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 ^{1}H NMR and HRMS. The insecticidal activities of them were evaluated by against *plutella xylostella* and c*hilo 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 $\mathbf{II_2}$ is higher than the control reagent chlorantraniliprole at the same concentration. Therefore, Compound $\mathbf{II_2}$ 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 $\mathbf{II_1}$ is comparable to the insecticidal activity of chlorantraniliprole, the insecticidal activity of compound $\mathbf{II_2}$ is higher than that of chlorantraniliprole.

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2. Design and Synthesis of the Target Compounds

2.1 Design of the Target Compound.

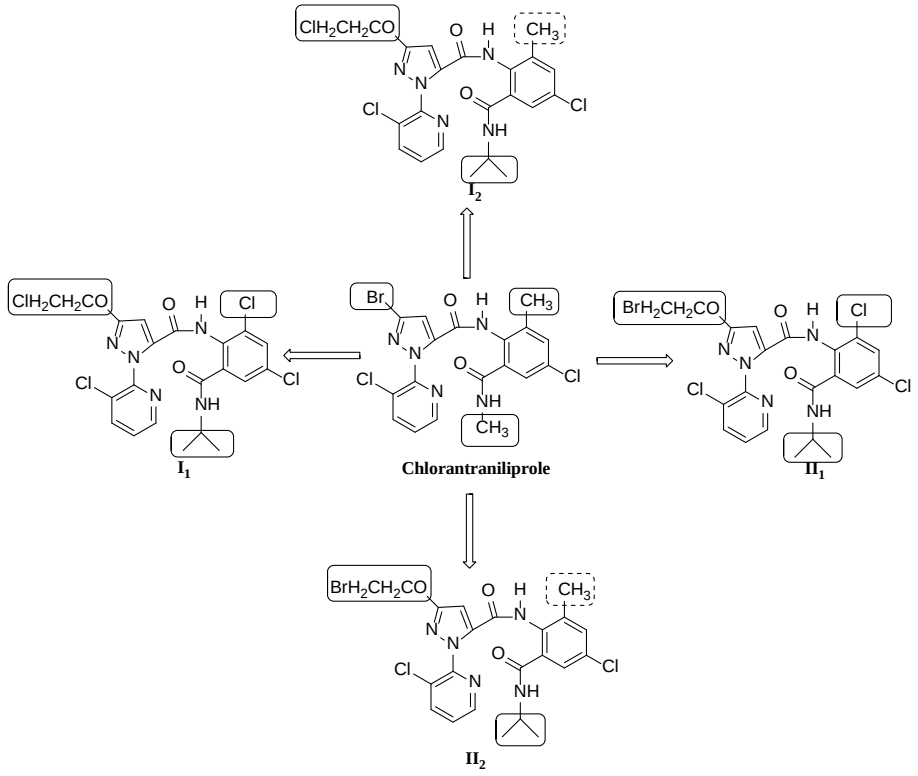

Figure.1 Design strategy of target compounds I and II

2.2 Synthesis of the Target Compounds.

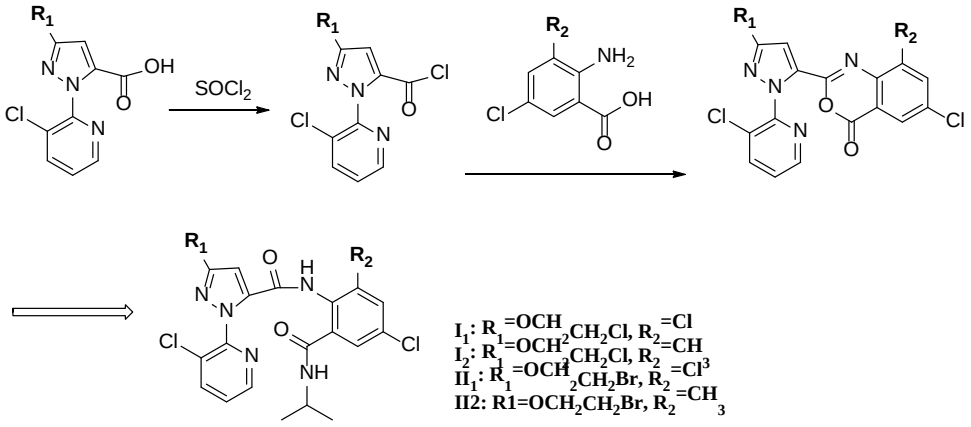

Figure.2 Synthetic route of target compounds

2.2.1 Synthesis of compound I_1 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℃ 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($\mathbf{I_1}$).

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.(**$\mathbf{I_1}$**) as a white powder.

2.3 Data for the Twenty Compounds.

2.3.1 Data for the compound $\mathbf{I_1}$.

White powder; yield, 83.5%; mp, 157.6～159.2°C; ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{21}H_{19}Cl_4N_5NaO_3$ $[M+Na]^+$ 552.0140, found 552.0146.

2.3.2 Data for the compound $\mathbf{I_2}$.

White powder; yield, 73.7%; mp, 192.6～194.3°C; ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{22}H_{22}Cl_3N_5NaO_3$ $[M+Na]^+$ 532.0686, found 532.0689.

2.3.3 Date for the compound $\mathbf{II_1}$.

White powder; yield, 70.6%; mp,140.5～142.4°C; ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{21}H_{19}BrCl_3N_5NaO_3$ $[M+Na]^+$ 595.9635, found 595.9639.

2.3.4 Date for the compound $\mathbf{II_2}$.

White powder; yield, 63.5%; mp, 171.2～173.1°C; ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{22}H_{22}BrCl_2N_5NaO_3[M+Na]^+$ 576.0181, found 576.0179.

3. Insecticidal Activity

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

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 1 Biological activities of target compounds

compound number	lethality rate against *plutella xylostella* (%)			lethality rate against *chilo suppressalis* (%)		
	10 mg/L	5 mg/L	1 mg/L	10 mg/L	5mg/L	1mg/L
I$_1$	91	67	34	90	69	36
I$_2$	94	76	39	92	78	41
II$_1$	96	81	42	94	84	44
II$_2$	100	90	69	100	92	71
chlorantraniliprole	100	89	66	100	91	68

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_2CH_2Br, 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.

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