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Syntheses and insecticidal activities of novel 2-fluorophenyl-5-aryl/cyclopropyl-1,3,4-oxadiazoles

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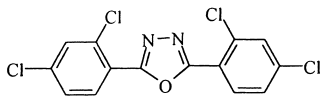
Abstract

Two 2-fluorophenyl-5-substitued cyclopropyl-1,3,4-oxadiazoles (**IIIa–b**) with *cis/trans* isomers were synthesized from the corresponding hydrazide (**Ia**) and aroyl chlorides by two-step reactions. Six asymmetrical 2-(2,4-dichloro-5-fluorophenyl)-5-aryl-1,3,4-oxadiazoles (**IIIc–h**) were obtained by one step reaction of 2,4-dichloro-5-fluorobenzoic acid hydrazide (**Ic**) with the corresponding aromatic carboxylic acid in the presence of phosphorus oxychloride under reflux. However, the similar reaction of 4-fluorophenoxyacetic acid hydrazide (**Ib**) with 2,4-dichloro-5-fluorobenzoic acid failed to yield the desired asymmetrical 2-(2,4-dichloro-5-fluorophenyl)-5-(fluorophenoxymethyl)-1,3,4-oxadiazole, and the resulting product was characterized as symmetrical 2,5-bis(2,4-dichloro-5-fluorophenyl)-1,3,4-oxadiazole (DCFPO). A possible reaction mechanism is suggested. Insecticidal activities of these nine new compounds against armyworms (*Pseudaletia separata Walker*) were determined.

Keywords: Fluoroaryl; 1,3,4-Oxadiazoles; *Cis/trans* isomers; One step reaction; Insecticidal activity; Armyworm

1. Introduction

Symmetrical 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole (DCPO) and analogs were found to be effective insecticides toward houseflies, faceflies and hornflies [1].



DCPO

However, DCPO's limited solubility in polar solvents made it commercially unattractive, therefore, it could be useful to find new 2,5-disubstituted-1,3,4-oxadiazoles which might show similar or enhanced biological activities and possess favorable solubility [2]. Since pyrethroids are efficient insecticides, we introduced one of their typical groups, 2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropyl, to synthesize two 2-fluorophenyl-5-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropyl]-1,3,4-oxadiazoles (**IIIa–b**, Scheme 1). In an experiment, a novel compound, 2,5-bis(2,4-dichloro-5-fluorophenyl)-1,3,4-oxadiazole (DCFPO), was accidentally synthesized (Scheme 2). It was found that DCFPO has better insecticidal activities toward armyworms and better solubility in a majority of organic polar solvents than DCPO [3]. In addition, organic fluorides have good and extensive biological activities allowing their possible application in pharmaceuticals and pesticides [4]. These facts prompted us to synthesize six other asymmetrical 2-(2,4-dichloro-5-fluorophenyl)-5-aryl-1,3,4-oxadiazoles (**IIIc–h**, Scheme 3). These new compounds might be expected to have good insecticidal activities and improved solubility.

2. Results and discussion

2.1. Synthesis

Starting from three different compounds **1**–**3**, hydrazides **Ia–c** were prepared (Scheme 4).

Asymmetrical 2,5-disubstituted-1,3,4-oxadiazoles are usually synthesized from *N,N′*-diacylhydrazines [2]. By this method, compounds **IIIa–b** were prepared from hydrazide **Ia** via *N,N′*-diacylhydrazines **IIa–b** (Scheme 1). The ^{1}H NMR spectra of compound **1** and the above compounds

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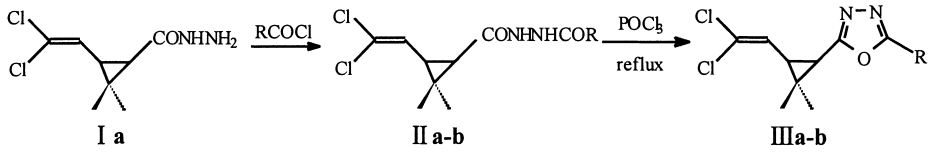
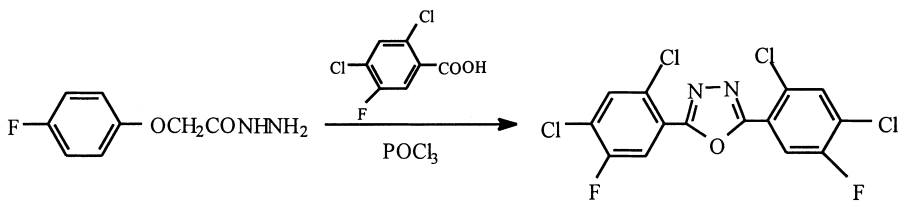


I a **II a-b** **IIIa-b**

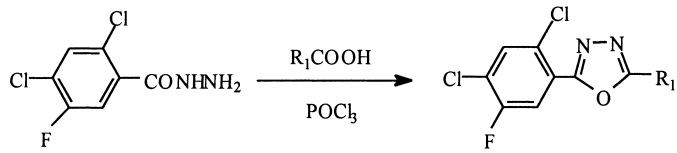
II a, **IIIa**: R = 3-fluorophenyl, **II b**, **IIIb**: R = 2,4-dichloro-5-fluorophenyl

Scheme 1. Conventional route for synthesis of asymmetrical 2,5-disubstituted-1,3,4-oxadiazoles (**IIIa–b**).



I b **DCFPO**

Scheme 2. Route for synthesis of DCFPO.

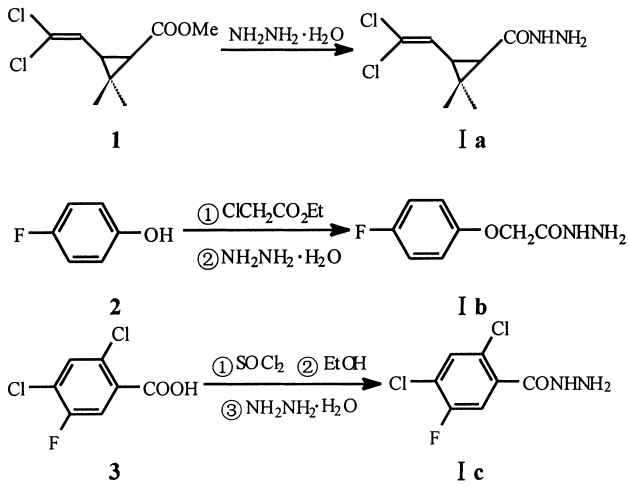


I c **IIIc-h**

IIIc: R' = 2-chloro-3-pyridyl, **IIId**: R' = 3-fluorophenyl, **IIIe**: R' = 6-chloro-3-pyridyl,

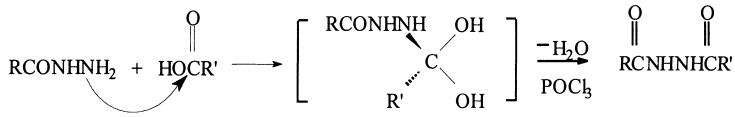
Scheme 3. Simple route for synthesis of asymmetrical 2,5-disubstituted-1,3,4-oxadiazoles (**IIIc–h**).

(except **IIIb**) showed two sets of signals at δ 1.00–7.00 ppm corresponding to *cis* and *trans* isomers on the three-membered cyclopropyl ring [5,6] (see data given in Section 3). Two doublets at δ 6.20–6.40 and 5.50–5.80 ppm for one proton are attributed to the dichlorovinyl CH. Examination of ^{1}H NMR data found in the literature for cyclopropyl compounds revealed that the chemical shifts of the dichlorovinyl hydrogen in *cis* and *trans* configurations followed the rule $\delta_{trans} < \delta_{cis}$ [6]. The doublet at δ 6.20–6.40 ppm (J = 8.50−9.00 Hz) is attributed to the *cis* isomer and the doublet at δ 5.50–5.80 ppm (J = 8.00−8.30 Hz) is attributed to the *trans* isomer. Because separation of *cis* and *trans* isomers is very difficult, they were not separated. However, according to the integration ratio of the dichlorovinyl CH in the ^{1}H NMR spectra of compounds **1**, **Ia**, **IIa–b** and **IIIa–b**, the *cis/trans* contents of these compounds can be estimated (*cis*: **1**, **Ia**, **IIa–b** about 40%; **IIIa** about 19%; **IIIb** zero). The closer the ratio of *cis*:*trans* is to 1:1, the longer the melting range is (see data given in Section 3). The formation of the oxadiazole ring makes steric hindrance increase more greatly in the *cis* configuration than in the *trans* configuration, so the content of *cis* isomer decreases in compound **IIIa** and becomes zero in compound **IIIb**.



Scheme 4. Routes for synthesis of three different hydrazides (**Ia–c**).

Later, we found a simple method by which oxadiazoles could be directly synthesized from carboxylic acids and hydrazides in one step. Although *N*,*N*′-diacylhydrazines need not be synthesized, it is likely that they are first produced by an intermolecular nucleophilic displacement reaction (Scheme 5) and then transformed into oxadiazoles. This view is supported by the fact that only *N*,*N*′-diacylhydrazines were obtained by this method in some experiments. For example, the similar reaction of 4-fluorophenoxyacetic acid hydrazide with trimethylacetic acid gave only



Scheme 5. A possible mechanism for formation of diacylhydrazines by one step method.

N-trimethylacetyl-*N*′-(4-fluorophenoxyacetyl)hydrazine. Because the simple method needs more time and the reaction condition of cyclization is harsh, it is necessary that the hydrazides should be stable. We found that this method might be unsuitable for aliphatic hydrazides (e.g. compound **Ia**) because a large amount of tar was produced and the yield was rather low.

It is interesting that symmetrical 2,5-bis(2,4-dichloro-5-fluorophenyl)-1,3,4-oxadiazole (DCFPO) was synthesized from 4-fluorophenoxyacetic acid hydrazide and 2,4-dichloro-5-fluorobenzoic acid because the expected product was asymmetrical 2-(2,4-dichloro-5-fluorophenyl)-5-(4-fluorophenoxymethyl)-1,3,4-oxadiazole (DCFPO and its analogs are being applied for a patent) [3]. Because 2,4-dichloro-5-fluorobenzoic acid was in excess, we believe that an exchange reaction occurs (Scheme 6) between the carboxylic acid and the diacylhydrazine which was formed via the mechanism shown in Scheme 5. Furthermore, we think that it might be more difficult to transform *N*-(2,4-dichloro-5-fluorobenzoyl)-*N*′-(4-fluorophenoxyacetyl)hydrazine into 2-(2,4-dichloro-5-fluorophenyl)-5-(4-fluorophenoxymethyl)-1,3,4-oxadiazole than to transform *N*,*N*′-bis(2,4-dichloro-5-fluorobenzoyl)hydrazine into DCFPO. With the continuous consumption of *N*,*N*′-bis(2,4-dichloro-5-fluorobenzoyl)hydrazine, the above exchange reaction is favorable for the formation of *N*,*N*′-bis(2,4-dichloro-5-fluorobenzoyl)hydrazine.

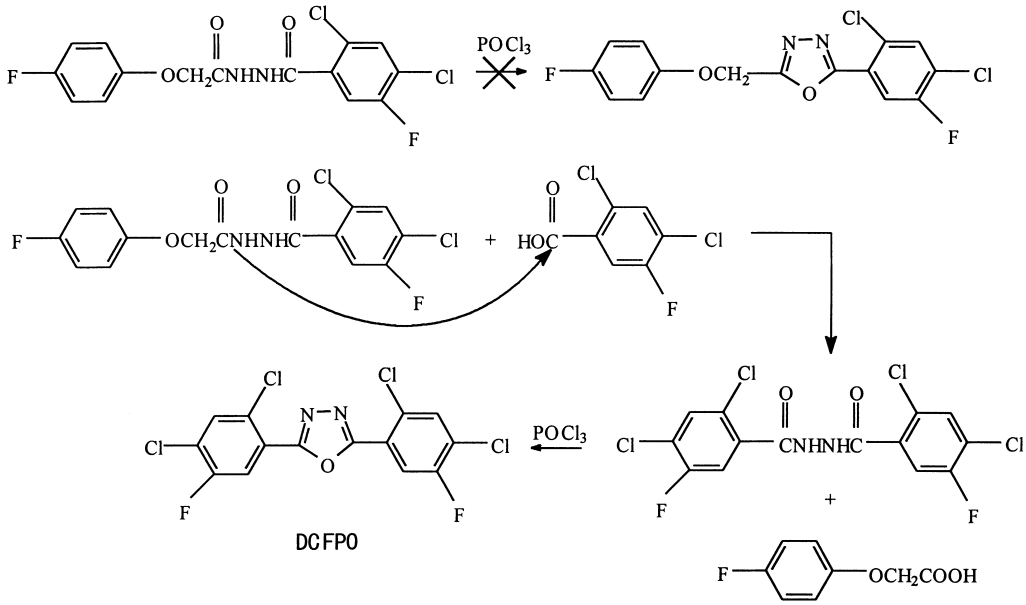
2.2. Insecticidal activities

The insecticidal activities against armyworms for compounds **IIIa–h**, DCFPO and the check sample DCPO are listed in Table 1.

By comparing the insecticidal activities of compounds **IIIa**, **IIIb**, **IIId**, **IIIf**, **IIIh**, DCFPO and DCPO, it was found that their activities against armyworms increased in the following order: **IIIh** < **IIIa** < **IIIb** << **IIId** < DCPO < **IIIf** < DCFPO. So it could be concluded that with the increase of electron-withdrawing power, insecticidal activity of oxadiazoles against armyworms increases. However, when a strong electron-withdrawing group $-NO_2$ was further introduced into DCFPO, the activity decreased greatly. In view of this, it might be implied that there is an optimum electron-withdrawing power or that $-NO_2$ is too big. In addition, the presence of a pyridyl ring is unfavorable for the activity against armyworms and the presence of a 2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropyl group does not obviously increase insecticidal activity.

3. Experimental

Melting points were taken on a digital melting point apparatus made in Shanghai and are uncorrected. ^1H NMR spectra were recorded with Bruker WP-500SY



Scheme 6. A possible reaction mechanism for formation of DCFPO.

Table 1
Percent mortality (%) and LC_{50} (mg/l) of oxadiazoles **IIIa–h**, DCFPO and DCPO against armyworms

Compounds	Conc. (mg/l)	Percent mortality (%)	LC_{50} (mg/l)
IIIa	500	31	>500
IIIb	500	43	>500
IIIc	500	0	–
IIId	125	100	51.18
	50	57	
	25	20	
	12.5	10	
IIIe	500	0	–
IIIf	25	100	5.22
	12.5	93	
	6.25	73	
	3.125	13	
IIIg	500	0	–
IIIh	500	0	–
	5	100	1.77
DCFPO	2.5	57	
	1.25	7	
DCPO	20	93	10.13
	10	27	
	5	17	

(500 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Infrared spectra were measured on KBr disks using a Nicolet FT-IR-20SX instrument. Mass spectra were obtained on a Hitachi M80 instrument. Combustion analyses for elemental composition were made with an Italian MOD.1106 analyzer. All reactions were monitored by TLC.

3.1. Preparation of hydrazides

3.1.1. Preparation of 2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarboxylic acid hydrazide (*Ia*)

A mixture of 2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarboxylic acid methyl ester (**1**) (2.23 g, 10 mmol) and hydrazine monohydrate (5 g, 100 mmol) was boiled under reflux for 12 h. After cooling to room temperature, the precipitate was collected, washed and dried to give a yellowish solid, yield 90%. The solid was recrystallized from ethanol to give yellowish grainy crystals, mp 54.4–70.1°C (*cis*:*trans* = 37.2:62.8). $R_f = 0.20$ (ethyl acetate). IR (KBr): 3300, 3050, 2950, 1645, 1615, 1540, 1430, 1380, 850, 810 cm^{-1}. ^1H NMR ($CDCl_3$): δ *cis*: 6.36 (d, J = 8.80 Hz, 1H, Cl_2CCH), 2.01 (dd, $J = 8.80$ Hz, 1H, CH), 1.58 (d, $J = 8.80$ Hz, 1H, CH), 1.10–1.27 (6H, $2CH_3$); *trans*: 5.62 (d, $J = 8.26$ Hz, 1H, Cl_2CCH), 2.27 (dd, $J = 8.26$ and 5.27 Hz, 1H, CH), 1.41 (d, $J = 5.27$ Hz, 1H, CH), 1.10–1.27 (6H, $2CH_3$). Analysis: Calc. for $C_8H_{12}Cl_2N_2O$ (223): C, 43.05; H, 5.38; N, 12.56%. Found: C, 42.87; H, 5.30; N, 12.44%.

3.1.2. Preparation of 4-fluorophenoxyacetic acid hydrazide (*Ib*)

4-Fluorophenol (**2**) (16.8 g, 150 mmol) was dissolved in anhydrous acetone (45 ml). To the solution were added ethyl chloroacetate (22.5 g, 180 mmol) and anhydrous potassium carbonate (41.25 g, 300 mmol). The reaction mixture obtained was refluxed for 20 h, while stirring. When hot, the reaction mixture was filtered under aspirator pressure. The solvent was removed from the filtrate under reduced pressure to give a reddish brown liquid. After the liquid had stood for a few hours, the resulting precipitate was filtered off to give the crude 4-fluorophenoxyacetic acid ethyl ester. A mixture of the above ester, hydrazine monohydrate (63.70 g, 1.25 mol) and ethanol (75 ml) was refluxed for 14 h. After cooling to room temperature, the resulting precipitate was filtered, washed and dried to produce white needles, yield 31%. The needles were recrystallized from ethanol to produce white needle crystals, mp 132.1–132.9°C. $R_f = 0.18$ (ethyl acetate). Analysis: Calc. for $C_8H_9FN_2O_2$ (184): C, 52.17; H, 4.92; N, 15.21%. Found: C, 52.22; H, 4.93; N, 15.27%.

3.1.3. Preparation of 2,4-dichloro-5-fluorobenzoic acid hydrazide (*Ic*)

A mixture of 2,4-dichloro-5-fluorobenzoic acid (**3**) (8.36 g, 40 mmol) and thionyl chloride (16 ml) was refluxed for 2 h. The excess thionyl chloride was removed by distillation under normal pressure. Benzene (5 ml) was added to the distillation pot and then distilled under reduced pressure to give crude 2,4-dichloro-5-fluorobenzoyl chloride. The crude acyl chloride was added dropwise to anhydrous ethanol (15 ml) over 45 min, while stirring. The reaction mixture was stirred for 12 h at room temperature. The excess ethanol was evaporated under reduced pressure to give the light yellow liquid, 2,4-dichloro-5-fluorobenzoic acid ethyl ester. A mixture of the above ester, hydrazine monohydrate (20.38 g, 400 mmol) and ethanol (20 ml) was refluxed for 10 h. After cooling to room temperature, the resulting precipitate was filtered, washed and dried to produce white needles, yield 72%. The solid was recrystallized from ethanol to give white needle crystals, mp 171.2–171.9°C. $R_f = 0.18$ (ethyl acetate). IR (KBr): 3300, 3050, 1650, 1610, 1560, 1520, 1460, 1380, 1000, 950, 880 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.93 (s 1H, NH), 7.65 (d, $J_{H,F}$ = 8.98 Hz, 1H, ArH), 7.62 (d, $J_{H,F} = 6.51$ Hz, 1H, ArH). Analysis: Calc. for $C_7H_5Cl_2FN_2O$ (223): C, 37.67; H, 2.24; N, 12.56%. Found: C, 37.46; H, 2.06; N, 12.37%.

3.2. General procedure for preparation of N-aroyl-N′-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarbonyl]-hydrazine

2,2-Dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarboxylic acid hydrazide (**Ia**) (1.56 g, 7 mmol), $NaHCO_3$ (0.588 g, 7 mmol), THF (8 ml) and H_2O (4 ml) were mixed. To the mixture was added dropwise a solution of the aroyl chloride

containing fluorine (7 mmol) in THF (6 ml) over 30 min, while stirring. The reaction mixture was stirred for 3 h at room temperature. The solvent was removed in vacuo and a solid obtained was washed and dried to give the crude product.

*3.2.1. N-(3-fluorobenzoyl)-N′-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarbonyl]hydrazine (**Ia**)*

This compound was obtained as a light orange solid from 3-fluorobenzoyl chloride, yield 92%. The solid was recrystallized from ethanol to give yellowish powdery crystals, mp 85.3–101.9°C (*cis*:*trans* = 38.9:61.1). $R_f = 0.36$ (ethyl acetate:petroleum ether = 1:2, v/v). IR (KBr): 3250, 3050, 2950, 1690, 1650, 1590, 1530, 1490, 1260, 890, 840, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ *cis*: 9.86–10.12 (m, 1H, NH), 9.50 (s, 1H,NH), 7.95 (m, 1H, ArH), 7.54 (m, 1H, ArH), 7.38 (m, 1H, ArH), 7.21 (m, 1H, ArH), 6.30 (d, J = 8.66 Hz, 1H, Cl_2CCH), 2.04 (dd, J = 8.66 Hz, 1H, CH), 1.81 (d, J = 8.66 Hz, 1H, CH), 1.15–1.27 (6H, $2CH_3$); *trans*: 9.86–10.12 (m, 1H, NH), 9.50 (s, 1H, NH), 7.95 (m, 1H, ArH), 7.54 (m, 1H, ArH), 7.38 (m, 1H, ArH), 7.21 (m, 1H, ArH), 5.56 (d, J = 8.23 Hz, 1H, Cl_2CCH), 2.30 (dd, J = 8.23 and 5.28 Hz, 1H, CH), 1.63 (d, J = 5.28 Hz, 1H, CH), 1.15–1.27 (6H, $2CH_3$). Analysis: Calc. for $C_{15}H_{15}Cl_2FN_2O_2$ (345): C, 52.17; H, 4.35; N, 8.12%. Found: C, 52.07; H, 4.37; N, 7.99%.

*3.2.2. N-(2,4-dichloro-5-fluorobenzoyl)-N′-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarbonyl] hydrazine (**IIb**)*

This compound was obtained as a gray solid from 2,4-dichloro-5-fluorobenzoyl chloride, yield 88%. The solid was recrystallized from ethanol to give white powdery crystals, mp 127.4–141.9°C (*cis*:*trans* = 39.0:61.0). $R_f = 0.36$ (ethyl acetate:petroleum ether = 1:2, v/v). IR (KBr): 3250, 3050, 2950, 1700, 1650, 1520, 1480, 1420, 1390, 1240, 890, 850, 730 cm^{-1}.^1H NMR ($CDCl_3$): δ *cis*: 9.75–9.94 (m, 1H, NH), 9.54 (s, 1H, NH), 7.61 (d, $J_{H,F}$ = 8.84 Hz, 1H, ArH), 7.53 (d, $J_{H,F}$ = 6.31 Hz, 1H, ArH), 6.35 (d, J = 8.99 Hz, 1H, Cl_2CCH), 2.10 (dd, J = 8.99 Hz, 1H, CH), 1.84 (d, J = 8.99 Hz, 1H, CH), 1.20–1.31 (6H, $2CH_3$); *trans*: 9.75–9.94 (m, 1H, NH), 9.54 (s, 1H,NH), 7.57 (d, $J_{H,F}$ = 8.84 *Hz*, 1H, ArH), 7.51 (d, $J_{H,F}$ = 6.31 Hz, 1H, ArH), 5.63 (d, J = 8.11 Hz, 1H, Cl_2CCH), 2.33 (dd, J = 8.11 and 4.70 Hz, 1H, CH), 1.63 (d, J = 4.70 Hz, 1H, CH), 1.20–1.31 (6H, $2CH_3$). Analysis: Calc. for $C_{15}H_{13}Cl_4FN_2O_2$ (414): C, 43.48; H, 3.14; N, 6.76%. Found: C, 43.19; H, 3.21; N, 6.55%.

3.3. Preparation of 2,5-disubstituted-1,3,4-oxadiazoles

*3.3.1. Preparation of 2-(3-fluorophenyl)-5-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropyl]-1,3,4-oxadiazole (**IIIa**)*

A mixture of *N*-(3-fluorobenzoyl)-*N*′-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarbonyl]hydrazine (**IIa**) (1.73 g, 5 mmol) and $POCl_3$ (10 ml) was refluxed for 3 h. After cooling to room temperature, it was poured slowly into an ice and water mixture. The resulting precipitate was filtered, washed, dried and recrystallized twice from ethanol to produce white needle crystals, yield 67%, mp 150.0–154.9°C (*cis*:*trans* = 18.7:81.3). $R_f = 0.72$ (ethyl acetate:-petroleum ether = 1:2, v/v). IR (KBr): 3100, 2900, 1600, 1570, 1560, 1490, 1240, 1190, 890, 870, 830 cm^{-1}. ^1H NMR ($CDCl_3$): δ *cis*: 7.83 (m, 1H, ArH), 7.73 (m, 1H, ArH), 7.49 (m, 1H, ArH), 7.23 (m, 1H, ArH), 6.28 (d, J = 8.76 Hz, 1H, Cl_2CCH), 2.38 (d, J = 8.76 Hz, 1H, CH), 2.27 (dd, J = 8.76 Hz, 1H, CH), 1.29–1.38 (6H, $2CH_3$); *trans*: 7.83 (m, 1H, ArH), 7.73 (m, 1H, ArH), 7.49 (m, 1H, ArH), 7.23 (m, 1H, ArH), 5.74 (d, J = 8.08 Hz, 1H, Cl_2CCH), 2.48 (dd, J = 8.08 and 5.57 Hz, 1H, CH), 2.13 (d, J = 5.57 Hz, 1H, CH), 1.29–1.38 (6H, $2CH_3$). Analysis: Calc. for $C_{15}H_{13}Cl_2FN_2O$ (327): C, 55.05; H, 3.98; N, 8.56%. Found: C, 54.85; H, 3.96; N, 8.66%.

*3.3.2. Preparation of 2-(2,4-dichloro-5-fluorophenyl)-5-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropyl]-1,3,4-oxadiazole (**IIIb**)*

This compound was prepared as white needle crystals from (**IIb**) as described in Section 3.3.1, yield 60%, mp 139.1–140.2°C. $R_f = 0.72$ (ethyl acetate:petroleum ether = 1:2, v/v). IR (KBr): 3050, 2950, 1570, 1500, 1480, 1360, 1250, 1090, 890, 830, 730 cm^{-1}. ^1H NMR ($CDCl_3$): δ *trans*: 7.84 (d, $J_{H,F}$ = 8.99 Hz, 1H, ArH), 7.63 (d, $J_{H,F}$ = 6.53 Hz, 1H, ArH), 5.76 (d, J = 8.11 Hz, 1H, Cl_2CCH), 2.49 (dd, J = 8.11 and 5.56 Hz, 1H, CH), 2.19 (d, J = 5.56 Hz, 1H, CH), 1.33–1.35 (6H, $2CH_3$). Analysis: Calc. for $C_{15}H_{11}Cl_4FN_2O$ (396): C, 45.45; H, 2.78; N, 7.07%. Found: C, 45.21; H, 2.70; N, 7.16%.

*3.3.3. Preparation of 2-(2,4-dichloro-5-fluorophenyl)-5-(2-chloro-3-pyridyl)-1,3,4-oxadiazole (**IIIc**)*

A mixture of 2,4-dichloro-5-fluorobenzoic acid hydrazide (**Ic**) (1.12 g, 5 mmol), 2-chloro-3-pyridinecarboxylic acid (0.70 g, 5 mmol) and $POCl_3$ (10 ml) was refluxed at 105–110°C for 6 h. After cooling to room temperature, it was poured slowly into an ice and water mixture (100 ml). The resulting precipitate was filtered, washed, dried and recrystallized from ethanol to produce off-white powdery crystals, yield 57%, mp 154.1–154.9°C. $R_f = 0.70$ (ethyl acetate:petroleum ether = 1:2, v/v). ^1H NMR ($CDCl_3$): δ 8.65 (dd, J = 4.76 and 1.96 Hz, 1H), 8.52 (dd, J = 7.78 and 1.96 Hz, 1H), 8.00 (d, $J_{H,F}$ = 8.89 Hz, 1H), 7.71 (d, $J_{H,F}$ = 6.50 Hz, 1H), 7.50 (dd, J = 4.76 and 7.78 Hz, 1H). Analysis: Calc. for $C_{13}H_5Cl_3FN_3O$ (344.5): C, 45.28; H, 1.45; N, 12.19%. Found: C, 45.62; H, 1.42; N, 12.59%.

*3.3.4. Preparation of 2-(2,4-dichloro-5-fluorophenyl)-5-(3-fluorophenyl)-1,3,4-oxadiazole (**IIId**)*

This compound was prepared as light brown grainy crystals from 3-fluorobenzoic acid as described in 3.3.3, yield 55%, mp 135.8–137.0°C. $R_f = 0.68$ (ethyl acetate: petroleum ether = 1:2, v/v). ^1H NMR ($CDCl_3$): δ 7.96 (m,

2H), 7.84 (m, 1H), 7.67 (d, $J_{H,F} = 6.52$ Hz, 1H), 7.55 (m, 1H), 7.30 (m, 1H). Analysis: Calc. for $C_{14}H_6Cl_2F_2N_2O$ (327): C, 51.38; H, 1.83; N, 8.56%. Found: C, 51.77; H, 1.79; N, 8.99%.

*3.3.5. Preparation of 2-(2,4-dichloro-5-fluorophenyl)-5-(6-chloro-3-pyridyl)-1,3,4-oxadiazole (**IIIe**)*

This compound was prepared as off-white powdery crystals from 6-chloro-3-pyridinecarboxylic acid as described in 3.3.3, yield 52%, mp 188.9–190.2°C. $R_f = 0.70$ (ethyl acetate:petroleum ether = 1:2, v/v). ^{1}H NMR ($CDCl_3$): δ 9.14 (dd, $J = 2.42$ and 0.63 Hz, 1H), 8.41 (dd, $J = 2.42$ and 8.36 Hz, 1H), 7.96 (d, $J_{H,F} = 8.86$ Hz, 1H), 7.68 (d, $J_{H,F} = 6.49$ Hz, 1H), 7.56 (dd, $J = 8.36$ and 0.63 Hz, 1H). Analysis: Calc. for $C_{13}H_5Cl_3FN_3O$ (344.5): C, 45.28; H, 1.45; N, 12.19%. Found: C, 45.29; H, 1.50; N, 12.47%.

*3.3.6. Preparation of 2-(2,4-dichloro-5-fluorophenyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole (**IIIf**)*

This compound was prepared as small yellowish needle crystals from 2,4-dichlorobenzoic acid as described in 3.3.3, yield 61%, mp 183.4–184.4°C. $R_f = 0.68$ (ethyl acetate:petroleum ether = 1:2, v/v). IR (KBr): 3060, 3020,1590, 1565, 1480, 1460, 1250, 1100, 1080, 880, 860, 730 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.09 (d, $J = 8.48$ Hz, 1H), 7.97 (d, $J_{H,F} = 8.92$ *Hz*, 1H), 7.68 (d, $J_{H,F} = 6.51$ Hz, 1H), 7.62 (d, $J = 2.02$ Hz, 1H), 7.45 (dd, $J = 8.48$ and 2.02 Hz, 1H). MS (EI 70 eV), (*m/e*, %): 376 (6.833) [M]; 378 (6.778) [M + 2]; 380 (5.367) [M + 4]; 382 (2.319), [M + 6]; 285 (18.673); 191 (63.399); 173 (100); 163 (26.375); 145 (29.431); 109 (25.552); 75 (22.700); 74 (23.836). Analysis: Calc. for $C_{14}H_5Cl_4FN_2O$ (378): C, 44.44; H, 1.32; N, 7.41%. Found: C, 44.72; H, 1.39; N, 7.67%.

*3.3.7. Preparation of 2-(2,4-dichloro-5-fluorophenyl)-5-(2,4-dichloro-3-nitro-5-fluorophenyl)-1,3,4-oxadiazole (**IIIg**)*

This compound was prepared as a yellow solid from 2,4-dichloro-3-nitro-5-fluorobenzoic acid as described in Section 3.3.3. The yellow solid was recrystallized from DMF to give white flake crystals, yield 49%, mp 167.1–167.8°C. $R_f = 0.80$ (ethyl acetate:petroleum ether = 1:2, v/v). ^{1}H NMR ($CDCl_3$): δ 8.17 (d, $J_{H,F} = 8.44$ Hz, 1H), 7.99 (d, $J_{H,F} = 8.79$ Hz, 1H), 7.69 (d, $J_{H,F} = 6.46$ Hz, 1H). Analysis: Calc. for $C_{14}H_3Cl_4F_2N_3O_3$ (441): C, 38.10; H, 0.68; N, 9.52%. Found: C, 37.65; H, 0.66; N, 9.48%.

*3.3.8. Preparation of 2-(2,4-dichloro-5-fluorophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (**IIIh**)*

This compound was prepared as a brown solid from 4-methoxybenzoic acid as described in Section 3.3.3. The brown solid was purified on silica gel by column chromatography with the solvent (petroleum ether:ethyl acetate = 4:1, v/v) as eluent to give a white solid, yield 28%. The solid was recrystallized from ethanol to give white powdery crystals, mp 167.4–168.1°C. $R_f = 0.64$ (ethyl acetate:petroleum ether = 1:2, v/v). IR (KBr): 2950, 2900,2850, 1610, 1500, 1460, 1260, 1100, 1080, 1010, 890, 860, 790, 730 cm^{-1}.^{1}H NMR ($CDCl_3$): δ 8.10 (d, $J = 7.88$ Hz, 2H, ArH), 7.96 (d, $J_{H,F} = 8.91$ Hz, 1H, ArH), 7.66 (d, $J_{H,F} = 6.53$ Hz, 1H, ArH), 7.05 (d, $J = 7.88$ Hz, 2H, ArH), 3.91 (s, 3H, OCH_3). MS (EI 70 eV), (*m/e*, %): 338 (21.501) [M]; 340 (15.070) [M + 2]; 342 (3.278) [M + 4]; 247 (7.335); 191 (15.076); 163 (6.470); 135 (100); 119 (8.299); 107 (5.864); 92 (16.394); 77 (19.426). Analysis: Calc. for $C_{15}H_9Cl_2FN_2O_2$ (339): C, 53.10; H, 2.65; N, 8.26%. Found: C, 52.96; H, 2.37; N, 8.32%.

3.3.9. Preparation of 2,5-bis(2,4-dichloro-5-flurophenyl)-1,3,4-oxadiazole (DCFPO)

The mixture of 4-fluorophenoxyacetic acid hydrazide (**Ib**) (1.84 g, 5 mmol), 2,4-dichloro-5-fluorobenzoic acid (4.18 g, 20 mmol) and $POCl_3$ (10 ml) was refluxed for 5 h. After cooling, it was poured into broken ice. The resulting white precipitate was filtered, washed with diluted sodium hydroxide water solution and then water, dried and recrystallized twice from ethanol to give white flake crystals, yield 58%, mp 176.1–176.2°C. $R_f = 0.80$ ($CHCl_3$). IR (KBr): 3080, 2920,1610, 1580, 1460, 1260, 1095, 890, 730, 670 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.33 (d, $J_{H,F} = 9.61$ Hz, 2H), 8.19 (d, $J_{H,F} = 6.57$ Hz, 2H). MS (EI 70 eV), (*m/e*, %): 393 (18.991) [M − 1]; 395 (21.946) [M + 1]; 397 (4.566) [M + 3]; 399 (3.381), [M + 5]; 305 (23.959); 191 (100); 163 (33.371); 143 (3.367). Analysis: Calc. for $C_{14}H_5Cl_4FN_2O$ (378): C, 44.44; H, 1.32; N, 7.41%. Found: C, 44.72; H, 1.39; N, 7.67%.

3.4. The method for investigation of effect on armyworms (pseudaletia separata walker)

A test solution was made by dissolving the compound in a small amount of DMF, then adding a few drops of surfactant, and finally adding water to a proper volume. Concentration is defined as mass (mg) of the compound per liter of solution. A moderate amount of corn leaves treated by the above test solution were placed on moistened filter paper in broad bottles. Each bottle was infested with 10 s-instar larvae of the Southern armyworm. Corn leaves treated were added daily. All treatments were maintained at about 20°C in a well ventilated room. The percent mortality was determined in 5 days.

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