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Syntheses, Antifeedant Activity, and QSAR Analysis of New Oxa(thia)diazolyl 3(2*H*)-Pyridazinones

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Twenty-eight new oxa(thia)diazolyl 3(2*H*)-pyridazinone derivatives were synthesized. Some compounds showed good chronic growth activities against the armyworm, *Pseudaletia separata* (Walker). Their EC_{50} values were determined in vivo. Nineteen 2-*tert*-butyl-4-chloro-5-[5′-aryl-2′-(1′,3′,4′-oxadiazolyl)methoxy]-3(2*H*)-pyridazinones were quantitatively analyzed using the QSAR procedure. The partial least squares method was applied to find relationships between activity and the physicochemical data. The results showed that dipole moment, molar refractivity, and log *P* are identified as critical parameters for chronic growth effects.

KEYWORDS: Syntheses; oxa(thia)diazolyl 3(2*H*)-pyridazinones; chronic growth activity; QSAR

INTRODUCTION

There has been much interest recently in natural products that exhibit antifeedant activity from an agricultural point of view (*1*, *2*). The best known example is azadirachtin, a potent antifeedant and insect growth regulator isolated from the seed of the Indian neem tree (*3*, *4*). However, their translation into a commercial product has been slow, partly because of the structural complexity, instability, and synthetic inaccessibility of those natural products.

In the course of screening compounds for novel and structurally simple antifeedants, we found some new oxadiazolyl 3(2*H*)-pyridazinones that showed chronic growth activity against the Asiatic corn borer, *Ostrinia furnacalis* (Guene**e**). The characteristic effects of the compounds to Asiatic corn borer were similar to those of azadirachtin. These data suggested that the oxadiazolyl 3(2*H*)-pyridazinones might be a new type of antifeedant (*5*−*7*).

Early work in this series concentrated on preparing less complex analogues of **IIIa** (**IIIb**−**t**, X^1 = O or S, X^2 = O, R^1 = *tert*-butyl, R^2 = substituted phenyl). In this paper, chemical transformations were conducted to modify three chemical moieties present in oxadiazolyl 3(2*H*)-pyridazinone and to synthesize four series of key derivatives. The structural modifications were made at the X^2, R^1, and R^2 positions of the skeletal structure shown in **Figure 1** and **Table 1** (**IVa**−**h**, **Va**−**h**, **VIa**−**c**, and **VIIa**−**f**).

Because the 1,3,4-thiadiazoles are bioisosteric analogues of the 1,3,4-oxadiazoles, which have chemical, physical, and biological similarities (*8*), some thiadiazolyl 3(2*H*)-pyridazinones (**IVa**−**h**, X^2 = S) were synthesized to elevate their activity.

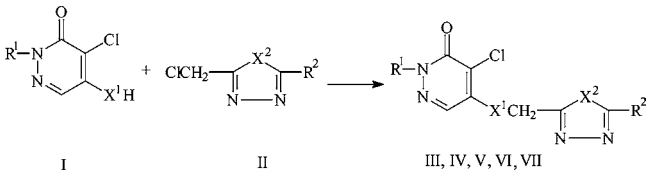

Figure 1. Synthesis of the final compounds.

The introduction of a fluorine, polyfluorine, or trifluoromethyl group into organic molecules frequently results in compounds that display more potent activity than the parent (*9*). Recently, polyfluorinated organic compounds have been widely employed in pharmaceuticals, agrochemicals, and new materials (*10*, *11*). In pesticide chemistry, several commercial polyfluorinated products with their unique properties have been manufactured and used worldwide. For example, Tefluthrin is a kind of synthetic pyrethroid that has been shown to bind to the sodium channels in insects and cause knockdown and death (*12*), and Flufenoxuron, an insect growth regulator (*13*), can interfere with chitin biosynthesis in insects. In our previous research, we reported that the monofluorinated oxadiazolyl pyridazinones (**IIIf**, **IIIj**, and **IIIk**) have potent chronic growth activities against the Asiatic corn borer. In light of the facts, we were interested in preparing polyfluorinated oxadiazolyl pyridazinones (**Va**−**h**) to investigate whether these might show suffciently enhanced chronic growth activity.

The next set of compounds, **VIa**−**c**, were prepared to study how the aromatic ring (R^2) affects the activity by replacing it with the alkyl group and heterocycles. Finally, compounds **VIIa**−**f** were designed to probe the effect of replacing the *tert*-butyl group by the aliphatic chain and benzene ring.

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Table 1. Chronic Growth Activity of Compounds **IIIa**–**w**, **IVa**–**h**, **Va**–**h**, **VIa**–**c**, **VIIa**–**f**, and Azadirachtin on Armyworm *P. separata* (Walker) as well as EC_{50} and PEC_{50} Values

compd	X^1	X^2	R^1	R^2	EC_{50} (mg/L) (mean ± SE)	pEC_{50}
IIIa	O	O	*tert*-butyl	C_6H_5	12.2 ± 1.0	4.914
IIIb	O	O	*tert*-butyl	C_6H_4 (4-NO_2)	>300	<3.523
IIIc	O	O	*tert*-butyl	C_6H_4 (3-CH_3)	116.2 ± 4.9	3.935
IIId	O	O	*tert*-butyl	C_6H_3 [3,5-$(CH_3)_2$]	>300	<3.523
IIIe	O	O	*tert*-butyl	C_6H_4 (4-CH_3)	19.9 ± 1.6	4.701
IIIf	O	O	*tert*-butyl	C_6H_4 (4-F)	5.2 ± 0.6	5.284
IIIg	O	O	*tert*-butyl	C_6H_4 (4-C_2H_5)	14.5 ± 1.5	4.838
IIIh	O	O	*tert*-butyl	C_6H_4 (4-Cl)	1.9 ± 0.6	5.721
IIIi	O	O	*tert*-butyl	C_6H_4 (4-OCH_3)	17.7 ± 0.5	4.752
IIIj	O	O	*tert*-butyl	C_6H_4 (3-F)	7.1 ± 0.6	5.149
IIIk	O	O	*tert*-butyl	C_6H_4 (2-F)	16.8 ± 2.8	4.775
IIIl	O	O	*tert*-butyl	C_6H_2 (2,4-di-Cl-5-F)	23.1 ± 3.5	4.636
IIIm	S	O	*tert*-butyl	C_6H_5	>300	<3.523
IIIn	S	O	*tert*-butyl	C_6H_4 (4-F)	150.4 ± 15.3	3.822
IIIo	S	O	*tert*-butyl	C_6H_4 (3-F)	243.4 ± 9.3	3.614
IIIp	S	O	*tert*-butyl	C_6H_4 (2-F)	269.4 ± 11.3	3.569
IIIq	S	O	*tert*-butyl	C_6H_4 (4-Cl)	180.4 ± 14.9	3.744
IIIr	S	O	*tert*-butyl	C_6H_3 [3,5-$(CH_3)_2$]	>300	<3.523
IIIs	S	O	*tert*-butyl	C_6H_4 (3-CH_3)	>300	<3.523
IIIt	S	O	*tert*-butyl	C_6H_4 (4-NO_2)	>300	<3.523
IIIu	O	O	*tert*-butyl	C_6H_4 (4-Br)	21.4 ± 1.7	4.669
IIIv	O	O	*tert*-butyl	C_6H_3 (2,4-di-Cl)	27.8 ± 2.3	4.556
IIIw	O	O	*tert*-butyl	C_6H_4 (2-Cl)	61.2 ± 3.8	4.213
IVa	O	S	*tert*-butyl	C_6H_5	200.4 ± 9.6	3.698
IVb	O	S	*tert*-butyl	C_6H_4 (4-F)	21.5 ± 2.3	4.667
IVc	O	S	*tert*-butyl	C_6H_4 (2-F)	120.7 ± 7.8	3.918
IVd	O	S	*tert*-butyl	C_6H_4 (4-Cl)	106.4 ± 5.7	3.973
IVe	O	S	*tert*-butyl	C_6H_3 (2,4-di-Cl)	62.2 ± 3.3	4.206
IVf	O	S	*tert*-butyl	C_6H_2 (2,4-di-Cl-5-F)	67.1 ± 4.2	4.173
IVg	O	S	*tert*-butyl	C_6H_4 (3-CH_3)	>300	<3.523
IVh	O	S	*tert*-butyl	C_6H_3 [3,5-$(CH_3)_2$]	>300	<3.523
Va	O	O	*tert*-butyl	C_6H_3 (2,6-di-F)	45.4 ± 2.8	4.343
Vb	O	O	*tert*-butyl	C_6H (2,4-di-Cl-3-NO_2-5-F)	>300	<3.523
Vc	O	O	*tert*-butyl	C_6 (2,3,4,5,6-penta-F)	270.7 ± 8.8	3.567
Vd	O	O	*tert*-butyl	C_6H_2 (2,4,5-tri-F)	75.7 ± 4.8	4.121
Ve	O	O	*tert*-butyl	C_6H (2,4,5-tri-F-3-CH_3O)	>300	<3.523
Vf	O	O	*tert*-butyl	C_6H_3 (2-F-4-Cl)	10.4 ± 2.2	4.983
Vg	O	O	*tert*-butyl	C_6H (2,3,4,5-tetra-F)	240.6 ± 11.5	3.619
Vh	O	O	*tert*-butyl	C_6H_4 (4-CF_3)	34.1 ± 0.8	4.471
VIa	O	O	*tert*-butyl	CH_3	>300	<3.523
VIb	O	O	*tert*-butyl	2-furyl	>300	<3.523
VIc	O	O	*tert*-butyl	2-thienyl	>300	<3.523
VIIa	O	O	C_6H_5	C_6H_5	91.5 ± 5.4	4.039
VIIb	O	O	*n*-butyl	C_6H_5	>300	<3.523
VIIc	O	O	*n*-butyl	C_6H_4 (4-F)	161.5 ± 7.6	3.792
VIId	O	O	*n*-butyl	C_6H_4 (4-Cl)	223.5 ± 13.6	3.651
VIIe	O	O	C_2H_5	C_6H_5	>300	<3.523
VIIf	O	O	C_2H_5	C_6H_4 (4-F)	>300	<3.523
azadirachtin					0.58 ± 0.05	6.237

The chronic growth inhibitory activity of the 48 synthesized compounds, including 20 earlier reported compounds (**IIIa**–**t**), was assessed using another insect, the armyworm, *Pseudaletia separata* (Walker). We also studied the quantitative structure–activity relationship of the recently and newly synthesized active compounds, and QSAR equations were established.

MATERIALS AND METHODS

Synthetic Procedures. 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 $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High-resolution mass spectra were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Combustion analyses for elemental composition were made with an Elementar vario EL III. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light.

N-Chloroacetyl-*N*′-aroylhydrazines were prepared according to procedures found in the literature (*14*). 5-Aryl-2-(chloromethyl)-1,3,4-oxadiazoles (**IIIi**–**v**) were prepared by the cyclodehydration of *N*-(chloroacetyl)-*N*′-aroylhydrazines in boiling $POCl_3$ (*5*). Syntheses of the target compounds, 2-alkyl-4-chloro-5-[5′-aryl-2′-(1′,3′,4′-oxa(thia)-diazolyl)methoxy]-3(2*H*)-pyridazinones (**IIIu**–**w**, **IVa**–**h**, **Va**–**h**, **VIa**–**c**, and **VIIa**–**f**) were realized as described previously (*5*).

Synthetic Procedure for 5-Aryl-2-(chloromethyl)-1,3,4-thiadiazoles (IIa–h). The mixture of the *N*-chloroacetyl-*N*′-aroylhydrazine (0.05 mmol), Lawesson reagent (0.05 mmol), and toluene (10 mL) was refluxed at 110 °C for 2 h under a nitrogen atmosphere. After cooling to room temperature, the mixture was treated with water (30 mL) and extracted with chloroform (3 × 10 mL). The organic layer was washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified on a silica gel column eluted with petroleum ether (60–90 °C)/ethyl acetate (4:1) to give **IIa**–**h**. The preparative and spectral data of **IIa**–**v** are listed in **Table 2**.

*Data for **IIIu**:* yield, 72%; mp, 144–145 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.55 (s, 2H, CH_2), 7.69 (d, 2H, ArH), 7.96 (d, 2H, ArH), 7.97 (s, 1H, PyH); EIMS, *m*/*z* (%) 438 (M^+, 3), 383 (39), 373 (67), 347 (48), 237 (69), 183 (100), 155 (17), 57 (15). HRMS for $C_{17}H_{16}N_4O_3ClBr$: calcd, 438.0094; found, 438.0098.

*Data for **IIIv**:* yield, 81%; mp, 148–149 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.58 (s, 2H, CH_2), 7.44 (dd, 1H, ArH), 7.61 (d, 1H, ArH), 7.99 (d, 1H, ArH), 7.96 (s, 1H, PyH); EIMS, *m*/*z* (%) 428 (M^+, 5), 393 (14), 373 (67), 337 (64), 227 (72), 173 (100), 147 (24), 57 (7). HRMS for $C_{17}H_{15}N_4O_3Cl_3$: calcd, 428.0210; found, 428.0177.

*Data for **IIIw**:* yield, 63%; mp, 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 1.68 [s, 9H, $(CH_3)_3C$], 5.60 (s, 2H, CH_2), 7.28–8.03 (m, 4H, ArH), 7.98 (s, 1H, PyH); EIMS, *m*/*z* (%) 394 (M^+, 3), 359 (6), 339 (21), 303 (32), 193 (29), 139 (100), 111 (20), 57 (24). HRMS for $C_{17}H_{16}Cl_2N_4O_3$: calcd, 394.0601; found, 394.0611.

*Data for **IVa**:* yield, 68%; mp, 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 1.62 [s, 9H, $(CH_3)_3C$], 5.70 (s, 2H, CH_2), 7.50–8.10 (m, 5H, ArH), 7.90 (s, 1H, PyH); EIMS, *m*/*z* (%) 376 (0.5, M^+), 341 (98), 284 (100), 175 (99), 121 (85). HRMS for $C_{17}H_{17}ClN_4O_2S$: calcd, 376.0761; found, 376.0772.

*Data for **IVb**:* yield, 71%; mp, 190–191 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 [s, 9H, $(CH_3)_3C$], 5.82 (s, 2H, CH_2), 7.20–7.80 (m, 4H, ArH), 7.83 (s, 1H, PyH); EIMS, *m*/*z* (%) 394 (0.2, M^+), 359 (78), 303 (47), 193 (100), 139 (82). HRMS for $C_{17}H_{16}ClFN_4O_2S$: calcd, 394.0667; found, 394.0674.

*Data for **IVc**:* yield, 62%; mp, 171–172 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 [s, 9H, $(CH_3)_3C$], 5.81 (s, 2H, CH_2), 7.83 (s, 1H, PyH), 7.20–7.90 (m, 4H, ArH); EIMS, *m*/*z* (%) 394 (0.2, M^+), 359 (100), 303 (55), 193 (90), 139 (90). HRMS for $C_{17}H_{16}ClFN_4O_2S$: calcd, 394.0667; found, 394.0661.

*Data for **IVd**:* yield, 65%; mp, 206–207 °C; ^{1}H NMR ($CDCl_3$) δ 1.62 [s, 9H, $(CH_3)_3C$], 5.70 (s, 2H, CH_2), 7.80 (s, 1H, PyH), 7.20–7.90 (m, 4H, ArH); EIMS, *m*/*z* (%) 410 (0.2, M^+), 375 (88), 319 (72), 209 (100), 155 (88). HRMS for $C_{17}H_{16}Cl_2N_4O_2S$: calcd, 410.0371; found, 410.0374.

*Data for **IVe**:* yield, 66%; mp, 160–161 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 [s, 9H, $(CH_3)_3C$], 5.84 (s, 2H, CH_2), 7.20–7.71 (m, 3H, ArH), 7.90 (s, 1H, PyH); EIMS, *m*/*z* (%) 444 (0.3, M^+), 409 (87) 353 (83), 243 (100), 189 (98). HRMS for $C_{17}H_{15}Cl_3N_4O_2S$: calcd, 443.9981; found, 444.0001.

*Data for **IVf**:* yield, 60%; mp, 176–177 °C; ^{1}H NMR ($CDCl_3$) δ 1.61 [s, 9H, $(CH_3)_3C$], 5.82 (s, 2H, CH_2), 7.51–7.90 (m, 2H, ArH), 7.90 (s, 1H, PyH); EIMS, *m*/*z* (%) 462 (0.4, M^+), 427 (81), 371 (86), 261 (97), 207 (100). HRMS for $C_{17}H_{14}Cl_3FN_4O_2S$: calcd, 461.9887; found, 461.9890.

*Data for **IVg**:* yield, 69%; mp, 126–127 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 [s, 9H, $(CH_3)_3C$], 2.45 (s, 3H, CH_3), 5.70 (s, 2H, CH_2), 7.80 (s, 1H, PyH), 7.20–7.90 (m, 4H, ArH); EIMS, *m*/*z* (%) 390 (0.1, M^+), 355 (77), 299 (79), 189 (81), 135 (100). HRMS for $C_{18}H_{19}ClN_4O_2S$: calcd, 390.0917; found, 390.0909.

*Data for **IVh**:* yield, 70%; mp, 148–149 °C; ^{1}H NMR ($CDCl_3$) δ 1.70 [s, 9H, $(CH_3)_3C$], 2.42 (s, 6H, CH_3), 5.71 (s, 2H, CH_2), 7.21–7.60 (m, 3H, ArH), 7.90 (s, 1H, PyH); EIMS, *m*/*z* (%) 404 (0.2, M^+),

Table 2. Melting Point, Yield, and Mass Spectral Data of 5-Aryl-2-(chloromethyl)-1,3,4-oxa(thia)diazoles (**IIa**–**v**)

compd	X^2	R^2	mp (°C)	yield (%)	*m/z*
IIa	S	C_6H_5	84–85	90	210 (M^+), 175, 135, 121, 103, 77
IIb	S	C_6H_4 (4-F)	118–119	82	228 (M^+), 193, 153, 139, 121, 95
IIc	S	C_6H_4 (2-F)	89–90	70	228 (M^+), 193, 153, 139, 121, 95
IId	S	C_6H_4 (4-Cl)	134–136	85	244 (M^+), 209, 169, 155, 137, 111
IIe	S	C_6H_3 (2,4-di-Cl)	116–117	77	278 (M^+), 243, 203, 189, 171
IIf	S	C_6H_2 (2,4-di-Cl-5-F)	153–154	84	296 (M^+), 261, 221, 207, 189, 163
IIg	S	C_6H_4 (3-CH_3)	82–83	80	224 (M^+), 189, 149, 135, 117, 91
IIh	S	C_6H_3 [3,5-$(CH_3)_2$]	92–93	75	238 (M^+), 203, 163, 149, 131, 105
IIi	O	C_6H_3 (2,6-di-F)	137–139	81	228 (M^+), 193, 153, 139, 121, 95
IIj	O	C_6H (2,4-di-Cl-3-NO_2-5-F)	177–179	78	210 (M^+), 175, 135, 121, 103, 77
IIk	O	C_6 (2,3,4,5,6-penta-F)	115–116	80	238 (M^+), 203, 163, 149, 131, 105
II1	O	C_6H_2 (2,4,5-tri-F)	139–140	85	244 (M^+), 209, 169, 155, 137, 111
IIm	O	C_6H (2,4,5-tri-F-3-CH_3O)	167–169	82	278 (M^+), 243, 203, 189, 171
IIn	O	C_6H_3 (2-F-4-Cl)	110–112	83	228 (M^+), 193, 153, 139, 121, 95
IIo	O	C_6H (2,3,4,5-tetra-F)	155–156	80	296 (M^+), 261, 221, 207, 189, 163
IIp	O	C_6H_4 (4-CF_3)	210–211	77	224 (M^+), 189, 149, 135, 117, 91
IIq	O	CH_3	135–137	70	132 (M^+), 83, 97, 43, 56, 15
IIr	O	2-furyl	81–82	75	184 (M^+), 149, 135, 93, 95, 67
IIs	O	2-thienyl	163–165	78	200 (M^+), 166, 151,109, 83, 111
IIt	O	C_6H_4 (4-Br)	187–188	70	274 (M^+), 237, 183, 155, 102
IIu	O	C_6H_3 (2,4-di-Cl)	108–110	80	262 (M^+), 213, 227,173, 145, 109
IIv	O	C_6H_4 (2-Cl)	200–201	71	228 (M^+), 179, 193,139, 111, 75

369 (98), 313 (69), 203 (92), 149 (100). HRMS for $C_{19}H_{21}ClN_4O_2S$: calcd, 404.1074; found, 404.1061.

Data for ***Va****:* yield, 63%; mp, 174−175 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.60 (s, 2H, CH_2), 7.02 (t, J = 8.55 Hz, 2H, ArH), 7.56−7.59 (m, 1H, ArH), 7.96 (s, 1H, PyH); EIMS, *m/z* (%) 396 (M^+, 3), 341 (57), 361 (9), 305 (51), 195 (42), 141 (100). HRMS for $C_{17}H_{15}N_4O_3F_2Cl$: calcd, 396.0801; found, 396.0781.

Data for ***Vb****:* yield, 57%; mp, 237−238 °C; ^{1}H NMR ($CDCl_3$) δ 1.57 [s, 9H, $(CH_3)_3C$], 5.92 (s, 2H, CH_2), 8.35 (s, 1H, PyH), 8.40 (d, J = 9.13 Hz, 1H, ArH); EIMS, *m/z* (%) 491 (M^+, 3), 436 (100), 400 (32), 236 (37), 190 (13). HRMS for $C_{17}H_{13}N_5O_5FCl$: calcd, 490.9966; found, 490.9951.

Data for ***Vc****:* yield, 68%; mp, 191−193 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.61 (s, 2H, CH_2), 7.97 (s, 1H, PyH); EIMS, *m/z* (%) 450 (M^+, 4), 395 (100), 359 (81), 331 (5), 249 (45), 195 (97). HRMS for $C_{17}H_{12}N_4O_3F_5Cl$: calcd, 450.0518; found, 450.0498.

Data for ***Vd****:* yield, 72%; mp, 174−175 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.60 (s, 2H, CH_2), 7.14−7.19 (m, 1H, Ar−H), 7.93−7.98 (m, 1H, Ar−H), 7.95 (s, 1H, Py-H); EIMS, *m/z* (%) 396 (M^+, 3), 341 (57), 361 (9), 305 (51), 195 (42), 141 (100). HRMS for $C_{17}H_{15}N_4O_3F_2Cl$: calcd, 396.0801; found, 396.0781.

Data for **Ve***:* yield, 63%; mp, 140−141 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 4.12 (s, 3H, OCH_3), 5.57 (s, 2H, CH_2), 7.59−7.64 (m, 1H, ArH), 7.95 (s, 1H, PyH); EIMS, *m/z* (%) 396 (M^+, 3), 341 (57), 361 (9), 305 (51), 195 (42), 141 (100). HRMS for $C_{17}H_{15}N_4O_3F_2Cl$: calcd, 396.0801; found, 396.0781.

Data for ***Vf****:* yield, 66%; mp, 119−120 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.57 (s, 2H, CH_2), 7.27−7.35 (m, 2H, ArH), 7.96 (s, 1H, PyH), 8.04−8.07 (m, 1H, ArH); EIMS, *m/z* (%) 412 (M^+, 3), 377 (9), 357 (53), 321 (50), 211 (63), 157 (100). HRMS for $C_{17}H_{15}N_4O_3FCl_2$: calcd, 412.0505; found, 412.0503.

Data for ***Vg****:* yield, 70%; mp, 186−187 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.59 (s, 2H, CH_2), 7.77−7.79 (m, 1H, ArH), 7.94 (s, 1H, PyH); EIMS, *m/z* (%) 432 (M^+, 6), 377 (100), 341 (44), 177 (93), 57 (18). HRMS for $C_{17}H_{13}N_4O_3F_4Cl$: calcd, 432.0612; found, 432.0616.

Data for ***Vh****:* yield, 64%; mp, 193−194 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.58 (s, 2H, CH_2), 7.84 (d, J = 8.23 Hz, 2H, ArH), 7.97 (s, 1H, PyH), 8.23 (d, J = 8.23 Hz, 2H, Ar-H); EIMS, *m/z* (%) 428 (M^+, 5), 373 (85), 337 (66), 173 (100), 145 (30). HRMS for $C_{18}H_{16}N_4O_3F_3Cl$: calcd, 428.0863; found, 428.0896.

Data for ***VIa****:* yield, 57%; mp, 188−189 °C; ^{1}H NMR ($CDCl_3$) δ 1.57 [s, 9H, $(CH_3)_3C$], 2.53 (s, 3H, CH_3), 5.37 (s, 2H, CH_2), 7.85 (s, 1H, PyH); EIMS, *m/z* (%) 298 (M^+, 7), 263 (17), 243 (100), 207 (92), 147 (57), 97 (17), 57 (13). HRMS for $C_{12}H_{15}N_4O_3Cl$: calcd, 298.0833; found, 298.0830.

Data for ***VIb****:* yield, 70%; mp, 141−142 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.53 (s, 2H, CH_2), 6.63−6.64 (m, 1H, furan-H), 7.26 (d, J = 3.81 Hz, 1H, furan-H), 7.69 (d, J = 1.35 Hz, 1H, furan-H), 7.95 (s, 1H, Py-H); EIMS, *m/z* (%) 350 (M^+, 4), 315 (13), 295 (35), 259 (31), 149 (100), 95 (45), 57 (7). HRMS for $C_{15}H_{15}N_4O_4Cl$: calcd, 350.0782; found, 350.0785.

Data for ***VIc****:* yield, 75%; mp, 190−191 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 [s, 9H, $(CH_3)_3C$], 5.53 (s, 2H, CH_2), 7.21−7.22 (m, 1H, thiophenyl-H), 7.63 (dd, J = 0.81 Hz, J = 0.81 Hz, 1H, thiophenyl-H), 7.69 (dd, J = 0.88 Hz, J = 0.88 Hz, 1H, thiophenyl-H), 7.98 (s, 1H, Py-H); EIMS, *m/z* (%) 366 (M^+, 3), 331 (17), 311 (32), 275 (34), 165 (100), 111 (69), 57 (9). HRMS for $C_{15}H_{15}N_4O_3SCl$: calcd, 366.0553; found, 366.0591.

Data for ***VIIa****:* yield, 50%; mp, 177−178 °C; ^{1}H NMR ($CDCl_3$) δ 5.58 (s, 2H, CH_2), 7.39−7.62 (m, 5H, ArH), 7.56−8.12 (m, 5H, ArH), 8.03 (s, 1H, PyH); EIMS, *m/z* (%) 380 (M^+, 4), 345 (18), 304 (36), 105 (100), 77 (20). Anal. Calcd (%) for $C_{19}H_{13}ClN_4O_3$: C, 59.93; H, 3.44; N, 14.71. Found: C, 59.73; H, 3.27; N, 14.84.

Data for ***VIIb****:* yield, 58%; mp, 143−145 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.35 Hz, 3H, CH_3), 1.37−1.38 (m, 2H, CH_2), 1.77−1.79 (m, 2H, CH_2), 4.20 (t, J = 7.34 Hz, 2H, CH_2N), 5.57 (s, 2H, CH_2), 7.53−8.09 (m, 5H, ArH), 8.03 (s, 1H, PyH); EIMS, *m/z* (%) 360 (M^+), 359 (6), 339 (21), 303 (32), 193 (29), 139 (100), 111 (20), 57 (24). Anal. Calcd (%) for $C_{17}H_{17}ClN_4O_3$: C, 56.59; H, 4.75; N, 15.52. Found: C, 56.72; H, 4.78; N, 15.73.

Data for ***VIIc****:* yield, 64%; mp, 140−142 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.12 Hz, 3H, CH_3), 1.35−1.37 (m, 2H, CH_2), 1.77−1.78 (m, 2H, CH_2), 4.19 (t, J = 7.21 Hz, 2H, CH_2N), 5.58 (s, 2H, CH_2), 7.21−8.11 (m, 4H, ArH), 8.04 (s, 1H, PyH); EIMS, *m/z* (%) 378 (M^+), 201 (12), 177 (8), 123 (100), 95 (32). Anal. Calcd (%) for $C_{17}H_{16}ClFN_4O_3$: C, 53.90; H, 4.26; N, 14.79. Found: C, 53.81; H, 4.12; N, 14.49.

Data for ***VIId****:* yield, 59%; mp, 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.02 Hz, 3H, CH_3), 1.30−1.31 (m, 2H, CH_2), 1.70−1.72 (m, 2H, CH_2), 4.12 (t, J = 6.92 Hz, 2H, CH_2N), 5.49 (s, 2H, CH_2), 7.44−7.96 (m, 4H, ArH), 7.94 (s, 1H, PyH); EIMS, *m/z* (%) 395 (M^+), 201 (20), 177 (8), 139 (100), 111 (32), 75 (16), 41 (18). Anal. Calcd (%) for $C_{17}H_{16}Cl_2N_4O_3$: C, 51.66; H, 4.08; N, 14.18. Found: C, 51.52; H, 3.88; N, 14.24.

Data for ***VIIe****:* yield, 66%; mp, 165−168 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.23 Hz, 3H, CH_3), 4.27 (q, J = 7.22 Hz, 2H, CH_2N), 5.57 (s, 2H, CH_2), 7.53−8.09 (m, 5H, ArH), 8.04 (s, 1H, PyH); EIMS, *m/z* (%) 332 (M^+), 297 (100), 194 (12), 159 (28), 105 (32), 103 (18). Anal. Calcd (%) for $C_{15}H_{13}ClN_4O_3$: C, 54.14; H, 3.94; N, 16.84. Found: C, 54.42; H, 3.88; N, 16.56.

Table 3. Reactions of Polyfluoro Aromatic Esters with Hydrazine Hydrate

R^2	reaction time (h)	reaction temp (°C)
C_6H (2,4-di-Cl-3-NO_2-5-F) C_6H_3 (2-F-4-Cl) C_6H_4 (4-CF_3)	8	80–85
C_6H_3 (2,6-di-F)	2–3	25–30
C_6H_2 (2,4,5- tri-F) C_6H (2,4,5-tri-F-3-CH_3O) C_6H (2,3,4,5-tetra-F)	4–5	0–5
C_6 (2,3,4,5,6-penta-F)	no desired product obtained	

Data for ***VIIf****:* yield, 58%; mp, 195−197 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7.12 Hz, 3H, CH_3), 4.26 (q, J = 7.11 Hz, 2H, CH_2N), 5.56 (s, 2H, CH_2), 7.22−8.11 (m, 4H, ArH), 8.02 (s, 1H, PyH); EIMS, *m*/*z* (%) 350 (M^+), 315 (14), 177 (18), 123 (100), 107 (11), 95 (45). Anal. Calcd (%) for $C_{15}H_{12}ClFN_4O_3$: C, 51.37; H, 3.45; N, 15.97. Found: C, 51.26; H, 3.49; N, 16.05.

Insect. Larvae of the armyworm, *P. separata* (Walker), were reared continuously on freshly cut maize seedling under standard laboratory conditions (25 °C, 60% relative humidity, and a 16:8 h light/dark photoperiod).

Chronic Growth Bioassay. Effects of all 48 compounds and azadirachtin on larval growth were further assessed using second-instar larvae of the armyworm, *P. separata* (Walker). Fresh leaves containing the test substance and pure azadirachtin were prepared as described by Ismann (*15*, *16*). Second-instar larvae of the armyworm (n = 30) were released on leaves with various concentrations of the analyzed compounds (0.01−500 mg/L). Three replicates were prepared for each concentration with 10 larvae in each replicate. Control diets were prepared in a similar way but with only solvent. After 5 days of exposure, all larvae were individually weighed to obtain EC_{50} values (effective concentration to inhibit growth by 50% relative to controls). Data were mean values from triplicates [± standard error (SE)] and subjected to probit analysis. The data of EC_{50} and the reciprocal logarithm of EC_{50}, pEC_{50}, are presented in **Table 1**.

RESULTS AND DISCUSSION

Synthesis. Starting from various aromatic esters, a set of aroylhydrazines, *N*-chloroacetyl-*N*′-aroylhydrazines and 5-aryl-2-chloromethyl-1,3,4-oxadiazoles, were synthesized following the procedure reported previously (*5*). With only a few exceptions, aroylhydrazines were synthesized by treatment of aromatic ester with excess hydrazine hydrate in ethanol at 80 °C for 7−8 h. However, attempts to obtain the polyfluoroaroylhydrazines under the above-mentioned experimental conditions were found to be unsuccessful due to hydrazino group substitution occurring on the benzene ring. Therefore, the aroylhydrazines containing polyfluorine atoms were prepared by modification of the conventional method. Conditions for hydrazinolysis of polyfluoro aromatic ester are given in **Table 3**.

2,3,4,5,6-Pentafluorobenzoylhydrazine could not be prepared directly by hydrazinolysis of ethyl 2,3,4,5,6-pentafluorobenzoate with hydrazine hydrate in ethanol. For this reason, 5-(2,3,4,5,6-pentafluorophenyl)-2-(chloromethyl)-1,3,4-oxadiazole (**IIk**) could not be obtained by the general synthetic route. Thus, we adjusted our protocol and sought another practical approach for the synthesis of **IIk** (*17*, *18*). Heating 4-nitrophenol with chloroacetyl chloride at 40 °C in ethyl ether for 0.5 h led to chloroacetic acid 4-nitrophenyl ester, and subsequent treatment with hydrazine hydrate at 0 °C for 0.5 h in THF gave chloroacetylhydrazine. Further acylation of chloroacetylhydrazine with 2,3,4,5,6-pentafluorobenzoyl chloride followed by cyclodehydration in boiling $POCl_3$ afforded 5-(2,3,4,5,6-pentafluorophenyl)-2-(chloromethyl)-1,3,4-oxadiazole (**IIk**). The procedure is outlined in **Figure 2**.

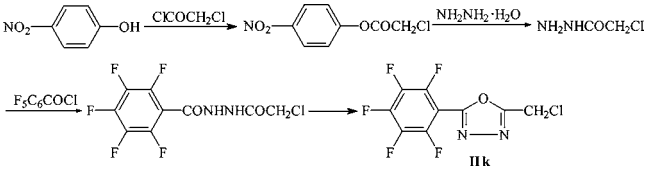

Figure 2. New synthetic route for 5-(2,3,4,5,6-pentafluorophenyl)-2-(chloromethyl)-1,3,4-oxadiazole.

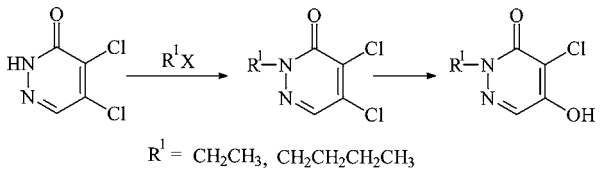

Figure 3. Synthetic route for 2-ethyl(or *n*-butyl)-4-chloro-5-hydroxy-3(2*H*)-pyridazinone.

Different from the synthesis of 2-*tert*-butyl-4-chloro-5-hydroxy-3(2*H*)-pyridazinone, which we described previously (*5*), 2-ethyl-4-chloro-5-hydroxy-3(2*H*)-pyridazinone and 2-*n*-butyl-4-chloro-5-hydroxy-3(2*H*)-pyridazinone are prepared by first alkylating 4,5-dichloro-3(2*H*)-pyridazinone followed by hydroxylation (*19*), as shown in **Figure 3**.

Chronic Growth Activity. Previously we reported the chronic growth activities against Asiatic corn borer, *Ostrinia furnacalis* (Guenee), of **IIIa**−**t** and also discussed the effects of the changes of gross structure on the chronic growth activity. In this study, we measured the chronic growth activity of 48 oxadiazolyl 3(2*H*)-pyridazinone derivatives having various substitutents against the armyworm, *P. separata* (Walker).

Among the 48 compounds, compound **IIIh** was the most active. It was only slight weaker than azadirachtin. Compared to **IIIa**, with the introduction of F and Cl at the para position, increased activity, but a bulkier halogen (Br) and an electron-withdrawing group such as CF_3 or NO_2 decreased activity. Furthermore, the position of fluorine substituent in aryl derivatives (R^2 = aryl) played an important positive role in their potency in the order para > meta > ortho. Substitution by such groups as alkyl and alkoxy at meta and para positions somewhat reduced activity. The disubstituted analogues were found to be inferior to their respective nonsubstituted (**IIIa**) and mono (para) substituted ones generally, except for the 2-F-4-Cl derivative (**Vf**). Replacement of the oxo bridge by a mercapto bridge (**IIIm**−**t**) remarkably decreased the activity. These present results for *P. separata* are similar to those obtained earlier for *O. furnacalis*. The introduction of more than one fluorine atom on the benzene ring seems to be unfavorable to the activity to various degrees; the activity was found to fall off with increasing number of fluorine atoms. Thiadiazole compounds (**IVa**−**h**) exhibited lower activities compared to the corresponding oxadiazoles. The exchange of the *tert*-butyl group in the parent compounds (**IIIa**) for *n*-butyl (**VIIb**,**c**), ethyl (**VIIe**,**f**), or phenyl groups (**VIIa**) led to diminishing biological activity. These results indicate that the *tert*-butyl group on the nitrogen atom is very important for the insecticidal activity of the compounds. Loss of activity was also observed when the phenyl rings (R^2) were replaced by methyl (**VIa**), furyl (**VIb**), or thienyl (**VIc**) groups. **Table 1** summarizes the insecticidal screening results of the studied compounds.

Physicochemical Parameters. To further explore the structural requirements of oxadiazolyl 3(2*H*)-pyridazinones for the activity, the activity values were quantitatively analyzed using

Table 4. Activity Observed (pEC_{50}) and Predicted and Residual Values for 19 Oxadiazolyl 3(2*H*)-Pyridazinones and Physicochemical Parameters for PLS Regression

compd	activity obsd (pEC_{50})	eq 2 PLS predicted	PLS residuals	dipole-mag	log *P*	MR
IIIa	4.914	4.821	0.093	6.07	2.95	50.605
IIIh	5.721	5.107	0.614	6.32	3.09	53.216
IIIf	5.284	5.264	0.020	6.34	2.69	50.729
IIIc	3.94	4.363	–0.428	5.72	3.02	53.979
IIIe	4.701	4.534	0.167	5.85	3.01	53.979
IIIg	4.838	4.830	0.008	6.22	3.52	54.612
IIIi	4.752	4.853	–0.101	6.24	3.52	54.202
IIIj	5.149	5.226	–0.077	6.31	2.69	50.729
IIIk	4.775	4.974	–0.199	6.17	2.89	50.729
IIIl	4.636	4.596	0.040	5.99	3.36	55.501
IIIu	4.669	4.917	–0.248	6.18	3.21	59.168
IIIv	4.556	4.292	0.264	5.78	3.52	59.826
IIIw	4.213	4.122	0.091	5.58	3.19	54.216
Va	4.343	4.327	0.016	5.63	2.75	50.853
Vc	3.567	3.451	0.116	5.21	3.06	12.168
Vd	4.121	4.183	–0.062	5.69	2.96	25.526
Vf	4.983	5.025	–0.042	6.29	3.23	54.601
Vg	3.619	3.684	–0.065	5.41	3.18	15.347
Vh	4.471	4.677	–0.206	6.15	3.66	52.571

physicochemical parameters and a regression method. All computations were done on a Silicon Graphics workstation running on the IRIX 6.5 operating system. Relevant computational modules were accessed from the Drug Discovery Workbench (DDW) of Cerius[2] (version 4.8). Molecular geometries were optimized under the universal force field (UFF) provided by Open Force Field (OFF) within Cerius[2].

The above qualitative structure−activity relationship analysis revealed that there were four possible regions governing the activity: the oxo bridge, the *tert*-butyl group, the oxadiazole ring, and the substituted phenyl. Therefore, particular attention was paid to those compounds, 2-*tert*-butyl-4-chloro-5-[5′-aryl-2′-(1′,3′,4′-oxadiazolyl)methoxy]-3(2*H*)-pyridazinones, and used for the regression analysis. Some compounds were excluded from the regression analysis because these compounds did not give acceptable EC_{50} values. Nineteen 3(2*H*)-pyridazinones (X^1 = O, X^2 = O, R^1 = *tert*-butyl, R^2 = substituted phenyl) were used for quantitative analysis. The biological activities and physicochemical parameters of 19 compounds are summarized in **Table 4**.

To find out which of the parameters are important to activity, several equations were obtained according to different combinations of the parameters. The data matrix was analyzed by the partial least squares (PLS) method. The quality of each of the regression models was evaluated using the square of the correlation coefficient (r^2); we examined only regressions with $r^2 > 0.80$. The most significant combination of physicochemical parameters affecting activity were dipole moment (μ), molar refractivity (MR), and log *P*.

The physical parameters dipole moment, molar refractivity, and log *P* are the independent variables of the regression, and the biological activity pEC_{50} is the dependent variable. Finally, it was found that there was significant correlation between the pEC_{50} and dipole moment and molar refractivity as showed by eq 1:

$$pEC_{50} = -3.49825 + 1.32928(\mu) + 0.0036254(MR) \quad (1)$$

$$r^2 = 0.803,\ XVr^2 = 0.684,\ PRESS = 1.687$$

In this and the following equations, important indices of goodness of fit are given: correlation coefficient, r^2; cross-validation correlation coefficient, XVr^2; and predicted sum of squares, PRESS. The cross-validation correlation coefficient XVr^2 is a measure of the predictive power of the equation. To investigate the need for a hydrophobic term in QSAR, we have used log *P* as an additional correlating parameter for obtaining a model for this set of 19 compounds. Addition of log *P* to the above model (eq 1) gave significant improvement in the statistics, yielding the following regression expression:

$$pEC_{50} = -2.2994 + 1.28423(\mu) + 0.0055719(MR) - 0.329534(\log P) \quad (2)$$

$$r^2 = 0.840,\ XVr^2 = 0.761,\ PRESS = 1.272$$

The coefficients of indicator parameters (dipole moment and MR) in eq 2 are positive. This indicates that the higher the dipole moment and MR values, the higher the activity. The negative coefficient of the log *P* term indicates that as molecular hydrophobicity (log *P*) of the present 19 compounds decreased, if substitution patterns are acceptable, their activity increased. The entire correlation matrix of the regression variables is shown in **Table 5**. The activities calculated by eq 2 are listed in **Table 4**. The correlation relationship between observed values and estimated values for eq 2 of the insecticidal activity is shown in **Figure 4**. The results indicate that log *P*, dipole moment, and MR values can be used to help predict the activity. Although a small set of analogues was used to develop these QSAR models, the models will provide insight in designing chronic growth activity oxadiazolyl 3(2*H*)-pyridazinones.

A relatively large number of the oxa(thia)diazolyl 3(2*H*)-pyridazinones have been prepared and characterized. Chronic growth activity (EC_{50}) against the armyworm, *P. separata* (Walker), was evaluated by comparison with the natural

Table 5. Correlation Matrix for Variables Used To Derive Equation 2

	dipole-mag	MR	log *P*	activity
dipole-mag	1.000			
MR	0.672	1.000		
log *P*	0.027	0.158	1.000	
activity	0.894	0.651	–0.151	1.000

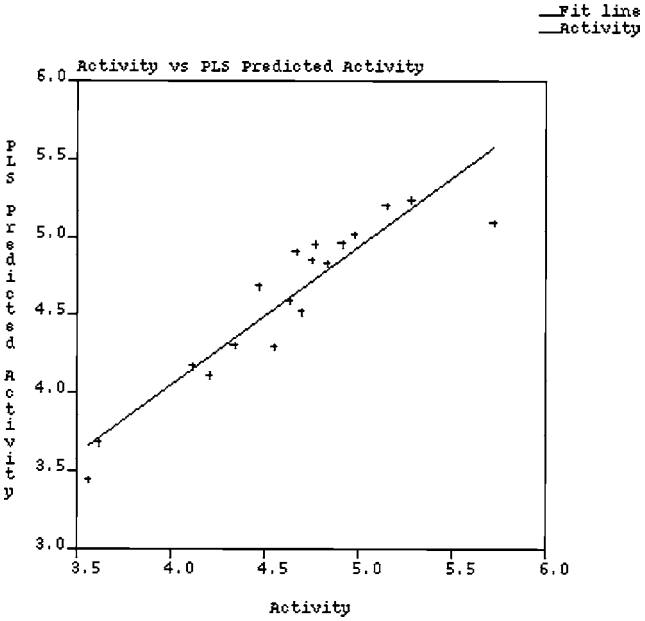

Figure 4. Correlation between observed and estimated activities of 18 oxadiazolyl 3(2*H*)-pyridazinones using eq 2.

antifeedent, azadirachtin. The results show that most of the oxa(thia)diazolyl 3(2*H*)-pyridazinones are able to inhibit armyworm growth to more or less extent depending on the structure of the compounds. Structure−activity relationship analysis of all of these oxadiazolyl 3(2*H*)-pyridazinones revealed that the $-OCH_2$ group, the *tert*-butyl group on the nitrogen atom, the oxadiazole ring, and the substituted benzene ring would be essential for the activity. Nineteen 2-*tert*-butyl-4-chloro-5-[5′-aryl-2′-(1′,3′,4′-oxadiazolyl)methoxy]-3(2*H*)-pyridazinones were subjected to a multiple linear regression analysis using the growth inhibition data pEC_{50} values. Significant relationships were found between those three parameters and the activity against the armyworm. The chronic growth activities of oxadiazolyl 3(2*H*)-pyridazinones against the armyworm depend on the following factors: the dipole moment (μ), molar refractivity (MR), and log *P*. We hope that this model will be used in the future to design new effective antifeedants.

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