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Synthesis and Insecticidal Activity of a New Benzenedicarboxamide Derivative

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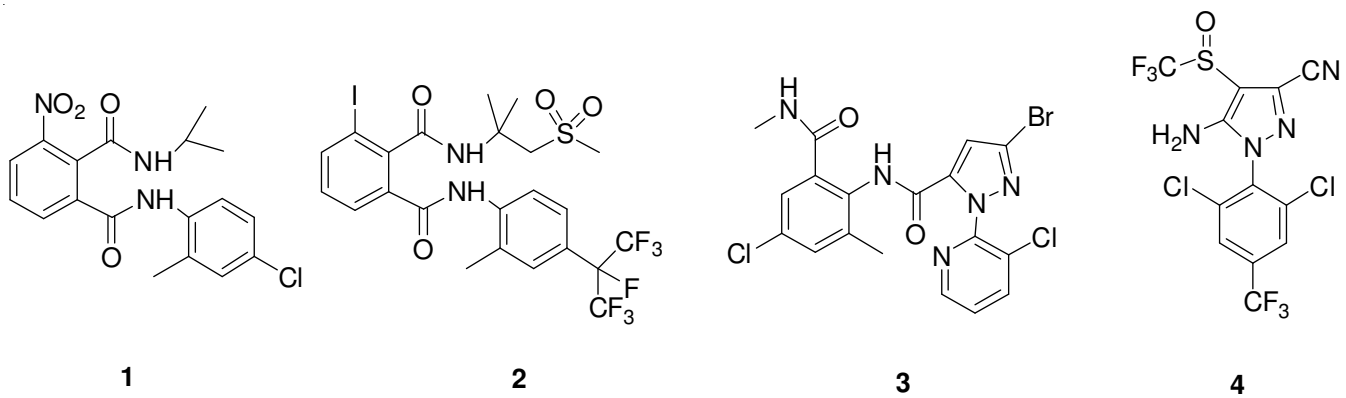
A benzenedicarboxamide derivative was designed and synthesized. Its structure was characterized by ^{1}H NMR. Biological assay showed compound **9** was much potent to beet armyworm (*Spodoptera exigua*) than the positive control. The synthesized compound might be a better candidate of new insecticide against beet armyworm.

Key Words: Benzenedicarboxamide, Synthesis, Biological assay, Beet armyworm.

INTRODUCTION

The use of synthetic insecticides is one of the most effective solutions for controlling pest organisms considered harmful to crop growth in the current agricultural system. Nihon Nohyaku Research Center has found an insecticidal benzenedicarboxamide derivative[1] (**1**, Fig. 1) with novel chemical structure and intriguing insecticidal symptoms. The optimization of a series of benzenedicarboxamide derivatives led to the first commercial phthalic acid diamide insecticide fubendiamide (**2**, Fig. 1)[2]. Fubendiamide is also the first artificially synthesized insecticide targeting RyRs and was discovered by Nihon Nohyaku and jointly developed with Bayer CropScience. It represents a novel class of insecticides with extremely high activity against a broad spectrum of lepidopterous insect pest species. Chlorantraniliprole (**3**, Fig. 1) is another representative commercial introduction of the RyRs insecticides[3], which showed exceptional insecticidal activity on a broad range of Lepidoptera[4].

The chemical structure of flubendiamide is characterized by three parts: a phthaloyl moiety, an aliphatic amide moiety and an aromatic amide moiety. This new molecule possesses a combination of excellent insecticidal activity and ecofriendly characteristics with a skeleton structure of phthalic acid diamide. In order to discover new insecticide, we sought to incorporate the active substructural unit of fipronil[5a,5b] (**4**, Fig. 1) which is an outstanding new insecticide for crop protection with good selectivity between insects and mammals, into the backbone structure of flubendiamide. On the basis of molecular similarity and the principle of combining active substructures, we designed and synthesized the title compound **9**. This paper describes the syntheses and bioactivities against three lepidopteran insects of the designed compound **9**.

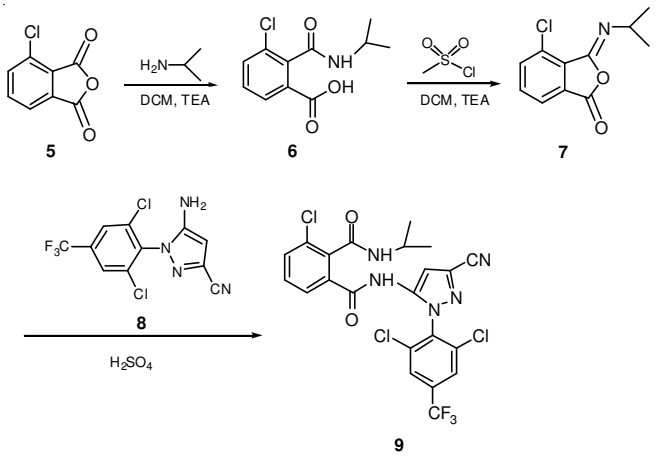


1 **2** **3** **4**

Fig. 1. Chemical structures of four commercial insects

EXPERIMENTAL

Melting points were determined with an electrothermal digital melting point apparatus and were uncorrected. ^{1}H NMR spectra were run on a Varian-400. All raw materials were purchased from commercial sources. Reagents were all analytically or chemically pure. All the solvents and liquid reagents were dried by standard methods in advance or distilled before use. The title compound was synthesized according to literature procedures[6]. The synthetic routes were outlined in **Scheme-I**.



Scheme-I: Synthetic procedure of the title compound

Preparation of 3-chloro-2-(isopropylcarbamoyl)-benzoic acid (6): A mixture of isopropylamine (1.18 g, 20 mmol) and triethylamine (2.02 g, 20 mmol) was slowly added to a solution of **5** (3.65 g, 20 mmol) in dichloromethane (30 mL) at 0-5 ºC. The reaction mixture was stirred for 0.5 h and acidified with 1 mol/L hydrochloric acid until pH = 1 then the white solid appeared. The mixture was filtrated to give part of **6** as a white solid. The filtrate was concentrated and purified by silica gel column chromatography to give another part of product. The combined product: 3.78 g (yield 78.2 %), m.p. 139-140 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (s, 1H, COOH), 7.92 (d, *J* = 8 Hz, 1H, Ph-H), 7.55 (d, *J* = 8 Hz, 1H, Ph-H), 7.36 (t, *J* = 8 Hz, 1H, Ph-H), 5.75 (d, *J* = 8 Hz, *J* = 8 Hz 1H, NH), 4.31 (m, 1H, CH), 1.25 (d, *J* = 6.4 Hz, 6H, $2CH_3$).

Preparation of 4-chloro-3-(isopropylimino)isobenzofuran-1(3*H*)-one (7): A slurry of compound **6** (0.24 g, 1 mmol) in dichloromethane (10 mL) was cooled in an ice bath, then a solution of triethylamine (0.10 g, 1 mmol) in dichloromethane (5 mL) was added dropwise with stirring. The solution was stirred and cooled to < 10 ºC followed by addition of methylsulfonyl chloride (0.11 g, 1 mmol) in dichloromethane (5 mL) at a rate so as to maintain the temperature below 10 ºC. The progress of the reaction was monitored by TLC. The reaction solution was washed with water, dried over anhydrous magnesium sulfate, filtered and the filtrate containing compound **7** was used in the subsequent reaction without further purification.

Preparation of 3-chloro-N^1-(3-cyano-1-(2,6-dichloro-4-(trifluoro methyl)phenyl-1*H*-pyrazol-5-yl)-N^2-isopropylphthalamide (9): To above obtained solution was added compound **8** (0.32 g, 1 mmol) and a drop of concentrated sulfuric acid. The reaction mixture was stirred for 2 h at room temperature. 10 mL of water was added and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The obtained residue was washed with ethyl acetate (3 mL), filtered to give part of **9** as a light-yellow solid. The filtrate was concentrated and purified by silica gel column chromatography to give another part of product. The combined product **9**, 0.37 g (yield 68.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.07 (s, 1H, NH), 8.35 (d, *J* = 8 Hz, 1H, NH), 8.05 (s, 2H, Ph-H), 7.37-7.56 (m, 3H, Ph-H), 7.25 (s, 1H, Pyrazole-H), 4.03 (m, 1H, CH), 1.16 (d, *J* = 6.4 Hz, 6H, $2CH_3$).

Biological assay: The insecticidal activity of the synthesized compound against Diamondback moth (*Plutella xylostella* L.), Beet Armyworm (*Spodoptera exigua*) and *Chilo suppressalis* Walker was tested. Assessments were made on a dead/alive basis and mortality rates were corrected using Abbott's formula[7]. Evaluations are based on a percentage scale of 0-100, in which 0 = no activity and 100 = total kill. The larvae with abnormal symptoms such as body contraction, feeding cessation, or paralysis were included in the number of dead.

RESULTS AND DISCUSSION

Larvicidal activity against Diamondback moth (*Plutella xylostella* L.) and Beet Armyworm (*Spodoptera exigua*): The larvicidal activities of the target compounds against beet armyworm and diamondback moth were tested by the leaf-dip method[8]. One commercial product, chlorantraniliprole was used as control. Leaf disks (1.8 cm in diameter) were cut from fresh cabbage leaves and then dipped into the test solution for 30 s. After air-drying, the treated leaf disks were placed in a Petri dish (60 cm in diameter) lined with a piece of filter paper and then 15 third-instar beet armyworm larvae and diamondback moth larvae were transferred to the Petri dish. The tests were maintained under a 14L-10D photoperiod, at 24-26 ºC and approx. 70 % relative humidity. Percentage mortalities were evaluated 48 h or 72 h after treatment and four replicates were carried out. The results were shown in Tables 1 and 2.

TABLE-1
LARVICIDAL ACTIVITIES AGAINST DIAMONDBACK MOTH OF COMPOUND **9**

Compound	Concentration (mg/L)	Mortality rate (%)
Compd. **9**	20	10.42
	10	9.09
	5	6.82
Chlorantraniliprole	20	100
	10	100
	5	100

The results in Table-1 indicated that compound **9** showed certain larvicidal activity, but much lower than controls. For example, the larvicidal activity of compound **9** against diamondback moth at 20 mg/L was only 10 % as compared to 100 % mortality of chlorantraniliprole in 48 h.

The results in Table-2 indicated that the target compound **9** displayed a litter lower larvicidal activities against beet

TABLE-2
LARVICIDAL ACTIVITIES AGAINST BEET ARMYWORM OF COMPOUND **9**

Compound	Concentration (mg/L)	Mortality rate	
		48 h	72 h
9	160	22.73	45.39
	40	22.73	34.85
Chlorantraniliprole	160	52.27	55.79
	40	26.67	52.22

TABLE-3
STOMACH TOXICITY OF COMPOUND **9** TO *Chilo suppressalis* WALKER LARVAE

Concentration (mg/L)	Mortality rate (%)
2000	30.77
650	25.64
400	10.26
80	0
65	0

armyworm than chlorantraniliprole. The larvicidal activity of compound **9** against beet armyworm at 160 mg/L was 45.39 % as compared to 55.79 % mortality of chlorantraniliprole in 72 h.

Larvicidal activity against *Chilo suppressalis* Walker: The synthesized compound **9** (0.065 g) was dissolved in 1 mL of DMF, then diluted to generate a serial dilutions with distilled water (3% Tween contained). The control treatment received the solvent without tested compound. All tests were maintained at 27 ± 1 ºC.

The stomach toxicity of the compound **9** to *Chilo suppressalis* Walker was tested by seedling-dip method with nine serial dilutions (0.65-2000 mg/mL). Nanjing No. 11 rice cultivar was used. Twenty seedlings as a group were immersed individually into each of these dilutions for 5 min. After natural air drying, two second-instar larvae were inoculated per seedling. Then the seedlings were placed into test tube with water in the bottom to maintain wetness of the rice seedling roots. For each dilution, 40 insects were treated. Mortality was recorded after 72 h.

The results outlined in Table-3 showed that low corrected mortality of 30.77 % at 2000 mg/mL and LD_{50} was supposed to higher than 2000 mg/mL, which indicated that the stomach toxicity to *Chilo suppressalis* Walker larvae of compound **9** was low.

In conclusion, a new benzenedicarboxamide derivative was designed and synthesized and its larvicidal activities against diamondback moth, beet armyworm and *Chilo suppressalis* Walker were evaluated. The preliminary bioassays indicated the title compound exhibited relatively good insecticidal activities against beet armyworm. The mortality can reach to 45.39 % when chlorantraniliprole possesses the mortality of 55.79 % at the same concentration.

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