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Design, synthesis, and insecticidal activity of novel isoxazole derivatives containing bisamide moiety

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Abstract

In this study, a total of 31 novel isoxazole derivatives containing bisamide moiety were synthesized and evaluated for their insecticidal activity against *Plutella xylostella* (*P. xylostella*). Bioassays indicated that some of the target compounds exhibited good insecticidal activity against *P. xylostella*. In particular, compound **E26** revealed excellent insecticidal activity against *P. xylostella*, with a 50% lethal concentration (LC_{50}) value of 4.6 μg/mL, which was even better than those of chlorpyrifos (7.7 μg/mL), beta-cypermethrin (12.8 μg/mL), and azadirachtin (10.2 μg/mL). These results indicated that isoxazole derivatives containing bisamide moiety could be developed as novel and promising insecticides. To the best of our knowledge, it is the first report on the insecticidal activity of this series of novel isoxazole derivatives containing bisamide moiety.

1 | INTRODUCTION

Plutella xylostella, one of the most widespread and harmful Lepidoptera pests, posed significant threats to cruciferous vegetables in the world and had been causing an estimated annual loss of USD 1.0 billion throughout the world.[1,2] At present, *P. xylostella* had been become a significant challenge for farmers due to it is difficult to prevent and control.[3–6] Nowadays, some of available traditional insecticides, such as chlorpyrifos, beta-cypermethrin, and azadirachtin, were used to control plant harmful pests.[7,8] However, long-term use of available traditional insecticides could lead to the drug resistance as well as result in a negative effect on the environment and plants safety. Therefore, it is an urgent task to develop novel and promising insecticides with a new mode of action.[9,10]

Isoxazole, an important scaffold for synthesis of various active molecules and their derivatives, had a broad spectrum of bioactivities, such as antibacterial,[11] antifungal,[12–14] insecticide,[15,16] and antiviral[17] activities. Meanwhile, amide and their derivatives, which represented a key moiety in heterocyclic chemistry, played a leading role in pharmaceuticals and pesticides chemistry due to their potent bioactivities including antifungal,[18,19] antibacterial,[20–22] anticancer,[23,24] antioxidant,[25] and insecticidal[26] activities. In our previous work, we had reported a series of novel isoxazole

derivatives containing an amide moiety (Figure 1) with potent antiviral activity against tobacco mosaic virus (TMV).[27]

As a continuation of our efforts to discover and develop "me-better" active molecules, in this study, we aimed to replace the pyrazole and acylhydrazone with phenyl and amide, respectively, shown in Figure 2, to build some new isoxazole derivatives containing bisamide moiety as active antiviral agents. Insecticidal activity results indicated that some of the target compounds exhibited potent insecticidal activity against *P. xylostella*. To the best of our knowledge, it is the first report on isoxazole derivatives containing bisamide moiety with potent insecticidal activity against *P. xylostella*.

2 | EXPERIMENTAL

2.1 | General information

Melting points uncorrected were measured by a XT-4 binocular microscope (Beijing Tech Instrument Co., China). The ^{1}H NMR and ^{13}C NMR spectra were determined on an ECX 500 NMR spectrometer (JEOL, Tokyo, Japan) running at room temperature at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR, and dimethyl sulfoxide (DMSO) was used as solvent. Elemental analysis was carried out using an Elemental Vario-III CHN analyzer (Elementar, Hanau, German). Analytical thin-layer chromatography (TLC) was performed on silica gel GF_{254}. All solvents were dried by standard methods in advance and distilled before use.

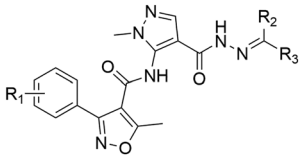


FIGURE 1 Compounds previously reported against tobacco mosaic virus (TMV)

2.2 | General procedure for the preparation of the key intermediate D

As shown in Scheme 1, 3-(2-chlorophenyl)-5-methylisoxazole-4-carboxylic acid **A** (0.02 mol) was added to distillated $SOCl_2$ (50 mL) and reacted at 80°C for 5 hours to obtain intermediate **B**. Then, intermediate **B** (0.02 mol) was added dropwise to a stirred solution of substituted anthranilic acid (0.02 mol) in anhydrous tetrahydrofuran (THF, 100 mL) and trimethylamine (TEA), and the reaction mixture was stirred at room temperature for 2 hours. After that, the reaction mixture was poured into cold 5.0% dilute HCl solution (200 mL). The solid obtained was filtered, washed with water, dried to give the crude product, and then further recrystallized from ethanol to give intermediate **C**. After that, a mixture of intermediate **C** (0.02 mol) and acetic anhydride (Ac_2O, 0.2 mol) was reacted under reflux for 4 hours. At the end of the reaction, the solvent was removed under reduced pressure. The residue was washed with water and the separated solid was collected by filtration, washed with water, recrystallized from ethanol, and dried to give the key intermediate **D**.

2.3 | General procedure for the preparation of the target compounds E1 to E31

Different aliphatic amines (1.5 mmol) were added to intermediate **D** (1.0 mmol) in THF (10 mL), and the suspension stirred at room temperature for 2 hours. Upon completion of the reaction, the mixture was concentrated under vacuum. The residue was dried and recrystallized from ethanol to gain the target compounds **E1** to **E31**.

2.4 | Insecticidal activity test against *P. xylostella*

The insecticidal activities of the target compounds against *P. xylostella* were evaluated using previously reported methods.[28–30] Fresh cabbage leaf discs (diameter 2 cm) were dipped for approximately 10 seconds with the test compound solutions. After drying in air at room

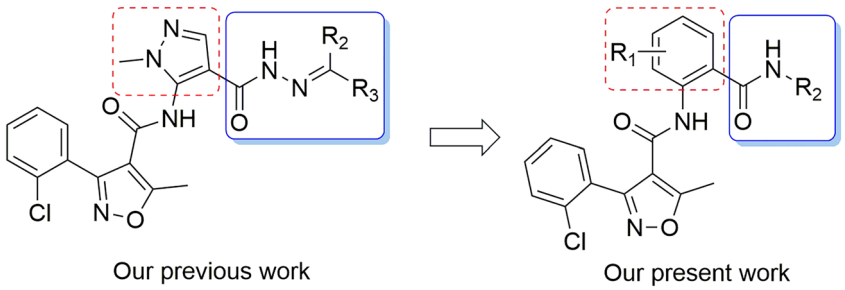
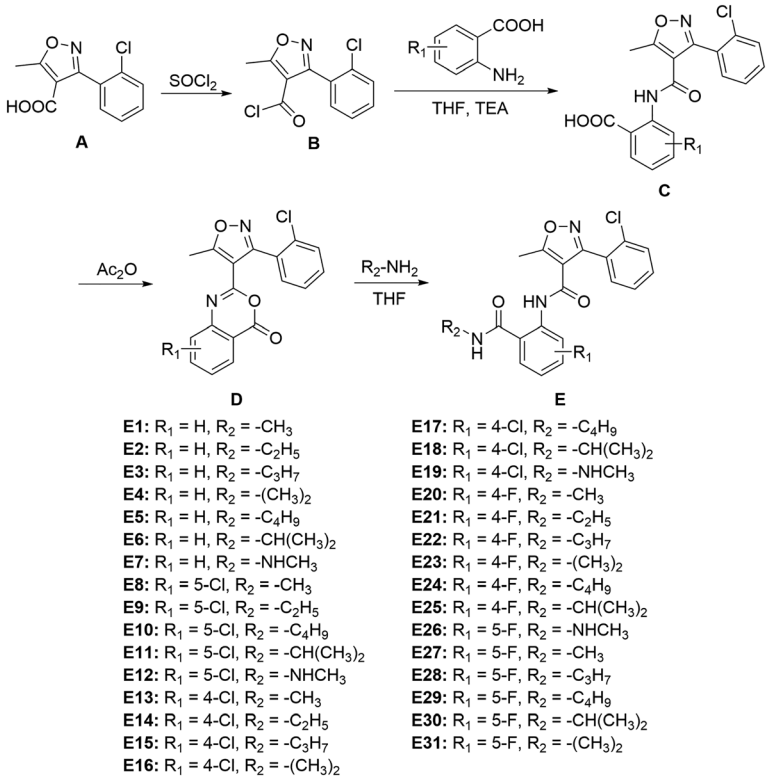


FIGURE 2 Design route of the target compounds [Color figure can be viewed at wileyonlinelibrary.com]



E1: R_1 = H, R_2 = -CH_3
E2: R_1 = H, R_2 = -C_2H_5
E3: R_1 = H, R_2 = -C_3H_7
E4: R_1 = H, R_2 = -$(CH_3)_2$
E5: R_1 = H, R_2 = -C_4H_9
E6: R_1 = H, R_2 = -$CH(CH_3)_2$
E7: R_1 = H, R_2 = -$NHCH_3$
E8: R_1 = 5-Cl, R_2 = -CH_3
E9: R_1 = 5-Cl, R_2 = -C_2H_5
E10: R_1 = 5-Cl, R_2 = -C_4H_9
E11: R_1 = 5-Cl, R_2 = -$CH(CH_3)_2$
E12: R_1 = 5-Cl, R_2 = -$NHCH_3$
E13: R_1 = 4-Cl, R_2 = -CH_3
E14: R_1 = 4-Cl, R_2 = -C_2H_5
E15: R_1 = 4-Cl, R_2 = -C_3H_7
E16: R_1 = 4-Cl, R_2 = -$(CH_3)_2$
E17: R_1 = 4-Cl, R_2 = -C_4H_9
E18: R_1 = 4-Cl, R_2 = -$CH(CH_3)_2$
E19: R_1 = 4-Cl, R_2 = -$NHCH_3$
E20: R_1 = 4-F, R_2 = -CH_3
E21: R_1 = 4-F, R_2 = -C_2H_5
E22: R_1 = 4-F, R_2 = -C_3H_7
E23: R_1 = 4-F, R_2 = -$(CH_3)_2$
E24: R_1 = 4-F, R_2 = -C_4H_9
E25: R_1 = 4-F, R_2 = -$CH(CH_3)_2$
E26: R_1 = 5-F, R_2 = -$NHCH_3$
E27: R_1 = 5-F, R_2 = -CH_3
E28: R_1 = 5-F, R_2 = -C_3H_7
E29: R_1 = 5-F, R_2 = -C_4H_9
E30: R_1 = 5-F, R_2 = -$CH(CH_3)_2$
E31: R_1 = 5-F, R_2 = -$(CH_3)_2$

SCHEME 1 Synthetic route of the target compounds **E1** to**E31**.

temperature, the treated cabbage leaf discs were placed in a petri dish (diameter 9 cm). Then, 10 larvae of second-instar *P. xylostella* were carefully transferred to the petri dish. Chlorpyrifos, beta-cypermethrin, and azadirachtin were used as controls and tested under the same conditions. All bioassays were performed on representative test organisms reared in the laboratory at 25 ± 1°C for 72 hours. Three replicates were performed for each treatment. Percentage mortalities for all test compounds were determined and corrected using Abbott's formula.[31]

3 | RESULTS AND DISCUSSION

3.1 | Synthesis

Using 3-(2-chlorophenyl)-5-methyl isoxazole-4-carboxylic acid as the starting material, the target compounds **E1** to **E31** were obtained in 83% to 90% yields. The structures of the target compounds were identified by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. The physical characteristics data for all the target compounds **E1** to **E31** were listed in the Supporting Information, and the data for the representative compound **E26** (Figure 3) were shown below.

3-(2-Chlorophenyl)-*N*-(5-fluoro-2-(2-methylhydrazinecarbonyl)phenyl)-5-methylisoxazole-4-carboxamide (**E26**). White solid; mp 193°C to 195°C; yield 88%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.80 (s, 1H, isoxazole —CONH), 7.70 (s, 1H, Ar—CONH), 7.61 to 7.37 (m, 6H, Ar—H), 6.99 (s, 1H, Ar—H), 4.75 (s, 1H, —NH—), 3.08 (s, 3H, —CH_3), 2.72 (s, 3H, isoxazole—CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 171.70, 169.14, 160.19, 159.84, 132.99, 132.28 (d, J = 11.25 Hz), 131.93, 130.32, 128.07, 127.61, 124.58, 114.11, 110.71, 110.59, 109.55, 109.34, 38.77, 12.88; IR (KBr, cm^{-1}) ν: 3443, 3339, 3181, 3051, 2994, 2961, 2870, 1684, 1672, 1645, 1622, 1607, 1539, 1493, 1506, 1450, 1416, 1404, 1391, 1387, 1335, 1300, 1256, 1238; Anal. Calcd. for $C_{19}H_{16}ClFN_4O_3$: C 56.65%, H 4.00%, N 13.91%, Found: C 56.75%, H 4.17%, N 13.98%.

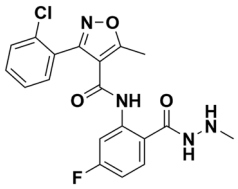


FIGURE 3 The structure of the target compound **E26**

3.2 | Insecticidal activity and structure-activity relationship analysis

The preliminary insecticidal activities of the target compounds **E1** to **E31** against *P. xylostella* were determined via the leaching method and the results were summarized in Table 1. The results of the preliminary

TABLE 1 The insecticidal activity of the target compounds **E1** to **E31** against *Plutella xylostella*

Compounds	Preliminary Biological Activity (%)						
	500 μg/mL	250 μg/mL	100 μg/mL	50 μg/mL	25 μg/mL	12.5 μg/mL	6.25 μg/mL
E1	76.7 ± 2.1	53.3 ± 1.2	30.0 ± 1.3	/	/	/	/
E2	60.0 ± 1.9	40.0 ± 1.4	/	/	/	/	/
E3	56.7 ± 2.2	33.3 ± 1.8	/	/	/	/	/
E4	66.7 ± 1.5	46.7 ± 1.7	/	/	/	/	/
E5	50.0 ± 2.1	26.7 ± 1.1	/	/	/	/	/
E6	43.3 ± 1.4	/	/	/	/	/	/
E7	86.7 ± 2.4	63.3 ± 1.6	43.3 ± 1.0	/	/	/	/
E8	90.0 ± 2.8	76.7 ± 1.9	60.0 ± 2.3	43.3 ± 2.5	/	/	/
E9	83.3 ± 3.0	70.0 ± 2.6	56.7 ± 1.8	36.7 ± 2.1	/	/	/
E10	70.0 ± 3.2	53.3 ± 2.3	40.0 ± 1.5	/	/	/	/
E11	66.7 ± 2.5	50.0 ± 1.4	30.0 ± 1.7	/	/	/	/
E12	100.0 ± 2.9	100.0 ± 3.4	100.0 ± 2.6	93.3 ± 3.7	80.0 ± 2.4	66.7 ± 1.8	43.3 ± 1.9
E13	100.0 ± 3.1	86.7 ± 2.2	70.0 ± 0.9	60.0 ± 1.2	46.7 ± 0.8	/	/
E14	90.0 ± 1.5	73.3 ± 1.8	60.0 ± 1.1	40.0 ± 2.1	/	/	/
E15	83.3 ± 2.0	66.7 ± 1.3	46.7 ± 0.9	/	/	/	/
E16	93.3 ± 1.0	63.3 ± 2.2	46.7 ± 1.4	/	/	/	/
E17	66.7 ± 1.5	50.0 ± 2.0	36.7 ± 1.2	/	/	/	/
E18	63.3 ± 2.1	46.7 ± 1.7	/	/	/	/	/
E19	100.0 ± 1.6	93.3 ± 2.1	83.3 ± 2.5	40.0 ± 1.6	/	/	/
E20	93.3 ± 2.2	80.0 ± 1.7	70.0 ± 1.4	56.7 ± 2.2	30.0 ± 1.9	/	/
E21	90.0 ± 3.1	76.7 ± 2.0	60.0 ± 1.7	43.3 ± 2.6	/	/	/
E22	86.7 ± 1.8	63.3 ± 2.6	46.7 ± 2.1	/	/	/	/
E23	100.0 ± 3.3	90.0 ± 3.4	76.6 ± 1.3	60.0 ± 1.6	46.7 ± 1.0	/	/
E24	80.0 ± 3.5	60.0 ± 2.1	46.7 ± 2.7	/	/	/	/
E25	73.3 ± 1.7	60.0 ± 2.5	40.0 ± 2.1	/	/	/	/
E26	100.0 ± 2.6	100.0 ± 3.0	100.0 ± 2.0	93.3 ± 2.7	80.0 ± 1.9	70.0 ± 2.8	56.7 ± 1.5
E27	100.0 ± 2.0	100.0 ± 2.5	90.0 ± 1.7	60.0 ± 1.4	40.0 ± 2.3	/	/
E28	76.7 ± 1.9	60.0 ± 1.2	46.7 ± 1.3	/	/	/	/
E29	70.0 ± 1.2	60.0 ± 1.6	40.0 ± 2.3	/	/	/	/
E30	67.7 ± 2.1	50.0 ± 2.1	30.0 ± 1.5	/	/	/	/
E31	100.0 ± 3.5	93.3 ± 3.2	80.0 ± 2.4	60.0 ± 1.9	50.0 ± 2.0	/	/
Chlorpyrifos	100.0 ± 1.8	100.0 ± 2.2	100.0 ± 1.4	90.0 ± 1.9	83.3 ± 2.3	66.7 ± 1.6	43.3 ± 2.1
beta-Cypermethrin	100.0 ± 1.3	100.0 ± 2.0	100.0 ± 1.1	83.3 ± 1.9	70.0 ± 2.8	60.0 ± 1.9	40.0 ± 1.5
Azadirachtin	100.0 ± 1.4	100.0 ± 1.6	100.0 ± 1.5	90.0 ± 1.9	80.0 ± 2.8	56.7 ± 1.5	40.0 ± 2.0

bioassays showed that the target compounds **E1** to **E31** against *P. xylostella* with the values of 43.3% to 100% and 20.0% to 100% at 500 and 250 μg/mL, respectively. Meanwhile, compounds **E12**, **E13**, **E19**, **E23**, **E26**, **E27**, and **E31** at 500 μg/mL, compounds **E12**, **E26**, and **E27** at 250 μg/mL, and compounds **E12** and **E26** at 100 μg/mL revealed 100% insecticidal activity against *P. xylostella*, which was equally to those of chlorpyrifos (100%), beta-cypermethrin (100%), and azadirachtin (100%). In particular, compound **E26** still revealed 56.7% insecticidal activity against *P. xylostella* at 6.25 mg/L, which was even better than those of chlorpyrifos (43.3%), beta-cypermethrin (40.0%), and czadirachtin (40.0%). Moreover, the 50% lethal

concentration (LC_{50}) values of some of the target compounds were also evaluated and listed in Tables 2. As shown in Table 2, compounds **E12** and **E26** displayed excellent insecticidal activities against *P. xylostella*, with the LC_{50} values of 6.4 and 4.6 μg/mL, respectively, which were even better than those of chlorpyrifos (7.7 μg/mL), beta-cypermethrin (12.8 μg/mL), and azadirachtin (10.2 μg/mL). These results indicated that isoxazole derivatives containing bisamide moiety could be developed as novel and promising insecticides.

Based on the insecticidal activities of the target compounds against *P. xylostella*, the preliminary structure-activity relationship (SAR) showed that the type and position of the substituent group R had an important effect on the insecticidal activity of the target compounds against *P. xylostella*. First, compared with the same substituent on the R_2 substituent group, with the presence of electron-drawing groups (—Cl, —F) at the R_1 substituent group on phenyl, the corresponding compounds presented better bioactivity against *P. xylostella* (**E8** > **E1**, **E13** > **E1**, and **E9** > **E2**). Second, compared with the same substituent on the R_2 substituent group, with the presence of —Cl at the R_1 substituent group on phenyl, the insecticidal activities against *P. xylostella* of the corresponding compounds with the —Cl substituent group at 4-position were higher than those of at 5-position in the order of **E13** > **E8** and **E14** > **E9**. Third, compared with the same substituent on the R_2 substituent group, with the presence of —F at the R_1 substituent group on phenyl, the insecticidal activities against *P. xylostella* of the corresponding compounds with the —F substituent group at 5-position were higher than those of at 4-position in the order of **E27** > **E20** and **E31** > **E23**.

TABLE 2 The LC_{50} values of the testing compounds against *Plutella xylostella*

Compounds	y = ax + b	r	LC_{50} (μg/mL)
E12	y = 1.56x + 3.74	0.99	6.4 ± 1.4
E13	y = 1.12x + 3.36	0.99	29.0 ± 1.9
E20	y = 1.41x + 2.60	0.98	48.4 ± 2.2
E23	y = 1.30x + 3.13	0.99	27.6 ± 2.0
E26	y = 1.33x + 4.11	0.99	4.6 ± 1.2
E27	y = 1.67x + 2.65	0.96	25.6 ± 2.7
E31	y = 1.37x + 3.12	0.98	23.8 ± 2.5
Chlorpyrifos	y = 1.07x + 4.05	0.98	7.7 ± 1.5
beta-Cypermethrin	y = 1.32x + 3.53	0.98	12.8 ± 2.3
Azadirachtin	y = 1.06x + 3.93	0.96	10.2 ± 3.1

4 | CONCLUSIONS

In conclusion, a total of 31 novel isoxazole derivatives containing bisamide moiety were designed and synthesized. Insecticidal bioassays indicated that some of the target compounds exhibited excellent insecticidal activity against *P. xylostella*. Especially, compound **E26** exhibited the best insecticidal activity against *P. xylostella*, with a LC_{50} value of 4.6 μg/mL, which was superior to those of chlorpyrifos (7.7 μg/mL), beta-cypermethrin (12.8 μg/mL), and azadirachtin (10.2 μg/mL). The results provided a practical tool for guiding the design and synthesis of novel and more potent isoxazole derivatives containing bisamide moiety.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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