Synthesis and Quantitative Structure−Activity Relationships of New 2,5-Disubstituted-1,3,4-oxadiazoles

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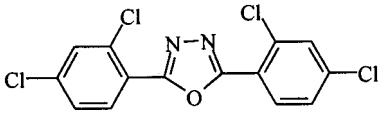
Fourteen new 2,5-disubstituted-1,3,4-oxadiazoles, namely (i) six 2-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropyl]-5-substituted-1,3,4-oxadiazoles and (ii) eight 2-substituted-phenoxymethyl-5-substituted-aryl-1,3,4-oxadiazoles, were synthesized and evaluated for their insect growth regulatory activity against second-instar larvae of armyworm (*Pseudaletia separata* Walker). Two of these compounds (**7** and **8**) showed good insecticidal activities, with LC_{50} values of 14.33 and 15.85 μg/mL, respectively. Steric parameters (e.g., the molecular length d and the ratio of the nonpolar surface area and polar surface area V_1/V_2) and semiempirical quantum parameters (e.g., the molecular total energy E_t and the lowest unoccupied molecular orbital energy E_{LUMO} and so on) of these compounds, as well as those of six other 2,5-disubstituted-1,3,4-oxadiazoles reported, were acquired by the molecular modeling method and the PM3-SCF-MO method, respectively. With the help of the synthons' activity contribution method based on the Free−Wilson approach in its Fujita−Ban variant, quantitative structure−activity relationships were studied by regressing half-lethal concentrations against the above parameters.

Keywords: *2,5-Disubstituted-1,3,4-oxadiazoles; insect growth regulatory activity; armyworm; QSAR*

INTRODUCTION

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



DCPO

(Arrington and Wade, 1980). This type of compound was shown to inhibit chitin synthesis in *Drosophlia* and in *Musca domestica* in both in vitro and in vivo studies. Moreover, 100 ppm of the oxadiazole DCPO was shown to result in up to a 50% reduction in the uptake and incorporation of [6-^{3}H]thymidine into DNA in housefly tissue preparation and a 30% reduction in protein synthesis (Cunn, 1985).

However, it was also felt that only a very small percent of the intrinsic activity of those substances was being observed as a result of their limited solubility in polar media. This solubility problem made DCPO commercially unattractive; therefore, the discovery of new analogues of DCPO, which might show similar or enhanced biological activity and possess favorable solubility characteristics, could be significant (Idoux et al., 1988; Qian and Idoux, 1991; Qian and Zhang, 1996; Shi et al., 2000).

The semiempirical quantum chemical method was used to study the structure−activity relationship of oxadiazoles against wild fruitfly (Qian and Zhang, 1996). The molecular modeling method and the synthons' activity contribution method based on the Free−Wilson approach in its widely applied Fujita−Ban variant were also used to study the structure−activity relationship of some insecticides (Qian, 1996, 1999). By these methods, good quantitative structure−activity relationship equations were established to predict the biological activity of new analogues.

In this work, we have synthesized two series of asymmetrical 2,5-disubstituted-1,3,4-oxadiazoles (**1**−**14**) via two different synthetic routes (Schemes 1 and 2) and measured their insecticidal activity against armyworm. The structure−activity relationship of oxadiazoles against armyworm (*Pseudaletia separata* Walker) was also studied by the three above methods. To enrich structure−activity relationships in the oxadiazoles, we cited six other oxadiazoles (**15**−**20**) with LC_{50} values (Shi et al., 2000). The formulas of all synthesized or cited oxadiazoles are listed in Table 1.

MATERIALS AND METHODS

Experimental Chemistry. All melting points (mp) were obtained with an electrothermal digital apparatus made in Shanghai and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP-500SY (500 MHz) spectrometer with $CDCl_3$/DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. Infrared spectra were measured on a Nicolet FT-IR-20SX instrument using a potassium bromide (KBr) disk, scanning from 625 to 4000 cm^{-1}. Mass spectra were recorded under electron-impact (70 eV) condition using a Hitachi M80 instrument. Combustion analyses for elemental composition were

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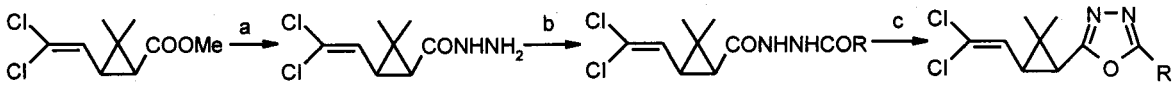
Scheme 1. General Synthetic Route for 2-Cyclopropyl-5-substituted-1,3,4-oxadiazoles (1−6)

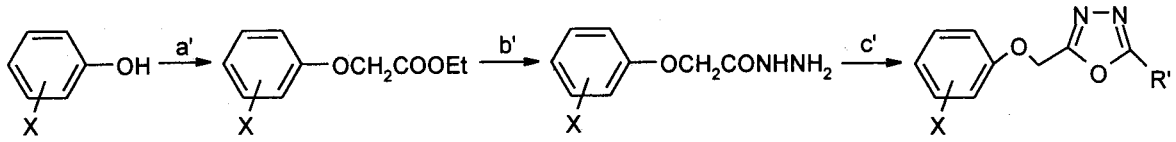


A **B** **C1-C6** **1-6**

a) $NH_2NH_2 \cdot H_2O$ b) $NaHCO_3$, H_2O, THF, RCOCl c) $POCl_3$

C1: R=phenyl; **C2**: R=2-thiophenyl; **C3**: R=2,4-dichlorophenyl; **C4**: R=4-chlorophenyl; **C5**: R=4-methoxylphenyl; **C6**: R=cinnamenyl.

Scheme 2. General Synthetic Route for 2-Phenoxymethyl-5-aryl-oxadiazoles (7−14)



D1-D3 **E1-E3** **F1-F3** **7-14**

a') $ClCH_2CO_2Et$, K_2CO_3, acetone b') $NH_2NH_2 \cdot H_2O$, EtOH c') R'COOH, $POCl_3$

D1, **E1**, **F1**: X=2-Cl; **D2**, **E2**, **F2**: X=4-Cl; **D3**, **E3**, **F3**: X=2,4-Cl_2;

made with an Italian MOD.1106 analyzer. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light.

General Synthetic Procedure for 2-[2,2-Dimethyl-3-(2,2-dichlorovinyl)cyclopropyl]-5-substituted-1,3,4-oxadiazoles (1−6). A mixture of 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylic acid methyl ester (**A**) (2.23 g, 10 mmol) and hydrazine monohydrate (5 g, 100 mmol) was boiled under reflux for 12 h. After the mixture had cooled to room temperature, a precipitate was collected, washed, and dried to give a yellowish solid, 2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarboxylic acid hydrazide (**B**) (90% yield). Compound **B** (without purification) (1.56 g, 7 mmol), $NaHCO_3$ (0.588 g, 7 mmol), THF (8 mL), and H_2O (4 mL) were mixed. To this mixture was added dropwise a solution of the corresponding acyl chloride (7 mmol) in THF (6 mL) over 30 min, with stirring. The reaction mixture was stirred for 3 h at room temperature. The solvent was removed in vacuo, and the solid obtained was washed and dried to give *N*-acyl-*N′*-[2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarbonyl]hydrazines (**C1**−**C6**) in ∼92% yield, which was submitted to the cyclization reaction without further purification. The mixture of the hydrazine **C1**−**C6** (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 from ethanol twice to produce the pure oxadiazoles **1**−**6**. The recrystallized yields for cyclization reactions are listed below.

Data for ***1*** *(**trans**):* yield 55%; obtained as white needle crystals; mp 163.1−163.9 °C; R_f = 0.68 (ethyl acetate/petroleum ether = 1:2, v/v); IR (KBr, cm^{-1}) υ_{max} 3050, 2950, 1650, 1570, 1560, 1490, 1450, 890, 830; ^1H NMR ($CDCl_3$) δ 8.03 (m, 2H, 2ArH), 7.52 (m, 3H, 3ArH), 5.74 (d, J = 8.09 Hz, 1H, Cl_2C=CH), 2.47 (dd, J = 8.09 and 5.56 Hz, 1H, CH), 2.15 (d, J = 5.56 Hz, 1H, CH), 1.29−1.32 (6H, $2CH_3$). Anal. Calcd (%) for $C_{15}H_{14}Cl_2N_2O$: C, 58.25; H, 4.53; N, 9.06. Found: C, 58.25; H, 4.47; N, 9.03.

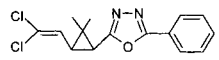
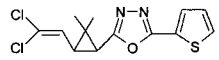
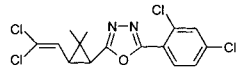
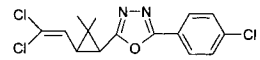
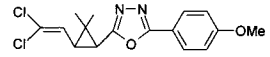
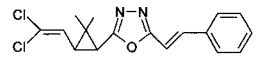
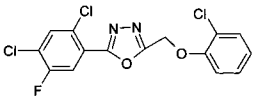
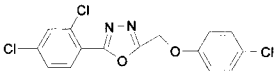
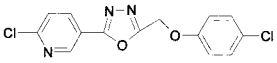
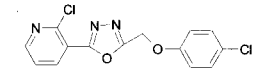
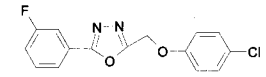
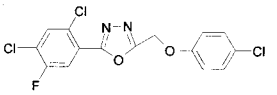
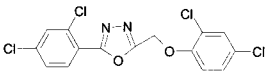
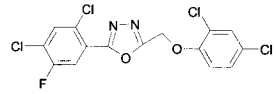
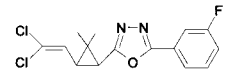
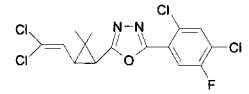
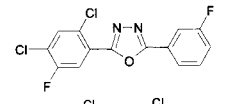
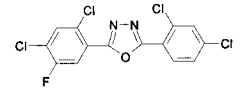
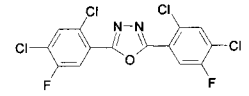
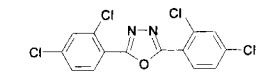
Data for ***2*** *(cis/trans = 6.6:93.4):* yield 60%; obtained as white powdery crystals; mp 149.0−150.2 °C; R_f = 0.74 (ethyl acetate/petroleum ether = 1:2, v/v); IR (KBr, cm^{-1}) υ_{max} 3050, 2950, 1600, 1560, 1495, 1430, 830, 710; ^1H NMR ($CDCl_3$) δ (cis) 7.74 (dd, J = 1.19 and 3.67 Hz, 1H, ArH), 7.56 (dd, J = 1.19 and 5.02 Hz, 1H, ArH), 7.18 (dd, J = 3.67 and 5.02 Hz, 1H, ArH), 6.29 (d, J = 8.80 Hz, 1H, Cl_2C=CH), 2.38 (d, J = 8.80 Hz, 1H, CH), 2.29 (dd, J = 8.80 Hz, 1H, CH), 1.30−1.40 (6H, $2CH_3$); (trans) δ 7.74 (dd, J = 1.19 and 3.67 Hz, 1H, ArH), 7.56 (dd, J = 1.19 and 5.02 Hz, 1H, ArH), 7.18 (dd, J = 3.67 and 5.02 Hz, 1H, ArH), 5.75 (d, J = 8.07 Hz, 1H, Cl_2C=CH), 2.47 (dd, J = 8.07 and 5.58 Hz, 1H, CH), 2.14 (d, J = 5.58 Hz, 1H, CH), 1.30−1.40 (6H, $2CH_3$). Anal. Calcd (%) for $C_{13}H_{12}Cl_2N_2OS$: C, 49.53; H, 3.84; N, 8.89. Found: C, 49.20; H, 3.70; N, 8.90.

Data for ***3*** *(trans):* yield 68%; obtained as white powdery crystals; mp 129.2−129.8 °C; R_f = 0.77 (ethyl acetate/petroleum ether = 1:2, v/v); IR (KBr, cm^{-1}) υ_{max} 3050, 2950, 1590, 1570, 1480, 1380, 1100, 890, 830; ^1H NMR ($CDCl_3$) δ (trans) 7.97 (d, J = 8.48 Hz, 1H, ArH), 7.59 (d, J = 2.03 Hz, 1H, ArH), 7.45 (dd, J = 8.48 and 2.03 Hz, 1H, ArH), 5.77 (d, J = 8.14 Hz, 1H, Cl_2C=CH), 2.49 (dd, J = 8.14 and 5.57 Hz, 1H, CH), 2.21 (d, J = 5.57 Hz, 1H, CH), 1.34 (6H, $2CH_3$). Anal. Calcd (%) for $C_{15}H_{12}Cl_4N_2O$: C, 47.62; H, 3.17; N, 7.41. Found: C, 47.19; H, 3.14; N, 7.40.

Data for ***4*** *(cis/trans = 28.1:71.9):* yield 63%; obtained as white needle crystals; mp 120.5−137.6 °C; R_f = 0.74 (ethyl acetate/petroleum ether = 1:2, v/v); IR (KBr, cm^{-1}) υ_{max} 3050, 2950, 1610, 1590, 1570, 1490, 1410, 1090, 890, 830, 730; ^1H NMR ($CDCl_3$) δ (cis) 8.00 (d, J = 8.55 Hz, 2H, 2ArH), 7.55 (d, J = 8.55 Hz, 2H, 2ArH), 6.30 (d, J = 8.76 Hz, 1H, Cl_2C=CH), 2.40 (d, J = 8.76 Hz, 1H, CH), 2.29 (dd, J = 8.76 Hz, 1H, CH), 1.31−1.41 (6H, $2CH_3$); (trans) δ 8.00 (d, J = 8.55 Hz, 2H, 2ArH), 7.55 (d, J = 8.55 Hz, 2H, 2ArH), 5.76 (d, J = 8.02 Hz, 1H, Cl_2C=CH), 2.49 (dd, J = 8.02 and 5.52 Hz, 1H, CH), 2.15 (d, J = 5.52 Hz, 1H, CH), 1.31−1.41 (6H, $2CH_3$). Anal. Calcd (%) for $C_{15}H_{13}Cl_3N_2O$: C, 52.40; H, 3.79; N, 8.15. Found: C, 51.88; H, 3.66; N, 8.22.

Data for ***5*** *(cis/trans = 23.4:76.6):* yield 61%; obtained as white needle crystals; mp 154.9−165.6 °C; R_f = 0.80 (ethyl acetate/petroleum ether = 1:2, v/v); IR (KBr, cm^{-1}) υ_{max} 3050, 2950, 1610, 1590, 1570, 1500, 1470, 1270, 1030, 890, 830; ^1H NMR ($CDCl_3$) δ (cis) 7.98 (d, J = 8.77 Hz, 2H, 2ArH), 7.02 (d, J = 8.77 Hz, 2H, 2ArH), 6.31 (d, J = 8.81 Hz, 1H, Cl_2C=CH), 3.90 (s, 3H, OCH_3), 2.39 (d, J = 8.81 Hz, 1H, CH), 2.26 (dd, J = 8.81 Hz, 1H, CH), 1.30−1.40 (6H, $2CH_3$); δ (trans) 7.98 (d, J = 8.77 Hz, 2H, 2ArH), 7.02 (d, J = 8.77 Hz, 2H, 2ArH), 5.75 (d, J = 8.11 Hz, 1H, Cl_2C=CH), 3.90 (s, 3H, OCH_3), 2.47 (dd, J = 8.11 Hz and 5.55 Hz, 1H, CH), 2.15 (d, J = 5.55 Hz, 1H, CH), 1.30−1.40 (6H, $2CH_3$). Anal. Calcd (%) for $C_{16}H_{16}Cl_2N_2O_2$: C, 56.64; H, 4.72; N, 8.26. Found: C, 56.71; H, 4.64; N, 8.40.

Table 1. Structure Formulas, Molecular Parameters, and Experimental and Calculated Inecticidal Activities of Synthesized or Cited Oxadiazoles

		Descriptor Variable					Synthons			pLC_{50}			
Compound	Structure Formula	d (Å)	V_1/V_2	E_L (a.u.)	E_{LUMO} (eV)	%trans	S_1	S_2	S_3	Exptl	Calcd[a]	Calcd[b]	Calcd[c]
1		13.897	10.75	-119.1	-0.818	100	0	0	0	2.86	3.03	2.87	2.92
2		13.320	9.82	-116.0	-0.860	93	0	0	0	< 3.0 (0%)*	2.05	2.04	2.35
3		14.581	11.29	-141.2	-1.165	100	0	0	0	3.91	3.61	3.79	3.68
4		14.512	10.89	-130.2	-1.109	72	0	0	0	< 3.0 (0%)*	3.18	3.22	3.24
5		16.161	8.47	-135.4	-0.731	77	0	0	0	< 3.0 (0%)*	0.63	1.35	1.31
6[#]		15.940	10.39	-128.9	-1.296	67	0	0	0	< 3.0 (0%)*	2.65	2.78	3.23
7		14.186	9.60	-154.3	-1.465	100	1	0	0	4.84	1.82	4.93	4.85
8		14.772	9.98	-138.7	-1.293	100	1	0	0	4.80	2.22	4.91	4.90
9		14.636	6.17	-128.6	-1.432	100	1	0	0	< 3.0 (7%)*	-1.80	1.56	2.54
10		14.163	6.44	-128.6	-1.392	100	1	0	0	< 3.0 (0%)*	-1.51	1.79	2.68
11		14.679	8.58	-132.2	-1.191	100	1	1	0	< 3.0 (0%)*	0.74	2.88	3.13
12		14.776	9.44	-154.3	-1.500	100	1	1	0	4.26	1.65	4.06	4.05
13		14.726	9.83	-149.8	-1.299	100	1	0	1	3.11	2.07	3.02	3.04
14		14.780	10.11	-165.4	-1.506	100	1	1	1	2.77	2.36	2.85	2.74
15		13.883	10.63	-134.7	-1.052	81	0	0	0	3.12	2.90	3.10	3.10
16		14.574	11.26	-156.8	-1.377	100	0	1	0	3.25	3.57	3.36	3.17
17		13.113	12.06	-142.6	-1.617	100	0	0	0	4.29	4.41	4.45	4.69
18		13.909	13.05	-149.1	-1.630	100	0	0	0	5.28	5.46	5.40	5.36
19		13.908	12.88	-164.7	-1.773	100	0	0	0	5.75	5.28	5.60	5.42
20(DCPO)		13.908	12.80	-133.5	-1.476	100	0	0	0	4.99	5.20	4.86	5.03

[a] Calculated by eq 1. [b] Calculated by eq 7. [c] Calculated by eq 8. *The values in parentheses are the percentage killed at that concenration. [#] The double bond in **6** is the *E* configuration.

Data for ***6*** *(cis/trans = 33.1:66.9):* yield 66%; obtained as white needle crystals; mp 120.8−134.4 °C; R_f = 0.77 (ethyl acetate/petroleum ether = 1:2, v/v); IR (KBr, cm^{-1}) υ_{max} 3080, 3050, 2950, 1650, 1570, 1530, 1450, 970, 890, 830, 750; ^1H NMR ($CDCl_3$) δ (cis) 7.57 (m, 2H, ArH), 7.50 (d, J = 16.22 Hz, 1H, C=CH), 7.43 (m, 3H, ArH), 7.02 (d, J = 16.22 Hz, 1H, C=CH), 6.30 (d, J = 8.76 Hz, 1H, Cl_2C=CH), 2.37 (d, J = 8.76 Hz, 1H, CH), 2.27 (dd, J = 8.76 Hz, 1H, CH), 1.31−1.40 (6H, $2CH_3$); δ (trans) 7.57 (m, 2H, ArH), 7.50 (d, J = 16.22 Hz, 1H, C=CH), 7.43 (m, 3H, ArH), 7.02 (d, J = 16.22 Hz, 1H, C=CH), 5.75 (d, J = 8.10 Hz, 1H, Cl_2C=CH), 2.48 (dd, J = 8.10 and 5.33 Hz, 1H, CH), 2.12 (d, J = 5.33 Hz, 1H, CH), 1.31−1.40 (6H, $2CH_3$). Anal. Calcd (%) for $C_{17}H_{16}Cl_2N_2O$: C, 60.90; H, 4.78; N, 8.36. Found: C, 61.05; H, 4.69; N, 8.48.

General Synthetic Procedure for Substituted Phenoxyacetic Acid Hydrazides (F1−F3). The substituted phenol (**D1**−**D3**) (100 mmol) was dissolved by anhydrous acetone (30 mL). To the solution were added ethyl chloroacetate (15 g, 120 mmol) and anhydrous potassium carbonate (22.7 g, 200 mmol). The reaction mixture obtained was refluxed for 20 h, with stirring. When hot, the reaction mixture was filtered under aspirator pressure. The solvent was removed from the filtrate under reduced pressure to give the crude substituted phenoxyacetic acid ethyl esters (**E1**−**E3**). A mixture of the above ester (**E1**−**E3**) (without further purification), hydrazine monohydrate (42.30 g, 0.83 mol), and ethanol (50 mL) was refluxed for 14 h. After the mixutre had cooled to room temperature, the resulting precipitate was filtered, washed, and dried to give the crude products, which were recrystallized from ethanol to produce the pure substituted phenoxyacetic acid hydrazides (**F1**−**F3**). The total yields for two-step reactions are given below.

Data for ***F1****:* yield 67%; obtained as a white floc; mp 110.5−111.1 °C; R_f = 0.20 (ethyl acetate). Anal. Calcd (%) for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; N, 13.96. Found: C, 47.81; H, 4.45; N, 13.90.

Data for ***F2****:* yield 74%; obtained as white needle crystals; mp 159.8−162.6 °C (Volovel'skii and Soedin, 1965); R_f = 0.15 (ethyl acetate); IR (KBr, cm^{-1}) υ_{max} 3320, 1680, 1490, 1240, 840. Anal. Calcd (%) for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; N, 13.96. Found: C, 47.69; H, 4.47; N, 13.84.

Data for ***F3****:* yield 66%; obtained as white powdery crystals; mp 155.8−157.4 °C (Zhang et al., 1989); R_f = 0.17 (ethyl acetate). Anal. Calcd (%) for $C_8H_8Cl_2N_2O_2$: C, 40.85; H, 3.40; N, 11.91. Found: C, 40.53; H, 3.28; N, 11.85.

General Synthetic Procedure for 2-Substituted Phenoxymethyl-5-substituted-aryl-1,3,4-oxadiazoles (7−14). A mixture of the substituted phenoxyacetic acid hydrazide (**F1**−**F3**) (10 mmol), the corresponding substituted aromatic carboxylic acid (10−20 mmol), and $POCl_3$ (10 mL) was refluxed for 5−6 h. After cooling, it was poured into broken ice. The resulting precipitate was filtered, washed with diluted sodium hydrate water solution and then water, dried, and recrystallized from ethanol to give the desired products (**7**−**14**).

Data for ***7****:* yield 40%; obtained as light brown powdery crystals; mp 119.5−120.0 °C; R_f = 0.52 (dichloromethane); ^1H NMR (DMSO-d_6) δ 8.15 (d, $J_{H,F}$ = 6.70 Hz, 1H, ArH), 8.05 (d, $J_{H,F}$ = 9.31 Hz, 1H, ArH), 7.35−7.45 (m, 3H, 3ArH), 7.05 (dd, J = 6.75 and 2.44 Hz, 1H, ArH), 5.65 (s, 2H, OCH_2). Anal. Calcd (%) for $C_{15}H_8Cl_3FN_2O_2$: C, 48.22; H, 2.16; N, 7.50. Found: C, 48.08; H, 2.08; N, 7.68.

Data for ***8****:* yield 31%; obtained as white needle crystals; mp 130.2−130.5 °C; R_f = 0.55 (dichloromethane); ^1H NMR (DMSO-d_6) δ 8.00 (d, J = 7.80 Hz, 1H, ArH), 7.92 (s, 1H, ArH), 7.68 (d, J = 7.80 Hz, 1H, ArH), 7.38 (d, J = 7.56 Hz, 2H, 2ArH), 7.15 (d, J = 7.56 Hz, 2H, 2ArH), 5.50 (s, 2H, OCH_2). Anal. Calcd (%) for $C_{15}H_9Cl_3N_2O_2$: C, 50.66; H, 2.55; N, 7.88. Found: C, 50.71; H, 2.47; N, 7.96.

Data for ***9****:* yield 31%; obtained as light brown needle crystals; mp 129.5−130.0 °C; R_f = 0.48 (dichloromethane); IR (KBr, cm^{-1}) υ_{max} 3080, 2880, 1580, 1490, 1230, 1120, 1030, 830, 760; ^1H NMR ($CDCl_3$) δ 8.98 (d, J = 2.40 Hz, 1H, ArH), 8.26 (dd, J = 2.40 and 5.45 Hz, 1H, ArH), 7.43 (d, J = 5.45 Hz, 1H, ArH), 7.20 (d, J = 6.30 Hz, 2H, 2ArH), 6.85 (d, J = 6.30 Hz, 2H, 2ArH), 5.25 (s, 2H, OCH_2). Anal. Calcd (%) for $C_{14}H_9Cl_2N_3O_2$: C, 52.20; H, 2.82; N, 13.04. Found: C, 52.43; H, 2.78; N, 13.12.

Data for ***10****:* yield 30%; obtained as small off-white ball crystals; mp 186.2−186.6 °C; R_f = 0.50 (dichloromethane); ^1H NMR ($CDCl_3$) δ 8.55 (d, J = 5.05 Hz, 1H, ArH), 8.25 (d, J = 2.25 Hz, 1H, ArH), 7.56 (d, J = 5.05 and 2.25 Hz, 1H, ArH), 7.37 (d, J = 9.00 Hz, 2H, 2ArH), 7.05 (d, J = 9.00 Hz, 2H, 2ArH), 4.75 (s, 2H, OCH_2). Anal. Calcd (%) for $C_{14}H_9Cl_2N_3O_2$: C, 52.20; H, 2.82; N, 13.04. Found: C, 52.19; H, 2.74; N, 13.01.

Data for ***11****:* yield 40%; obtained as brilliant yellow needle crystals; mp 100.6−101.5 °C; R_f = 0.57 (dichloromethane); IR (KBr, cm^{-1}) υ_{max} 3100, 2910, 1580, 1490, 1240, 1070, 870, 830, 780, 720; ^1H NMR ($CDCl_3$) δ 7.85 (m, 1H, ArH), 7.75 (m, 1H, ArH), 7.50 (m, 1H, ArH), 7.28 (m, 1H, ArH), 7.25 (d, J = 8.70 Hz, 2H, 2ArH), 6.95 (d, J = 8.70 Hz, 2H, 2ArH), 5.50 (s, 2H, OCH_2). Anal. Calcd (%) for $C_{15}H_{10}ClFN_2O_2$: C, 59.13; H, 3.31; N, 9.20. Found: C, 59.30; H, 3.28; N, 9.26.

Data for ***12****:* yield 45%; obtained as light brown thin flake crystals; mp 126.2−126.8 °C; R_f = 0.50 (dichloromethane); IR (KBr, cm^{-1}) υ_{max} 3090, 2910, 1610, 1580, 1490, 1240, 1090, 1040, 880, 830, 730, 680; ^1H NMR ($CDCl_3$) δ 7.90 (d, $J_{H,F}$ = 6.93 Hz, 1H, ArH), 7.65 (d, $J_{H,F}$ = 9.10 Hz, 1H, ArH), 7.30 (d, J = 8.90 Hz, 2H, 2ArH), 7.00 (d, J = 8.90 Hz, 2H, 2ArH), 5.70 (s, 2H, OCH_2); MS, m/z (relative intensity) 374 (M^+, 7), 245 (41), 194 (75), 191 (100), 165 (11), 128 (10), 111 (10), 99 (16). Anal. Calcd (%) for $C_{15}H_8Cl_3FN_2O_2$: C, 48.22; H, 2.16; N, 7.50. Found: C, 47.91; H, 1.96; N, 7.54.

Data for ***13****:* yield 33%; obtained as white needle crystals; mp 160.9−162.5 °C; R_f = 0.55 (dichloromethane); ^1H NMR (DMSO-d_6) δ 8.00 (s, 1H, ArH), 7.90 (d, J = 1.85 Hz, 1H, ArH), 7.70 (s, 1H, ArH), 7.65 (d, J = 1.85 Hz, 1H, ArH), 7.45 (d, J = 1.40 Hz, 1H, ArH), 7.43 (d, J = 1.40 Hz, 1H, ArH), 5.65 (s, 2H, OCH_2). Anal. Calcd (%) for $C_{15}H_8Cl_4N_2O_2$: C, 46.19; H, 2.07; N, 7.18. Found: C, 46.19; H, 2.05; N, 7.23.

Data for ***14****:* yield 32%; obtained as a white floc; mp 164.6−165.0 °C; R_f = 0.50 (dichloromethane); ^1H NMR (DMSO-d_6) δ 8.15 (d, $J_{H,F}$ = 6.71 Hz, 1H, ArH), 8.05 (d, $J_{H,F}$ = 9.15 Hz, 1H, ArH), 7.65 (d, J = 2.14 Hz, 1H, ArH), 7.40−7.45 (m, 2H, 2ArH), 5.65 (s, 2H, OCH_2). Anal. Calcd (%) for $C_{15}H_7Cl_4FN_2O_2$: C, 44.12; H, 1.72; N, 6.86. Found: C, 44.18; H, 1.68; N, 6.96.

Bioassays. *Insecticidal Activities against Armyworm (P. 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 (micrograms) of the compound per milliliter of solution. A moderate amount of mealie leaves, which were treated with the above test solution, was placed on moistened filter paper in three broad bottles. Each bottle was infested with 10 second-instar larvae of the southern armyworm. The treated mealie leaves were added everyday. All treatments were maintained at ~20 °C in a well-ventilated room. The percent mortality was determined by the number and size of live larvae in the treated bottles relative to that in the untreated controls in 5 days. Insecticidal activity data of the compounds were taken as the dependent variable and were expressed as pLC_{50} (i.e., $-\log LC_{50}$). The standard deviation in pLC_{50} found among three replicate measurements for a compound should be <0.05; otherwise, the value of pLC_{50} for the compound must be remeasured. These data of pLC_{50} are presented in Table 1 along with the activity of 10 oxadiazoles cited. Compound **20**, that is, DCPO, was included for reference purposes.

Descriptor Variables. The molecular shape parameter V_1/V_2, where V_1 and V_2 stand for the nonpolar surface area and polar surface area (Å^2) of water solvation shell, respectively, and the molecular length d (Figure 1) were calculated by using a molecular modeling program, PCMODEL (4th ed., June 1990) of Serena software. Before the above parameters of a compound were calculated, its spatial molecular conformation was optimized with PCMODEL to acquire its most relaxed conformation. The parameter d indicates the maximally extended molecular length between two end atoms in the most relaxed conformation, including hydrogen atoms if present. For electronic parameters the molecular total energy (E_t) and the

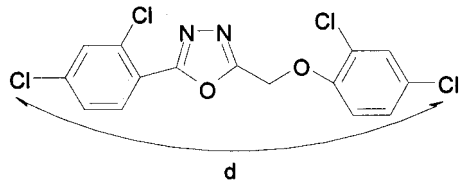


Figure 1. Demonstration of the molecular length *d* (e.g., compound **8**).

energy of the lowest unoccupied molecular orbital (E_{LUMO}) were calculated by using the PM3-SCF-MO method with HyperChem software (1993 edition) of Hypercube, Inc. Also, the energy of the highest occupied molecular orbital (E_{HOMO}) and the net charge on the five-member ring of oxadiazole were calculated. However, the latter two parameters were not listed because they gave poor correlations with pLC_{50}. Before electronic parameters of a compound were calculated, its spatial molecular conformation was also optimized with HyperChem to acquire its most relaxed conformation. In addition, the descriptor "%trans" accounts for the content of the trans isomer in a stereoisomeric mixture. It is defined that if a compound has no cis/trans isomers, its %trans is 100. All descriptor data are listed in Table 1.

Multiple Linear Regression (MLR) Analysis. The regression analysis was done with a computer software package known as "Origin (version 5.0)" of Microcal Software, Inc. The regression was done in a stepwise manner, with the parameter minimizing the sum of squared deviations being introduced step by step and the analysis being stopped when the introduction of the new parameter was no longer statistically significant as evidenced by Student's *t* test.

RESULTS AND DISCUSSION

Synthesis. 2,2-Dimethyl-3-(2,2-dichlorovinyl)cyclopropyl, a "classical" moiety of pyrethrin insecticides, was introduced to synthesize new 1,3,4-oxadiazole analogues (**1**−**6**) by a two-step reaction of 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylic acid hydrazide (**B**) with the corresponding acyl chloride (Scheme 1). The reaction intermediates are the corresponding *N*,*N*′-diacylhydrazines (**C1**−**C6**). Except for **1** and **3**, the experimental cyclopropyl compounds were mixtures of cis and trans isomers, considering the cleavage of the ^{1}H NMR signals corresponding to the dichlorovinyl hydrogen and the cyclopropyl hydrogens. Two diagnostic one-proton doublets at δ 5.50−6.50 ($Cl_2C{=}CH$) were conspicuous in the ^{1}H NMR spectra of all cyclopropyl compounds with cis and trans isomers. 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 $\delta_{trans} < \delta_{cis}$ (Chen et al., 1987). The dichlorovinyl hydrogen in the cis configuration was deshielded by ~0.55 ppm when compared with the same hydrogen in the trans configuration. According to the ratio of the integration of the dichlorovinyl hydrogen in the ^{1}H NMR spectra, the cis/trans contents of all cyclopropyl compounds can be estimated, as can be observed from the data presented under Materials and Methods. Because the cis contents of compounds **4**−**6** are higher (>20%), their melting ranges are longer (>10 °C). The R_f values of cis and trans isomers are indeed close to each other, so they are inseparable by conventional chromatographic techniques. The cyclopropyl oxadiazoles with cis and trans isomers were bioassayed as mixtures of both isomers.

Some aryloxymethyl groups were introduced to synthesize new 1,3,4-oxadiazole analogues (**7**−**14**) with the oxo bridge. The oxo bridge was introduced to increase the molecular flexility. They were prepared by a one-step reaction c′ of the hydrazides (**F1**−**F3**) with the corresponding aryloxy acetic acids (Scheme 2), without the synthesis of the intermediates *N*,*N*′-diacylhydrazines separately (that is, omitting reaction b, Scheme 1). The cyclized product (oxadiazole) can be distinguished from the diacylhydrazine intermediate by their infrared spectra: the latter has a strong N−H absorption peak at $\upsilon_{max} = 3250$ cm^{-1}, but the former has no absorption peak at this wavenumber. Although the diacylhydrazine intermediates were not synthesized separately, it is likely that *N*,*N*′-diacylhydrazines are first produced and then directly transformed into oxadiazoles during the course of the reaction. This view is supported by the experimental fact that the similar one-step reaction of 4-fluorophenoxyacetic acid hydrazide with trimethylacetic acid gave only the intermediate, *N*-trimethylacetyl-*N*′-(4-fluorophenoxyacetyl)-hydrazine. Just because the intermediates do not need to be synthesized separately, the one-step cyclized reaction c′ needs more time than the normal cyclized reaction c (Scheme 1) and so it is necessary that the hydrazides should be stable under the fierce reaction condition of cyclization. We found that this method might be unsuitable for aliphatic hydrazides (e.g., compound **B**) because a large amount of tar was produced and the yield was rather low. All aryloxymethyl oxadiazoles were recrystallized and obtained in a very pure form for the biological assays.

Table 2. Correlation Matrix of the Regression Variables

	V_1/V_2	E_t	E_{LUMO}	S_1	S_2	S_3
V_1/V_2	1					
E_t	0.0558	1				
E_{LUMO}	0.408	0.471	1			
S_1	0.803	0.375	0.0960	1		
S_2	0.345	0.533	0.173	0.318	1	
S_3	0.372	0.373	0.0345	0.539	0.272	1

Biological Activity. The results of the multiple regression analysis are given along with the statistical values (n = number of compounds; r = correlation coefficient; s = standard deviation; F = significance index with respect to the equation). The figures in parentheses are the confidence intervals of the regression coefficient and intercept. All items included in eqs 1, 2, and 7 are significant at the 98% level on the basis of Student's *t* test. Except that E_{LUMO} is significant at the 90% level, all other items included in eq 8 are significant at the 95% level on the basis of Student's *t* test. The entire correlation matrix of the regression variables is listed in Table 2.

Seven compounds, **2**, **4**−**6**, **9**, **10**, and **11**, were excluded from the regression analysis because these compounds did not give measurable LC_{50} values. However, we could not derive a satisfactory regression equation for the activity of the remaining 13 compounds yet. Considering that the $-OCH_2-$ group might have a special activity contribution, we continued to eliminate five compounds, **7**, **8**, and **12**−**14**, with the $-OCH_2-$ group from the regression analysis to derive eq 1:

$$pLC_{50} = \underset{(\pm 1.419)}{-8.309} + \underset{(\pm 0.120)}{1.055}\ V_1/V_2 \qquad (1)$$

$$n = 8,\ r = 0.964,\ s = 0.312,\ F = 77.91$$

Experimental values and values calculated by eq 1 are given in Table 1. Equation 1 explains that the activity of oxadiazole mainly depends on the lipophilicity. The

Table 3. Development of Equation 2

intercept	V_1/V_2	E_t	n	r	s	F
−7.867	1.022		8	0.967	0.303	73.07
−8.603	0.804	−0.0237	7	0.994	0.148	161.00

higher the value of V_1/V_2, the better the lipophilicity, so the higher the activity.

By analyzing the relationship between the activity data of 13 oxadiazoles with the LC_{50} values and the molecular length d values, it was found that when the d value is <14.5 Å, the introduction of fluorine is associated with an improved insecticidal activity. For example, the sequence of the activities of compounds **18**, **19**, and **20** is **20** < **18** < **19**, but when the d value is >14.5 Å, the result is contrary. Compounds **12**, **14**, and **16** are less active than compounds **8**, **13**, and **3**, respectively. Because a replacement of hydrogen by fluorine changes not only the lipophilicity but also the geometry and electronic properties in its environment, a plausible explanation might be that when the d value is <14.5 Å, the introduction of fluorine improves the lipophilicity to increase the activity, but when the d value is >14.5 Å, the increase of steric bulk and the change of electronic properties are unfavorableto the activity. In view of the above facts, it is implied that there is a turning point of molecular length (∼14.5 Å) for the effect of the introduction of fluorine. It is difficult to find a continuous physiochemical parameter to represent this kind of nonlinear relationship. Therefore, compound **16** was excluded from the regression analysis on the basis of eq 1 to derive eq 2:

$$\underset{}{pLC_{50}} = \underset{(\pm 0.722)}{-8.603} + \underset{(\pm 0.079)}{0.804}\ V_1/V_2 - \underset{(\pm 0.00577)}{0.0237E_t} \quad (2)$$

$$n = 7,\ r = 0.994,\ s = 0.148,\ F = 161.00$$

The stepwise development of eq 2 is presented in Table 3. Equation 2 explains that the lower the molecular total energy, the more stable the molecule, so the higher the activity.

By comparing the activity data of compounds **13** and **14** with those of compounds **7**, **8**, and **12**, it is found that the presence of 2,4-dichlorophenoxymethyl could decrease the activity by ∼30−50-fold relative to the presence of 2- or 4-chlorophenoxymethyl. We think that there is a critical molecular length d while an oxadiazole molecule binds to the receptor and its critical value is ∼14.5 Å. When the d value is close to the critical value, the relationship between the steric bulk and the activity is abrupt. The minor increase of the steric bulk could lead to the major decrease of the activity.

To give the quantitative activity contributions of the three moieties [(1) the $-OCH_2-$ group; (2) m-fluorine, d > 14.5 Å; (3) 2,4-dichlorophenoxymethyl, d > 14.5 Å], we adopted the synthons' activity contribution method based on the Free−Wilson approach in its Fujita−Ban variant (Qian, 1999). According to the literature, pLC_{50} is correlated with the mathematical sum of activity contributions (Q_i) of the synthons (S_i).

$$pLC_{50} = q + \sum_i Q_i S_i \quad (3)$$

Here, q is the activity contribution of a specified common parent synthon. When the synthon S_i is present, S_i = 1; when absent, S_i = 0. Herein, (1) the $-OCH_2-$ group, (2) m-fluorine, d > 14.5 Å, and (3) 2,4-dichlorophenoxymethyl, d > 14.5 Å, were treated as synthons, having activity contributions of Q_1, Q_2, and Q_3, respectively. Equation 3 can be written as eq 4.

$$pLC_{50} = q + Q_1 + Q_2 + Q_3 \quad (4)$$

In general, the activity contribution (Q_i) is a linear function of some physiochemical parameters. According to eq 2, we think that Q_i is correlated with the known parameters V_1/V_2 and E_t and some unknown parameters, which are specified as X_i, Y_i, and so on. Thus, the activity contribution Q_i is given by the following general eq 5.

$$Q_i = f(V_1/V_2, E_t, X_i, Y_i, \cdots) = a_i + b_i V_1/V_2 + c_i E_t + d_i X_i + e_i Y_i + \cdots \quad (5)$$

pLC_{50} can now be described as eq 6 by substituting eq 5 into eq 4.

$$pLC_{50} = a + bV_1/V_2 + cE_t + Q_1' + Q_2' + Q_3' = q(a, V_1/V_2, E_t) + \sum_i Q_i' S_i \quad (6)$$

According to eq 6, the calculated result of the regression analysis is given by eq 7.

$$\underset{}{pLC_{50}} = \underset{(\pm 0.772)}{-8.522} + \underset{(\pm 0.076)}{0.819V_1/V_2} - \underset{(\pm 0.00539)}{0.0217E_t} + \underset{(\pm 0.205)}{2.245(S_1)} - \underset{(\pm 0.144)}{0.740(S_2)} - \underset{(\pm 0.151)}{2.002(S_3)} \quad (7)$$

$$n = 13,\ r = 0.992,\ s = 0.161,\ F = 91.44$$

The 14.5 Å threshold for d used in defining S_2 and S_3 is a hidden variable that accounts for 2 degrees of freedom. Therefore, the total degree of freedom for eq 7 is not 7 (13 − 1 − 5), but 5 (13 − 1 − 5 − 2). Thus, the confidence interval, r, s, and F were revised to acquire eq 7′.

$$\underset{}{pLC_{50}} = \underset{(\pm 0.913)}{-8.522} + \underset{(\pm 0.090)}{0.819V_1/V_2} - \underset{(\pm 0.00638)}{0.0217E_t} + \underset{(\pm 0.243)}{2.245(S_1)} - \underset{(\pm 0.170)}{0.740(S_2)} - \underset{(\pm 0.179)}{2.002(S_3)} \quad (7')$$

$$n = 13,\ r' = 0.838,\ s' = 0.190,\ F' = 65.32$$

The activity contribution (Q_1') of the synthon S_1, that is, the $-OCH_2-$ group, is 2.245. The positive value indicates that the introduction of the $-OCH_2-$ group is favorable for the insecticidal activity against armyworm and compensates for the decrease of the lipophilicity. The activity contribution (Q_2') of the synthon S_2, that is, m-fluorine, d > 14.5 Å, is −0.740, which means that the presence of the m-fluorine brings about an adverse effect on the activity when the molecular length d value is more than the critical value. The activity contribution (Q_3') of the synthon S_3, that is, 2,4-dichlorophenoxymethyl, d > 14.5 Å, is −2.002, which has an absolute value greater than that of the activity contribution of S_2. Therefore, the presence of 2,4-dichlorophenoxymethyl decreases the activity more greatly than that of the m-fluorine when the d value is >14.5 Å. According to Table 1, however, it is found that S_3 can be nonzero only if S_1 is not nil. It should be admitted that having this sort of contingent relationship between two regression variables makes the proper

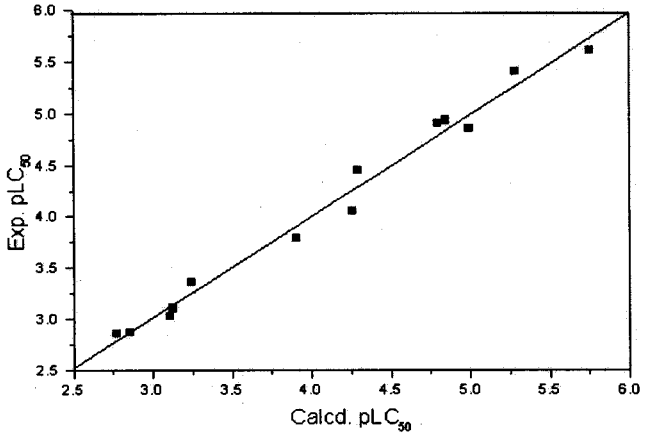


Figure 2. Correlation between experimental and calculated values of insecticidal activities of oxadiazoles.

interpretion of MLR statistics very difficult. The reason for this is that the introduction of the 2,4-dichlorophenoxymethyl group brings about two contradictory effects: on the one hand, the existence of the $-OCH_2-$ group is favorable to the activity; on the other hand, it increases the molecular length to make the minor increment of the steric bulk at one end of the molecule unfavorable to the activity.

Submitting E_{LUMO} for E_t on the basis of eq 7, we derive eq 8.

$$\begin{aligned} pLC_{50} = {} & \underset{(\pm 1.601)}{-5.114} + \underset{(\pm 0.186)}{0.661V_1/V_2} - \underset{(\pm 0.551)}{1.136E_{LUMO}} + \\ & \underset{(\pm 0.439)}{1.951(S_1)} - \underset{(\pm 0.197)}{0.614(S_2)} - \underset{(\pm 0.229)}{1.772(S_3)} \quad (8) \end{aligned}$$

$$n = 13,\ r = 0.984,\ s = 0.232,\ F = 43.53$$

For the same reason as eq 7, eq 8 needs to be revised to get eq 8′.

$$\begin{aligned} pLC_{50} = {} & \underset{(\pm 1.894)}{-5.114} + \underset{(\pm 0.220)}{0.661V_1/V_2} - \underset{(\pm 0.652)}{1.136E_{LUMO}} + \\ & \underset{(\pm 0.519)}{1.951(S_1)} - \underset{(\pm 0.233)}{0.614(S_2)} - \underset{(\pm 0.271)}{1.772(S_3)} \quad (8') \end{aligned}$$

$$n = 13,\ r' = 0.832,\ s' = 0.275,\ F' = 31.09$$

Values calculated by eqs 7 and 8 are given in Table 1 for comparison. The correlation relationship between experimental values and calculated values for eq 7 of the insecticidal activity is shown in Figure 2.

CONCLUSIONS

The insecticidal activity of 2,5-disubstituted-1,3,4-oxadiazoles against armyworm depends on the following factors: the lipophilicity (V_1/V_2), the molecular total energy (E_t) or the energy of the lowest unoccupied molecular orbital (E_{LUMO}), and the molecular length (d). Corresponding to the effects of both *m*-fluoro and 2,4-dichlorophenoxymethyl, it is likely that there are two critical values d_{cri} and d'_{cri} (both estimated to be ~14.5 Å) for the molecular length, respectively, which might be unequal to each other. When d is less than d_{cri} and d'_{cri}, the introduction of a group that increases the value of V_1/V_2 and/or decreases the value of E_t and E_{LUMO} would improve the insecticidal activity of oxadiazole against armyworm. When the introduction of a group makes the molecular length close to or more than d_{cri} and d'_{cri}, however, the electronic property and the steric bulk affect the activity more obviously. In general, when the molecular length increases, the "dumbbell" molecular structure, which has one larger moiety at either end, and the negative meta-group on the phenyl ring at the 2- or 5-position on the oxadiazole ring are unfavorable to the activity.

In addition, it seems that when d is less than d_{cri} and d'_{cri}, the presence of the benzene ring with two withdrawing groups or more (e.g., Cl, F) at the 2- or 5-position on the oxadiazole ring would be essential for the activity because it is favorable to the decrease of E_t or E_{LUMO}.

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