t	1.94 m, 2.02 m	29.5 t	1.70 m, 1.86 m	28.9 t	1.81 m, 2.36 m
13	45.4 d	2.21 m	42.9 d	1.61 m	37.4 d	2.43 m	43.0 d	2.29 m
14	82.1 d	3.11 m	75.2 d	4.21 t (4.8)	75.5 d	4.14 m	75.7 d	4.73 m
15	41.6 t	1.95 m, 2.00 m	36.6 t	2.08 m, 2.31 m	37.6 t	2.10 m, 2.41 m	36.2 t	1.99 m, 2.08 m
16	82.2 d	3.29 m	82.0 d	3.46 m	82.1 d	3.48 m	83.4 d	3.20 m
17	61.7 d	3.09 s	56.4 d	3.59 s	62.7 d	4.14 s	61.3 d	2.75 s
18	70.1 t	3.95 m, 4.09 m	66.9 t	4.40 d (12.0) 4.69 d (12.0)	68.0 t	4.27 m, 4.29m	71.1 t	3.88 m, 3.93 m
19	53.3 t	2.35 m, 3.11 m	173.3 s	-	163.2 d	7.29 brs	52.4 t	1.88 m, 2.41 m
21	49.1 t	2.77 m, 2.91 m	-	-	-	-	49.1 t	2.34 m, 2.42 m
22	11.4 q	1.18 t (7.2)	-	-	-	-	13.4 q	1.03 t (7.2)
1-OMe	57.5 q	3.32 s	56.1 q	3.22 s	56.2 q	3.20 s	56.3 q	3.32 s
14-OMe	56.1q	3.27 s	-	-	-	-	-	-
16-OMe	55.8 q	3.25 s	56.8q	3.37s	56.7 q	3.37 s	56.3q	3.24 s
8-OEt	-	-	-	-	-	-	55.6 t	3.27 m, 3.29 m
	-	-	-	-	-	-	16.3 q	1.08 t (6.8)
14-OAc	-	-	-	-	-	-	171.4 s	-
	-	-	-	-	-	-	21.4 q	2.02 s
18-OCO	168.0 s	-	164.5 s	-	164.8 s	-	164.7 s	-
1′	140.9 s	-	137.7 s	-	137.8 s	-	137.7 s	-
2′	115.3 s	-	128.8 s	-	128.4 s	-	128.5 s	-
3′	130.7 d	7.97 d (7.2)	132.5 d	8.22 d (8.0)	132.5 d	8.23 d (8.0)	132.4 d	8.21 m
4′	123.0 d	7.13 t (8.0)	129.8 d	7.29 t (6.4)	129.9 d	7.31 t (8.0)	129.7 d	7.28 m
5′	134.7 d	7.56 t (8.0)	129.8 d	7.64 t (8.0)	130.1 d	7.65 t (8.0)	129.9 d	7.64 t (8.0)
6′	120.5 d	8.69 d (8.0)	134.2 d	7.75 m	134.4 d	7.78 m	134.7 d	7.78 m
1′-*N*H	-	11.87 s	-	-	-	-	-	-
*N*H*CO*C_6H_4	167.5 s	-	-	-	-	-	-	-
1″	120.2 s	-	-	-	-	-	-	-
2″	140.0 s	-	154.2 s	-	154.0 s	-	153.9 s	-
3″	121.3 d	8.57 d (8.0)	-	-	-	-	-	-
4″	132.8 d	7.44 t (8.0)	162.3 s	-	162.2 s	-	162.1 s	-
5″	123.3 d	7.15 t (8.0)	127.2 d	8.29 d (8.0)	127.1 d	8.26 d (8.0)	127.0 d	8.26 d (8.0)
6″	126.9 d	7.76 d (8.0)	126.9 d	7.51 t (6.8)	126.9 d	7.51 t (8.0)	126.6 d	7.48 t (8.0)
7″	-	-	134.8 d	7.79 d (8.0)	134.9 d	7.81 m	134.1 d	7.71 d (8.0)
8″	25.1 q	2.15 s	127.2 d	7.73 d (8.0)	127.1 d	7.73 m	127.0 d	7.73 m
9″	-	-	147.7 s	-	147.7 s	-	147.6 s	-
10″	-	-	120.9 s	-	120.9 s	-	120.8 s	-
2″-Me	-	-	24.3 q	2.25 s	24.3 q	2.24 s	24.1 q	2.23 s
2″-*N*H	-	11.10 s	-	-	-	-	-	-
*N*H*CO*Me	168.7 s	-	-	-	-	-	-	-

Compounds **1–7** were evaluated for their inhibitory activities against LPS–induced NO production in RAW 264.7 cell line by Griess method,[3] celecoxib (30 μM) as positive control. However, none of them showed obviously inhibitory activities.

General experimental procedures.

Optical rotations were recorded on a Perkin–Elmer 341 polarimeter. UV spectra were collected on a Persee TU-1905 spectrometer. 1D- and 2D- NMR spectra were measured by a Bruker AV 400 NMR spectrometer. HR–ESIMS were carried out on a Q–TOF micro mass spectrometer (Waters, USA). Silica gel (Qingdao Haiyang Chemical Co., Ltd., China, 200–300 mesh) were used for column chromatography (CC). The TLC plates were precoated with silica gel GF_{254} (Qingdao Haiyang Chemical Co., Ltd., China).

Plant Material

Aconitum novoluridum were collected in Linzhi City, Tibet Autonomous Region, China, in July 2019, and were identified by Prof. LiangKe Song of Yunnan University of Traditional Chinese Medicine. A voucher specimen (Swjtu-novol-201907) was deposited in the School of Life Science and Engineering, Southwest Jiaotong University.

Extraction and isolation

Dried and powder roots of *A. novoluridum* (30 kg) were extracted with 95% EtOH five times at room temperature, with each soaking process lasting seven days. Evaporation of the solvent under reduced pressure provided a 95% EtOH extract. The extract was treated with 0.5 N hydrochloric acid (2 L) and successively extracted with light petroleum (4 × 2 L) and EtOAc (4 × 2 L) to remove non-alkaloid constituents. Then, 28% aqueous ammonia solution (2 L) was added to the acidic solution to adjust to pH 10. The solutions were extracted with CH_2Cl_2 (5 × 3 L) to afford the alkaloids (198 g). The crude alkaloids were chromatographed over silica gel column eluted with CH_2Cl_2–MeOH (200:1-0:1) gradient system to give six fractions A-F. Fraction C was chromatographed on a silica gel column eluted with petroleum ether-EtOAc-diethylamine (30:1:1%-1:1:1%) to give fractions C_1-C_8. Fraction C_1 was chromatographed on a silica gel column eluted with petroleum ether-EtOAc-diethylamine (60:1:1%-10:1:1%) to afford compound **1** (15 mg). Fraction C_2 was chromatographed on a silica gel column eluted with petroleum ether-CH_2Cl_2-diethylamine (60:1:1%-20:1:1%) to afford compound **5** (28 mg) and compound **6** (8 mg). Fraction C_3 was chromatographed on a silica gel column eluted with petroleum ether-diethylamine (40:1-20:1) to afford compound **7** (12 mg). Fraction C_4 was chromatographed on a silica gel column elutied with petroleum ether-EtOAc-diethylamine (40:1:1%-20:1:1%) to give six fractions $C_{4\text{-}1}$-$C_{4\text{-}6}$; fraction $C_{4\text{-}3}$ was chromatographed on a silica gel column eluted with petroleum ether-CH_2Cl_2-diethylamine (30:1:1%-10:1:1%) to afford compound **4** (16 mg). Fraction D was chromatographed on a silica gel column eluted

with petroleum ether-CH_2Cl_2-diethylamine (120:1:1%-10:1:1%) to give fractions D_1-D_3. Fraction D_3 was chromatographed on a silica gel column eluted with petroleum ether-CH_2Cl_2-diethylamine (30:1:1%-1:1:1%) to afford compound **2** (12 mg) and compound **3** (21 mg).

Inhibitory activity of NO production

RAW 264.7 cells were cultured in the growth medium containing DMEM high sugar medium at 37 ℃ in humidified 5% CO_2/95% air. The cytotoxicity of the compound to RAW 264.7 was evaluated by MTT test.[3] The ability of RAW 264.7 macrophages to inhibit LPS-induced NO production was measured with Griess method.[3] RAW 264.7 cells (2 per well×10^4 cells) were incubated in 96 well plates for 12 h, pretreated with medicated medium for 2 h, then added with LPS, and incubated in the incubator for 24 h. Absorb 50 μL of the supernatant, and then add it into Griess reagent kit in turn for mixing. The absorbance was measured at 562 nm by enzyme immunoassay. With Celecoxib as the positive control, calculate the inhibitory effect of the compound on NO production.

Novolunine D (1)

White amorphous powder; $[\alpha]_D^{25}$ +1.6 (*c* 0.45, MeOH); UV (MeOH) λ_{max} (log ε): 259 (3.87), 298 (3.33) nm; HR-ESI-MS (*m/z*): 702.3770 $[M+H]^+$ (calcd for $C_{40}H_{51}N_3O_8^+$, 702.3754); see Table 1.

Novolunine E (2)

White amorphous powder; $[\alpha]_D^{25}$ -5.0 (*c* 0.45, MeOH); UV (MeOH) λ_{max} (log ε): 258 (3.88), 298 (3.38) nm; HR-ESI-MS (*m/z*): 656.2956 $[M+H]^+$ (calcd for $C_{37}H_{41}N_3O_8^+$, 656.2972); see Table 1.

Novolunine F (3)

White amorphous powder; $[\alpha]_D^{25}$ -5.1 (*c* 0.45, MeOH); UV (MeOH) λ_{max} (log ε): 258 (3.88), 298 (3.38) nm; HR-ESI-MS (*m/z*): 640.3026 $[M+H]^+$ (calcd for $C_{37}H_{41}N_3O_7^+$, 640.3023); see Table 1.

8-O-ethylbrevicanine C (4)

White amorphous powder; $[\alpha]_D^{25}$ +5.7 (*c* 0.45, MeOH); UV (MeOH) λ_{max} (log ε): 259 (3.86), 298 (3.38) nm; HR-ESI-MS (*m/z*): 740.3933 $[M+H]^+$ (calcd for $C_{43}H_{53}N_3O_8^+$, 740.3911); see Table 1.

SUPPLEMENTARY DATA

NMR spectra for compounds **1** – **4** were available in the Supporting Information.

Supplementary (UV, ^1H and ^{13}C NMR, HR-MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27918/106/6.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (82073734).

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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