农药学学报 2016, 18(3): 291-298
Chinese Journal of Pesticide Science http://www.nyxxb.com.cn

· Research Report · **DOI**: 10.16801/j.issn.1008-7303.2016.0040

Synthesis and bioactivity of (*S, S*)-2,8-diazabicyclo [4.3.0] nonane containing benzimidazole moiety

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Abstract: A series of novel (*S*, *S*)-2,8- diazabicyclo [4.3.0] nonane containing benzimidazole moiety was synthesized and their structures were determined by ^{1}H NMR and HRMS. The biological activity results showed that these compounds possessed moderate antifungal activity to some plant pathogenous fungi and moderate insecticidal activity against *Mythimna separata* Walker and *Culex pipiens pallens*. Compounds **6e** and **6f** exhibited good antibacterial activity against *Sclerotinia sclerotiorum*, *Phytophthora infestans* and *Fusarium graminearum*. The lethality rates of compounds **6e** and **6k** against *Mythimna separata* Walker were 100% at 200 mg/L and the lethality rates of compounds **6h** and **6k** against *C. pippiens pallens* were 75% at 2 mg/L.

Keywords: (*S*, *S*)-2, 8-diazabicyclo[4.3.0]nonane; benzimidazole; antifungal activity; insecticidal activity

新型含苯并咪唑的 (*S, S*)-2,8-二氮杂双环 [4.3.0] 壬烷类衍生物的合成及生物活性

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摘 要：通过 *N*-烷基化反应合成了一系列新型含苯并咪唑的 *(S, S)*-2,8- 二氮杂双环 [4.3.0] 壬烷类衍生物，中间体化合物通过环化反应和酰化反应合成得到。所有新型化合物的结构均通过熔点测定、核磁共振氢谱和高分辨质谱确认。生物活性测试结果显示，目标化合物拥有中等的抗植物真菌活性，对东方粘虫 *Mythimna separata* Walker 和蚊幼虫 *Culex pipiens pallens* 具有中等到良好的杀虫活性。其中化合物 **6e** 和 **6f** 对油菜菌核 *Sclerotinia sclerotiorum*、马铃薯晚疫 *Phytophthora infestans*、小麦赤霉 *Fusarium graminearum* 等真菌具有良好的抗菌活性。化合物 **6e** 和 **6k** 在 200 mg/L 下对东方粘虫的致死率为 100%，化合物 **6h** 和 **6k** 在 2 mg/L 下对蚊幼虫的致死率为 75%。

Received: Feb. 2, 2016; **Accepted:** March. 15, 2016.

Fond project: Project supported by the National Science Foundation of China (No.31370039).

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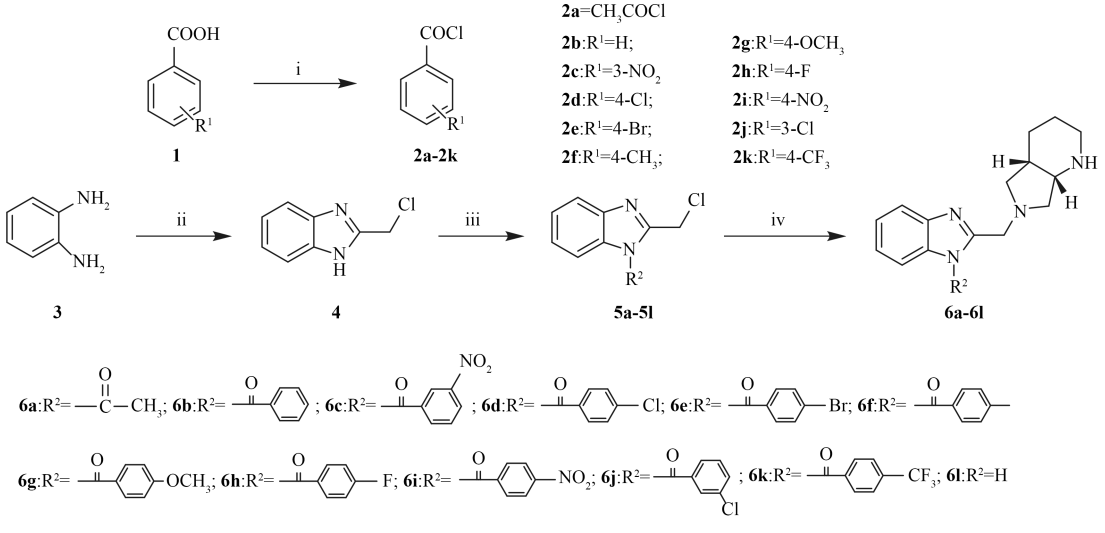
关键词: 苯并咪唑; (*S, S*)-2,8- 二氮杂双环 [4.3.0] 壬烷; 抗真菌活性; 杀虫活性
中图分类号: O626.22; S482.3 **文献标志码:** A **文章编号:** 1008-7303(2016)03-0291-07

In recent years, due to the increasing resistance of fungi to fungicides, it is necessary to develop new environmentally friendly fungicide. Moxifloxacin is the fourth-generation fluoroquinolone drug with broad-spectrum antifungal activity, good pharmacokinetics property, low drug resistance, and safe to use[1-2]. It also has very broad application prospect, and huge market potential[3]. As the branched-chain, (*S*, *S*)-2, 8-diazabicyclo [4.3.0] nonane is the key intermediate for the synthesis of moxifloxacin. Its special diazabicyclo structure strengthens moxifloxacin's activity against gram-positive bacteria, and also reduces adverse reaction while keeps the original activity [4].

Heterocyclic compounds with benzimidazole moiety usually showed high biological activity[5-6], including antiparasitic, antiviral, antifungal and anticancer activity. Aromatic heterocyclic ring containing two nitrogen atoms, can form hydrogen bonds with receptors[6-7]. The synthesis of 1-substituted and 2-substituted benzimidazole derivatives has become a hot research topic recently[7-13].

Since (*S*, *S*)-2,8- diazabicyclo [4.3.0] nonane and benzimidazole have special nitrogen heterocyclic structures, we designed and synthesized a series of novel hetereocycles with 2, 8-diazabicyclo [4.3.0] nonane and benzimidazole moiety by using active substructure splicing method (**Scheme 1**). The antifungal activity and insecticidal activity of these compounds were also evaluated.



Reagents and conditions: (i) $(COCl)_2$, DMF, CH_2Cl_2, rt; (ii) $ClCH_2COOH$, HCl, H_2O, re- flux, $NH_3 \cdot H_2O$; (iii) compounds **2a-2k**, Et_3N, CH_2Cl_2, 0 ℃; reflux; (iv) (*S*, *S*)-2, 8-diazabicyclo [4.3.0] nonane, K_2CO_3, CH_3CN, rt.

Scheme 1 Synthesis of compounds 6a-6l

1 Materials and methods

1.1 Instruments

All chemicals and reagents were of analytical grade. Reactions were monitored with analytical thin-layer chromatography (TLC). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker AV 400 spectrometer in a $CDCl_3$ solution with tetramethylsilane as the internal standard. High resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument.

1.2 Synthetic procedures

1.2.1 General procedure for synthesis of compounds 2b-2k To a solution of acid **1** (10 mmol) and oxalyl

chloride (20 mmol) in dry CH_2Cl_2 (20 mL), 0.1 mL DMF was added. The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure. The crude acid chloride **2** was used in the subsequent step without further purification [16-17].

1.2.2 General synthetic procedure for compound 4 Compounds **4** were prepared according to the literature procedures [14-16].

1.2.3 General procedure for synthesis of compounds 5a-5k To a solution of 2-(chloromethyl)-1*H*-benzo [d] imidazole **4** (10 mmol) and triethylamine (15 mmol) in CH_2Cl_2 (20 mL), acyl chlorides **2** (10 mmol) was added dropwise at 0 ℃. The reaction mixture was allowed to warm to room temperature, and was then refluxed for 2 h. After the reaction completed, the mixture was diluted with CH_2Cl_2, washed with 1 mol/L HCl (50 mL×3), followed by brine (10 mL×3). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography on silica gel to afford **5a-5k**[18].

(2-chloromethyl-benzoimidazol-1-yl)-ethanone (**5a**): yield 80%, a yellow solid, m. p. 80-81 ℃; ^{1}H NMR, δ: 7.82 (dd, J = 6.4, 2.6 Hz, 1H, Ar-H), 7.71 (dd, J = 6.7, 2.4 Hz, 1H, Ar-H), 7.45-7.39 (m, 2H, Ar-H), 5.11 (s, 2H, CH_2), 2.89 (s, 3H, CH_3).

(2-chloromethyl-benzoimidazol-1-yl)-phenyl-methanone (**5b**): yield 83%, a yellow solid, m. p. 80-81 ℃; ^{1}H NMR, δ: 8.16 (d, J = 7.3 Hz, 2H, Ar-H), 7.79-7.51 (m, 3H, Ar-H), 7.50 (t, J = 7.7 Hz, 2H, Ar-H), 7.34-7.31 (m, 2H, Ar-H), 4.93 (s, 2H, CH_2).

(2-chloromethyl-benzoimidazol-1-yl)-(3-nitro-phenyl)-methanone (**5c**): yield 85%, a yellow solid, m. p. 128-129 ℃; ^{1}H NMR, δ: 8.70 (s, 1H, Ar-H), 8.60 (d, J = 8.2 Hz, 1H, Ar-H), 8.11 (d, J = 7.7 Hz, 1H, Ar-H), 7.84-7.77 (m, 2H, Ar-H), 7.36 (t, J = 7.7 Hz, 1H, Ar-H), 7.17 (t, J = 7.8 Hz, 1H, Ar-H), 6.60 (d, J = 8.3 Hz, 1H, Ar-H), 5.10 (s, 2H, CH_2).

(2-chloromethyl-benzoimidazol-1-yl)-(4-chloro-phenyl)-methanone (**5d**): yield 80%, a yellow solid, m. p. 110-111 ℃; ^{1}H NMR, δ: 7.79 (t, J = 8.8 Hz, 3H, Ar-H), 7.54 (d, J = 8.4 Hz, 2H, Ar-H), 7.33 (t, J = 7.7 Hz, 1H, Ar-H), 7.1 (t, J = 7.8 Hz, 1H, Ar-H), 6.71 (d, J = 8.3 Hz, 1H, Ar-H), 5.08 (s, 2H, CH_2).

(2-chloromethyl-benzoimidazol-1-yl)-(4-bromo-phenyl)-methanone (**5e**): yield 80%, a yellow solid, m. p. 108-109 ℃; ^{1}H NMR, δ: 7.80 (d, J = 8.1 Hz, 1H, Ar-H), 7.75-7.61 (m, 4H, Ar-H), 7.33 (t, J = 7.5 Hz, 1H, Ar-H), 7.18 (t, J = 7.7 Hz, 1H, Ar-H), 6.71 (d, J = 8.3 Hz, 1H, Ar-H), 5.07 (s, 2H, CH_2).

(2-chloromethyl-benzoimidazol-1-yl)-p-tolyl-methanone (**5f**): yield 87%, a yellow solid, m. p. 73-74 ℃; ^{1}H NMR, δ: 7.79 (d, J = 8.1 Hz, 1H, Ar-H), 7.72 (d, J = 7.8 Hz, 2H, Ar-H), 7.37-7.28 (m, 3H, Ar-H), 7.16 (t, J = 7.8 Hz, 1H, Ar-H), 6.76 (d, J = 8.3 Hz, 1H, Ar-H), 5.07 (s, 2H, CH_2), 2.50 (s, 3H, CH_3).

(2-chloromethyl-benzoimidazol-1-yl)-(4-methoxy-phenyl)-methanone (**5g**): yield 83%, a yellow solid, m. p. 77-78 ℃; ^{1}H NMR, δ: 7.80 (t, J = 8.7 Hz, 3H, Ar-H), 7.31 (t, J = 7.7 Hz, 1H, Ar-H), 7.17 (t, J = 7.8 Hz, 1H, Ar-H), 7.02 (d, J = 8.1 Hz, 2H, Ar-H), 6.83 (d, J = 8.2 Hz, 1H, Ar-H), 5.07 (s, 2H, CH_2), 3.93 (s, 3H, CH_3).

(2-chloromethyl-benzoimidazol-1-yl)-(4-fluoro-phenyl)-methanone (**5h**): yield 80%, a yellow solid, m. p. 77-78 ℃; ^{1}H NMR, δ: 7.98-7.77 (m, 3H, Ar-H), 7.37-7.18 (m, 4H, Ar-H), 6.73 (d, J = 8.3 Hz, 1H, Ar-H), 5.11 (s, 2H, CH_2).

(2-chloromethyl-benzoimidazol-1-yl)-(4-nitro-phenyl)-methanone (**5i**): yield 85%, a yellow solid, m. p. 80-81 ℃; ^{1}H NMR, δ: 8.44 (d, J = 7.1 Hz, 2H, Ar-H), 8.02 (d, J = 7.1 Hz, 2H, Ar-H), 7.84 (d, J = 8.1 Hz, 1H, Ar-H), 7.38 (t, J = 7.7 Hz, 1H, Ar-H), 7.20 (t, J = 7.8 Hz, 1H, Ar-H), 6.59 (d, J = 8.3 Hz, 1H, Ar-H), 5.12 (d, J = 1.5 Hz, 2H, CH_2).

(2-chloromethyl-benzoimidazol-1-yl)-(3-chloro-phenyl)-methanone (**5j**): yield 80%, a yellow solid, m. p. 87-88 ℃; ^{1}H NMR, δ: 8.14 (t, J = 1.8 Hz, 1H, Ar-H), 8.08-8.00 (m, 1H, Ar-H), 7.65 (dt, J = 6.6, 3.3 Hz, 2H, Ar-H), 7.60-7.57 (m, 1H, Ar-H), 7.44 (t, J = 7.9 Hz, 1H, Ar-H), 7.37-7.30 (m, 2H, Ar-H), 4.94 (s, 2H,

CH_2).

(2-chloromethyl-benzoimidazol-1-yl)-(4-trifluoromethyl-phenyl)-methanone (**5k**): yield 86%, a yellow solid, m. p. 78-79 ℃; ^{1}H NMR, δ: 7.97 (d, J = 8.1 Hz, 2H, Ar-H), 7.85 (dd, J = 10.3, 8.3 Hz, 3H, Ar-H), 7.42-7.31 (m, 1H, Ar-H), 7.25-7.16 (m, 1H, Ar-H), 6.63 (d, J = 8.3 Hz, 1H, Ar-H), 5.12 (s, 2H, CH_2).

1.2.4 General procedure for the synthesis of compounds 6a-6l To a mixture of (*S, S*)-2,8-diazabicyclo [4.3.0] nonane (10 mmol) and anhydrous K_2CO_3 (15 mmol) in CH_3CN (20 mL), compound **5** (5 mmol) was added. After the reaction completed, the mixture was filtrated. The solvent was removed and the residue was dissolved by CH_2Cl_2. The mixture was washed with saturated $NaHCO_3$ solution and water. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography on silica gel to afford title compounds **6a-6l**[19-20].

1.3 Bioassays

1.3.1 Antifungal activity The fungicidal activity of title compounds was tested *in vitro* against *Physalospora piricala*, *Fusarium graminearum*, *Phytophthora infestans*, *Rhizoctonia cerealis*, *Sclerotinia sclerotiorum*, *Cochliobolus heterostrophus* and *Fusarium moniliforme*, their relative inhibitory rates (%) were determined by the mycelium growth rate method[21]. Carbendazim, chlorothalonil and thiram were used as controls. After the mycelia grew completely, the diameters of the mycelia were measured and the inhibition rate was calculated according to the formula:

$$I/\% = [(D_1 - D_2)/D_1] \times 100$$

In the formula, I is the inhibition rate, D_1 is the average diameter of mycelia in the blank test, and D_2 is the average diameter of mycelia in the presence of one of those compounds.

1.3.2 Insecticidal activity Insecticidal activity against *Mythimna separata* Walker was tested in a greenhouse [22]. The bioassay was operated at (25±1) ℃ by statistical requirements. The compounds were dissolved with acetone at various concentrations, 0.306 μL of the tested solution was applied to the thoracic tergite of fourth-instar larva with a platinum loop. After the treatment, the insects were observed under standard rearing conditions. Mortalities were calculated after 72 h. Each treatment was performed in triplicate.

Insecticidal activity against *Culex pipiens pallens*[22] was also evaluated. compounds (1 mL) was added to water (99 mL) to get the test solutions of different concentrations. 20 fourth-instar mosquito larva were transferred into 10 mL of the test solution and raised for 2 d, and the results were expressed by the lethality rate.

2 Results and discussion

2.1 Synthesis and analytical spectral data

The physical and chemical data of the title compounds **6a-6l** were shown in Table 1. The ^{1}H NMR data of the title compounds **6a-6l** were shown in Table 2. The ^{13}C NMR data of the title compounds **6d**, **6e**, **6g** and **6i** were shown in Table 3.

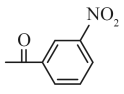
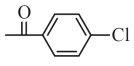
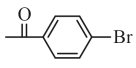
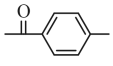
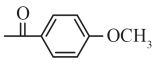
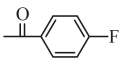
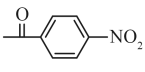
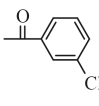
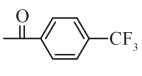
The synthetic route of the intermediates and title compounds are illustrated in **Scheme 1**. Compound **4** was prepared from *o*-phenylenediamine and chloroacetic acid via a cyclization reaction in the acidic environment, followed by the ammonia neutralization. It can be conveniently obtained with high yields. Compounds **5a-5l** can be obtained through the acylation reaction in CH_2Cl_2 with Et_3N as base with high yields.

It was noteworthy that the target compounds **6a-6l** can't be obtained in acetone with anhydrous K_2CO_3 and KI, while they were formed in the *N*-alkylation reaction in CH_3CN. It might indicated the poor activity of the reactants in acetone.

2.2 Antifungal activity

The antifungal activities of the target compounds against seven pathogenic fungis were listed in Table 4. Most of them showed moderate activity at the concentration of 50 μg/mL. Inhibition rate against *P.*

Table 1 Physical and chemical data of the title compounds 6a-6l

Compd.	R^2	Appearance	Yield/%	m. p./℃	ESI-FTICR-MS found (Calcd.)
6a		White solid	30	91-92	298.1798 (298.1794) $[M+H]^+$
6b		White solid	50	87-88	361.2029 (361.2023) $[M+H]^+$
6c		White solid	45	87-88	405.1804 (405.1801) $[M+H]^+$
6d		White solid	38	70-71	395.1639 (395.1633) $[M+H]^+$
6e		White solid	40	102-103	439.1127 (439.1128) $[M+H]^+$
6f		White solid	35	65-66	375.2184 (375.2179) $[M+H]^+$
6g		White solid	37	81-82	391.2131 (391.2129) $[M+H]^+$
6h		White solid	30	88-89	378.1861 (378.1856) $[M+H]^+$
6i		White solid	48	98-99	406.1877 (406.1874) $[M+H]^+$
6j		White solid	43	90-91	394.1564 (394.1560) $[M+H]^+$
6k		White solid	50	105-106	428.1827 (428.1824) $[M+H]^+$
6l	H	White solid	25	89-90	256.1691 (256.1688) $[M+H]^+$

infestans ranged from 50.0% to 62.5% for compounds **6d-6g.** Compounds **6d-6h** exhibited activity toward *S. sclerotiorum*, however, all of them were less effective than chlorothaloni. Inhibition rates against *P. piricala* of compounds **6h-6i** were as good as carbendazim. Compounds **6d-6l** exhibited inhibition rates of 55.0%-67.6% against *R. cerealis*. Compounds **6d-6g** were less effective than carbendazim against *C. heterostrophus* and *F. moniliforme*. However, the fungicidal activities of other title compounds are not notable.

2.3 Insecticidal activity

The insecticidal activity was evaluated against *M. separata* and *C. pipiens pallens*. Chloratraniliprole was used as control. We found that the insecticidal activities of most new compounds against *M. separata* were over 50% at the concentration of 200 mg/L. Among them, compounds **6e** and **6k** showed higher activities. Most of the target compounds also exhibited insecticidal activity against *C. pipiens pallens* at the concentration of 2 mg/L. Compounds **6h, 6i** and **6k** showed higher lethality rates against *C. pipiens pallens*.

In conclusion, a series of 2, 8-diazabicyclo [4.3.0] nonane containing benzimidazole moiety has been synthesized and characterized. All 12 compounds showed moderate antifungal activity against seven pathogenic fungi and moderate insecticidal activity against *M. separata* and *C. pipiens pallens*. 2,8-Diazabicyclo [4.3.0] nonane and benzimidazole are developed and applied widely in the field of fungicide. Interestingly, to a certain extent, these novel structures exhibited insecticidal activity, which means they are worth for our further modification.

Table 2 ^{1}H NMR data of the title compounds 6a-6l

Compd.	^{1}H NMR (400 MHz, $CDCl_3$), δ
6a	7.58 (s, 2H, Ar-H), 7.31-7.17 (m, 2H，Ar-H), 4.15-3.97 (m, 2H, CH_2), 3.79-3.69 (m, 1H, CH), 3.66-3.36 (m, 4H, CH_2), 3.15-2.99 (m, 1H, CH), 2.91-2.78 (m, 1H, NH), 2.52-2.32 (m, 2H, CH_2), 1.98 (d, J = 86.2 Hz, 3H, CH_3), 1.82-1.52 (m, 4H, CH_2).
6b	7.80-7.51 (m, 3H, Ar-H), 7.49-7.41 (m, 2H, Ar-H), 7.37-7.18 (m, 4H, Ar-H), 4.52-4.07 (m, 1H, CH_2), 4.03-3.79 (m, 1H, CH_2), 3.75-3.37 (m, 4H, CH_2), 3.07 (t, J = 17.9 Hz, 1H, CH), 2.92-2.73 (m, 1H, CH), 2.60-2.25 (m, 2H, CH_2), 1.75 (s, 1H, NH), 1.67-1.43 (m, 3H, CH_2), 1.38-1.29 (m, 1H, CH_2).
6c	8.46-8.23 (m, 1H, Ar-H), 8.03 (dd, J = 79.9, 8.0 Hz, 1H, Ar-H), 7.69-7.46 (m, 3H, Ar-H), 7.33-7.20 (m, 3H, Ar-H), 4.42-4.10 (m, 1H, CH_2), 3.96-3.81 (m, 1H, CH), 3.76-3.64 (m, 1H, CH), 3.61-3.45 (m, 2H, CH_2), 3.12 (d, J = 17.5 Hz, 1H, CH_2), 2.93-2.83 (m, 1H, NH), 2.60-2.31 (m, 2H, CH_2), 1.93-1.74 (m, 2H, CH_2), 1.70-1.50 (m, 3H, CH_2), 1.29 (d, J = 11.5 Hz, 1H, CH_2).
6d	7.67-7.48 (m, 3H, Ar-H), 7.40 (d, J = 8.3 Hz, 1H, Ar-H), 7.30-7.25 (m, 2H , Ar-H), 7.23 (d, J = 8.3 Hz, 1H, Ar-H), 7.15 (d, J = 8.3 Hz, 1H, Ar-H), 4.09-4.43 (m, 1H, CH_2), 3.90-3.82 (m, 1H, CH_2), 3.72-3.60 (m, 1H, CH), 3.56-3.41 (m, 2H, CH_2), 3.06 (s, 1H, CH), 2.89-2.80 (m, 1H, CH_2), 2.57-2.27 (m, 2H, CH_2), 1.75 (d, J = 4.3 Hz, 1H, NH), 1.66-1.47 (m, 3H, CH_2), 1.37-1.28 (m, 2H, CH_2).
6e	7.56 (d, J = 8.4 Hz, 2H, Ar-H), 7.44 (d, J = 8.4 Hz, 2H, Ar-H), 7.30 (d, J = 8.4 Hz, 2H, Ar-H), 7.13 (d, J = 8.4 Hz, 2H, Ar-H), 4.44-4.09 (m, 1H, CH_2), 3.91-3.82 (m, 1H, CH_2), 3.74-3.37 (m, 4H, CH_2), 3.07 (s, 1H, CH), 2.93-2.78 (m, 1H, CH), 2.57-2.27 (m, 2H, CH_2), 1.76 (s, 1H, NH), 1.67-1.45 (m, 3H, CH_2), 1.36-1.25 (m, 1H, CH_2).
6f	7.56 (s, 2H, Ar-H), 7.48 (d, J = 8.0 Hz, 2H, Ar-H), 7.31-7.20 (m, 3H, Ar-H), 7.02 (d, J = 7.9 Hz, 1H, Ar-H), 4.52-4.09 (m, 1H, CH_2), 3.96-3.79 (m, 1H, CH_2), 3.74-3.36 (m, 4H, CH_2), 3.03 (s, 1H, NH), 2.87-2.76 (m, 1H, CH), 2.545-2.462 (m, 1H, CH), 2.33 (d, J =19.2 Hz, 3H, CH_3), 1.84-1.67 (m, 2H, CH_2), 1.64-1.43 (m, 3H, CH_2), 1.35-1.27 (m, 1H, CH_2).
6g	7.56 (d, J = 8.6 Hz, 3H, Ar-H), 7.31 (d, J = 8.6 Hz, 1H, Ar-H), 7.32-7.28 (m, 2H, Ar-H), 6.91 (d, J = 8.6 Hz, 1H, Ar-H), 6.68 (d, J = 8.6 Hz, 1H, Ar-H), 4.53-4.08 (m, 1H, CH_2), 3.95-3.79 (m, 3H, CH_2), 3.75 (s, 1H, CH_2), 3.67-3.51 (s, 3H, CH_3), 3.45-3.40 (m, 1H, CH), 3.00 (s, 1H, CH), 2.86-2.77 (m, 1H, CH_2), 2.47 (d, J = 4.6 Hz, 1H, CH_2), 2.39-2.24 (m, 1H, CH_2), 1.74 (s, 1H, NH), 1.65-1.50 (m, 2H, CH_2), 1.43 (s, 1H, CH_2), 1.25-1.29 (m, 1H, CH_2).
6h	7.61-7.57 (m, 3H, Ar-H), 7.33-7.23 (m, 3H, Ar-H), 7.11 (t, J = 8.6 Hz, 1H, Ar-H), 6.85 (t, J = 8.6 Hz, 1H, Ar-H), 4.51-4.05 (m, 1H, CH_2), 3.92-3.82 (m, 1H, CH_2), 3.76-3.35 (m, 4H, CH_2), 3.06 (s, 1H, CH), 2.89-2.79 (m, 1H, CH), 2.57-2.27 (m, 2H, CH_2), 1.75 (d, J = 4.7 Hz, 1H, NH), 1.66-1.44 (m, 3H, CH_2), 1.34-1.24 (m, 1H, CH_2).
6i	8.29 (d, J = 8.7 Hz, 1H, Ar-H), 7.96 (d, J = 8.7 Hz, 1H, Ar-H), 7.71 (d, J = 8.7 Hz, 1H, Ar-H), 7.57 (d, J = 32.3 Hz, 2H, Ar-H), 7.33 (d, J = 8.7 Hz, 1H, Ar-H), 7.30 (d, J = 4.0 Hz, 1H, Ar-H), 7.27 (d, J = 3.2 Hz, 1H, Ar-H), 4.40-4.05 (m, 1H, CH_2), 3.92-3.78 (m, 1H, CH_2), 3.75-3.63 (m, 2H, CH_2), 3.60-3.35 (m, 3H, CH_2), 3.07-3.13 (m, 1H, CH), 2.89-2.84 (m, 1H, CH), 2.58 - 2.43 (m, 2H, CH_2), 1.79-1.72 (m, 1H, NH), 1.65 (d, J = 5.7 Hz, 1H, CH_2), 1.53 (d, J = 5.3 Hz, 2H, CH_2).
6j	7.56 (d, J = 1.5 Hz, 2H, Ar-H), 7.44 (d, J = 8.0 Hz, 2H, Ar-H), 7.36 (t, J = 7.8 Hz, 2H, Ar-H), 7.16-7.09 (m, 2H, Ar-H), 4.40-4.08 (m, 1H, CH_2), 3.90-3.84 (m, 1H, CH_2), 3.56-3.42 (m, 4H, $2CH_2$), 3.12-3.01 (m, 1H, CH), 2.92-2.76 (m, 1H, CH), 2.57-2.26 (m, 2H, CH_2), 1.80-1.71 (m, 1H, NH), 1.67-1.46 (m, 3H, CH_2), 1.38-1.22 (m, 1H, CH_2).
6k	7.68-7.63 (m, 2H, Ar-H), 7.53 (s, 2H, Ar-H), 7.39 (d, J = 8.1 Hz, 1H, Ar-H), 7.32 (d, J = 8.0 Hz, 1H, Ar-H), 7.28-7.22 (m, 2H, Ar-H), 4.40-4.07 (m, 1H, CH_2), 3.88-3.80 (m, 1H, CH_2), 3.73-3.35 (m, 4H, $2CH_2$), 3.05 (d, J = 16.8 Hz, 1H, CH), 2.88-2.80 (m, 1H, CH), 2.56-2.26 (m, 2H, CH_2), 1.73 (s, 1H, NH), 1.60-1.50 (m, 3H, CH_2), 1.28 (d, J = 19.4 Hz, 1H, CH_2).
6l	7.45-7.39 (m, 2H, Ar-H), 7.45-7.39 (m, 2H, Ar-H), 5.47-5.26 (m, 1H, CH_2), 5.18-5.00 (m, 1H, CH_2), 4.84 (d, J = 13.1 Hz, 1H, CH_2), 4.23-4.14 (m, 2H, CH_2), 3.70 (s, 1H, CH), 3.14 (d, J = 11.3 Hz, 1H, CH), 2.68-2.62 (m, 1H, CH_2), 2.28 (s, 1H, NH), 1.86-1.67 (m, 2H, CH_2), 1.59 (d, J = 12.8 Hz, 1H, CH_2), 1.35-1.02 (m, 2H, CH_2), 0.93-0.82 (m, 1H, CH_2).

Table 3 ^{13}C NMR data of the title compounds 6

Compd.	^{13}C NMR (100 MHz, $CDCl_3$), δ
6d	170.23, 169.25, 152.69, 152.23, 136.38, 135.95, 134.48, 133.71, 128.94, 128.64, 128.55, 128.31, 62.87, 60.36, 54.38, 53.24, 51.60, 38.16, 36.39, 22.97.
6e	170.30, 169.48, 152.64, 151.39, 134.89, 134.54, 131.63, 131.48, 129.07, 128.50, 124.76, 124.49, 63.22, 60.54, 54.41, 53.31, 51.38, 38.11, 36.38, 22.97.
6g	170.45, 161.18, 160.64, 152.70, 152.14, 129.54, 128.81, 128.26, 128.34, 128.11, 122.11, 113.55, 63.14, 60.14, 55.38, 54.02, 53.95, 53.13, 38.16, 36.55, 23.14.
6i	169.42, 167.95, 152.65, 148.39, 148.01, 142.10, 141.30, 128.32, 127.51, 123.65, 123.39, 122.45, 63.58, 60.52, 54.59, 53.49, 48.16, 37.79, 36.35, 29.59.

Table 4 Anti-fungal activity (inhibition rate, %) of title compounds at 50 μg/mL

Compd.	*Physalospora piricala*	*Fusarium graminearum*	*Phytophthora infestans*	*Rhizoctonia cerealis*	*Sclerotinia sclerotiorum*	*Cochliobolus heterostrophus*	*Fusarium moniliforme*
6a	21.4	7.1	6.3	11.3	8.6	2.6	12.5
6b	33.3	14.3	6.3	28.8	11.4	2.6	18.8
6c	0.0	7.1	18.8	17.5	37.1	0.0	15.6
6d	0.0	32.1	50.0	55.0	57.1	59.0	62.5
6e	45.2	50.0	62.5	67.5	68.6	61.5	62.5
6f	19.0	46.4	62.5	61.3	71.4	56.4	59.4
6g	50.0	46.4	56.3	55.0	68.6	56.4	65.6
6h	95.7	48.3	36.8	43.2	62.5	25.0	39.3
6i	93.5	10.3	42.1	58.1	35.7	41.7	57.1
6j	65.2	17.2	5.3	44.6	10.7	13.9	21.4
6k	43.5	27.6	21.1	59.5	26.8	22.2	21.4
6l	82.6	17.2	5.3	67.6	23.2	13.9	21.4
carbendazim	100					100	100
chlorothalonil		73.1	81.0	100	96.4	100	

Table 5 Insecticidal activity (lethality rates, %) of title compounds

Compd.	*Mythimna separata*		*Culex pipiens pallens*
	200 mg/L	100 mg/L	2 mg/L
6a	35		30
6b	5		20
6c	50		15
6d	30		5
6e	100	40	25
6f	10		25
6g	25		25
6h	50		75
6i	80		65
6j	50		20
6k	100	0	75
6l	50		5
chlorantraniliprole	100	100	100

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(Ed.JIN Shuhui)