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DITERPENOID ALKALOIDS FROM *ACONITUM LEUCOSTOMUM* AND THEIR ANTIFEEDANT ACTIVITY

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Abstract – Two new diterpenoid alkaloids and eight known ones were isolated from the root of *Aconitum leucostomum*. Their structures were elucidated on the basis of extensive spectroscopic analyses such as HR-ESI-MS, 1D NMR and 2D NMR spectra. Compounds **1**, **2**, **5**, **6** and **8** were tested for their antifeedant activity against *Spodoptera exigua* Hübner, and compound **2** showed antifeedant activity with an effective concentration for 50% feeding reduction (EC_{50}) at 1.54 mg/cm^2.

Aconitum (Ranunculaceae) is a large genus comprising 400 species, and about 76 *Aconitum* species in China are used as folk medicines, which are mainly used for the treatment of rheumatoid arthritis and various types of pains.[1] *Aconitum leucostomum* Worosch grows at altitudes 1400-2550 meters and distributes in the Gansu and Xinjiang Provinces of China, which is belonging to the *Aconitum* genus.[2] *Aconitum leucostomum* Worosch has been used as folk medicines in Kazak, which has the functions of dispelling wind and dehumidifying, reducing swelling and relieving pain.[3] The isolation of thirty-seven diterpenoid alkaloids from this plant had been reported, including twenty-two C_{18} diterpenoid alkaloids,[1,2,4] eight C_{19} diterpenoid alkaloids[1,5] and seven C_{20} diterpenoid alkaloids.[1,6] Our further chemical investigation of this plant led to the isolation of two new diterpenoid alkaloids, leucostosine A (**1**) and leucostosine B (**2**), together with eight known ones, chasmaconitine (**3**), songoramine (**4**), 14-acetyl-8-methyltalatisamine (**5**), brochyponine A (**6**), cammaconine (**7**), delphicrispuline (**8**), pseudaconine (**9**) and delphatine (**10**). The antifeeding activities of compounds **1**, **2**, **5**, **6** and **8** against the larvae of *Spodoptera exigua* Hübner were tested by choice of leaf-disc method. In this paper, we report the isolation, structure elucidation and antifeedant activities of these alkaloids.

Compound **1** was isolated as a white amorphous powder and gave a positive reaction to *Dragendorff's* reagent. Its molecular formula was determined as $C_{22}H_{35}NO_4$ [*m/z* 378.2643 $(M + H)^+$, calcd. for

$C_{22}H_{35}NO_4$, 378.2639]. The IR spectrum indicated the presence of hydroxyl groups (3446 cm^{-1}). The ^{1}H-NMR, ^{13}C-NMR and DEPT spectra of **1** (Table 1) showed characteristic signals for an *N*-ethyl group [δ_H 1.13 (3H, t, J = 7.2 Hz), δ_C 48.6 (t) and 12.9 (q)], and two methoxy groups [δ_H 3.35 (3H, s), 3.41 (3H, s), δ_C 56.3 (q), 57.8 (q)]. Besides the signal of an *N*-ethyl group and two methoxy groups in the ^{13}C-NMR spectrum, there were 18 carbons remained which including two quaternary carbons [δ_C 48.2 (s), 75.2 (s)], ten methenyl [δ_C 33.2 (d), 37.2 (d), 40.2 (d), 43.7 (d), 45.2 (d), 45.8 (d), 63.9 (d), 72.4 (d), 83.0 (d), 85.1 (d)] and six methylene [δ_C 23.6 (t), 28.9 (t), 29.8 (t), 30.0 (t), 43.1 (t), 54.2 (t)], consistent with the molecular formula of $C_{22}H_{35}NO_4$. These data indicated that **1** was a lappaconitine-type C_{18}-diterpenoid.[7] In the HMBC spectrum, two methoxy groups [δ_H 3.35 (3H, s), 3.41 (3H, s)] had long-range correlations between C-16 [δ_C 83.0 (d)] and C-14 [δ_C 85.1 (d)], so the two methoxy groups were assigned to C-14 and C-16. The 1-OH was assigned an α-position based on the signal of H-1 [δ_H 3.76 (1H, brs)] and the resonance of C-1 [δ_C 72.4 (d)] in the NMR spectra.[8] The stereo-configuration of compound **1** was further confirmed by analysis of the coupling constants and NOESY spectrum. The coupling constant of H-14 [δ_H 3.73, t, J = 4.4 Hz] and the correlation of H-10β/H-14 in NOESY indicated that the methoxy group at C-14 was assigned an α-position.[8] The correlation of H-16/H-17 and the coupling constant of H-16 [δ_H 3.29, t, J = 8.0 Hz] showed that the 16-OMe was β-position.[8] Therefore, the structure of compound **1** was determined as shown in Figure 1, named as leucostosine A.

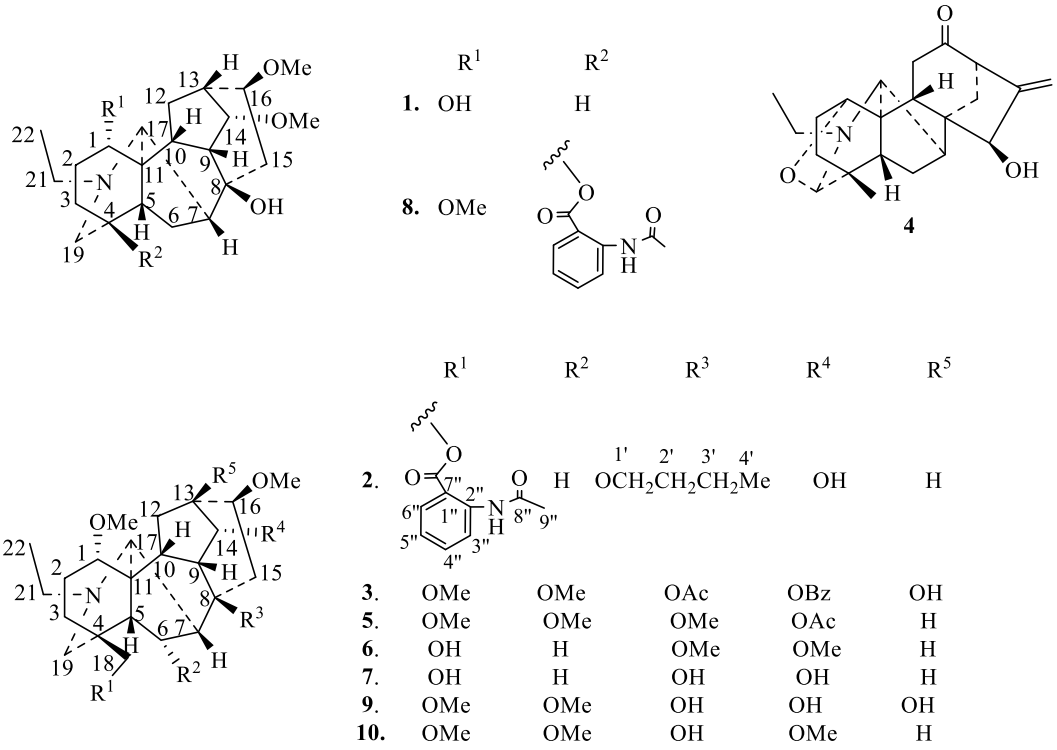

Figure 1. Structures of compounds **1-10**

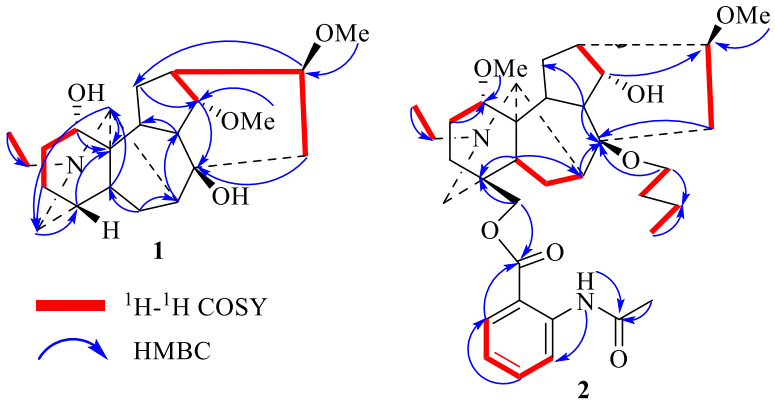

Figure 2. Key HMBC and ^{1}H-^{1}H COSY correlations of compounds **1**, **2**

Compound **2** was isolated as a white amorphous powder and gave a positive reaction to *Dragendorff's* reagent. Its molecular formula was determined as $C_{36}H_{52}N_2O_7$ [*m/z* 625.3840 $(M + H)^+$, calcd. for $C_{36}H_{52}N_2O_7$, 625.3847]. The IR data indicated the presence of hydroxyl group (3449 cm^{-1}), an aromatic ring (1586, 1523 and 1445 cm^{-1}) and an *ortho*-disubstituted benzene (754 cm^{-1}). The NMR data (Table 1) revealed the presence of *N*-ethyl group [δ_H 1.03 (3H, t, *J* = 6.8 Hz), δ_C 49.4 (t), 13.7 (q)], two methoxy groups [δ_H 3.22 (3H, s), 3.30 (3H, s), δ_C 56.5 (q), 56.5 (q)], a butoxy group [δ_H 0.83 (3H, t, *J* = 7.6 Hz), 1.26 (2H, t, *J* = 6.8 Hz), δ_C 14.1 (q), 19.7 (t), 32.6 (t), 60.4 (t)], an *ortho*-disubstituted benzene [δ_H 8.63 (1H, d, *J* = 8.4 Hz), 7.49 (1H, t, *J* = 6.8 Hz), 7.03 (1H, t, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 9.6 Hz), δ_C 114.9 (s), 141.8 (s), 120.6 (d), 134.9 (d), 122.6 (d), 130.6 (d)], an *N*H [δ_H 10.90 (1H, s)] and an acetyl group [δ_H 2.17 (3H, s), δ_C 25.6 (q), 169.2 (s)]. The presence of *ortho*-disubstituted benzene, *N*H, and acetyl group indicated that compound **2** has an *o*-acetamidobenzoate moiety (-OCOC_6H_4-*o*-NHAc). The NMR data showed that compound **2** was an aconitine-type diterpenoid alkaloid.[9] Comparison of the NMR data of **2** with those of known compound talassicmine A, indicated that the oxyethyl group at C-8 was replaced by a butoxy group.[9] In the HMBC, two methoxy groups [δ_H 3.22 (3H, s), 3.30 (3H, s)] were located at C-1 [δ_C 85.6 (d)] and C-16 [δ_C 82.6 (d)], the butoxy group H-1' [δ_H 3.24 (2H, d, *J* = 5.6 Hz)] showed long-range correlation with C-8 [δ_C 78.0 (s)], the *o*-acetamidobenzoate moiety located at C-18 based on the H-18 [δ_H 3.98 (2H, ABq, *J* = 10.8 Hz)] had correlations with C-7" [δ_C 168.4 (s)], and the *N*H [δ_H 10.90 (1H, s)] with C-8" [δ_C 169.2 (s)] and C-3" [δ_C 120.6 (d)]. The 1-OMe was assigned an α-position, which was confirmed by the NOE correlations of H-1/H-5β and H-1/H-10β. The hydroxyl at C-14 was α-position based on the correlation of H-10β/H-14. The NOE correlation of H-16/H-17 suggested that the 16-OMe was β-position. Thus, the structure of compound **2** was determined as shown in Figure 1, named as leucostosine B, and the full assignment of its spectroscopic data was achieved based on 1D and 2D NMR analyses.

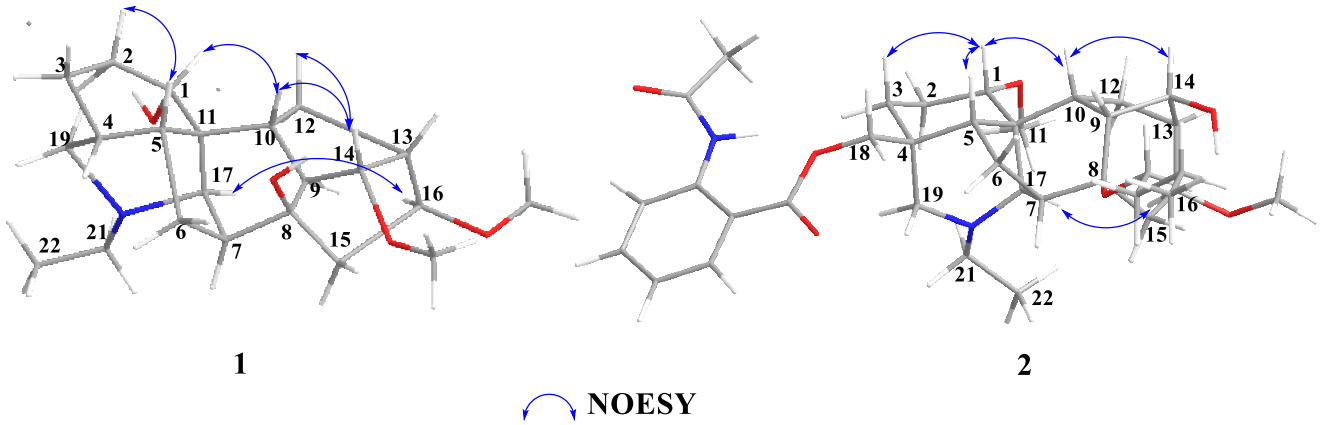

Figure 3. Key NOESY correlations of compounds **1**, **2**

Eight known compounds, chasmaconitine (**3**),[10] songoramine (**4**),[11] 14-acetyl-8-methyltalatisamine (**5**),[12] brochyponine A (**6**),[13] cammaconine (**7**),[9] delphicrispuline (**8**),[14] pseudaconine (**9**)[15] and delphatine (**10**)[16] were first time isolated from *Aconitum leucostomum* Worosch.

Compounds **1**, **2**, **5**, **6** and **8** were tested for their antifeedant activity against *S. exigua* (Hübner) Linne using aconitine (EC_{50} values of 0.03 mg/cm^2) as a positive control by choice of leaf-disc method.[17] The results showed that compound **2** showed strongest antifeedant activity with a low EC_{50} (1.54 mg/cm^2), compounds **5**, **6** and **8** showed low antifeedant activity (EC_{50} values of 8.89, 4.69, 5.24 mg/cm^2), compound **1** showed weak activity (EC_{50} values of 19.77 mg/cm^2).

Table 1. ^{1}H and ^{13}C NMR Spectroscopic Data for Compounds **1**, **2** [a]

No.	**1** [b]			**2** [b]		
	δ_H	δ_C	HMBC(H→C)	δ_H	δ_C	HMBC(H→C)
1	3.76 br.s	72.4 d	C-3, C-10, C-11	3.07 m	85.6 d	1-OMe
2	1.62 *	29.8 t	C-1	1.99 *, 2.23 m	26.1 t	C-1, C-3
3	1.62 *, 1.89 *	23.6 t	C-1, C-19	1.40 *, 1.80 *	32.9 t	C-5
4	1.89 *	33.2 d	C-11	—	38.2 s	
5	2.06 m	40.2 d	C-17	1.65 d (6.8)	46.4 d	C-4, C-7, C-17, C-18, C-19
6	1.47 m, 2.03 m	28.9 t	C-8, C-5, C-7, C-11	1.35 d (6.8), 1.90 m	24.2 t	C-4, C-5
7	2.17 *	45.2 d	C-5, C-9, C-17	2.35 *	40.8 d	C-5, C-8, C-11, C-17
8	—	75.2 s		—	78.0 s	
9	2.17 *	45.8 d	C-7, C-10	1.77 m	45.5 d	C-8, C-12
10	1.89 *	43.7 d	C-8	2.28 m	38.9 d	C-9
11	—	48.2 s		—	49.0 s	
12	1.99 m	30.0 t	C-14	1.80 *, 1.99 *	28.9 t	C-9, C-16
13	2.45 m	37.2 d		2.15 m	45.9 d	C-14, C-16

14	3.73 t (4.4)	85.1 d	C-8, C-13, 14-OMe	3.93 m	75.2 d	C-8, C-16
15	1.96 m, 2.25 m	43.1 t	C-8, C-13, C-16	1.99 *, 2.07 *	34.6 t	C-7, C-8
16	3.29 t (8.0)	83.0 d	C-12, C-14, 16-OMe	3.27 m	82.6 d	C-14, 16-OMe
17	2.76 s	63.9 d	C-5, C-8, C-11, C-19,	2.96 s	62.4 d	C-5, C-6, C-19, C-21
18	—	—		3.98 ABq (10.8)	71.0 t	C-3, C-4, C-5, C-19 C-7"
19	2.45 *, 2.52 *	54.2 t	C-4, C-5, C-17	2.56 m, 2.07 *	52.8 t	
21	2.45 *, 2.52 *	48.6 t		2.48 m, 2.35 *	49.4 t	
22	1.13 t (7.2)	12.9 q	C-21	1.03 t (6.8)	13.7 q	C-21
1-OMe	—	—		3.22 s	56.5 q	C-1
1'	—	—		3.24 d (5.6)	60.4 t	C-2', C-3', C-8
2'	—	—		1.40 m	32.6 t	C-1', C-3', C-4'
3'	—	—		1.26 d (6.8)	19.7 t	C-1', C-2', C-4'
4'	—	—		0.83 t (7.6)	14.1 q	C-2', C-3'
14-OMe	3.41 s	57.8 q	C-14	—	—	
16-OMe	3.35 s	56.3 q	C-16	3.30 s	56.5 q	C-16
1"	—	—		—	114.9 s	
2"	—	—		—	141.8 s	
3"	—	—		8.63 d (8.4)	120.6 d	C-1", C-2", C-5"
4"	—	—		7.49 t (6.8)	134.9 d	C-2", C-6",
5"	—	—		7.03 t (8.0)	122.6 d	C-1", C-3", C-4", C-6"
6"	—	—		7.90 d (9.6)	130.6 d	C-2", C-4", C-7"
7"	—	—		—	168.4 s	
8"	—	—		—	169.2 s	
9"	—	—		2.17 s	25.6 q	C-8"
*N*H	—	—		10.90 s	—	C-3", C-8"

a. Data are based on DEPT, ^{1}H-^{1}H COSY, HMQC and HMBC experiments. Spectra were recorded in $CDCl_3$.
b. ^{1}H NMR (400 MHz, $CDCl_3$, δ, J in Hz in parentheses), ^{13}C NMR (100 MHz, $CDCl_3$, δ).
* Means overlapped.

EXPERIMENTAL

General experimental procedure. The chromatographic (CC) stationary phases were diatomite (Qingdao Ocean Chemical Co., Ltd.), silica gel (200-300 mesh, 100-200 mesh, 60-80 mesh) and alumina (100-200 mesh, Qingdao Ocean Chemical Co., Ltd.). The mobile phase of the chromatography (CC) was petroleum ether (PE), ethyl acetate (EA), acetone, diethylamine (DEA), CH_2Cl_2 and MeOH. TLC plates (Qingdao Haiyang Chemical Co., Ltd., China). TLC has the same mobile phase as chromatography (CC).

It can be observed under 254 nm or 365 nm UV lamps or spray the diterpene alkaloid exclusive color reagent *Dragendorff's* reagent or iodine. HR-ESI-MS was measured by Q-TOF micromass spectrometer (Waters, USA). Measurements of optical rotation with a Perkin-Elmer 341 polarimeter. The 1D and 2D NMR spectra of the compounds were measured by Brucker AVANCE DRX-400 NMR spectrometer (TMS). IR spectra on a FT-IR, BRUKER Tensor II spectrometer (KBr discs, cm^{-1}).

Plant Material.

A. leucostomum were collected in Nileke county, Xinjiang Uygur Autonomous Region of China, in August 2019, and were identified by Prof. Qing-Er Yang of the Institute of Botany, Chinese Academy of Sciences. A voucher specimen (C. Ren & L. Wang 735) was deposited in the School of Life Science and Engineering, Southwest Jiaotong University.

Extraction and Isolation. The roots of *Aconitum leucostomum* plant (600 kg) were dried and crushed and soaked in 95% EtOH at room temperature for 3 times (3 days each time). After removal of EtOH under reduced pressure, make it dissolved in 2% HCl solution. The acidic solution, after extraction with EtOAc, was made alkaline with concentrated NaOH, adjusted to pH 11, and then extracted with EtOAc. Then, the EtOAc was removed by reduced pressure concentration to obtain the crude alkaloid (3 kg).

The crude alkaloid (3 kg) was subjected to column chromatography on diatomite in a gradient manner PE/EA (10:1 to 1:1, *v*/*v*) to afford four fractions: S_{1-1} to S_{1-4} based on TLC analyses. S_{1-1} was subjected to CC on silica gel eluted in a gradient manner PE/CH_2Cl_2/MeOH (10:1:0.1 to 1:1:0.4, *v*/*v*/*v*) to afford six fractions: S_{2-1} to S_{2-6} based on TLC analyses. S_{2-1} was subjected to CC on silica gel eluted in a gradient manner PE/EA/DEA (35:1:0.1 to 1:1:0.2, *v*/*v*/*v*) to afford four fractions: A to D based on TLC analyses. B was subjected to CC on silica gel eluted in a gradient manner PE/CH_2Cl_2/MeOH (12:4:0.2 to 4:4:0.2, *v*/*v*/*v*) to afford four fractions: B_1 to B_4 based on TLC analyses. B_2 was subjected to CC on silica gel eluted in PE/CH_2Cl_2/DEA (100:3:0.4, *v*/*v*/*v*) to obtain compound **10** (10 mg).

C was subjected to CC on silica gel eluted in a gradient manner PE/EA/DEA (20:1:0.1 to 1:1:0.1, *v*/*v*/*v*) to afford two fractions: C_1 to C_2 based on TLC analyses. C_2 was subjected to CC on silica gel eluted in PE/DEA (150:1 to 20:1, *v*/*v*) to afford five fractions: C_{2-1} to C_{2-5} based on TLC analyses. C_{2-2} was subjected to CC on silica gel eluted in CH_2Cl_2/MeOH (200:1 to 10:1, *v*/*v*) to afford five fractions: C_{2-2-1} to C_{2-2-5} based on TLC analyses. C_{2-2-5} was subjected to CC on silica gel eluted in PE/acetone/DEA (25:1:0.02, *v*/*v*/*v*) to obtain compound **1** (26 mg). C_{2-2-3} was subjected to CC on silica gel eluted in CH_2Cl_2/MeOH (150:1 to 10:1, *v*/*v*) to obtain compound **2** (37 mg). C_{2-2-2} was subjected to CC on silica gel eluted in PE/CH_2Cl_2/MeOH (5:5:0.1, *v*/*v*/*v*) to obtain compound **8** (18 mg). C_{2-3} was subjected to CC on silica gel eluted in CH_2Cl_2/MeOH (300:1 to 10:1, *v*/*v*) to afford two fractions: C_{2-3-1} to C_{2-3-2} based on TLC analyses. C_{2-3-1} was subjected to CC on silica gel eluted in PE/acetone/DEA (30:1:0.1 to 25:1:0.1, *v*/*v*/*v*) to obtain compounds **4** (16 mg) and **5** (10 mg). C_{2-3-2} was subjected to CC on silica gel eluted in

PE/CH_2Cl_2/DEA (60:1:0.1 to 50:1:0.1, *v*/*v*/*v*) to obtain compounds **3** (28 mg) and **6** (12 mg). $C_{2\text{-}4}$ was subjected to CC on silica gel eluted in CH_2Cl_2/MeOH (200:1 to 10:1, *v*/*v*) to afford five fractions: $C_{2\text{-}4\text{-}1}$ to $C_{2\text{-}3\text{-}5}$ based on TLC analyses. $C_{2\text{-}4\text{-}2}$ was subjected to CC on silica gel eluted in PE/CH_2Cl_2/MeOH (150:1:0.1, *v*/*v*/*v*) to obtain compound **9** (11 mg). $C_{2\text{-}4\text{-}5}$ was subjected to CC on silica gel eluted in PE/CH_2Cl_2/DEA (100:3:0.5 to 80:3:0.5, *v*/*v*/*v*) to obtain compound **7** (373 mg).

Leucostosine A (1)

White amorphous powder; $[\alpha]_D^{25}$: -0.2 (c 0.66, $CHCl_3$); HR-ESI-MS *m/z* 378.2643 $[M + H]^+$ (calcd. for $C_{22}H_{35}NO_4$, 378.2639); ^1H and ^{13}C NMR data see Table 1. IR (KBr) ν_{max}: 3446, 2926, 1642, 1458, 1398, 1229, 1213, 1093, 965 cm^{-1}.

Leucostosine B (2)

White amorphous powder; $[\alpha]_D^{25}$: +1.4 (c 0.73, $CHCl_3$); HR-ESI-MS *m/z* 625.3840 $[M + H]^+$ (calcd. for $C_{36}H_{52}N_2O_7$, 625.3847); ^1H and ^{13}C NMR data see Table 1. IR (KBr) ν_{max}: 3449, 2933, 1688, 1586, 1523, 1445, 1386, 1258, 1083, 754 cm^{-1}.

Antifeedant activity

The antifeedant activity of the compounds were tested by the choice of leaf-disc method. The tested compounds and positive control were dissolved with acetone to 10 mg/mL and diluted to 5, 2.5, 1.25, 0.613 mg/mL. Cut the fresh cabbage leaves into plates 5 cm in diameter and treated with emulsion of 15 μL test substance or deionized water containing acetone and Tween-20 as control. Air dry all the leaves. Under the conditions of temperature 27 ± 1 ºC, relative humidity 70%-80% and photoperiod of 14:10 h (L:D), the *Spodoptera exigua* (Hübner) colony (Henan Jiyuan Baiyun Industry Co., Ltd.) was reared until third-instar. The third-instar larvae with uniform body, robust were selected for the test. Two leaves from the treatment and control groups were placed in each petri dish (15 cm in diameter). Each dish was put in four healthy larvae that had been starved for 6 h. This was repeated three times. After 24 h, the feeding area was measured by square paper method. The food reduction (%FR) was calculated by the following formula: %FR = (CK-T)/CK × 100 (CK is the control leaf disc area eaten and T is the treated leaf disc area eaten). Compounds with %FR > 50% were tested in a dose-response experiment to calculate their relative potency (EC_{50}) by linear regression analysis (%FR of the logarithmic concentration).

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SUPPLEMENTARY DATA

Key ^{1}H-^{1}H COSY, HMBC and NOESY correlations, and 1D and 2D NMR spectra of compounds **1** and **2** are available in the Supporting Information.

CONFLICT OF INTEREST REFERENCES

All the authors have no conflict of interest to declare.

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