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Synthesis and Biological Activities of 2,2-Dichloro-1-(4-ethoxyphenyl)-*N*-Substituted Phenyl Cyclopropanecarboxamide

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Some new amide-type compounds are synthesized from 1-(4-ethyoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylic acid and substituted anilline. Their structures were confirmed by ^{1}H NMR, MS and elemental analysis. The bioassay results indicated that they showed moderate fungicidal and insecticidal activities.

Key Words: Pyrethroid, Amide, Synthesis, Fungicidal activity, Insecticidal activity.

INTRODUCTION

Cyclopropane derivatives, as a kind of highly bioactive compounds, have been studied broadly for many years[1]. At the end of 1940s, cyclopropane compounds, such as pyrethroids, were marketed as low toxic insecticides. Since the first pyrethroids insecticide-Allethrin was found, a large variety of pyrethroids derivatives have been synthesized and lots of them, such as deltamethrin, cypermethrin, bifenthrin, fenvalerate, tefluthrin and so on, are commercially available[2]. From then on, many biologically active and structurally stable cyclopropane compounds had been synthesized[3].

In recent years, synthesis of broader spectrum and highly bioactive substituted cyclopropane compounds. Due to the amide group exhibited the good biological activity, such as herbicidal activity, fungicidal activity, insecticide activity, *etc.*[4]. In line with our continuous efforts to synthesize bioactive lead compounds for crop protection, the title compounds were designed by introducing amide pharmacophore into the cyclopropane scaffold and their biological activity tested. Then, the single crystal of the title compound was determined. The preliminary biological test showed that the synthesized compound has moderate fungicidal and insecticidal activities.

EXPERIMENTAL

Melting points were determined by an X-4 apparatus and uncorrected. ^{1}H NMR spectra were measured on a Bruker Avance 400 DMX instrument using TMS as an internal standard and $CDCl_3$ as the solvent. Mass spectra were recorded on a HP 5989B mass detector instrument. Elemental analyses were performed on a Carlo erba EA1110 elemental analyzer. All the reagents are of analytical grade or freshly prepared before use.

1-(4-Ethyoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylic acid was synthesized in our laboratory according to literature. Thionyl chloride (100 mL) was added into 1-(4-ethyoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (10 mmol) and the mixture was refluxed for 8 h. The excessive thionyl chloride was distilled off under reduced pressure. The desired acid chloride was not purified. Dropwised the acid chloride to substituted substituted aniline (10 mmol) and Et_3N (12 mmol), then vigorously stirred at ambient temperature. TLC was employed to trace the process. Stop the reaction and cool the resultant mixture under room temperature. The corresponding amide precipitated immediately. The product was filtered, washed with diluted acetic acid, dried and purified by silica-gel column eluted with ethyl acetate/petroleum ether to give the title compounds **4**.

2,2-Dichloro-1-(4-ethoxyphenyl)-*N*-phenylcyclopropane carboxamide(4a). White crystal;yield, 80.5 %; m.p., 148-151 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, J = 7.2 Hz, 3H, CH_3), 2.22 (d, J = 8.0 Hz, 1H, cyclopropane H), 2.72 (d, J = 8.4 Hz, 1H, cyclopropane H), 4.00-4.04 (m, 2H, CH_3CH_2O), 6.93-6.95 (m, 2H, Ph), 7.21-7.25 (m, 3H, Ph), 7.56 (s, 1H, NH), 7.70-7.72 (m, 2H, Ph), 7.92-7.94 (m, 2H, Ph); Ms *m/z* (relative intensity/%): 350 (M^+, 36), 315 (21), 279 (14), 258 (100), 187 (39), 165 (74), 92 (17), 77 (9); Anal. calcd. for $C_{18}H_{17}NO_2Cl_2$ (%): C 61.73, H 4.89, N 4.00, found: C 61.45, H 4.87, N 4.02.

2,2-Dichloro-1-(4-ethoxyphenyl)-*N*-(3-methylphenyl)-cyclopropane carboxamide(4b). White crystal; yield, 78.4 %;

m.p., 128-131 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.37 (t, *J* = 7.2 Hz, 3H, CH_3), 2.25 (d, *J* = 8.0 Hz, 1H, cyclopropane H), 2.38 (s, 3H, CH_3), 2.81 (d, *J* = 8.8 Hz, 1H, cyclopropane H), 3.98-4.02 (m, 2H, CH_3CH_2O), 6.96-6.98 (m, 2H, Ph), 7.31-7.35 (m, 3H, Ph), 7.56 (s, 1H, NH), 7.81-7.93 (m, 3H, Ph); Ms *m/z* (relative intensity/%): 364 (M^+, 29), 330 (49), 294 (20), 258 (100), 187(12), 165 (68), 92 (12), 77 (6). Anal. calcd. for $C_{19}H_{19}NO_2Cl_2$(%): C 62.65, H 5.26, N 3.85, found: C 62.70, H 5.23, N 3.79.

2,2-Dichloro-1-(4-ethoxyphenyl)-N-(4-methylphenyl)-cyclopropane carboxamide(4c). White crystal; yield, 77.8 %; m.p., 120-123 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.40 (t, *J* = 7.2 Hz, 3H, CH_3), 2.26 (d, *J* = 8.0 Hz, 1H, cyclopropane H), 2.39 (s, 3H, CH_3), 2.79 (d, *J* = 8.8 Hz, 1H, cyclopropane H), 3.99-4.03 (m, 2H, CH_3CH_2O), 6.99-7.01 (m, 2H, Ph), 7.28-7.30 (m, 2H, Ph), 7.66 (s, 1H, NH), 7.88-8.02 (m, 4H, Ph); Ms *m/z* (relative intensity/%): 364 (M^+, 36), 330 (20), 294 (39), 258 (100), 187 (40), 165 (56), 92 (18), 77 (11). Anal. calcd. for $C_{19}H_{19}NO_2Cl_2$ (%): C 62.65, H 5.26, N 3.85, found: C 62.77, H 5.24, N 3.81.

2,2-Dichloro-1-(4-ethoxyphenyl)-*N*-(2-methylphenyl)-cyclopropane carboxamide(4d). White crystal; yield, 81.6 %; m.p., 132-134 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, *J* = 7.2 Hz, 3H, CH_3), 2.26 (d, *J* = 8.4 Hz, 1H, cyclopropane H), 2.40 (s, 3H, CH_3), 2.88 (d, *J* = 8.8 Hz, 1H, cyclopropane H), 3.98-4.01 (m, 2H, CH_3CH_2O), 6.95-6.97 (m, 2H, Ph), 7.40-7.45 (m, 3H, Ph), 7.59 (s, 1H, NH), 7.82-7.95 (m, 3H, Ph); Ms *m/z* (relative intensity/%): 364 (M^+, 22), 330 (40), 294 (36), 258 (100), 187 (29), 165 (76), 92 (24), 77 (18). Calcd. for $C_{19}H_{19}NO_2Cl_2$ (%): C 62.65, H 5.26, N 3.85, found: C 62.58, H 5.21, N 3.93.

2,2-Dichloro-1-(4-ethoxyphenyl)-*N*-(4-nitrophenyl)-cyclopropane carboxamide(4e). White crystal; yield, 70.2 %; m.p., 134-136 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.41 (t, *J* = 7.2 Hz, 3H, CH_3), 2.26 (d, *J* = 8.0 Hz, 1H, cyclopropane H), 2.79 (d, *J* = 8.8 Hz, 1H, cyclopropane H), 3.98-4.03 (m, 2H, CH_3CH_2O), 6.91-6.93 (m, 2H, Ph), 7.29-7.31 (m, 2H, Ph), 7.78 (s, 1H, NH), 8.01-8.12 (m, 3H, Ph); Ms *m/z* (relative intensity/%): 395 (M^+, 41), 360 (22), 324 (36), 258 (100), 187 (11), 165 (44), 92 (19), 77 (28). Calcd. for $C_{18}H_{16}N_2O_4Cl_2$ (%): C 54.70, H 4.08, N 7.09, found: C 54.54, H 4.05, N 7.13.

2,2-Dichloro-1-(4-ethoxyphenyl)-*N*-(2,4-difluoro-phenyl)cyclopropane carboxamide(4f). White crystal; yield, 76.4 %; m.p., 126-129 ºC; ^{1}H NMR ($CDCl_3$) δ: 1.41 (t, *J* = 7.6 Hz, 3H, CH_3), 2.31 (d, *J* = 8.0 Hz, 1H, cyclopropane H), 2.79 (d, *J* = 8.4 Hz, 1H, cyclopropane H), 4.00-4.04 (m, 2H, CH_3CH_2O), 7.00-7.02 (m, 2H, Ph), 7.45-7.47 (m, 2H, Ph), 7.70 (s, 1H, NH), 7.82-7.90 (m, 3H, Ph); Ms *m/z* (relative intensity/%): 386 (M^+, 28), 350 (31), 315 (12), 258 (100), 187 (32), 165 (48), 92 (20), 77 (29); Calcd. for $C_{18}H_{15}NO_2Cl_2F_2$ (%): C 55.98, H 3.91, N 3.63, found: C 56.08, H 3.86, N 3.69.

Biological activities

Bioassay of fungicidal activities: The method for testing the primary biological activities was performed in an isolated culture. Under a sterile condition, 1 mL DMSO of title compound was added to the culture plates, followed by the addition of 9 mL of culture medium. The final mass concentration of the title compound was 50 μg/mL. The blank assay was performed with 1 mL of sterile water. Circle mycelium with a diameter of 4 mm was cut using a drill. The culture plates were cultivated at (24 ± 1) ºC. The extended diameters of the circle mycelium were measured after 72 h. The relative inhibition rate of the circle mycelium compared to blank assay was calculated *via* the following equation:

Relative inhibition rate (%) = [(CK - PT) / CK] × 100 %

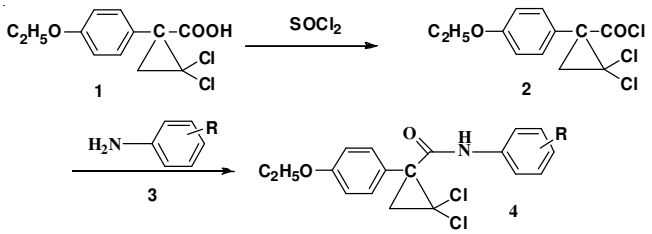
where, CK is the extended diameter of the circle mycelium during the blank assay; and PT, is the extended diameter of the circle mycelium during testing.

Bioassay of insecticidal activities: Insecticidal activities against *Nilaparvata legen, Mythimna separate, Tetranychus cinnabarnus* and *Aphis medicagini* were performed in the greenhouse. The bioassay was operated at 25 ± 1 ºC according to statistical requirements. Assessments were made on a dead/alive basis and mortality rates were corrected according to Abbott's formula. Percent mortality was evaluated. Error of the experiments was 5 %. For comparative purpose, compound **5** were tested as control under the same conditions.

The insecticidal activities of compounds **4** were evaluated according FAO procedure. The insecticidal activity against oriental armyworm was tested by foliar application, individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. Then every 10 fourth-instar oriental armyworm larvae were put into each dish. Percent mortalities were evaluated 2 days after treatment. Each treatment was replicated for three times.

RESULTS AND DISCUSSION

The synthetic routes of title compounds were illustrated as outlined in **Scheme-I**. The starting material lambda cyhalthrin acid **1** was treated with $SOCl_2$ as chlorination reagent to generate acid chloride **2**. The excess thionyl chloride was removed by reduced pressure distillation. For the next step the acyl chloride was used without additional purification. Then it reacted with substituted aniline at room temperature as shown in **Scheme-I**.



4a, R=H; 4b, R=3-Me; 4c, R=4-Me; 4d, R=2-Me; 4e, R=4-NO_2; 4f, R=2,4-F_2

Scheme-I: Synthetic route of title compounds

The chemical structures of the title compounds were confirmed by ^{1}H NMR, mass and elemental analysis. The ^{1}H NMR, mass spectra and elemental analysis data of the compounds are in agreement with the proposed structures. In the ^{1}H NMR spectra, the N-H protons of the amide derivatives were observed as singlets at 7.38-7.82 ppm. All other aromatic protons were observed in the expected regions. All the title compounds of mass spectra are molecular ion peak.

Fungicidal activity: The *in vivo* fungicidal results of all of the compounds against *Rhizoctonia solani, Pseudoperonospora cubensis, Sphaerotheca fuliginea* and *Botrytis cinerea* were

listed in Table-1. As shown in Table-1, all these compounds did not display obvious fungicidal activities against *Rhizoctonia solani, Pseudoperonospora cubensis, Sphaerotheca fuliginea* and *Botrytis cinerea*. Surprisingly, compound **4a** exhibited good activity against *Botrytis cinerea* (61.2 %). As shown in Table-1, compound displayed moderate activity against *Botrytis cinerea*. For the *Sphaerotheca fuliginea* and *Rhizoctonia solani*, it was found that most of them had low activity.

TABLE-1
FUNGICIDAL ACTIVITIES OF 4 (INHIBITION/%)

Compd.	*Sphaerotheca fuliginea*	*Pseudoperonospora cubensis*	*Botrytis cinerea*	*Rhizoctonia solani*
4a	16.3	15.6	61.2	19.8
4b	8.5	8.9	23.5	6.3
4c	6.8	7.8	36.8	6.9
4d	7.8	3.6	20.1	9.2
4e	0	0	15.6	0
4f	0	2.1	10.8	0

Insecticidal activity: The insecticidal activity of compounds **4** against *Nilaparvata legen, Mythimna separate, Tetranychus cinnabarnus* and *Aphis medicagini* was summarized in Table-2. In general, all the title compounds exhibited no insecticidal activity against *Aphis medicagini*. Also, title compounds showed low insecticidal activities against *Nilaparvata legen, Mythimna separate, Tetranychus cinnabarnus*. Surprisingly, only compounds **4b** displayed moderate insecticidal activity against *Mythimna separate* (48.5 %).

TABLE-2
INSECTICIDAL ACTIVITIES OF 4 (MORTALITY/%)

Compd.	*Nilaparvata legen*	*Mythimna separate*	*Tetranychus cinnabarnus*	*Aphis medicagini*
4a	5.3	16.3	0	0
4b	10.1	48.5	16.1	0
4c	0	18.4	4.6	0
4d	8.3	26.4	3.1	0
4e	7.1	36.1	0	0
4f	13.5	20.3	7.8	0

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