HETEROCYCLES, Vol. 102, No. 12, 2021, pp. -. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 24th August, 2021, Accepted, 17th September, 2021, Published online, 4th October, 2021
DOI: 10.3987/COM-21-14544

SEMI-SYNTHETIC CHASMANTHININE ANALOGUES WITH ANTIFEEDANT EFFECTS AGAINST *SPODOPTERA EXIGUA*

Ziyu Song,[1‡] Ke Xu,[1‡] Jing Li,[2] Yayun Xie,[1] Xiang Li,[1] Shuai Huang,[1] Feng Gao,[1] Lin Chen,[1,2]* and Xianli Zhou[1]*

[1] School of Life Science and Engineering, Southwest Jiaotong University, Chengdu 610031, Sichuan, P.R. China. [2] Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, School of Chemistry and Chemical Engineering, China West Normal University, Nanchong, 637002, Sichuan, P.R. China.
***** Corresponding Author: Phone +86-28-887603201; E-mail: linch@swjtu.edu.cn; zhouxl@swjtu.edu.cn. [‡] These authors contributed equally to this work and should be considered co-first authors.

Abstract – The synthesis and structure modification of active natural lead compounds is an important approach for the discovery of novel green pesticides. Nineteen derivatives of chasmanthinine, a natural C_{19}-diterpenoid alkaloids, were prepared, and their structures were unambiguously determined by ^{1}H NMR, ^{13}C NMR, and HR-ESI-MS. Moreover, the antifeedant activities of title compounds were evaluated against larvae of *Spodoptera exigua* (Hübner). The results illustrated that compounds **p** with a thienyl group at the C-14 position (EC_{50} = 0.10 mg/cm^2) showed the strongest antifeedant activities among all tested compounds. This present study is the first report on the antifeedant effects of synthetic chasmanthinine analogs aganist *S. exigua* (Hübner) larvae.

INTRODUCTION

There are about 0.16 million species of Lepidoptera, which is the largest group of plant-feeding insects.[1] The widely distributed pest, *Spodoptera exigua* (Hübner) (Lepidoptera: Noctuidae) is a polyphagous agricultural pest that feeds on cotton, ornamental plants, and vegetables and so on, causing harm for economy.[2] Lepidopteran pests such as *S. exigua* were generally controlled by using chemical pesticides, such as pyrethroids, organophosphates, carbamates, endosulfan, and diamides.[3] However, it is reported that due to insecticide resistance, many insecticides failed to control *S. exigua* (Hübner).[4] Therefore, the development of potential alternatives to control insect pests effectively and selectively is urgent. Plant

original bio-pesticide has received much attention because of their reduced persistence in the environment and lessened threats to humans and non-target organisms.[5]

The extract of genus *Delphinium* and *Aconitum*, well-known poisonous herb grown widely in China, has been used as an insecticide for a long time.[6] From 1980s, methyllycaconitine, a typical diterpenoid alkaloid of the genus *Delphinium*, was found to exhibit insecticide activity and a high affinity for the insect cholinergic receptor, [7] these compounds has raised considerable attention in agricultural chemistry in recent years because of its complicated structure and interesting biological activities. Actually, tons of natural or synthetic diterpenoid alkaloids showed important biological activities, such as anti-inflammatory, inhibiting acetylcholinesterase, cytotoxic properties, analgesic, anti-arrhythmia, anti-tumor, insecticidal and antifeedant activities.[8] In our previous work, we found that chasmanthinine (**Figure 1**), a typical C_{19}-diterpenoid alkaloid which was isolated from *Aconitum franchetii* var. *villosulum*, showed effective antifeedant activity against larvae of *S. exigua* (Hübner). Furthermore, the comprehensive analysis of structural features and activities indicated that esterification of HO-8 and/or HO-14 in a C_{19}-diterpenoid alkaloid would enhance the antifeedant activity. [9] Based upon the above results, and to discover natural product-based pesticides, herein we first designed and synthesized a series of chasmanthinine derivatives with characteristic hydroxyl at C-8 and different ester substituents at C-14. Their antifeedant and insecticidal activities were also evaluated against the typically crop-threatening pests, larvae of *S. exigua*.

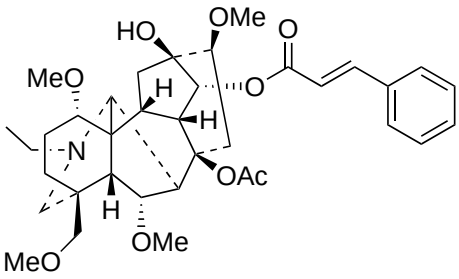


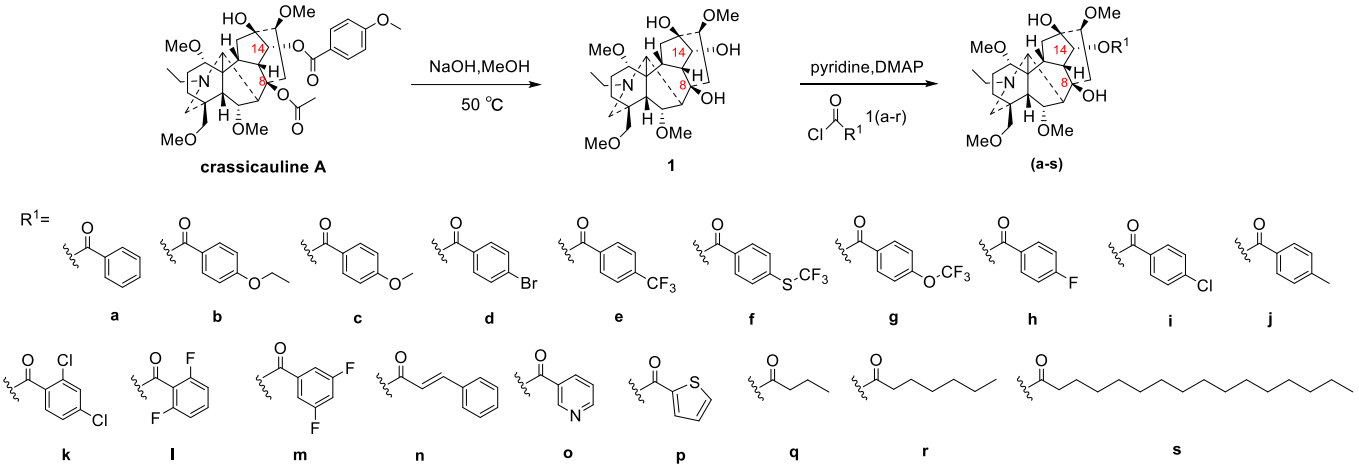
Figure 1. Structure of chasmanthinine

RESULTS AND DISCUSSION

Chemistry. Nineteen chasmanthinine derivatives, including fourteen substituted benzoyl (**a**~**n**), two heterocyclic (**o** and **p**) and three long chain fatty acyl ester derivatives (**q**, **r** and **s**), were successfully prepared in two steps as shown in Scheme 1. Intermediate compound **1** was obtained from crassicauline **A** by hydrolysis reaction as described previously,[10] and the structure was elucidated by comparison with data reported in the literature.[11] The target compounds were obtained by esterification reaction of intermediate **1** with different acyl chlorides in 14%~77% yields. Pyridine was used as acid binding agent. The secondary alcohol (at C-14) hydroxyl group of intermediate **1** is relatively active than tertiary alcohol (at C-8 and C-13) hydroxyl groups in esterification reaction. Therefore, when preparing the target compounds, the reaction conditions, such as the rate of adding acid chloride, the reaction temperature, and the reaction time should be strictly controlled to ensure the occurrence of the reaction and increase the yield.

All the title compounds were identified by ^{1}H NMR, ^{13}C NMR, DEPT and HR-ESI-MS. The spectral data of compounds **a**~**s** were given in the supplemental material. In the ^{13}C NMR spectra of the title compounds

a~s, the typical ester carbonyl signal at 174~162 ppm and oxygenated quaternary carbons resonances at 76 and 73 ppm strongly indicated that the ester group was located at C-14 and the appearance of hydroxyl groups at C-8 and C-13.[12] This conclusion was also supported by the molecular masses difference between the title compounds and intermediate **1**.



Scheme 1. Synthetic route to the title compounds

Antifeedant activities of the target compounds a~s.

In this study, all chasmanthinine derivatives were screened for their antifeedant activities against *S. exigua*, and the preliminary screening results were outlined in Table 1. Generally, the monoester compound **p** with thiophenecarbonyl at the C-14 position (FR = 93.6%) showed the strongest antifeedant activities in all tested compounds when the dosage was 5 mmol/L. Compounds **f**, **g**, **h**, **k**, **l**, **m**, **n**, **q**, **r**, and **s** (FR > 70%) showed moderate antifeedant activity, while antifeedant effect of compounds **b** (containing *p*-ethoxybenzoyl) and **o** (containing a nicotinoyl) were negligible.

For *para*-benzoyl derivatives explored various electron-donating and electron-withdrawing substituents based around commercially available benzoyl chloride. An electron-donating substituent in the 4-position, such as an ethoxy, methoxy or methyl group, showed only moderate to weak activity (**b**, **c**, and **j**). By contrast, electron-withdrawing groups were required for good activity (i.e., **e**, **f**, **g**, and **h**). Notably, compound **h** (*p*-fluorobezoyl, FR (food reduction) = 81.2%) showed the best activity among these compounds, which indicted incorporation of fluorine at the phenyl ring was feasible. However, only the effect of 2,6-difluoro and 3,5-difluorobenzoyl derivative were evaluated for synthesis reason. Compound **m** (3,5-difluoro, FR = 92.5%) showed better activity while compound **l** (2,6-difluoro, FR = 70.7%) was lower than compound **h**. In order to enrich the structure of the target compound, two heterocyclic compounds (**n** and **o**) and three long chain fatty acyl derivatives (**q**, **r** and **s**) were synthesized. Antifeedant assays indicated that compound **p** exhibited excellent activity (FR = 93.6%) while compound **o** shows weak activity (FR = 31.1%). Compounds **q**, **r** and **s** exhibited moderate antifeedant activity (FR = 75.3, 72.7, 70.2%, respectively).

Table 1. The antifeedant activity of title compounds against *S. exigua* larvae (at 5 mmol/L, n = 12)

Comp.	R	FR (%)	Comp.	R	FR (%)
a	benzoyl	64.1	**l**	2,6-difluorobenzoyl	70.7
b	*p*-ethoxybenzoyl	43.6	**m**	3,5-difluorobenzoyl	92.5
c	*p*-methoxybenzoyl	58.5	**n**	cinnamoyl	72.1
d	*p*-bromobenzoyl	58.7	**o**	nicotinoyl	31.1
e	*p*-trifluoromethylbenzoyl	65.6	**p**	thiophenecarbonyl	93.6
f	*p*-trifluoromethylthiobenzoyl	76.5	**q**	butyryl	75.3
g	*p*-trifluoromethoxybenzoyl	80.4	**r**	heptanoyl	72.7
h	*p* -fluorobenzoyl	81.2	**s**	octadecanoyl	70.2
i	*p* -chlorobenzoyl	53.2	**CHA**[a]	—	96.2
j	*p* -methylbenzoyl	61.5	**AZA**[a]	—	100
k	2,4-dichlorobenzoyl	76.4			

[a] CHA: chasmanthinine; AZA: azadirachtin A, used as positive control.

To further investigate the potential antifeedant activities, we selected some compounds like **g**, **h**, **m**, and **p** (FR > 80%) to have further exploration in such a situation, and compared the values of EC_{50} with chasmanthinine and azadirachtin A at different concentrations. The antifeedant activities expressed as EC_{50} values for highly potential compounds are listed in Table 2. The results indicated that low insecticidal activity than chasmanthinine though the activities of compounds **m** and **p** were almost close to it. These results suggested that **p** would be the lead compound for further investigation precursor. Esterification is a commonly used drug design method.[13] Our previous research also shows that esterification and/or etherification of HO-8 and/or HO-14 in a C_{19}-diterpenoid alkaloid enhance the antifeedant activity.[9] However, the compounds synthesized in this study unfortunately does not exceed the activity of chasmanthinine. We speculate that this may be related to the substituents at C-8, which can be further modified to obtain compounds with higher activity. The antifeedant mechanism of DAs also needs to be further explored.

Table 2. EC_{50} Values of title compounds against *S. exigua* (Hübner)

Comp.	Antifeedant regression equation	EC_{50} (95% CI) (mg cm^{-2})	r	Comp.	Antifeedant regression equation	EC_{50} (95% CI) (mg cm^{-2})	r
g	y=0.92x+2.86	0.22 (0.11-0.42)	0.9858	**p**	y=0.49x+4.01	0.10 (0.06-0.18)	0.9904
h	y=0.84x+3.06	0.21 (0.13-0.32)	0.9935	**CHA**[a]	y=1.17x+3.62	0.07 (0.03-0.18)	0.9787
m	y=0.60x+3.78	0.11 (0.08-0.15)	0.9968	**AZA**[a]	y=0.86x+4.45	0.02(0.01-0.07)	0.9954

[a] CHA: chasmanthinine; AZA: azadirachtin A

EXPERIMENTAL

General information

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV 400 nuclear magnetic resonance instrument (400 MHz). Chemical shifts were recorded in parts per million (ppm) relative to tetramethyl silane as the internal standard. Thin-layer chromatography silica gel GF254 and column chromatography silica gel G and H (200~400 mesh) were produced by Qingdao Ocean Chemical Plant. HRMS (ESI) were carried out on a Q-TOF micro mass spectrometer (Waters, USA). Unless otherwise specified, the reagents and solvents used in this article are all commercially available analytical or chemical grades and used directly without any purification.

Synthetic Procedures

General Synthetic Procedure for the Intermediate Compound 1. Crassicauline **A** (95% purity, Wuhan yuancheng technology development Co., Ltd.) 402 mg (0.62 mmol) was dissolved in a solution of 5% NaOH/MeOH (20 mL). The reaction solution was stirred at 50 °C for 30 min. After cooling down to room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in H_2O (15 mL) and extracted with DCM (15 mL × 3). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the intermediate **1** as a white amorphous powder in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (d, J = 6.8 Hz, 1H), 3.96 (d, J = 4.5 Hz, 1H), 3.66 (d, J = 8.5 Hz, 1H), 2.38 (brs, 3H), 3.28-3.26 (m, 6H), 3.20 (brs, 3H), 2.99-2.94 (m, 1H), 1.05 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.0, 84.6, 82.4, 80.7, 79.6, 77.2, 72.6, 62.7, 59.3, 57.7, 57.3, 56.3, 53.7, 52.3, 50.6, 50.2 (2C), 49.4, 42.3, 39.6, 39.5, 35.9, 35.2, 25.9, 13.8. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{42}NO_7$: 468.2961, found: 468.2973.

General Synthetic Procedure for Compounds a to s. Intermediate **1** (0.5 mmol) and 4-dimethylaminopyridine (DMAP, 0.5 mmol) were dissolved in pyridine, and the corresponding acyl chloride (1.5 mmol) was slowly added dropwise to the solution while stirring at room temperature. After continuing stirring for 8-12 h at room temperature, and the reaction was monitored by TLC. At the end of the reaction, the mixture was treated with aq. $NaHCO_3$ solution (10%, 10 mL) to adjust the pH to 10. The products were extracted with DCM (5 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, and evaporated to give compounds **a~s** after purification by column chromatography over silica gel (petroleum ether-acetone = 50:1-15:1).

Compound a. pale yellow amorphous powder, yield 14%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 6.0 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 5.17 (d, J = 5.0 Hz, 1H), 4.04 (d, J = 6.8 Hz, 1H), 3.66 (d, J = 8.4 Hz, 1H), 3.38 (s, 3H), 3.29 (s, 3H), 3.27 (s, 3H), 3.26 (s, 3H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 133.2, 130.3, 129.9 (2C), 128.7 (2C), 85.4, 83.4, 82.6, 80.6, 80.5, 76.3,

73.9, 62.4, 59.3, 58.4, 57.7, 56.4, 54.2, 53.8, 50.4, 49.4, 48.4, 42.5, 42.4, 42.0, 39.4, 37.2, 36.6, 26.0, 13.6. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{46}NO_8$: 572.3217, found: 572.3313.

Compound b. pale yellow amorphous powder, yield 14%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.14 (d, J = 5.0 Hz, 1H), 4.14 (q, J = 4.0 Hz, 2H), 4.03 (d, J = 6.8 Hz, 1H), 3.89 (brs, 1H), 3.66 (d, J = 8.5 Hz, 1H), 3.36 (s, 3H), 3.29 (s, 3H), 3.26 (s, 3H), 3.25 (s, 3H), 1.71 (s, 3H), 1.42 (t, J = 7.0 Hz, 3H), 1.08 (q, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 163.1, 131.9 (2C), 122.3, 114.4 (2C), 85.7, 83.5, 82.7, 80.8, 80.3, 76.4, 73.9, 63.9, 62.4, 59.3, 58.4, 57.6, 56.4, 53.9, 53.7, 50.4, 50.0, 49.4, 48.7, 42.5, 42.0, 39.5, 36.7, 35.2, 26.3, 14.8, 13.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{50}NO_9$: 616.3480, found: 616.3484.

Compound c. white amorphous powder, yield 16%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H), 5.29 (brs, OH), 5.13 (d, J = 5.0 Hz, 1H), 4.03 (d, J = 6.8 Hz, 1H), 3.89 (brs, 1H), 3.86 (s, 3H), 3.66 (d, J = 8.4 Hz, 1H), 3.37 (s, 3H), 3.29 (s, 3H), 3.26 (s, 3H), 3.25 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 163.7, 132.0 (2C), 122.6, 114.0 (2C), 85.7, 83.5, 82.7, 80.8, 80.3, 76.4, 73.9, 62.4, 59.4, 58.5, 57.7, 56.4, 55.6, 54.0, 53.7, 50.4, 50.0, 49.4, 48.7, 42.5, 42.1, 39.5, 36.7, 35.2, 26.3, 13.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{48}NO_9$: 602.3323, found: 602.3322.

Compound d. pale yellow amorphous powder, yield 38%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 5.11 (d, J = 4.8 Hz, 1H), 4.03 (d, J = 6.8 Hz, 1H), 3.38 (s, 3H), 3.28 (s, 3H), 3.26 (s, 3H), 3.25 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 132.0 (2C), 131.4 (2C), 129.2, 128.3, 85.3, 83.4, 82.6, 80.6, 76.2, 73.9, 62.4, 59.3, 58.5, 57.7, 56.3, 54.1, 54.1, 50.4, 50.4, 49.5, 49.4, 48.1, 42.3, 42.0, 39.4, 36.5, 35.1, 26.0, 13.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{45}BrNO_8$: 650.2323, found: 650.2326.

Compound e. pale yellow amorphous powder, yield 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 5.06 (d, J = 5.0 Hz, 1H), 3.96 (d, J = 6.8 Hz, 1H), 3.78 (brs, 1H), 3.36 (s, 3H), 3.23 (s, 3H), 3.21 (s, 6H), 1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 134.9-133.9 (q, J = 32 Hz), 133.5, 130.2 (2C), 127.7-119.6 (-CF_3, q, J = 271 Hz), 125.5-125.4 (2C, q, J = 3 Hz), 85.4, 83.3, 82.6, 80.7, 80.6, 76.0, 73.7, 62.2, 59.2, 58.3, 57.6, 56.2, 54.3, 53.8, 50.3, 49.6, 49.3, 47.9, 42.2, 41.8, 39.3, 36.3, 35.1, 26.2, 13.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{45}F_3NO_8$: 640.3091, found: 640.3091.

Compound f. pale yellow amorphous powder, yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H),7.68 (d, J = 8.0 Hz, 2H), 5.07 (d, J = 5.0 Hz, 1H), 3.99 (d, J = 6.8 Hz, 1H), 3.64 (d, J = 8.4 Hz, 1H), 3.38 (s, 3H), 3.26 (s, 3H), 3.24 (s, 3H), 3.23 (s, 3H), 1.07 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 135.5 (2C), 132.3, 130.6 (2C), 130.0-129.9 (q, J = 2 Hz), 133.9-124.7 (-SCF_3, q, J = 302 Hz), 85.3, 83.4, 82.6, 80.7, 80.5, 76.0, 73.7, 62.2, 59.1, 58.3, 57.6, 56.2, 54.2, 53.9, 50.3, 49.6, 49.2, 47.9,

42.2, 41.8, 39.3, 36.3, 34.9, 26.1, 13.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{45}F_3NO_8S$: 672.2812, found: 672.2812.

Compound g. pale yellow amorphous powder, yield 37%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 5.07 (d, J = 5.0 Hz, 1H), 3.99 (d, J = 6.8 Hz, 1H), 3.64 (d, J = 8.4 Hz, 1H), 3.38 (s, 3H), 3.26 (s, 3H), 3.24 (s, 3H), 3.23 (s, 3H), 1.07 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 152.6 (q, J = 3 Hz), 131.8 (2C), 128.6, 120.3 (2C), 124.1-116.4 (-OCF_3, q, J = 257 Hz), 85.3, 83.3, 82.5, 80.5, 80.5, 75.9, 73.7, 62.1, 59.1, 58.3, 57.5, 56.1, 54.1, 53.8, 50.2, 49.5, 49.2, 47.9, 42.2, 42.1, 39.3, 36.3, 34.9, 26.1, 13.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{45}F_3NO_9$: 656.3040, found: 656.3042.

Compound h. white amorphous powder, yield 52%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, J = 8.0 Hz, 2H), 7.07 (t, J = 8.0 Hz, 2H), 5.09 (d, J = 5.0 Hz, 1H), 3.99 (d, J = 7.0 Hz, 1H), 3.80 (brs, 1H), 3.64 (d, J = 8.5 Hz, 1H), 3.36 (s, 3H), 3.26 (s, 3H), 3.23 (s, 3H), 3.22 (s, 3H), 1.06 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1-164.6 (d, J = 253 Hz), 166.0, 132.4 (2C, d, J = 10 Hz), 126.6 (d, J = 3 Hz), 115.8-115.6 (2C, d, J = 22 Hz), 85.5, 83.4, 82.7, 80.7, 80.5, 76.2, 73.8, 62.3, 59.2, 58.4, 57.6, 56.3, 54.0, 53.9, 50.4, 49.8, 49.3, 48.2, 42.4, 41.9, 39.4, 36.5, 35.1, 26.2, 13.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{45}FNO_8$: 590.3123, found: 590.3215.

Compound i. pale yellow amorphous powder, yield 26%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 6.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 5.12 (d, J = 5.0 Hz, 1H), 4.02 (d, J = 6.8 Hz, 1H), 3.39 (s, 3H), 3.30 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 1.13 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 139.8, 131.3 (2C), 129.0 (2C), 128.8, 85.0, 83.4, 82.6, 80.5, 80.5, 76.1, 73.9, 62.4, 59.3, 58.5, 57.8, 56.4, 54.5, 54.1, 50.5, 49.5, 49.4, 48.0, 42.2, 42.1, 39.3, 36.7, 36.5, 25.8, 13.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{45}ClNO_8$: 606.2828, found: 606.2891.

Compound j. pale yellow amorphous powder, yield 21%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 4.2 Hz, 2H), 7.42 (d, J = 8.0Hz, 2H), 5.12 (d, J = 5.2 Hz, 1H), 4.06 (d, J = 6.8 Hz, 1H), 3.42 (s, 3H), 3.30 (s, 9H), 1.12 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 144.1, 129.9 (2C), 129.4(2C), 127.3, 83.8, 83.1, 82.3, 80.1, 80.0, 76.0, 74.0, 62.2, 59.3, 58.6, 57.9, 56.3, 55.1, 53.8, 50.5, 49.6, 47.6, 42.4, 41.9, 39.1, 36.8, 36.4, 24.9, 21.8, 12.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{48}NO_8$: 586.3374, found: 586.3437.

Compound k. pale yellow amorphous powder, yield 17%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 4.35 (d, J = 5.2 Hz, 1H), 3.31 (s, 6H), 3.30 (s, 3H), 3.25 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 138.4, 134.9, 132.6, 131.1, 129.1, 127.2, 87.0, 84.9, 82.3, 80.6, 80.4, 77.8, 72.9, 62.4, 59.4, 58.1, 57.7, 56.1, 54.7, 52.3, 50.4, 49.6, 49.2, 48.8, 43.0, 40.6, 39.4, 35.9, 34.0, 25.2, 13.2. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{44}Cl_2NO_8$: 640.2438, found: 640.2438.

Compound l. pale yellow amorphous powder, yield 16%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 1H), 6.99 (t, J = 8.5 Hz, 2H), 5.18 (d, J = 4.7 Hz, 1H), 4.07 (d, J = 7.0 Hz, 1H), 3.68 (d, J = 8.4 Hz, 1H), 3.30 (s, 6H), 3.27 (s, 3H), 3.25 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6-160.0 (2C, dd, J = 257, 6 Hz), 162.5, 133.8-133.7 (t, J = 10 Hz), 112.7-112.5 (2C, dd, J = 23, 4 Hz), 112.8-112.5 (t, J = 14 Hz), 85.8, 83.5, 83.1, 82.6, 80.9, 77.0, 73.2, 62.3, 59.4, 58.3, 57.6, 56.5, 53.9, 53.3, 50.4, 49.9, 49.6, 49.4, 42.6, 41.1, 39.5, 37.4, 35.2, 26.2, 13.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{44}F_2NO_8$: 608.3029, found: 608.3029.

Compound m. white amorphous powder, yield 18%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 9.7 Hz, 2H), 7.03 (t, J = 8.5 Hz, 1H), 5.31 (brs, 2H), 5.09 (d, J = 5.0 Hz, 1H), 4.01 (d, J = 7.0 Hz, 1H), 3.68 (d, J = 8.4 Hz, 1H), 3.45 (s, 3H), 3.31 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 1.09 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8 (t, J = 4 Hz), 164.2-161.6 (2C, dd, J = 248, 12 Hz), 133.8-133.6 (t, J = 10 Hz), 113.2-112.9 (2C, dd, J = 20, 7 Hz), 108.8-108.3 (t, J = 25 Hz), 85.5, 83.3, 82.7, 80.8, 80.7, 76.0, 73.9, 62.4, 59.3, 58.3, 57.8, 56.4, 54.5, 53.9, 50.4, 49.8, 49.4, 47.8, 42.3, 41.9, 39.4, 36.2, 35.1, 26.3, 13.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{44}F_2NO_8$: 608.3029, found: 608.3055.

Compound n. white amorphous powder, yield 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 5.6 Hz, 1H), 7.50 (m, 2H), 7.35 (m, 3H), 6.40 (d, J = 5.6 Hz, 1H), 5.01 (d, J = 6.0 Hz, 1H), 4.01 (d, J = 6.0 Hz, 1H), 3.65 (d, J = 8.4 Hz, 1H), 3.35 (s, 3H), 3.28 (s, 6H), 3.22 (s, 3H), 1.07 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 145.9, 134.3, 130.6, 129.0 (2C), 128.3 (2C), 117.7, 85.6, 83.6, 82.6, 80.8, 80.7, 76.5, 73.7, 62.2, 59.2, 58.5, 57.6, 56.3, 53.9, 53.5, 50.3, 49.8, 49.3, 48.8, 42.5, 41.8, 39.4, 37.0, 35.1, 26.2, 13.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{48}NO_8$: 598.3389, found: 598.3380.

Compound o. pale yellow amorphous powder, yield 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.76-8.74 (m, 1H), 8.29-8.27 (m, 1H), 7.39-7.36 (m, 1H), 5.28 (s, 1H), 5.12 (d, J = 4.8 Hz, 1H), 4.00 (d, J = 6.8 Hz, 1H), 3.40 (brs, 3H), 3.28 (brs, 3H), 3.25-3.24 (m, 6H), 1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 153.5, 151.3, 137.4, 126.3, 123.5, 85.4, 83.4, 82.7, 80.6 (2C), 76.1, 73.9, 62.3, 59.3, 58.5, 57.8, 56.4, 54.4, 54.0, 53.5, 50.4, 49.4, 47.9, 42.3, 42.0, 39.4, 36.4, 35.0, 26.2, 13.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{45}N_2O_8$: 573.3176, found: 573.3145.

Compound p. white amorphous powder, yield 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 2.5 Hz, 1H), 7.56 (d, J = 4.8 Hz, 1H), 7.10-7.08 (m, 1H), 5.08 (d, J = 4.5 Hz, 1H), 4.08 (d, J = 6.6 Hz, 1H), 3.59 (d, J = 8.2 Hz, 1H), 3.39 (s, 3H), 3.29 (m, 6H), 3.26 (brs, 3H), 1.21 (t, J = 5.9 Hz, 3H).^{13}C NMR (100 MHz, CDCl3) δ 162.1, 134.1, 133.4, 132.9, 128.1, 83.5, 82.8, 82.0, 80.1, 79.7, 75.8, 73.7, 62.5, 59.3, 58.3, 57.9, 56.1, 55.7, 53.6, 50.5, 49.5, 47.0, 42.1, 42.0, 41.6, 38.9, 36.4, 31.6, 24.2, 12.3. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{44}NO_8S$: 578.2788, found: 578.2800.

Compound q. pale yellow oil, yield 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (d, J = 4.9 Hz, 1H), 3.68 (d, J = 8.4 Hz, 1H), 3.33 (s, 3H), 3.29 (brs, 6H), 3.22 (s, 3H), 1.07 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.4 Hz,

3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 85.7, 83.8, 82.6, 81.4, 80.8, 76.9, 73.6, 62.3, 59.4, 58.6, 57.6, 56.4, 53.9, 53.2, 50.3, 49.9, 49.4, 49.3, 42.6, 41.7, 39.5, 37.5, 36.6, 35.3, 26.2, 18.3, 13.8 (2C). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{48}NO_8$: 538.3380, found: 538.3388.

Compound r. yellow oil, yield 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (d, J = 4.9 Hz, 1H), 4.03-4.01 (m, 2H), 3.68 (d, J = 8.4 Hz, 1H), 3.33 (s, 3H), 3.29 (brs, 6H), 3.23 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 85.7, 83.8, 82.6, 81.4, 80.8, 77.4, 73.6, 62.3, 59.4, 58.6, 57.6, 56.4, 53.9, 53.2, 50.4, 49.9, 49.4, 49.3, 42.6, 41.7, 39.5, 37.5, 35.2, 34.7, 31.6, 28.9, 26.1, 24.8, 22.6, 14.1, 13.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{54}NO_8$ 580.3849, found: 580.3885.

Compound s. pale yellow oil, yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (d, J = 4.9 Hz, 1H), 4.03-4.01 (m, 2H), 3.68 (d, J = 8.5 Hz, 1H), 3.33 (s, 3H), 3.29 (brs, 6H), 3.22 (s, 3H), 1.07 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 85.7, 83.3, 82.6, 81.4, 80.8, 77.4, 73.6, 62.3, 59.4, 58.6, 57.6, 56.4, 53.9, 53.2, 50.4, 49.9, 49.4, 49.3, 42.6, 41.7, 39.5, 37.5, 35.3, 34.7, 32.1, 29.8 (4C), 29.7 (2C), 29.6, 29.5, 29.4, 29.3, 26.2, 24.9, 22.8, 14.2, 13.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{72}NO_8$ 706.5258, found: 706.5272.

Antifeedant Bioassays.

The *S. exigua* (Hübner) colony (Henan Jiyuan Baiyun Industry Co., Ltd.) was reared on cabbage foliage and maintained at 24 ± 1 °C and >70% relative humidity with a photoperiod of 16:8 h (L:D) in a growth chamber. The newly emerged third-instar larvae of *S. exigua* was used in the antifeedant bioassays.

The antifeedant properties of the derivatives were evaluated using a no choice leaf-disc method.[14] The compounds were dissolved in acetone to prepare a 5 mmol/L stock solution for the following test. Fresh cabbage leaves were cut into leaf discs (2 cm diameter) and then treated on the upper surface with 15 μL of either the test substance emulsions or acetone as a control. After air drying, four treated leaves and control leaves were arranged on 2% agar beds (2-3 mm) in 15 cm diameter Petri dishes separately. Four healthy and starved 6 h instars were placed in each dish and allowed to feed in a growth chamber (environmental conditions as described above). Progressive consumption of treated and control leaves by the larvae after 24 h was assessed using a leaf area meter, and food reduction (FR) in each dish was determined using the equation FR = (CK − T)/CK ×100% (CK is the control leaf disc area eaten and T is the treated leaf disc area eaten). Three replicates were prepared for each treatment (total n = 12). Acetone were used as negative controls, whereas azadirachtin **A** was used as the positive control.

EC_{50} values (the effective dose for 50% feeding reduction) were calculated by a dose-response experiment. The software Origin 2019 was used for linear regression analysis (% FR on log dose) to obtain EC_{50} values and 95% confidence interval.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (21807089), the Science and Technology Support Programs of Sichuan Province (2021YJ0222), and the Fundamental Research Funds for Central Universities (2682021CX085) and the Scientific Research and Training Program for college students of Southwest Jiaotong University (211504).

REFERENCES

1. X. F. Zhao, *J. Integr. Agric*., 2020, **19**, 1417; M. M. Rabelo, S. V. Paula-Moraes, J. G. Pereira Eliseu, and B. D. Siegfried, *Pest Manag. Sci.*, 2020, **76**, 4240.
2. S. H. Liu, X. H. Yao, X. Xiang, Q. F. Yang, X. G. Wang, T. Xin, and S. Y. Yu, *Pest Manag. Sci*., 2021, **77**, 1739; W. Che, T. Shi, Y. Wu, and Y. Yang, *J. Econ. Entomol.*, 2013, **106**, 1855; T. C. Lai, J. Li, and J. Y. Su, *Pestic. Biochem. Physiol*., 2011, **101**, 198; G. Wu, J. Guo, F. H. Wan, and N. W. Xiao, *J. Insect. Sci*., 2010, **10**, 165.
3. D. M. Soderlund and J. R. Bloomquis, *Annu. Rev. Entomol*., 1989, **34**, 77.
4. M. M. Rabelo, S. V. Paula-Moraes, E. J. G. Pereira, and B. D. Siegfried, *Pest Manag. Sci.*, 2020, **76**, 4240; D. M. Suckling, D. E. Conlong, J. E. Carpenter, K. A. Bloem, P. Rendon, and M. J. B. Vreysen, *Biol. Invasions*, 2016, **19**, 1107; J. M. Bonmatin, E. A. D. G. Mitchell Glauser, E. Lumawig-Heitzman, F. Claveria, V. L. M. Bijleveld, K. Taira, and F. Sánchez-Bayo, *Sci. Total Environ*., 2021, **757**, 143822.
5. L. W. Zhang, O. E. Fasoyin, I. Molnár, and Y. Q. Xu, *Nat. Prod. Rep*., 2020, **37**, 1181; P. H. Tschoeke, E. E. Oliveira., M. S. Dalcin, M. C. A. C. Silveira-Tschoeke, R. A. Sarmento, and G. R. Santos, *Environ. Pollut*., 2019, **251**, 591.
6. F. P. Wang, Q. H. Chen, and X. Y. Liu, *Nat. Prod. Rep.*, 2010, **27**, 529.
7. K. R. Jennings, D. G. Brown, and D. P. Wright, *Cell Mol. Life Sci.*, 1986, **42**, 611.
8. J. Wang, J. B. Xu, H. B. Yang, F. Gao, X. L. Zhou, L. Chen, and S. Huang, *Heterocycles*, 2021, **102**, 1579; Q. L. Guo, H. Xia, Y. Z. Wu, S. Shao, C. B. Xu, T. T. Zhang, and J. G. Shi, *Acta Pharm. Sin. B*, 2020, **10**, 1954; L. H. Shan, L. Chen, F. Gao, and X. L. Zhou, *Nat. Prod. Res*., 2019, **33**, 3254; J. F. Zhang, L. Chen, and X. L. Zhou, *Heterocycles*, 2018, **96**, 304; W. L. Xu, L. Chen, F. Gao, and X. L. Zhou, *Heterocycles*, 2018, **96**, 1631; M. Y. Ren, Q. T. Yu, C. Y. Shi, and J. B. Luo, *Molecules*, 2017, **22**, 267; X. Y. Liu and Y. Qin, *Nat. Prod. Rep*., 2017, **34**, 1044; G. H. Zhou, L. Y. Tang, X. D. Zhou, T. Wang, Z. Z. Kou, and Z. J. Wang, *J. Ethnopharmacol*., 2015, **160**, 173; M. A. Turabekova, B. F. Rasulev, F. N. Dzhakhangirov, D. Leszczynska, and J. Leszczynski, *Eur. J. Med. Chem*., 2010, **45**, 3885.
9. J. F. Zhang, L. Chen, S. Huang, L. H. Shan, F. Gao, and X. L. Zhou, *J. Nat. Prod.*, 2017, **80**, 3136.
10. J. L. Wang, X. L. Shen, Q. H. Chen, G. Qi, W. Wang, and F. P. Wang, *Chem. Pharm. Bull.*, 2009, **5**,

801.

11. J. B. Hanuman and A. Katz, *Phytochemistry*, 1994, **36**, 1527.
12. F. P. Wang and Q. H. Chen, 'The C19-Diterpenoid Alkaloids, The Alkaloids: Chemistry and Biology', Vol. 69, ed. by G. A. Cordell, Academic Press, Inc., London, 2010, pp. 1-577.
13. Y. Cheng, Y. S. Gong, Y. S. Liu, B. S. Song, and Q. Zou, *Brief. Bioinform.*, 2021, doi:10.1093/bib/bbab344.
14. A. González-Coloma, M. Reina, R. Cabrera, P. Castaera, and C. Gutiérrez. *J. Chem. Ecol*., 1995, **21**, 1255.