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ARTICLE

Design, Synthesis, and Insecticidal Activities of Phthalamides Containing a Hydrazone Substructure

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Fluobendiamide is the first commercialized artificial synthetic insecticide acting on the ryanodine receptor. This new molecule possesses a combination of excellent insecticidal activity and eco-friendly characteristics with a skeleton structure of phthalamide. In this study, we incorporated hydrazone, present in many pesticidal compounds reported during the last two decades, into phthalamide derivatives via Schiff-base condensation and aminolysis to obtain 21 new compounds; these compounds were characterized by proton nuclear magnetic resonance (^{1}H NMR), infrared spectroscopy (IR), and high-resolution mass spectrometry (HRMS) or elemental analysis. A preliminary bioassay against peach aphids (*Myzus persicae*) revealed that the title compounds exhibited good stomach toxicity at 600 mg/L. Twelve new compounds were found to display higher activity than postive control flubendiamide (LC_{50}=184.099 mg/L), however, LC_{50} was less than 100 mg/L only for compounds **4e, 4o, 4s, 4t** (59−77 mg/L). That is, combinations of a *p*-fluorophenyl or (methyl)thienyl group at the Ar position with an isopropyl or cyclohexyl group at the R position might improve the lethality of the designed phthalamide derivative. Preliminary results of a bioassay at 600 mg/L against diamondback moth (*Plutella xylostella*, Linnaeus) showed that only the title compound **4e** possessed good larvicidal activity. On comparison of the bioassay results of stomach toxicity and larvicidal activity, it is noteworthy that the compound incorporating phenylpyrazolyl exhibited good larvicidal activity and poor stomach activity.

KEYWORDS: Phthalamides; hydrazone; synthesis; insecticidal activity

INTRODUCTION

The use of synthetic pesticides is one of the most effective solutions for controlling pest organisms considered harmful to crop growth in the current agricultural system. However, over time, some pests become pesticide-resistant due to annual applications. That is, they adapt to the specific chemical and are no longer affected by it. In addition, due to environmental concerns associated with the accumulation of pesticides in food products and water supplies, there is a great demand for environmentally friendly products. Pesticide resistance and environmental concerns compel us to choose alternative or new products; therefore, we must discover novel active molecules with new modes of action and eco-friendly properties such as being easily degradable into nontoxic residues, being harmless to human beings, and beneficial in meeting the demands of crop protection.

The ryanodine receptor (RyR), also known as the calcium ion channel receptor, derives its name from the plant metabolite ryanodine from *Ryania speciosa* (*1*). The calcium ion, a secondary messenger, plays a special role in the nervous system and behavior of insects (*2*,*3*). Thus, the ryanodine receptor has been regarded as one of the potential targets for novel insecticide discovery ever since it was found that natural ryanodine possessed insecticidal activity. Although a large number of studies have been conducted in the last several decades to reduce the mammalian toxicity of ryanodine by modifying it to uncover new insecticides, all of these attempts eventually failed (*4*−*7*). However, in 1989, when phthalamide derivatives were designed and synthesized as candidate herbicides (*8*,*9*), Tsuda et al. discovered not only that a compound **B** found during the optimization of compound **A** possessed good insecticidal activity but also that tested insects exhibited poisoning symptoms remarkably similar to those caused by natural ryanodine. Subsequently in 1998, Tohnishi et al. further optimized the structure of compound **B** and conducted numerous studies to find the active molecule flubendiamide (**C**)-the first artificially synthesized insecticide acting on the ryanodine receptor (*10*−*15*)-which was commercialized in 2008. A brief summary of the discovery process of flubendiamide is shown in **Scheme 1**.

Phthalamide has the skeleton structure of flubendiamide and is also a new active structure for insecticide discovery. The

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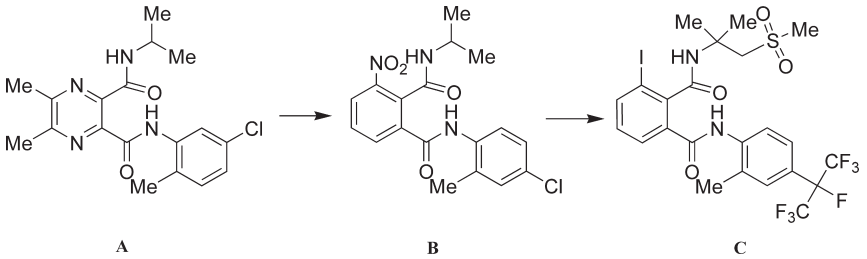
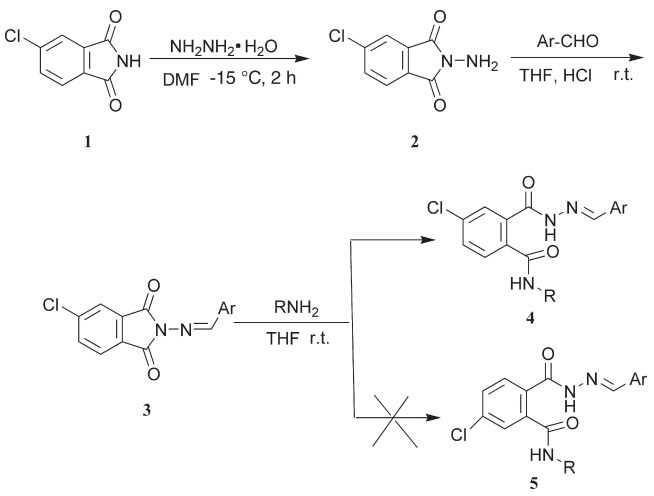
Scheme 1. The Brief Discovery Process of Flubendiamide



Scheme 2. General Synthetic Route for Title Compounds **4a**−**u**



functional group hydrazone exists as an active substructure in many biologically active compounds. For example, hydramethylnon, the first insecticide containing hydrazone, was launched in 1980 to control ants and black beetles. Subsequently, many active pesticidal molecules incorporating the functional group hydrazone (*16*−*20*) were reported in the 1990s as follows: benzophenone hydrazone derivatives were reported in 1993 by Syngenta to control *Diabrotica balteata* on corn and in 1996 by Bayer to control *Plutella xylostella* on cabbage. In addition, some heteroaryl hydrazone compounds as acaricides and insecticides were introduced in 2000 by Sankyo Pharmaceuticals Co., Ltd., and Nippon Kayaku Co., Ltd. In order to discover new molecules acting on the ryanodine receptor, we sought to incorporate the active substructural unit hydrazone into the backbone structure of flubendiamide. On the basis of molecular similarity and the principle of combining active substructures, we designed and synthesized the title compounds. This paper describes the syntheses and bioactivities of the designed compounds.

MATERIALS AND METHODS

Instruments. Melting points were measured using a Fisher-Johns melting point apparatus (Cole-Parmer Co.) without correcting the thermometer. ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Advance DPX 300 (Bruker Co.) spectrometer using tetramethylsilane (TMS) as an internal reference. Chemical shift values (δ) were given in parts per million (ppm). Infrared spectra were obtained on Bruker IR-Tensor 27 spectrophotometer (Bruker Co.) using potassium bromide pellets and were reported as wavenumbers (cm^{-1}). Elemental analysis was performed on a Yanaco Corder MT-3 (Yanaco Co., Ltd.) elemental analyzer. Mass spectra were recorded using a high-resolution mass spectrometry (HRMS) spectrometer HPLC-1100/TOF MS (Agilent Co.).

Reagents. All solvents and liquid reagents were of analytical reagent grade and were dried in advance and redistilled before use. Flash column chromatography with silica gel was used to purify the crude product.

Table 1. Types of Ar and R Groups in Title Compounds **4a**−**4u**

compd	Ar	R
4a	2-chlorophenyl	isopropyl
4b	2-chlorophenyl	cyclohexyl
4c	2-fluorophenyl	butyl
4d	2-fluorophenyl	cyclohexyl
4e	4-fluorophenyl	isopropyl
4f	4-fluorophenyl	butyl
4g	4-(trifluoromethyl)phenyl	butyl
4h	4-hydroxyphenyl	isopropyl
4i	4-hydroxyphenyl	cyclohexyl
4j	2-furanyl	isopropyl
4k	2-furanyl	butyl
4l	2-furanyl	cyclohexyl
4m	2-methyl-5-furanyl	isopropyl
4n	2-methyl-5-furanyl	cyclohexyl
4o	2-thienyl	isopropyl
4p	2-thienyl	butyl
4q	2-thienyl	cyclohexyl
4r	3-methyl-2-thienyl	isopropyl
4s	3-methyl-2-thienyl	cyclohexyl
4t	5-methyl-2-thienyl	isopropyl
4u	5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl	cyclohexyl

General Synthetic Procedure for Compound 2. A mixture of 5-chloroisoindoline-1,3-dione (**1**; 18.15 g, 100.0 mmol) in *N*,*N*-dimethylformamide (DMF; 100 mL) was cooled to −15 °C and stirred for 2 h after the addition of 99% hydrazine hydrate (5.50 g, 110.0 mmol). When the reaction was completed, the mixture was poured into 300 mL of water, and the resulting precipitate was filtered to obtain a yellow solid (**2**; 6.48 g, 33.0%); mp 178−179 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.93−7.92 (m, 1H, Ph H), 7.90−7.86 (m, 2H, Ph H), 4.97 (s, 2H, NNH_2).

General Synthetic Procedure for the Title Compounds 4a−**u (Scheme 2 and Table 1).** *Synthesis of* (*E*/*Z*)*-2-*(*Cyclohexylcarbamoyl*)*-5-chloro-N′-*((*5-methylfuran-2-yl*)*methylene*)*benzohydrazide* (***4n***). To a solution of **2** (1.97 g, 10 mmol) and 5-methyl-2-furanal (1.10 g, 10 mmol) in 1,4-dixoane (100 mL) was added 12 N HCl (0.1 mL) at room temperature. After the reaction mixture was stirred for 5−10 min, a solution of cyclohexanamine (1.98 g, 20 mmol) in tetrahydrofuran (THF; 10 mL) was added, and the reaction mixture was stirred overnight at room temperature. When the reaction was complete, the solvent was evaporated under reduced pressure, and the resulting mixture was dissolved in ethyl acetate (80 mL); this was followed by washing with H_2O (3 × 30 mL) and drying with anhydrous sodium sulfate. Ethyl acetate was evaporated under reduced pressure to give a yellow solid as the crude product, which was recrystallized with a mixture of THF and *n*-hexane (1:1, v/v) to obtain the pure product **4n** (2.40 g). Yield: 61.9%; light yellow solid. Mp: 123−124 °C. ^{1}H NMR (DMSO-d_6): δ 11.65 (br s, 1H, CON*H*N=CH), 8.32−8.17 (m, 1H, Ph H), 8.05 (s, 0.7H, N=C*H*), 7.77 (s, 0.3H, N=C*H*), 7.64−7.40 (m, 3H, CON*H*CH + Ph H), 6.80−6.16 (m, 2H, furanyl), 3.65 (br s, 0.7H, CONHC*H*), 3.62 (br s, 0.3H, CONHC*H*), 2.35 (s, 2H, CH_3), 2.26 (s, 1H, CH_3), 1.82−1.54 (m, 5H, cyclohexyl), 1.25−1.05 (m, 5H, cyclohexyl). HRMS: *m*/*z* calcd for $C_{20}H_{23}ClN_3O_3$ (M + H)$^+$ 388.1428, found 388.1976.

The title compounds **4a**−**m**,**o**−**u** were prepared by the same reaction procedure as that described above. However, when R in the amine was an *n*-butyl group, the crude products of compounds **4c, 4f, 4g, 4k, 4p** were

purified by flash column chromatography with a mixture of ethyl acetate and n-hexane (1:1 v/v) as the effluent.

Data for (*E*/*Z*)-*2*-(*Isopropylcarbamoyl*)-*N*′-(*2-chlorobenzylidene*)-*5-chlorobenzohydrazide* (***4a***). Yield: 64.6%; white solid. Mp: 199−202 °C. ^{1}H NMR (DMSO-d_6): δ 12.04−11.83 (m, 1H, CONHN=CH), 8.67 (s, 0.5H, N=CH), 8.35 (s, 0.5H, N=CH), 8.39−8.35 (m, 1H, Ph H), 8.01−7.97 (m, 0.5H, Ph H), 7.69−7.26 (m, 6.5H, CONHCH + Ph H), 4.00−3.77 (m, 1H, CONHCH), 1.13 (d, J = 6.57 Hz, 2.7H, CH(CH_3)$_2$), 0.92 (d, J = 6.57 Hz, 3.3H, CH(CH_3)$_2$). HRMS: m/z calcd for $C_{18}H_{18}Cl_2N_3O_2$ (M + H) $^+$ 378.0776, found 378.1127.

Data for (*E*/*Z*)-*2*-(*Cyclohexylcarbamoyl*)-*N*′-(*2-chlorobenzylidene*)-*5-chlorobenzohydrazide* (***4b***). Yield: 33.5%; white solid. Mp: 206−209 °C. ^{1}H NMR (DMSO-d_6): δ 11.80 (br s, 1H, CONHN=CH), 8.68 (s, 0.45H, N=CH), 8.36 (s, 0.55H, N=CH), 8.36−8.30 (m, 1H, Ph H), 8.02−7.99 (m, 1H, Ph H), 7.67−7.26 (m, 6H, CONHCH + Ph H), 3.63, 3.48 (br s, 1H, CONHCH), 1.82−1.47 (m, 5H, cyclohexyl), 1.29−0.86 (m, 5H, cyclohexyl). Anal. Calcd for $C_{21}H_{21}Cl_2N_3O_2$: C, 60.30; H, 5.06; N, 10.05. Found: C, 60.27; H, 5.10; N, 10.06.

Data for (*E*/*Z*)-*2*-(*Butylcarbamoyl*)-*N*′-(*2-fluorobenzylidene*)-*5-chlorobenzohydrazide* (***4c***). Yield: 5.3%; white solid. Mp: 84−86 °C. ^{1}H NMR (DMSO-d_6): δ 11.75 (br s, 1H, CONHN=CH), 8.51 (s, 0.5H, N=CH), 8.51−8.46 (m, 1H, Ph H), 8.18 (s, 0.5H, N=CH), 7.94−7.87 (m, 0.5H, Ph H), 7.69−7.13 (m, 6.5H, CONHCH$_2$ + Ph H), 3.21−3.15 (m, 1H, CONHCH$_2$), 3.00−2.96 (m, 1H, CONHCH$_2$), 1.50−1.09 (m, 4H, CH$_2$CH$_2$CH$_2$CH$_3$), 0.87 (t, J = 7.2 Hz, 1.5H, CH$_2$CH$_3$), 0.68 (t, J = 5.67 Hz, 1.5H, CH$_2$CH$_3$). Anal. Calcd for $C_{19}H_{19}ClFN_3O_2$: C, 60.72; H, 5.10; N, 11.18. Found: C, 60.48; H, 5.14; N, 11.07.

Data for (*E*/*Z*)-*2*-(*Cyclohexylcarbamoyl*)-*N*′-(*2-fluorobenzylidene*)-*5-chlorobenzohydrazide* (***4d***). Yield: 45.1%; white solid. Mp: 157−160 °C. ^{1}H NMR (DMSO-d_6): δ 11.00 (br s, 1H, CONHN=CH), 8.53 (s, 0.5H, N=CH), 8.38−8.32 (m, 1H, Ph H), 7.98−7.92 (m, 0.5H, Ph H), 8.18 (s, 0.5H, N=CH), 7.70−7.14 (m, 6.5H, CONHCH + Ph H), 3.65 (br s, 0.5H, CONHCH), 3.49 (br s, 0.5H, CONHCH), 1.83−1.47 (m, 5H, cyclohexyl), 1.30−0.96 (m, 5H, cyclohexyl). HRMS: m/z calcd for $C_{21}H_{22}ClFN_3O_2$ (M + H) $^+$ 402.1385, found 402.1744.

Data for (*E*/*Z*)-*2*-(*Isopropylcarbamoyl*)-*N*′-(*4-fluorobenzylidene*)-*5-chlorobenzohydrazide* (***4e***). Yield: 42.0%; white solid. Mp: 109−111 °C. ^{1}H NMR (DMSO-d_6): δ 11.85−11.65 (m, 1H, CONHN=CH), 8.36−8.27 (m, 1H, Ph H), 8.27 (s, 0.5H, N=CH), 7.94 (s, 0.5H, N=CH), 7.78−7.11 (m, 7H, CONHCH + Ph H), 3.98−3.96 (m, 0.5H, CONHCH), 3.82−3.79 (m, 0.5H, CONHCH), 1.14 (d, J = 6.45 Hz, 3H, CH(CH_3)$_2$), 0.92 (d, J = 6.45 Hz, 3H, CH(CH_3)$_2$). HRMS: m/z calcd for $C_{18}H_{18}ClFN_3O_2$ (M + H)$^+$ 362.1072, found 362.1198.

Data for (*E*/*Z*)-*2*-(*Butylcarbamoyl*)-*N*′-(*4-fluorobenzylidene*)-*5-chlorobenzohydrazide* (***4f***). Yield: 37.8%; light yellow solid. Mp: 131−133 °C. ^{1}H NMR (DMSO-d_6): δ 11.79 (br s, 1H, CONHN=CH), 8.49−8.43 (m, 1H, Ph H), 8.27 (s, 0.5H, N=CH), 7.94 (s, 0.5H, N=CH), 7.80−7.12 (m, 7H, CONHCH$_2$ + Ph H), 3.19−3.15 (m, 1H, CONHCH$_2$), 3.01−2.97 (m, 1H, CONHCH$_2$), 1.50−1.12 (m, 4H, CH$_2$CH$_2$CH$_2$CH$_3$), 0.87 (t, J = 7.2 Hz, 1.5H, CH$_2$CH$_3$), 0.68 (t, J = 7.2 Hz, 1.5H, CH$_2$CH$_3$). HRMS: m/z calcd for $C_{19}H_{20}ClFN_3O_2$ (M + H)$^+$ 376.1228, found 376.1574.

Data for (*E*/*Z*)-*2*-(*Butylcarbamoyl*)-*N*′-(*4-(trifluoromethyl)benzylidene*)-*5-chlorobenzohydrazide* (***4g***). Yield: 17.8%; white solid. Mp: 169−171 °C. ^{1}H NMR (DMSO-d_6): δ 11.99, 11.83 (s, 1H, CONHN=CH), 8.49−8.45 (m, 1H, Ph H), 8.33 (s, 0.5H, N=CH), 8.01 (s, 0.5H, N=CH), 8.00−7.46 (m, 7H, CONHCH$_2$ + Ph H), 2.97−2.91 (m, 1.2H, CONHCH$_2$), 3.20−3.14 (m, 0.8H, CONHCH$_2$), 1.49−1.06 (m 4H, CH$_2$CH$_2$CH$_2$CH$_3$), 0.87 (t, J = 7.24 Hz, 1.4H, CH$_2$CH$_3$), 0.63 (t, J = 7.24 Hz, 1.6H, CH$_2$CH$_3$). Anal. Calcd for $C_{20}H_{19}ClF_3N_3O_2$: C, 56.41; H, 4.50; N, 9.87. Found: C, 56.37; H, 4.49; N, 9.83.

Data for (*E*/*Z*)-*2*-(*Isopropylcarbamoyl*)-*N*′-(*4-hydroxybenzylidene*)-*5-chlorobenzohydrazide* (***4h***). Yield: 36.1%; white solid. Mp: 139−140 °C. ^{1}H NMR (DMSO-d_6): δ 11.59 (s, 0.5H, CONHN=CH), 11.41 (m, 0.5H, CONHN=CH), 9.94 (s, 0.5H, OH), 9.78 (s, 0.5H, OH), 8.34−8.23 (m, 1H, Ph H), 8.15 (s, 0.5H, N=CH), 7.83 (s, 0.5H, N=CH), 7.65−7.41 (m, 4H, CONHCH + Ph H), 7.29−7.26 (d, J = 8.67 Hz, 1H, Ph H), 6.85−6.82 (d, J = 8.58 Hz, 1H, Ph H), 6.72−6.69 (d, J = 8.58 Hz, 1H, Ph H), 3.99−3.93 (m, 0.5H, CONHCH), 3.83−3.76 (m, 0.5H, CONHCH), 1.13 (d, J = 6.6 Hz, 3H, CH(CH_3)$_2$), 0.94 (d, J = 6.6 Hz, 3H, CH(CH_3)$_2$). HRMS: m/z calcd for $C_{18}H_{19}ClN_3O_3$ (M + H)$^+$ 360.1115, found 360.1588.

Data for (*E*/*Z*)-*2*-(*Cyclohexylcarbamoyl*)-*N*′-(*4-hydroxybenzylidene*)-*5-chlorobenzohydrazide* (***4i***). Yield: 58.5%; light yellow solid. Mp: 193−195 °C. ^{1}H NMR (DMSO-d_6): δ 11.64 (br s, 1H, CONHN=CH), 9.81 (br s, 1H, OH), 8.29−8.25 (m, 1H, Ph H), 8.15 (s, 0.5H, N=CH), 7.83 (s, 0.5H, N=CH), 7.65−7.41 (m, 4H, CONHCH + Ph H), 7.26 (d, J = 8.66 Hz, 1H, Ph H), 6.82 (d, J = 8.58 Hz, 1H, Ph H), 6.72 (d, J = 8.58 Hz, 1H, Ph H), 3.64 (br s, 0.5H, CONHCH), 3.50 (br s, 0.5H, CONHCH), 1.82−1.48 (m, 5H, cyclohexyl), 1.26−0.86 (m, 5H, cyclohexyl). HRMS: m/z calcd for $C_{21}H_{23}ClN_3O_3$ (M + H)$^+$ 400.1428, found 400.2010.

Data for (*E*/*Z*)-*2*-(*Isopropylcarbamoyl*)-*5-chloro-N*′-((*furan-2-yl*)*methylene*)-*benzohydrazide* (***4j***). Yield: 25.8%; yellow solid. Mp: 197−199 °C. ^{1}H NMR (DMSO-d_6): δ 11.76 (s, 0.6H, CONHN=CH), 11.58 (0.4H, CONHN=CH), 8.35−8.24 (m, 1H, Ph H), 8.15 (s, 0.6H, N=CH), 7.85 (s, 0.4H, N=CH), 7.85 (s, 0.6H, CONHCH), 7.68 (s, 0.4H, CONHCH), 7.64−7.40 (m, 3H, furanyl + Ph H), 6.94−6.53 (m, 2H, furanyl), 4.00−3.82 (m, 1H, CONHCH), 1.13 (d, J = 6.57 Hz, 3H, CH(CH_3)$_2$), 0.96 (d, J = 6.57 Hz, 3H, CH(CH_3)$_2$). HRMS: m/z calcd for $C_{16}H_{17}ClN_3O_3$ (M + H)$^+$ 334.0958, found 334.1331.

Data for (*E*/*Z*)-*2*-(*Butylcarbamoyl*)-*5-chloro-N*′-((*furan-2-yl*)*methylene*)-*benzohydrazide* (***4k***). Yield: 25.9%; brown solid. Mp: 123−125 °C. ^{1}H NMR (DMSO-d_6): δ 11.77−11.59 (m, 1H, CONHN=CH), 8.51−8.40 (m, 1H, Ph H), 8.13 (s, 0.5H, N=CH), 7.95−7.41 (m, 4.5H, CONHCH$_2$+ 0.5N=CH + furanyl + Ph H), 6.94−6.54 (m, 2H, furanyl), 3.20−3.13 (m, 1.1H, CONHCH$_2$), 3.03−3.00 (m, 0.9H, CONHCH$_2$), 1.49−1.17 (m 4H, CH$_2$CH$_2$CH$_2$CH$_3$), 0.88 (t, J = 7.2 Hz, 2H, CH$_2$CH$_3$), 0.75 (t, J = 7.2 Hz, 1H, CH$_2$CH$_3$). HRMS: m/z calcd for $C_{17}H_{19}ClN_3O_3$ (M + H)$^+$ 348.1115, found 348.1455.

Data for (*E*/*Z*)-*2*-(*Cyclohexylcarbamoyl*)-*5-chloro-N*′-((*furan-2-yl*)-*methylene*)*benzohydrazide* (***4l***). Yield: 18.7%; yellow solid. Mp: 137−138 °C. ^{1}H NMR (DMSO-d_6): δ 11.77−11.56 (m, 1H, CONHN=CH), 8.35−8.18 (m, 1H, Ph H), 8.15 (s, 0.6H, N=CH), 7.85 (s, 0.4H, N=CH), 7.85 (s, 0.6H, CONHCH), 7.67 (s, 0.4H, CONHCH), 7.64−7.40 (m, 3H, furanyl + Ph H), 6.94−6.53 (m, 2H, furanyl), 3.63−3.49 (m, 1H, CONHCH), 1.82−1.50 (m, 5H, cyclohexyl), 1.25−0.96 (m, 5H, cyclohexyl). HRMS: m/z calcd for $C_{19}H_{21}ClN_3O_3$ (M + H)$^+$ 374.1271, found 374.1649.

Data for (*E*/*Z*)-*2*-(*Isopropylcarbamoyl*)-*5-chloro-N*′-((*5-methylfuran-2-yl*)*methylene*)*benzohydrazide* (***4m***). Yield: 61.5%; light yellow solid. Mp: 168−170 °C. ^{1}H NMR (DMSO-d_6): δ 11.62 (br s, 1H, CONHN=CH), 8.33−8.25 (m, 1H, Ph H), 8.07 (s, 0.4H, N=CH), 7.77 (s, 0.4H, N=CH), 7.65−7.41 (m, 3H, CONHCH + Ph H), 6.81−6.79 (m, 0.6H, furanyl), 6.65−6.64 (m, 0.4H, furanyl), 6.27−6.26 (m, 0.6H, furanyl), 6.17−6.15 (m, 0.4H, furanyl), 3.99−3.80 (m, 1H, CONHCH), 2.35 (s, 2H, CH$_3$), 2.26 (s, 1H, CH$_3$), 1.13 (d, J = 6.57 Hz, 4H, CH(CH_3)$_2$), 0.98 (d, J = 6.57 Hz, 2H, CH(CH_3)$_2$). HRMS: m/z calcd for $C_{17}H_{19}ClN_3O_3$ (M + H)$^+$ 348.1115, found 348.1490.

Data for (*E*/*Z*)-*2*-(*Isopropylcarbamoyl*)-*5-chloro-N*′-((*thiophen-2-yl*)-*methylene*)*benzohydrazide* (***4o***). Yield: 69.1%; white solid. Mp: 110−111 °C. ^{1}H NMR (DMSO-d_6): δ 11.76 (s, 0.65H, CONHN=CH), 11.60 (s, 0.35H, CONHN=CH), 8.47 (s, 0.64H, N=CH), 8.36−8.23 (m, 1H, Ph H), 8.12 (s, 0.36H, N=CH), 7.71−7.32 (m, 5H, CONHCH + thienyl + Ph H), 7.16−7.13 (m, 0.65H, thienyl), 7.06−7.03 (m, 0.35H, thienyl), 3.97−3.81 (m, 1H, CONHCH), 1.13 (d, J = 6.57 Hz, 4H, CH(CH_3)$_2$), 0.96 (d, J = 6.54 Hz, 2H, CH(CH_3)$_2$). HRMS: m/z calcd for $C_{16}H_{17}ClN_3O_2S$ (M+H)$^+$ 350.0730, found 350.0806.

Data for (*E*/*Z*)-*2*-(*Butylcarbamoyl*)-*5-chloro-N*′-((*thiophen-2-yl*)*methylene*)-*benzohydrazide* (***4p***). Yield: 40.1%; light yellow solid. Mp: 119−121 °C. ^{1}H NMR (DMSO-d_6): δ 11.73 (br s, 1H, CONHN=CH), 8.47 (s, 0.7H, N=CH), 8.47−8.39 (m, 1H, Ph H), 8.12 (s, 0.3H, N=CH), 7.69−7.31 (m, 5H, CONHCH$_2$ + thienyl + Ph H), 7.16−7.13 (m, 0.65H, thienyl), 7.06−7.03 (m, 0.35H, thienyl), 3.2 (m, 1.3H, CONHCH$_2$), 3.05−3.00 (m, 0.7H, CONHCH$_2$), 1.49−1.14 (m 4H, CH$_2$CH$_2$CH$_2$CH$_3$), 0.88 (t, J = 7.17 Hz, 1H, CH$_2$CH$_3$), 0.75 (t, J = 7.17 Hz, 1H, CH$_2$CH$_3$). Anal. Calcd for $C_{17}H_{18}ClN_3O_2S$: C, 56.12; H, 4.99; N, 11.55. Found: C, 55.85; H, 4.94; N, 11.41.

Data for (*E*/*Z*)-*2*-(*Cyclohexylcarbamoyl*)-*5-chloro-N*′-((*thiophen-2-yl*)*methylene*)*benzohydrazide* (***4q***). Yield: 51.8%; yellow solid. Mp: 122−125 °C. ^{1}H NMR (DMSO-d_6): δ 11.77, 11.60 (br s, 1H, CONHN=CH), 8.47 (s, 0.7H, N=CH), 8.36 (d, J = 7.86 Hz, 0.7H, Ph H), 8.19 (d, J = 7.86 Hz, 0.3H, Ph H), 8.12 (s, 0.3H, N=CH), 7.71−7.32 (m, 5H,

CONHCH + thienyl + Ph H), 7.156−7.13 (m, 1H, thienyl), 7.06−7.03 (m, 1H, thienyl), 3.63−3.51 (m, 1H, CONHCH), 1.81−1.49 (m, 5H, cyclohexyl), 1.26−0.98 (m, 5H, cyclohexyl). HRMS: *m*/*z* calcd for $C_{19}H_{21}ClN_3O_2S$ (M + H)$^+$ 390.1043, found 390.1494.

Data for (*E*/*Z*)-*2*-(*Isopropylcarbamoyl*)-*5*-*chloro*-*N*′-((*3*-*methylthiophen*-*2*-*yl*)*methylene*)*benzohydrazide* (**4r**). Yield: 40.7%; light yellow solid. Mp: 132−134 °C. ^{1}H NMR (DMSO-d_6): δ 11.61 (br s, 1H, CONHN=CH), 8.54 (s, 0.7H, N=CH), 8.26 (s, 0.3H, N=CH), 8.34−8.16 (m, 1H, Ph H), 8.18 (s, 0.3H, N=CH), 7.71−7.39 (m, 4H, CONHCH + thienyl + Ph H), 6.97 (d, *J* = 5.03 Hz, 0.65H, thienyl), 6.87 (d, *J* = 5.03 Hz, 0.35H, thienyl), 4.00−3.73 (m, 1H, CONHCH), 2.30 (s, 2H, CH_3), 2.20 (s, 1H, CH_3), 1.13 (d, *J* = 6.57 Hz, 4H, CH(CH_3)$_2$), 0.98 (d, *J* = 6.57 Hz, 2H, CH(CH_3)$_2$). HRMS: *m*/*z* calcd for $C_{17}H_{19}ClN_3O_2S$ (M + H)$^+$ 364.0887, found 364.1257.

Data for (*E*/*Z*)-*2*-(*Cyclohexylcarbamoyl*)-*5*-*chloro*-*N*′-((*3*-*methylthiophen*-*2*-*yl*)*methylene*)*benzohydrazide* (**4s**). Yield: 11.4%; light yellow solid. Mp: 121−124 °C. ^{1}H NMR (DMSO-d_6): δ 11.68 (br s, 1H, CONHN=CH), 8.54 (s, 0.7H, N=CH), 8.37−8.29 (m, 0.7H, Ph H), 8.18 (s, 0.3H, N=CH), 8.08−8.06 (m, 0.3H, Ph H), 7.86−7.39 (m, 4H, CONHCH + thienyl + Ph H), 6.97 (d, *J* = 5.03 Hz, 0.65H, thienyl), 6.88 (d, *J* = 5.03 Hz, 0.35H, thienyl), 3.65−3.51 (m, 1H, CONHCH), 2.30 (s, 2H, CH_3), 2.20 (s, 1H, CH_3), 1.82−1.51 (m, 5H, cyclohexyl), 1.26−1.04 (m, 5H, cyclohexyl). HRMS: *m*/*z* calcd for $C_{20}H_{23}ClN_3O_2S$ (M + H)$^+$ 404.1200, found 404.1637.

Data for (*E*/*Z*)-*2*-(*Isopropylcarbamoyl*)-*5*-*chloro*-*N*′-((*5*-*methylthiophen*-*2*-*yl*)*methylene*)*benzohydrazide* (**4t**). Yield: 58.8%; light yellow solid. Mp: 166−169 °C. ^{1}H NMR (DMSO-d_6): δ 11.73 (br s, 1H, CONHN=CH), 8.37 (s, 0.7H, N=CH), 8.34−8.10 (m, 1H, Ph H), 8.01 (s, 0.3H, N=CH), 7.90−7.38 (m, 3H, CONHCH + Ph H), 7.27−6.58 (m, 2H, thienyl), 4.38−4.30 (m, 0.3H, CONHCH), 4.02−3.81 (m, 0.7H, CONHCH), 2.49 (s, 2H, CH_3), 2.38 (s, 1H, CH_3), 1.13 (d, *J* = 6.58 Hz, 3.3H, CH(CH_3)$_2$), 0.98 (d, *J* = 6.58 Hz, 1.7H, CH(CH_3)$_2$). HRMS: *m*/*z* calcd for $C_{17}H_{19}ClN_3O_2S$ (M + H)$^+$ 364.0887, found 364.0915.

Data for (*E*/*Z*)-*2*-(*Cyclohexylcarbamoyl*)-*5*-*chloro*-*N*′-((*5*-*chloro*-*3*-*methyl*-*1*-*phenyl*-*1H*-*pyrazol*-*4*-*yl*)*methylene*)*benzohydrazide* (**4u**). Yield: 57.8%; white solid. Mp: 207−208 °C. ^{1}H NMR (DMSO-d_6): δ 11.67 (br s, 1H, CONHN=CH), 8.33−8.15 (m, 1H, Ph H), 8.28 (s, 0.5H, N=CH), 8.16 (s, 0.5H, N=CH), 7.74−7.41 (m, 8H, CONHCH + Ph H), 3.57 (br s, 1H, CONHCH), 2.50 (s, 1.5H, CH_3), 1.92 (s, 1.5H, CH_3), 1.83−1.53 (m, 5H, cyclohexyl), 1.27−1.07 (m, 5H, cyclohexyl). HRMS: *m*/*z* calcd for $C_{25}H_{26}Cl_2N_5O_2$ (M + H)$^+$ 498.1464, found 498.2056.

Biological Assay. The bioassay was performed on a representative test organism reared in the laboratory, and it was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula (*21*). Evaluations were based on a percentage scale of 0−100, in which 0 = no activity and 100 = total kill.

Stomach Toxicity against Peach Aphids (*Myzus persicae*). Adult peach aphids were collected from vegetable fields of Haidian District, Beijing, and bred indoors. The insecticidal activity of the title compounds was tested against 3-day-old nymphs following foliar application. About 50 aphids were transferred to a shoot with cabbage leaves. The shoot with aphids was cut and dipped in a solution of 600 mg/L of the test compound for 5 s. After removing the extra solution on the leaves, the aphids were raised in the shoot at 25 ± 1 °C and 85% relative humidity for 24 h. Each treatment was carried out two times. Insecticidal activity was also tested with concentrations of 200, 50, and 12.5 mg/L. For comparative purposes, flubendiamide was tested as well. The corrected mortality rate was calculated by Abbott's formula.

Larvicidal Activity against Diamondback Moths (*Plutella xylostella* Linnaeus). Adult diamondback moths were collected from vegetable fields of Haidian District, Beijing, and bred indoors. The larvicidal activity of the title compounds against second instar larvae was tested by the leaf-dip method as follows, using a previously reported procedure (*22*, *23*). Leaf disks (2.0 cm in diameter) cut from fresh cabbage leaves were dipped in the test solution for 5 s. After air-drying, the treated leaf disks were placed in a tube (6.0 cm inner diameter) lined with a piece of filter paper, and then the instar diamondback moth larvae were transferred to the tube within 10 s. Mortality rates as percentages were evaluated 3 days after treatment, and two replications were carried out. For comparative purposes, flubendiamide was also tested.

Table 2. Optimization of Reaction Conditions for Preparation of Compound **2**

entry	solvent	time (min)	temp (°C)	yield (%)
1	EtOH	2	78	0
2	EtOH	40	30	15.0
3	EtOH	40	15	4.9
4	EtOH	120	15	3.1
5	DMF	40	15	19.0
6	DMF	120	15	15.4
7	DMF	40	5	25.2
8	DMF	120	5	24.8
9	DMF	40	−5	9.9
10	DMF	120	−5	10.1
11	DMF	40	−15	17.5
12	DMF	120	−15	33.0
13	DMF	150	−15	33.6

RESULTS AND DISCUSSION

Synthesis. As shown in **Scheme 2**, 5-chloroisoindoline-1,3-dione (**1**) reacted with 99% hydrazine hydrate in DMF to give *N*-amino-5-chloroisoindoline-1,3-dione (**2**). Compound **2** condensed with aldehydes via a Schiff base condensation to give compound **3**, which was followed by a ring-opening reaction with amines to afford the title compounds **4a**−**u**.

Sanz et al. reported in 2002 that compound **2** was prepared from compound **1** (R = H) and 99% hydrazine hydrate in ethanol at reflux (*24*). We followed this method and found that the obtained product was not the desired compound but the product isomer 6-chloro-2,3-dihydrophthalazine-1,4-dione after structural characterization with ^{1}H NMR (at 300 MHz in DMSO; δ 7.91−8.10 (m, 3H, Ph H), 11.71 (br s, 2H, NHNH)). When we sought to conduct this reaction at a temperature of 30 °C, the desired product was obtained with a yield of 15%. When the reaction temperature was further decreased to 15 °C, the reaction yield also decreased to 4.9%. However, when DMF was used as the solvent instead of ethanol, the reaction yield could reach 33.6% by varying the reaction time and temperature. The detailed yields under different conditions are listed in **Table 2**.

The title compounds could be prepared via condensation of compound **2** with different aldehydes and a ring-opening reaction of the substituted amine in two separate steps (*25*, *26*). In this study, we attempted to combine the two reactions into a single pot to obtain the desired products. When R in the amine was an *n*-butyl group, the title compounds **4c, 4f, 4g, 4k, 4p** were produced as characterized by LC/MS. However, these compounds decomposed easily during removal of the solvent 1,4-dioxane (bp 101.5 °C) via distillation. Subsequently, we attempted to use the low-boiling-point solvent THF (bp 65.4 °C) as the reaction solvent and obtained the corresponding products via purification of flash column chromatography instead of recrystallization with lower yields. Moreover, some title compounds such as **4j, 4l, 4s** were also obtained at lower yields (10−30%) after recrystallization because of their good solubility in a mixture of THF and *n*-hexane.

In principle, the reaction of unsymmetric compound **2** with aromatic aldehyde and amine could afford a pair of regioisomeric products **4** and **5** (**Scheme 2**). In practice, only **4** was found after the product was characterized using the heteronuclear multiple-bond correlation (HMBC) and heteronuclear single-quantum correlation (HSQC) techniques of NMR. However, ^{1}H NMR clearly showed that the product still constituted a pair of geometric trans and cis isomers because of the C=N double bond in hydrazone. Thus, there are two different chemical shifts for some protons in the ^{1}H NMR spectra of the product, particularly for protons in the C=N double bond.

Bioassay. *Stomach Toxicity against Peach Aphids* (*Myzus persicae*). The results of stomach toxicities of compounds **4a**−**u**

Table 3. Insecticidal Activities of Title Compounds **4a**−**u** Against *Myzus persicae*

compd	mortality (%)				
	600 mg/L	200 mg/L	50 mg/L	12.5 mg/L	LC_{50} (mg/L)
4a	92.9	28.2	12.5	16.3	170.644
4b	100	41.3	28.0	26.2	148.396
4c	94.6	39.6	34.0	9.7	121.941
4d	90.2	23.8	8.3	5.9	276.113
4e	91.3	57.8	52.8	21.9	68.055
4f	97.7	20.0	18.6	19.0	309.938
4g	96.6	49.3	22.9	12.5	130.043
4h	100	55.6	16.9	5.4	128.575
4i	92.6	24.6	19.4	25.7	244.229
4j	100	29.3	25.4	18.6	161.476
4k	100	20.0	11.7	0	234.069
4l	100	15.7	20.0	8.2	221.334
4m	96.4	50	16.9	13.8	121.636
4n	93.0	16.0	7.3	0	271.415
4o	98.7	45.5	30.3	24.0	70.515
4p	98.6	35.7	23.3	9.4	124.039
4q	98.8	37.8	13.5	19.6	113.217
4r	90.6	56.1	25.5	16.3	124.447
4s	90.6	45.2	41.7	22.4	58.903
4t	100	52.3	32.7	29.3	76.178
4u	91.9	9.5	9.1	16.7	266.287
flubendiamide					184.099

against peach aphid (*Myzus persicae*) in **Table 3** indicated that most of the compounds had excellent stomach toxicity against peach aphids at a concentration of 600 mg/mL, and 12 compounds were found to display higher activity than the control, flubendiamide (LC_{50} = 184.099 mg/L). However, the toxicities of those 12 decreased significantly when the concentrations of test compounds were reduced to 200 mg/mL or lower. Compounds **4e, 4o, 4s, 4t** exhibited slightly higher activity (LC_{50} < 77 mg/L) than other title compounds, suggesting that the introduction of *p*-fluorophenyl or (methyl)thienyl groups at the Ar position and isopropyl or cyclohexyl groups at the R position could have a positive effect on stomach toxicity. Since substituted pyrazolyl appears as a functional group in some commercial insecticidal molecules such as fipronil and chlorantraniliprole, in this study, we incorporated a substituted phenylpyrazolyl group into the designed structure. However, compound **4u** showed the lowest activity among all compounds at a concentration of 200 mg/mL and had a higher LC_{50} value (266 mg/L). This revealed that the introduction of a 5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl group could not improve stomach toxicity.

Larvicidal Activity against Diamondback Moths (*Plutella xylostella Linnaeus*). The bioassay results in **Table 4** showed that with the exception of compound **4e**, which had a mortality of 100%, most compounds had low larvicidal activity against diamondback moths at a concentration of 600 mg/mL. Moreover, compounds **4b, 4e, 4h, 4i, 4t, 4u** showed higher activity (mortality > 50%) than other compounds. That is, when the Ar in the title compound was a substituted phenyl or thienyl group with an isopropyl or cyclohexyl at the R position, *larvicidal activity* could be improved. However, all compounds had a lower larvicidal activity again diamondback moths compared to 95% mortality at 0.2 mg/L of the control, flubendiamide.

In conclusion, we designed and synthesized new phthalamides containing hydrazone using a combination of active substructures. Preliminary bioassays showed that the title compounds exhibited good stomach toxicity against peach aphids at a concentration of 600 mg/L, and 12 compounds were found to display better stomach toxicity than control fluobendiamide, but all compounds had lower larvicidal activity against diamondback moths compared to control flubendiamide. The bioassay results indicated that the toxicities of new compounds on the tested species did not exhibit the expected excellent biological activities. Nonetheless, the relationships between structure and activity obtained in this study, such as the incorporation of (un)substituted thienyl, (un)substituted phenyl and isopropyl, and cyclohexyl at different positions of *phthalamide* could be beneficial in achieving the further modification of designed structures for discovering new insecticidal molecules.

Table 4. Insecticidal Activities of Title Compounds **4a**−**u** against *Plutella xylostella* Linnaeus

compd	mortality at a concn of 600 mg/L (%)
4a	33.3
4b	66.7
4c	22.2
4d	33.3
4e	100
4f	33.3
4g	33.3
4h	55.6
4i	55.6
4j	44.4
4k	44.4
4l	33.3
4m	44.4
4n	33.3
4o	0
4p	44.4
4q	33.3
4r	44.4
4s	11.1
4t	55.6
4u	66.7

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