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Design, Synthesis, and Insecticidal Activities of New *N*-Benzoyl-*N*′-phenyl-*N*′-sulfenylureas

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A series of new *N*′-alkylaminothio, *N*′-arylaminothio (or dithio), and *N*′,*N*′-thio (or dithio) derivatives of *N*-benzoyl-*N*′-phenylureas were designed and synthesized as insect-growth regulators with sulfur dichloride or disulfur dichloride as the original reactant. The new compounds were identified by ^{1}H nuclear magnetic resonancee (NMR) spectroscopy, elemental analysis [or high-resolution mass spectrometry (HRMS)], and single-crystal X-ray diffraction analysis. The X-ray results demonstrated that there exist N−S−N or N−S−S−N bonds in these new compounds. In comparison to the parent *N*-benzoyl-*N*′-phenylureas, these derivatives displayed better solubility. The insecticidal activities of the target compounds were evaluated. The results of bioassays showed that compounds **1**−**24** retained the larvicidal activities of the corresponding benzoylphenylureas (BPUs) and some compounds exhibited better larvicidal activities against oriental armyworm and mosquitoes than the parent BPUs. The larvicidal activities of the selected target compounds **1** and **24** against diamondback moth were better than that of the corresponding parent compounds E and triflumuron.

KEYWORDS: Benzoylphenylureas (BPUs); *N*-sulfenate derivative; *N*-aminothio (or dithio) derivatives; *N*′, *N*′-thio (or dithio) derivatives; diflumuron; penfluoron; triflumuron; larvividal activity; insecticidal activity; insect-growth regulator

INTRODUCTION

Insect-growth regulators (IGRs) alter physiological processes, which are essential to insect development and appear to act specifically on insects. When used as pesticides, IGRs stop insect larva from developing into biting, reproducing adults. Therefore, IGRs are an effective tool to implement integrated pest management (IPM) programs (*1*). Benzoylphenylureas (BPUs) and *N*-*tert*-butyl-*N*,*N*′-diacylhydrazines are two familiar types of IGRs, and they have attracted considerable attention for decades (*1*−*14*). However, diacylhydrazines and BPUs both have low solubility in water and limited solubility in common organic solvents. The disadvantage impedes their field application (*9*, *10*, *15*, *16*).

It has been reported that *N*-benzoyl-*N*′-phenyl-*N*′-substituted ureas (compounds **A** and **B** in **Figure 1**) could retain the insecticidal activities of the parent BPUs and that the solubility of these BPU derivatives were improved obviously at the same time (*9*, *10*). Recently, we have reported a series of *N*-aminothio and *N*,*N*-dithio derivatives of *N*′-*tert*-butyl-*N*, *N*′-diacylhydrazines (compounds **C** and **D** in **Figure 1**), which possess comparable activities against oriental armyworm than the corresponding parent compounds (*17*). In comparison to the parent compounds, these derivatives displayed better solubility. Inspired by these reports, we developed an idea that substitution of the hydrogen on the nitrogen atom of BPUs with aminothio and aminodithio substituents could retain the insecticidal activity of parent BPUs, whereas solubility of these BPU derivatives would be improved. Therefore, a series of novel *N*′-alkylaminothio, *N*′-arylaminothio (or dithio), and *N*′,*N*′-thio (or dithio) derivatives of *N*-benzoyl-*N*′-phenylureas were designed and synthesized (compounds **1**−**25** in **Figure 1**). The insecticidal activities of the target compounds were evaluated. The larvicidal activities of the selected target compounds **1** and **24** and the corresponding parent compounds E and triflumuron against diamondback moth and beet armyworm were tested, and the median lethal concentrations (LC_{50}) were calculated.

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MATERIALS AND METHODS

Instruments. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained at 300 MHz using a Bruker AC-P300 spectrometer or at 400 MHz using a Varian Mercury Plus 400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical-shift values (δ) were given in parts per million (ppm). Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. High-resolution mass spectrometry (HRMS) data was obtained on a FTICR-MS instrument (Ionspec7.0T). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Yields were not optimized.

General Synthesis. The reagents were all analytically or chemically pure. All anhydrous solvents were dried and purified by

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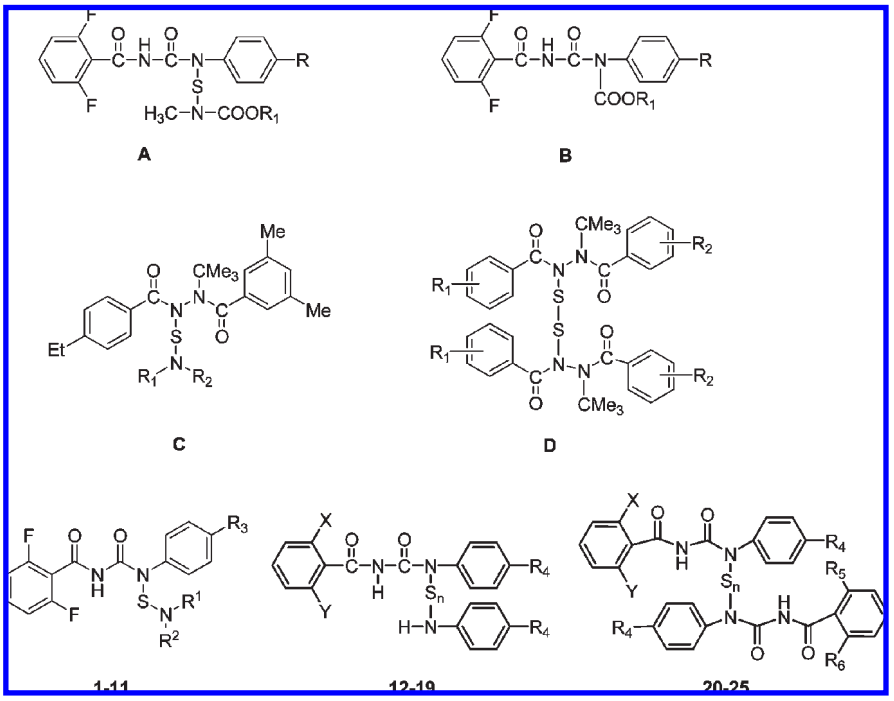

Figure 1. Chemical structures of compounds **A**−**D** and **1**−**25**.

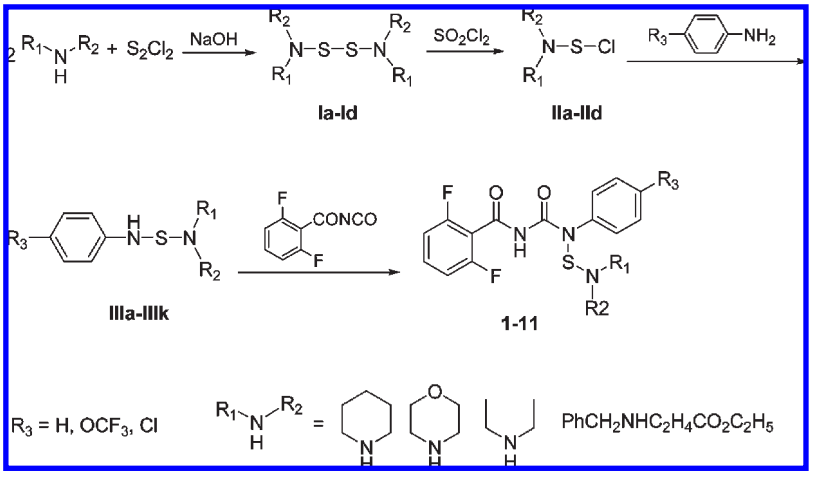

Figure 2. General synthetic route for the target compounds **1**−**11**.

standard techniques prior to use. Sulfur dichloride was prepared by the reaction of disulfur dichloride with chlorine (*18*). Disulfur dichloride was distilled just before use. Substituted benzoyl isocyanate was prepared by the method in the literature (*19*).

General Synthetic Procedure for the Target Compounds 1−**11** (Figure 2). *Synthesis of N,N′-Dithiobis-morpholine (**Ia**).* To a solution of sodium hydroxide (2.40 g, 60 mmol) in water (10 mL) was added dichloromethane (20 mL) and morpholine (2.61 g, 30 mmol) in one portion. Then, the mixture was cooled by an ice−water bath, and disulfur dichloride (2.02 g, 15 mmol) in dichloromethane (5 mL) was slowly added. After addition was complete, the mixture was stirred in an ice−water bath for 30 min. Then, the mixture was poured into the separatory funnel, and the aqueous phase was extracted by dichloromethane (10 mL × 2). The combined organic extract was washed with saturated brine (40 mL), then dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on a silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate as the eluent to afford **Ia** as a white solid (3.00 g, 84.7%); mp 118−120 °C. ^{1}H NMR (300 M, $CDCl_3$) δ: 2.82 [t, 8H, $^3J_{HH}$ = 4.2 Hz,2(CH_2NCH_2)], 3.33 [t, 8H, $^3J_{HH}$ = 4.6 Hz, 2(CH_2OCH_2)]. Intermediates **Ib**−**Id** were prepared by following the same procedure as for **Ia**.

*N,N′-Dithiobis-diethylamine (**Ib**).* Yield, 62%; yellow oil.

*N,N′-Dithiobis-piperidine (**Ic**).* Yield, 88%; white solid; mp 32−34 °C.

*N,N′-Dithiobis(ethyl 3-(benzylamino)propanoate) (**Id**).* Yield, 82%; colorless oil.

*Synthesis of N′-(2,6-Difluorobenzoyl)-N-(morpholinothio)-N-(4-(trifluoromethoxy)phenyl)urea (**1**).* To a solution of **Ia** (2.83 g, 12 mmol) in dichloromethane (20 mL) was slowly added sulfuryl dichloride (17.0 g, 12.6 mmol). After the addition was complete, the mixture was kept for 30 min. Then, the solvent was removed to give a crude product **IIa** as yellow oil, which was used in the next step without further purification.

A solution of **IIa** (0.46 g, 3 mmol) in anhydrous diethyl ether (5 mL) was dropwise-added to the mixture of 4-(trifluoromethoxy) benzenamine (0.53 g, 3 mmol) and triethylamine (0.30 g, 3 mmol) in anhydrous diethyl ether (25 mL) cooled in an ice−salt bath. Then, the mixture stood for 30 min after the addition was complete and filtered, and the residue was washed with anhydrous diethyl ether (5 mL × 2). The filtrate was concentrated under reduced pressure to give a crude product **IIIa** (0.86 g, 97.7%) as a white solid, which was

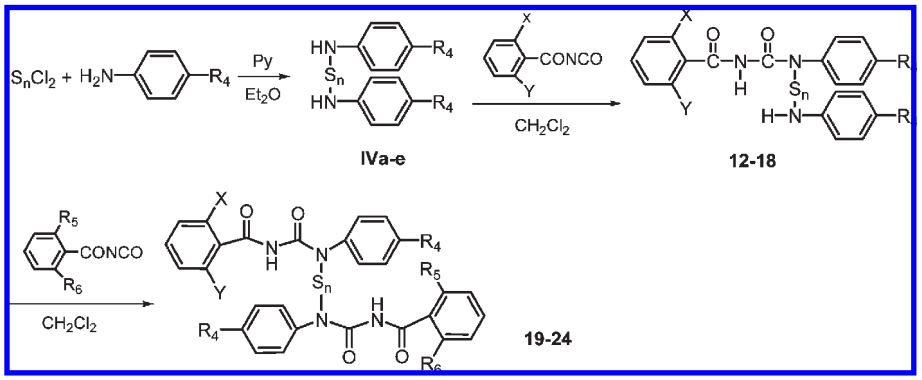

Figure 3. General synthetic route for the target compounds **12**−**24**.

recrystallized from a mixture of petroleum ether (60−90 °C) and ethyl acetate (7:1, v/v); mp 86−88 °C. ^{1}H NMR (300 M, $CDCl_3$) δ: 3.10 (t, 4H, $^3J_{HH}$ = 4.5 Hz, CH_2NCH_2), 3.69 (t, 4H, $^3J_{HH}$ = 4.5 Hz, CH_2OCH_2), 5.89 (s, 1H, Ar*NH*), 7.05−7.10 (m, 4H, Ar).

A solution of 2,6-difluorobenzoyl isocyanates (0.18 g, 1.0 mmol) in dry dichloromethane (5 mL) was added dropwise to a solution of compound **IIIa** (0.29 g, 1.1 mmol) in dry dichloromethane (10 mL) at room temperature. After the addition was complete, the mixture was stirred for 1 h at room temperature and concentrated under reduced pressure. The residue was purified by flash-column chromatography on a silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate as the eluent to afford the target compound **1** (0.35 g, 73.4%). Further recrystallization from a mixture of petroleum ether (60−90 °C) and dichloromethane gave a white solid; mp 86−88 °C. ^{1}H NMR (400 M, $CDCl_3$) δ: 3.21 (s, 4H, CH_2NCH_2), 3.65 (s, 4H, CH_2OCH_2), 6.94 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.3 Hz, Ar), 7.20 (d, 2H, $^3J_{HH}$ = 8.5 Hz, Ar), 7.34 (d, 2H, $^3J_{HH}$ = 8.5 Hz, Ar), 7.36−7.42 (m, 1H, Ar), 9.47 (s, 1H, CO*NH*CO). Anal. Calcd for $C_{19}H_{16}F_5N_3O_4S$: C, 47.80; H, 3.38; N, 8.80. Found: C, 47.62; H, 3.43; N, 8.78. The target compounds **2**−**11** were prepared by following the same procedure as for compound **1**.

*N-(4-Chlorophenyl)-N′-(2,6-difluorobenzoyl)-N-(morpholinothio)urea (**2**)*. Yield, 65%; white solid; mp 127−128 °C. ^{1}H NMR (400 M, $CDCl_3$) δ: 3.20 (s, 4H, CH_2NCH_2), 3.64 (s, 4H, CH_2OCH_2), 6.94 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.5 Hz, Ar), 7.24 (d, 2H, $^3J_{HH}$ = 8.6 Hz, Ar), 7.32 (d, 2H, $^3J_{HH}$ = 8.6 Hz, Ar), 7.36−7.42 (m, 1H, Ar), 9.40 (s, 1H, CO*NH*CO). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{16}ClF_2N_3O_3S$: $(M + Na)^+$ 450.0461, found 450.0464.

*N′-(2,6-Difluorobenzoyl)-N-phenyl-N-(piperidinylthio) urea (**3**)*. Yield, 61%; white solid; mp 84−86 °C. ^{1}H NMR (400 M, $CDCl_3$) δ: 1.07 [t, 6H, $^3J_{HH}$ = 7.1 Hz, 3(CH_2)], 3.13 (br, 4H, CH_2NCH_2), 6.91 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.1 Hz, Ar), 7.22−7.25 (m, 1H, Ar), 7.30−7.38 (m, 5H, Ar), 9.47 (s, 1H, CO*NH*CO). Anal. Calcd for $C_{19}H_{19}F_2N_3O_2S$: C, 58.30; H, 4.89; N, 10.73. Found: C, 58.11; H, 4.78; N, 10.79.

*N-(4-Chlorophenyl)-N′-(2,6-difluorobenzoyl)-N-(piperidinylthio)urea (**4**)*. Yield, 30%; white solid; mp 97−98 °C. ^{1}H NMR (400 M, $CDCl_3$) δ: 1.09 [t, 6H, $^3J_{HH}$ = 7.1 Hz, 3(CH_2)], 3.13 (br, 4H, CH_2NCH_2), 6.91 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.2 Hz, Ar), 7.20 (d, 2H, $^3J_{HH}$ = 8.6 Hz, Ar), 7.30 (d, 2H, $^3J_{HH}$ = 8.5 Hz, Ar), 7.33−7.39 (m, 1H, Ar), 9.62 (s, 1H, CO*NH*CO). Anal. Calcd for $C_{19}H_{18}ClF_2N_3O_2S$: C, 53.58; H, 4.26; N, 9.87. Found: C, 53.65; H, 4.43; N, 9.87.

*N′-(2,6-Difluorobenzoyl)-N-(piperidinylthio)-N-(4-(trifluoromethoxy)phenyl)urea (**5**)*. Yield, 39%; white solid; mp 96−98 °C. ^{1}H NMR (400 M, $CDCl_3$) δ: 1.08 [t, 6H, $^3J_{HH}$ = 7.1 Hz, 3(CH_2)], 3.09−3.18 (m, 4H, CH_2NCH_2), 6.92 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.2 Hz, Ar), 7.17 (d, 2H, $^3J_{HH}$ = 8.7 Hz, Ar), 7.29 (d, 2H, $^3J_{HH}$ = 8.7 Hz, Ar), 7.32−7.30 (m, 1H, Ar), 9.67 (s, 1H, CO*NH*CO). Anal. Calcd for $C_{20}H_{18}F_5N_3O_3S$: C, 50.53; H, 3.82; N, 8.84. Found: C, 50.10; H, 4.13; N, 8.82.

*N-(Diethylaminylthio)-N′-(2,6-difluorobenzoyl)-N-phenylurea (**6**)*. Yield, 39%; white solid; mp 109−111 °C. ^{1}H NMR (400 M, $CDCl_3$) δ: 1.50−1.60 [m, 6H, 2(CH_3)], 3.14−3.26 (m, 4H, CH_2NCH_2), 6.92 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.2 Hz, Ar), 7.27−7.39 (m, 6H, Ar), 9.53 (s, 1H, CO*NH*CO). Anal. Calcd for $C_{18}H_{19}F_2N_3O_2S$: C, 56.98; H, 5.05; N, 11.07. Found: C, 56.75; H, 5.05; N, 11.10.

*N-(4-Chlorophenyl)-N-(diethylaminylthio)-N′-(2,6-difluorobenzoyl)urea (**7**)*. Yield, 47%; white solid; mp 121−123 °C. ^{1}H NMR (400 M, $CDCl_3$) δ: 1.50−1.60 [m, 6H, 2(CH_3)], 3.10−3.25 (m, 4H, CH_2NCH_2), 6.92 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.2 Hz, Ar), 7.22 (d, 2H, *J* = 8.7 Hz, Ar), 7.30 (d, 2H, $^3J_{HH}$ = 8.7 Hz, Ar), 7.33−7.40 (m, 1H, Ar), 9.65 (s, 1H, CO*NH*CO). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{18}ClF_2N_3O_2S$: $(M + Na)^+$ 436.0669, found 436.0671.

*N-(Diethylaminylthio)-N′-(2,6-difluorobenzoyl)-N-(4-(trifluoromethoxy)phenyl)urea (**8**)*. Yield, 30%; white solid; mp 107−109 °C. ^{1}H NMR (400 M, $CDCl_3$) δ: 1.52−1.64 [m, 6H, 2(CH_3)], 3.12−3.30 (m, 4H, CH_2NCH_2), 6.93 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, Ar), 7.17 (d, 2H, $^3J_{HH}$ = 8.7 Hz, Ar), 7.32 (d, 2H, $^3J_{HH}$ = 8.7 Hz, Ar), 7.35−7.40 (m, 1H, Ar), 9.69 (s, 1H, CO*NH*CO). Anal. Calcd for $C_{19}H_{18}F_5N_3O_3S$: C, 49.24; H, 3.91; N, 9.07. Found: C, 49.12; H, 4.05; N, 8.92.

*N-((Ethyl propanoate)-3-yl-benzylaminylthio)-N′-(2,6-difluorobenzoyl)-N-phenylurea (**9**)*. Yield, 52%; yellow oil. ^{1}H NMR (400 M, $CDCl_3$) δ: 1.20 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3CH_2O), 2.47 (t, 2H, $^3J_{HH}$ = 6.9 Hz, CH_2CH_2CO), 3.30 (br, 2H, CH_3CH_2O), 4.04 (t, 2H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_2CO), 4.21 (br, 1H, NCH_2Ar), 4.32 (br, 1H, NCH_2Ar), 6.92 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.2 Hz, Ar), 7.01−7.15 (m, 3H, Ar), 7.26−7.32 (m, 5H, Ar), 7.33−7.41 (m, 3H, Ar), 8.99 (s, 1H, CO*NH*CO). Anal. Calcd for $C_{26}H_{25}F_2N_3O_4S$: C, 60.81; H, 4.91; N, 8.18. Found: C, 60.87; H, 4.80; N, 8.21.

*N-(4-Chlorophenyl)-N-((ethyl propanoate)-3-yl-benzylaminylthio)-N′-(2,6-difluorobenzoyl)urea (**10**)*. Yield, 61%; yellow oil. ^{1}H NMR (400 M, $CDCl_3$) δ: 1.21 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3CH_2O), 2.46 (t, 2H, $^3J_{HH}$ = 6.9 Hz, CH_2CH_2CO), 3.31 (br, 2H, CH_3CH_2O), 4.07 (t, 2H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_2CO), 4.21 (br, 1H, NCH_2Ar), 4.31 (br, 1H, NCH_2Ar), 6.92 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.2 Hz, Ar), 7.10−7.16 (m, 3H, Ar), 7.20 (d, 2H, $^3J_{HH}$ = 8.6 Hz, Ar), 7.26−7.41 (m, 5H, Ar), 9.21 (s, 1H, CO*NH*CO). HRMS (ESI) *m*/*z* calcd for $C_{26}H_{24}ClF_2N_3O_4S$: $(M + Na)^+$ 570.1036, found 570.1040.

*N-((Ethyl propanoate)-3-yl-benzylaminylthio)-N′-(2,6-difluorobenzoyl)-N-(4-(trifluoromethoxy)phenyl)urea (**11**)*. Yield, 59%; yellow oil. ^{1}H NMR (400 M, $CDCl_3$) δ: 1.21 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3CH_2O), 2.46 (t, 2H, $^3J_{HH}$ = 6.9 Hz, CH_2CH_2CO), 3.33 (br, 2H, CH_3CH_2O), 4.08 (t, 2H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_2CO), 4.22 (br, 1H, NCH_2Ar), 4.31 (br, 1H, NCH_2Ar), 6.92 (t, 2H, $^3J_{HH}$ = $^3J_{HF}$ = 8.2 Hz, Ar), 7.03−7.13 (m, 3H, Ar), 7.20 (d, 2H, $^3J_{HH}$ = 8.6 Hz, Ar), 7.26−7.40 (m, 5H, Ar), 9.29 (s, 1H, CO*NH*CO). Anal. Calcd for $C_{27}H_{24}F_5N_3O_5S$: C, 54.27; H, 4.05; N, 7.03. Found: C, 54.27; H, 3.94; N, 6.94.

General Synthetic Procedure for the Target Compounds 12−24 (Figure 3). *Synthesis of Bis(4-trifluoromethylphenylamino)disulfide (**IVa**)*. A mixture of 4-trifluoromethylaniline (1.61 g, 10 mmol) and pyridine (0.87 g, 11 mmol) in anhydrous diethyl ether was dropwise-added to a solution of disulfur dichloride

(0.68 g, 5 mmol) in anhydrous diethyl ether cooled in an ice−salt bath. The mixture was stirred for 1 h after the addition was complete and filtered. Then, the filtrate was washed by saturated brine and dried over anhydrous sodium sulfate. The filtrate was concentrated in vacuo to give an oil, which was purified by flash-column chromatography on a silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (12:1, v/v) as the eluent to obtain compound **IVa** as a pale yellow solid (1.30 g, 66.7%); mp 49−51 °C. ^{1}H NMR (300 M, $CDCl_3$) δ: 5.45 (s, 2H, NH), 6.98 (d, 4H, Ph), 7.40 (d, 4H, Ph). Intermediates **IVb**−**IVe** were prepared by following the same procedure as for **IVa**, and disulfur dichloride was displaced by sulfur dichloride when necessary.

*Bis(4-(trifluoromethoxy)phenylamine)disulfide (**IVb**).* Yield, 70.4%; mp 37−38 °C.

*Bis(4-(trifluoromethoxy)phenylamine)sulfide (**IVc**).* Yield, 69.3%; mp 55−57 °C.

*Bis(4-chloro-phenylamine)sulfide (**IVd**).* Yield, 77.2%; mp 99−101 °C (from ref *20*, 102−103 °C).

*Bis(4-(trifluoromethyl)phenylamine)sulfide (**IVe**).* Crude yield, 67.3%; oil.

*Synthesis of N′-(2,6-Difluorobenzoyl)-N-(4-(trifluoromethyl)phenyl)-N-((4-trifluoromethyl)benzenaminyldithio) urea (**12**).* A solution of 2,6-difluorobenzoyl isocyanates (0.18 g, 1.0 mmol) in dry dichloromethane (5 mL) was added dropwise to a solution of compound **IVa** (0.38 g, 1.0 mmol) in dry dichloromethane (10 mL), which was cooled with an ice bath, and the mixture was stirred for 1 h at room temperature. After removal of the solvent, the white solid was purified by recrystallization from diethyl ether to give compound **12** as a white solid (0.40 g, 71.4%); mp 122 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 6.17 (s, 1H, NH), 6.90 (t, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.07 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.35−7.48 (m, 5H, Ph), 7.63 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 9.13 (s, 1H, CONH). Anal. Calcd for $C_{22}H_{13}F_8N_3O_2S_2$: C, 46.56; H, 2.31; N, 7.40. Found: C, 46.57; H, 2.32; N, 7.30. The target compounds **13**−**18** were prepared by following the same procedure as for compound **12**.

*N′-(2,6-Difluorobenzoyl)-N-(4-(trifluoromethoxyl)phenyl)-N-((4-trifluoromethoxyl)benzenaminyldithio)urea (**13**).* Yield, 66.7%; white solid; mp 91 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 5.76 (s, 1H, NH), 6.92 (t, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 6.98 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.08 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.23 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.34−7.45 (m, 3H, Ph), 8.93 (s, 1H, CONH). Anal. Calcd for $C_{22}H_{13}F_8N_3O_4S_2$: C, 44.08; H, 2.19; N, 7.01. Found: C, 44.05; H, 2.17; N, 7.06.

*N′-(2-Chlorobenzoyl)-N-(4-(trifluoromethoxyl)phenyl)-N-((4-trifluoromethoxyl)benzenaminyldithio)urea (**14**).* Yield, 79.8%; white solid; mp 127 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 6.64 (s, 1H, NH), 6.94−7.11 (m, 5H, Ph), 7.18 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.30−7.39 (m, 3H, Ph), 7.46 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 9.39 (s, 1H, CONH). Anal. Calcd for $C_{22}H_{14}ClF_6N_3O_4S_2$: C, 44.19; H, 2.36; N, 7.03. Found: C, 44.50; H, 2.76; N, 7.24.

*N′-(2-Chlorobenzoyl)-N-(4-(trifluoromethyl)phenyl)-N-((4-trifluoromethyl)benzenaminyldithio)urea (**15**).* Yield, 60.2%; white solid; mp 135 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 6.94 (s, 1H, NH), 6.97−7.60 (m, 12H, Ph), 9.58 (s, 1H, CONH). Anal. Calcd for $C_{22}H_{14}ClF_6N_3O_2S_2$: C, 46.69; H, 2.49; N, 7.42. Found: C, 46.58; H, 2.44; N, 7.64.

*N-(4-Chlorophenylaminylthio)-N′-(2,6-difluorobenzoyl)-N-(4-chlorophenyl)urea (**16**).* Yield, 63.5%; white solid; mp 128−131 °C. ^{1}H NMR (300 M, $CDCl_3$) δ: 6.46 (s, 1H, NH), 6.75 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 6.96 (t, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.07 (t, 4H, $^3J_{HH}$ = 7.5 Hz, Ph), 7.30 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.42 (m, 1H, Ph), 9.52 (s, 1H, CONH). Anal. Calcd for $C_{20}H_{13}Cl_2F_2N_3O_2S$: C, 51.29; H, 2.80; N, 8.97. Found: C, 50.86; H, 2.82; N, 9.35.

*N′-(2,6-Difluorobenzoyl)-N-(4-(trifluoromethyl)phenylaminylthio)-N-(4-(trifluoromethyl)phenyl)urea (**17**).* Yield, 52.3%; white solid; mp 126−127 °C. ^{1}H NMR (300 M, $CDCl_3$) δ: 6.72 (s, 1H, NH), 6.83 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 6.98 (t, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.30−7.49 (m, 5H, Ph), 7.59 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 9.75 (s, 1H, CONH). Anal. Calcd for $C_{22}H_{13}F_8N_3O_2S$: C, 49.35; H, 2.45; N, 7.85. Found: C, 48.95; H, 2.55; N, 8.42.

*N′-(2,6-Difluorobenzoyl)-N-(4-(trifluoromethoxyl)phenylaminylthio)-N-(4-(trifluoromethoxyl)phenyl)urea (**18**).* Yield, 74.9%; white solid; mp 125 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 6.74 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 6.94 (m, 4H, Ph), 7.02 (s, 1H, NH), 7.14 (m, 4H, Ph), 7.46 (m, 1H, Ph), 9.53 (s, 1H, CONH). Anal. Calcd for $C_{22}H_{13}F_8N_3O_4S$: C, 46.57; H, 2.31; N, 7.41. Found: C, 46.30; H, 2.47; N, 7.58.

*Synthesis of Bis(N′-(2,6-difluorobenzoyl)-N-(4-(trifluoromethoxy)phenyl)urea)disulfide (**19**).* A solution of 2,6-difluorobenzoyl isocyanates (0.09 g, 0.5 mmol) in dry dichloromethane (3 mL) was added dropwise to a solution of compound **13** (0.30 g, 0.5 mmol) in dry dichloromethane (5 mL) at room temperature, and the mixture was stirred for 1 h after the addition was complete. After removal of the solvent, the white solid was purified by recrystallization from diethyl ether to give compound **19** as a white crystal (0.28 g, 71.8%); mp 109 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 6.95 (t, 4H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.32 (d, 4H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.37−7.46 (m, 2H, Ph), 7.57 (d, 4H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.85 [s, 2H, 2(CONH)]. Anal. Calcd for $C_{30}H_{16}F_{10}N_4O_6S_2$: C, 46.04; H, 2.06; N, 7.16. Found: C, 45.91; H, 2.02; N, 7.29. The target compounds **20**−**24** were prepared by following the same procedure as for compound **19**.

*1-(((3′-(2′-Chlorobenzoyl)-1′-(4′-(trifluoromethoxy)phenyl)urea)-1′-yl)dithio)-3-(2,6-difluorobenzoyl)-1-(4-(trifluoromethoxy)phenyl)urea (**20**).* Yield, 51.3%; white solid; mp 142 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 6.88 (t, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.32−7.43 (m, 8H, Ph), 7.65−7.71 (m, 5H, Ph), 7.88 (s, 1H, CONH), 8.24 (s, 1H, CONH). Anal. Calcd for $C_{30}H_{17}F_8N_4O_6S_2$: C, 46.13; H, 2.19; N, 7.17. Found: C, 45.95; H, 2.24; N, 7.17.

*Bis(N′-(2-chlorobenzoyl)-N-(4-(trifluoromethoxy)phenyl)urea)disulfide (**21**).* Yield, 64.1%; white solid; mp 131 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 7.28−7.38 (m, 10H, Ph), 7.71−7.76 (m, 6H, Ph), 8.30 [s, 2H, 2(CONH)]. Anal. Calcd for $C_{30}H_{18}Cl_2F_6N_4O_6S_2$: C, 46.22; H, 2.33; N, 7.19. Found: C, 46.18; H, 2.24; N, 7.04.

*Bis(N′-(2,6-difluorobenzoyl)-N-(4-(trifluoromethoxy)phenyl)urea)sulfide (**22**).* Yield, 69.3%; white solid; mp 144 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 6.94 (t, 4H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.26−7.43 (m, 10H, Ph), 9.10 [s, 2H, 2(CONH)]. Anal. Calcd for $C_{30}H_{16}F_{10}N_4O_6S$: C, 48.01; H, 2.15; N, 7.47. Found: C, 48.38; H, 2.42; N, 7.13.

*Bis(N-(4-chlorophenyl)-N′-(2,6-difluorobenzoyl)urea)sulfide (**23**).* Yield, 58.6%; white solid; mp 135 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 6.90 (t, 4H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.02 (d, 4H, $^3J_{HH}$ = 8.0 Hz, Ph), 7.25 (d, 4H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.35−7.42 (m, 2H, Ph), 9.58 [s, 2H, 2(CONH)]. Anal. Calcd for $C_{28}H_{16}Cl_2F_4N_4O_4S$: C, 51.63; H, 2.48; N, 8.60. Found: C, 51.80; H, 2.42; N, 8.56.

*1-(((3′-(2′-Chlorobenzoyl)-1′-(4′-(trifluoromethoxy)phenyl)urea)-1′-yl)thio)-3-(2,6-difluorobenzoyl)-1-(4-(trifluoromethoxy)phenyl)urea (**24**).* Yield, 62.3%; white solid; mp 139 °C (dec). ^{1}H NMR (300 M, $CDCl_3$) δ: 6.91 (t, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.01−7.59 (m, 13H, Ph), 8.82 (s, 1H, CONH), 10.48 (s, 1H, CONH). Anal. Calcd for $C_{30}H_{17}ClF_8N_4O_6S$: C, 48.11; H, 2.29; N, 7.48. Found: C, 48.00; H, 2.51; N, 7.32.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay 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 are based on a percentage scale of 0−100, in which 0 = no activity and 100 = total kill. The deviations of the tested biological values were ±5%.

Larvicidal Activity against Oriental Armyworm (*Mythimna separata*). The larvicidal activities of the target compounds **1**−**24** against oriental armyworm were evaluated by foliar application using the reported procedure (*16*, *22*, *23*). For the foliar armyworm tests, individual corn leaves were placed on moistened pieces of filter

Table 1. Larvicidal Activities against Oriental Armyworm and Mosquito of Compounds **1**−**11**, E, F, and Diflumuron

	toxicities against oriental armyworm		toxicities against mosquito	
compound	concentration (mg L^{-1})	larvicidal activity (%)	concentration (mg L^{-1})	larvicidal activity (%)
	1	100	0.01	100
1	0.5	100	0.005	100
	0.25	80	0.0025	20
	1	100	0.01	100
2	0.5	100	0.005	30
	0.25	80	0.0025	0
	200	90	5	100
3	100	40	2.5	70
	50	0	1	0
	1	100	0.01	90
4	0.5	100	0.005	0
	0.25	20	0.0025	0
	1	100	0.01	100
5	0.5	100	0.005	100
	0.25	50	0.0025	75
	200	70	5	100
6	100	40	2.5	100
	50	20	1	30
	1	100	0.01	100
7	0.5	70	0.005	10
	0.25	20	0.0025	10
	1	100	0.01	100
8	0.5	100	0.005	100
	0.25	60	0.0025	40
	200	70	5	100
9	100	40	2.5	60
	50	30	1	20
	1	100	0.01	60
10	0.5	50	0.005	0
	0.25	30	0.0025	
11	1	100	0.01	100
0.5	100	0.005	100	
0.25	40	0.0025	10	
	1	100	0.01	100
E	0.5	100	0.005	100
	0.25	80	0.0025	70
	200	80	5	100
F	100	30	2.5	100
	50	0	1	65
	1	100	0.01	100
diflubenzuron	0.5	100	0.005	50
	0.25	100	0.0025	10

paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Each treatment was performed 3 times. The biological data in **Table 1** was the average value of the three tested values. For comparative purposes, parent compounds E, F, G, diflubenzuron, penfluoron, and triflumuron were tested under the same condition.

Larvicidal Activity against Mosquito (*Culex pipiens pallens*). The larvicidal activities of the target compounds **1**−**11** against mosquito were evaluated by the reported procedure (*10*). Compounds **1**−**11** were prepared at different concentrations by dissolving **1**−**11** in acetone and adding distilled water. Then, 20 fourth-instar mosquito larvae were put into 10 mL of the test solution and raised for 8 days. The results were expressed by death percentage. The biological data in **Table 1** were the average value of the three tested values. For comparative purposes, compounds E, F, and diflubenzuron were tested under the same conditions.

Larvicidal Activity against Diamondback Moth (*Plutella xylostella* Linnaeus). The larvicidal activities of the target compounds **1** and **24** and the corresponding parent compounds E and triflumuron against diamondback moth were tested by the leaf-dip method using the reported procedure (*17*, *24*, *25*). Leaf disks (1.8 cm in diameter) were cut from fresh cabbage leaves and then dipped into the test solution for 5 s. After air-drying, the treated leaf disks were placed in a tube (9 × 3 cm inner diameter) lined with a piece of filter paper and then 10 s instar diamondback moth larvae were transferred to the tube. Percentage mortalities were evaluated 4 days after treatment, and three replicates were carried out. The data for the mortality regression lines of the compounds were subjected to probit analysis by Finney's method, and the median lethal concentrations (LC_{50}) of the compounds against diamondback moth larvae were calculated.

Larvicidal Activity against Beet Armyworm (*Spodoptera exigua*). The larvicidal activities of the target compounds **1** and **24** and the corresponding parent compounds E and triflumuron against beet armyworm were tested by the leaf-dip method using the reported procedure (*24*, *25*). Leaf disks (1.8 cm in diameter) were cut from fresh cabbage leaves and then dipped into the test solution for 5 s. After air-drying, the treated leaf disks were placed in a Petri dish (60 cm in diameter) lined with a piece of filter paper and then 10 third-instar beet armyworm larvae were transferred to the Petri dish. Percentage mortalities were evaluated 4 days after treatment, and three replicates were carried out. The data for the mortality

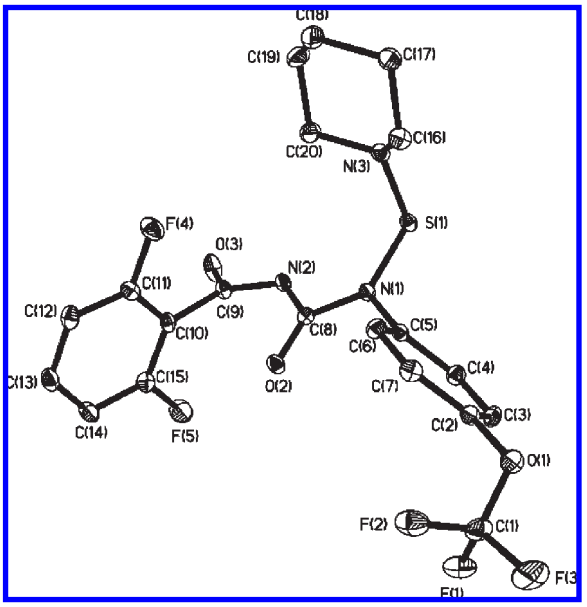

Figure 4. Molecular structure of compound **5**.

regression lines of the compounds were subjected to probit analysis by Finney's method, and the median lethal concentrations (LC_{50}) of the compounds against beet armyworm larvae were calculated.

RESULTS AND DISCUSSION

Synthesis. The target compounds **1**−**11** were synthesized from disulfur dichloride as shown in **Figure 2**. Disulfur dichloride was condensed with 2 equiv of secondary amine using sodium hydroxide as the acid acceptor to give intermediates **Ia**−**Id**, as shown in **Figure 2**. Then, intermediates **Ia**−**Id** were oxidized by sulfuryl dichloride to give intermediates **IIa**−**IId** without further purification (*26*), and subsequent reaction with aniline or substituted aniline yielded compounds **IIIa**−**IIIk**, which were combined with 2,6-difluorobenzoyl isocyanate to afford the target compounds **1**−**11**.

The target compounds **12**−**24** were prepared from disulfur dichloride or sulfur dichloride, as shown in **Figure 3**. At first, disulfur dichloride or sulfur dichloride reacted with substituted aniline using pyridine as the acid acceptor to give intermediates **IVa**−**IVe**, and subsequent reaction with substituted benzoyl isocyanate yielded compounds **12**−**18**, which were combined with another equivalent of substituted benzoyl isocyanate to afford compounds **19**−**24**. Compounds **IVc**−**IVe** were prepared by a reaction between appropriate aniline and sulfur dichloride using the reported method (*27*). Because there existed a balance between sulfur dichloride and disulfur dichloride at room temperature, compounds **IVc**−**IVe**, which were purified by flash-column chromatography on a silica gel, contained a little *N*,*N*′-dithiobis(arylamines). However, impure compound **IVc** or **IVd** was cooled in the refrigerator to be solidified, and the solid was washed with cool petroleum ether (30−60 °C) to give pure product because the polarity of *N*,*N*′-dithiobis (arylamines) was lower than that of *N*,*N*′-thiobis(arylamines). Pure intermediate **IVe** was not obtained from solidification of the impure product in the refrigerator, which was purified in the next step.

It was found that the substituted groups on the aromatic cycle had a great effect on the reaction activity in the synthesis of *N*′,*N*′-thio (or dithio) bis(BPUs) (**19**−**24**). For example, compounds **12**, **15**, and **17** did not react with substituted benzoyl isocyanate at or below room temperature. When heated to reflux, the reaction afford the corresponding parent *N*-benzoyl-*N*′-phenylureas from the break of the S−N bond in the structure of compounds **12**−**18** and no desired compounds **19**−**24**, which suggested that the withdrawing group ($-CF_3$) reduced the nucleophilic activity of the nitrogen atom in dithio (or thio) bis(arylamines). On the other hand, *N*,*N*′-dithiobis(4-trifluoromethoxybenzenamine) (**IVb**) was combined with 2,6-difluorobenzoyl isocyanate successfully at room temperature; however, the reaction with 2,6-dichlorobenzoyl isocyanate gave only the corresponding parent *N*-benzoyl-*N*′-phenylureas, which indicated that the electrophilic reaction activity of benzoyl isocyanate was reduced when the 2,6-difluoro group was replaced by the 2,6-dichlor group.

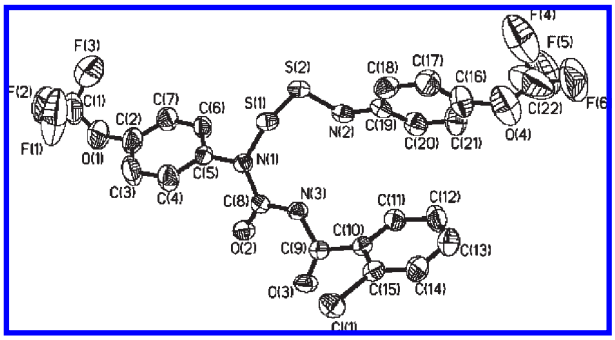

Figure 5. Molecular structure of compound **14**.

Table 2. Larvicidal Activities against Oriental Armyworm of Compounds **12**−**24**, E, G, Diflubenzuron, Penfluoron, and Triflumuron

	larvicidal activity (%) at concentration (mg L^{-1})			
compound	2.5	1.0	0.5	0.25
12		100	70	10
13		100	90	30
14		100	60	30
15	100	70	60	0
16		100	70	0
17		100	80	45
18		100	90	40
19		100	50	20
20		100	40	0
21	100	85	60	10
22		100	55	20
23		100	85	25
24		100	95	50
penfluoron		100	100	95
triflumuron	100	95	40	20
diflubenzuron		100	100	45
E		100	80	40
G	100	70	60	0

We found that the target compounds **1**−**24** have better solubility than the corresponding parent *N*-benzoyl-*N*′-phenylureas in organic solvents, such as diethylether, methylene dichloride, chloroform, toluene, xylene, petroleum ether, etc., which should make them easier to apply in the field.

Structure. Compound **5** was recrystallized from diethyl ether to give colorless crystals suitable for X-ray single-crystal diffraction (**Figure 4**), and compound **14** was recrystallized from dichloromethane to give colorless crystals suitable for X-ray single-crystal diffraction (**Figure 5**). It could be seen from the X-ray single-crystal figures that there exist N−S−N bonds in compound **5** and N−S−S−N bonds in compound **14**.

Table 3. Larvicidal Activities against Diamondback Moth and Beet Armyworm of Compounds **1**, **24**, E, and Triflumuron

compound	toxicities against diamondback moth LC_{50} (mg L^{-1})	toxicities against beet armyworm LC_{50} (mg L^{-1})
1	45.10	21.42
E	47.75	13.21
24	40.14	31.44
triflumuron	49.31	12.01

Bioassay. *Larvicidal Activities against Oriental Armyworm (M. separata) and Mosquito (C. pipiens pallens).* **Table 1** shows the larvicidal activities of compounds **1**−**11** and their corresponding parent compounds against oriental armyworm and mosquito. The results indicate that most of compounds **1**−**11** have excellent larvicidal activities against oriental armyworm and mosquito and the larvicidal activities of these compounds are about the same level as their corresponding parent BPUs. Compounds **3**, **6**, and **9** exhibit a little higher larvicidal activities against oriental armyworm than their parent BPUs (F), which suggests that the introduction of the sulfenyl amide groups in the structure of parent BPUs has a positive effect on the larvicidal activities.

Table 2 shows the larvicidal activities of compounds **12**−**24** and their corresponding parent compounds against oriental armyworm. The results indicate that compounds **12**−**24** have excellent larvicidal activities against oriental armyworm, which are parallel to those of their corresponding parent BPUs. On the whole, *N*′-aminothio derivatives (e.g., compound **17**) displayed better larvicidal activities than *N*′-aminodithio derivatives (e.g., compound **12**), possibly because much greater steric hindrance of *N*′-aminothio derivatives in the structures leads to easy release of the parent compounds in the body of the insect. On the other hand, *N*′-aminothio (or dithio) derivatives (compounds **12**−**18**) exhibited higher larvicidal activities than *N*′-aminothio (or dithio) bis(benzoylureas) (compounds **19**−**24**) because the molecular weight of compounds **19**−**24** was too high (MW > 500), which was in accordance with Lipinski's "Rule of Five" (*28*). For example, the larvicidal activity of compound **24** against oriental armyworm at 0.5 mg/L was 90% as compared to 40% mortality of compound **20** at the same concentration, and the larvicidal activities of compounds **13** and **18** against oriental armyworm at 0.5 mg/L were 90 and 90% respectively, whereas compounds **19** and **22** have only 50 and 55% mortality at the same concentration.

In addition, the results of **Tables 1** and **2** are obtained from two batchs of oriental armyworm larvae, which lead to little change in the larvicidal activities of compounds E and diflubenzuron in the two tables.

Table 3 shows the larvicidal activities of the target compounds **1** and **24** and the corresponding parent compounds E and triflumuron against diamondback moth and beet armyworm. The results in **Table 3** indicate that the target compounds **1** and **24** displayed comparable or a little higher larvicidal activities against diamondback moth than the corresponding parent compounds E and triflumuron from the values of LC_{50}. However, the results in **Table 3** indicate that the larvicidal activities against beet armyworm of the target compounds **1** and **24** were significantly low compared to that of the corresponding parent compounds E and triflumuron from the values of LC_{50}.

In summary, a series of novel *N*′-alkylaminothio, *N*′-arylaminothio (or dithio), and *N*′,*N*′-thio (or dithio) derivatives of *N*-benzoyl-*N*′-phenylureas were designed and synthesized as IGRs with sulfur dichloride or disulfur dichloride as the original reactant. The X-ray results demonstrated that there exist N−S−N or N−S−S−N bonds in these new compounds. These derivatives displayed better solubility compared to their corresponding parent BPUs, which should make them easier to apply in the field. The results of bioassays showed that compounds **1**−**24** retained the larvicidal activities of the corresponding BPUs and some compounds exhibited better larvicidal activities against oriental armyworm and mosquitoes than the parent BPUs. The larvicidal activities against diamondback moth of the selected target compound **24** were better than that of the corresponding parent compound triflumuron, but compounds **1** and **24** exhibited lower larvicidal activities against beet armyworm than that of the corresponding parent compounds E and triflumuron.

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