Synthesis and Biological Activity of a Novel O-Carboxamidobenzamide Compound Containing 2-Chloroethoxy (2-Bromoethoxy)

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Abstract: Chlorantraniliprole was used as a lead compound to design and synthesize 4 novel o-carboxamidobenzamide compounds containing 2-chloroethoxy (2-bromoethoxy). The structures of them were confirmed by ¹H NMR and HRMS. The insecticidal activities of them were evaluated by against *plutella xylostella* and *chilo suppressalis*. The preliminary results of the insecticidal activity test demonstrated that the target compounds showed excellent insecticidal activity against *plutella xylostella* and *chilo suppressalis*. In particular, the insecticidal activity of compound II₂ is higher than the control reagent chlorantraniliprole at the same concentration. Therefore, Compound II₂ has the value and potential for further research.

1. Introduction

Chlorantraniliprole is a high-efficiency o-amidobenzamide insecticide developed by DuPont company of the United States[^1,2]. Chlorantraniliprole has attracted widespread attention from pesticide researchers due to its excellent insecticidal effect[^3]. The most important feature of chlorantraniliprole was its unique chemical structure, efficient broad-spectrum insecticidal performance, environmental and ecological safety and so on[^4]. Chlorantraniliprole has the same mechanism of action as flubendiamide by controlling the ryanodine receptors (RyRs) of insect to control insects[^5,6]. Chlorantraniliprole could effectively control most of the important lepidopteran insects and some other kinds of insects, its highly efficient larvicidal activity and long-lasting efficacy features provide excellent protection for crops[^7]. In this paper we used chlorantraniliprole as a lead compound to design and synthesize 4 novel o-carboxamidobenzamide compounds containing 2-chloroethoxy (2-bromoethoxy). Preliminary biological activity tests indicated that among the 4 compound, the compound II₁ is comparable to the insecticidal activity of chlorantraniliprole, the insecticidal activity of compound II₂ is higher than that of chlorantraniliprole.
2. Design and Synthesis of the Target Compounds

2.1 Design of the Target Compound.

\[
\text{Chlorantraniliprole}
\]

\[
\text{R1: } R_1 = \text{OCH}_2\text{CH}_2\text{Cl}, R_2 = \text{Cl}
\]

\[
\text{R1: } R_1 = \text{OCH}_2\text{CH}_2\text{Br}, R_2 = \text{CH}_3
\]

Figure 1 Design strategy of target compounds I and II

2.2 Synthesis of the Target Compounds.

2.2.1 Synthesis of compound I1 as an example.

2.2.1.1 Synthesis of 3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbonyl chloride.

To a solution of 3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (15.1 g, 0.05 mol), thionyl chloride (9 g, 0.075 mol) in toluene (80 mL), then the reaction mixture was stirred at 110°C for 3 hrs, it was monitored by TLC until 3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid was consumed completely. After that the reaction mixture was concentrated under reduced pressure to give 3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbonyl chloride as a light yellow oily liquid (15.6 g).
2.2.1.2 Synthesis of 6,8-dichloro-2-(3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-4H-benzo[d][1,3]oxazin-4-one.

To a solution of 2-amino-3,5-dichlorobenzoic acid (10.3 g, 0.05 mol) and pyridine (8 g, 0.1 mol) in acetonitrile (150 mL), then a solution of 3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbonyl chloride (19.2 g, 0.06 mol) in acetonitrile (10 mL) was added dropwise at 25℃. The reaction mixture was stirred at 25℃ for 3 hrs. A solution of methanesulfonyl chloride (6.85 g, 0.06 mol) in acetonitrile (20 mL) was added dropwise, then, the reaction mixture was stirred at 25°C for 8 hrs, it was monitored by TLC until 2-amino-3,5-dichlorobenzoic acid was consumed completely. The reaction mixture was filtered and the filter cake was washed with 30 mL of acetonitrile and 80 mL of water, dried to give 6,8-dichloro-2-(3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-4H-benzo[d][1,3]oxazin-4-one as a light yellow powder (20 g).

2.2.1.3 Synthesis of 3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-N-(2,4-dichloro-6-(isopropylcarbamoyl)phenyl)-1H-pyrazole-5-carboxamide(I1).

To a solution of 6,8-dichloro-2-(3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-4H-benzo[d][1,3]oxazin-4-one (4.5 g, 0.01 mol) and isopropylamine (0.72g, 0.012 mol) in ethyl acetate (40 mL). The reaction mixture was stirred at 25℃ for 3 hrs, it was monitored by TLC until 6,8-dichloro-2-(3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-4H-benzo[d][1,3]oxazin-4-one was consumed completely. The reaction mixture was filtered and the filter cake was dried to give 3-(2-chloroethoxy)-1-(3-chloropyridin-2-yl)-N-(2,4-dichloro-6-(isopropylcarbamoyl)phenyl)-1H-pyrazole-5-carboxamide 4.42g. as a white powder.

2.3 Data for the Twenty Compounds.

2.3.1 Data for the compound I1.

White powder; yield, 83.5%; mp, 157.6～159.2°C; ¹H NMR (500 MHz, DMSO-d₆) δ (ppm) 8.88 (s, 1H), 8.42 (dd, J = 3.3, 1.4 Hz, 1H), 8.10 (ddd, J = 17.7, 8.1, 1.7 Hz, 1H), 8.05 (dd, J = 8.0, 1.5 Hz, 1H), 7.70 (dd, J = 5.4, 2.5 Hz, 1H), 7.52 (d, J = 2.6 Hz, 1H), 7.50–7.46 (m, 1H), 6.72 (d, J = 1.3 Hz, 1H), 4.43–4.35 (m, 2H), 3.98–3.95 (m, 1H), 3.94–3.82 (m, 2H), 1.04 (d, J = 6.5 Hz, 6H). HRMS: calculated for C21H19Cl4N5NaO3 [M+Na]+ 552.0140, found 552.0146.

2.3.2 Data for the compound I2.

White powder; yield, 73.7%; mp, 192.6～194.3°C; ¹H NMR (500 MHz, DMSO-d₆) δ (ppm) 10.10 (s, 1H), 8.44 (dd, J = 4.7, 1.9 Hz, 1H), 8.12 (dd, J = 8.0, 5.1 Hz, 1H), 8.10 − 8.07 (m, 1H), 7.53 (dt, J = 8.3, 4.2 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 6.83 − 6.73 (m, 1H), 4.49 (dd, J = 11.6, 6.2 Hz, 2H), 3.95 − 3.81 (m, 2H), 3.31 (s, 1H), 2.16 (d, J = 2.4 Hz, 3H), 1.04 (d, J = 6.6 Hz, 6H). HRMS: calculated for C22H22Cl3N5NaO3 [M+Na]+ 532.0686, found 532.0689.

2.3.3 Date for the compound II1.

White powder; yield, 70.6%; mp, 140.5～142.4°C; ¹H NMR (500 MHz, DMSO-d₆) δ (ppm) 10.15 (s, 1H), 8.44 (dd, J = 4.6, 1.6 Hz, 1H), 8.28 (t, J = 8.3 Hz, 1H), 8.08 (dd, J = 8.0, 1.6 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 8.0, 4.7 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 6.90 (s, 1H), 4.48 − 4.39 (m, 2H), 4.07 − 3.95 (m, 2H), 3.89 (dp, J = 13.3, 6.6 Hz, 1H), 1.03 (d, J = 6.6 Hz, 6H). HRMS: calculated for C₂₁H₁₀BrCl₃N₅NaO₃ [M+Na]+ 595.9635, found 595.9639.

2.3.4 Date for the compound II2.

White powder; yield, 63.5%; mp, 171.2～173.1°C; ¹H NMR (500 MHz, DMSO-d₆) δ (ppm)
10.12 (s, 1H), 8.44 (dd, J = 4.7, 1.7 Hz, 1H), 8.10 (d, J = 1.6 Hz, 1H), 8.08 (d, J = 1.5 Hz, 1H), 7.53 (dd, J = 8.1, 4.6 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 6.77 (s, 1H), 4.53 – 4.45 (m, 2H), 3.83 (t, J = 5.4 Hz, 1H), 3.32 (d, J = 10.9 Hz, 2H), 2.16 (s, 3H), 1.04 (d, J = 6.6 Hz, 6H). HRMS: calculated for C_{22}H_{22}BrCl_{2}N_{5}NaO_{3}[M+Na]^+ 576.0181, found 576.0179.

3. Insecticidal Activity

3.1 Insecticidal Activity of the Target Compounds Against *Plutella xylostella*.

Adopted leaf dip method, which put forward by International Resistance Action Committee (IRAC), was the method to test the control effect of target compounds on *plutella xylostella* and *chilo suppressalis*.

4. Results and Discussion

Form the data in Table 1 we can see that the four target compounds all have certain insecticidal activity against *plutella xylostella* and *chilo suppressalis*. Especially compound II_2_ showed 69% lethality rate against *plutella xylostella* and 71% lethality rate against *chilo suppressalis* at 1 mg/L, which was higher than that of chlorantraniliprole. In addition, compound II_1_ also showed excellent insecticidal activity against *plutella xylostella* and *chilo suppressalis*.

<table>
<thead>
<tr>
<th>compound number</th>
<th>lethality rate against <em>plutella xylostella</em> (%)</th>
<th>lethality rate against <em>chilo suppressalis</em> (%)</th>
</tr>
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<tr>
<td></td>
<td>10 mg/L</td>
<td>5 mg/L</td>
</tr>
<tr>
<td>I_1_</td>
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<td>67</td>
</tr>
<tr>
<td>I_2_</td>
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<td>76</td>
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<tr>
<td>chlorantraniliprole</td>
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<td>89</td>
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</table>

5. Conclusions

In summary, four novel o-carboxamidobenzamide compounds containing 2-chloroethoxy (2-bromoethoxy) were designed and synthesized. The preliminary insecticidal activity test reveals that the compound II_1_, II_2_ showed superior insecticide activity against *plutella xylostella* and *chilo suppressalis*. These results indicating that when R_1_ was OCH_2_CH_2_BR_, R_2_ was CH_3_, it is helpful to increase the insecticidal activity of the compound. The present work revealed that the compound II_2_ could be used as novel lead structures for the development of new pesticide.

References


