

Design, Synthesis, and Insecticidal Evaluation of New Benzoylureas Containing Isoxazoline and Isoxazole Group

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S Supporting Information

ABSTRACT: Twenty-two new benzoylphenylureas containing isoxazoline and the isoxazole group were designed and synthesized, and their structures were characterized by ^1H NMR and elemental analysis (or HRMS). The larvicidal activities against Oriental armyworm, mosquito, and diamondback moth of the new compounds were evaluated. Compounds **I-1** and **III-1** showed nearly the same level of insecticidal activity against Oriental armyworm as commercial insecticide Flucycloxuron and surprisingly exhibited much higher larvicidal activities against diamondback moth than Flucycloxuron.

KEYWORDS: Benzoylphenylureas, benzoyl urea, isoxazole, isoxazoline, insecticidal activity, insect growth regulator

INTRODUCTION

Agrochemical research has resulted in the discovery of novel insecticides that act on selective biochemical sites present in specific insect groups, such as the insect growth regulators of the benzoylphenylurea (BPU) type, which inhibit chitin formation in insects.¹ Chitin is an important component of the insect's cuticle. Insects treated with BPUs cannot make chitin and so cannot molt. Because molting must take place for the insect to reach the adult stage, a BPU poisoned insect also cannot reproduce. Eventually, the insect dies.² Because humans do not make chitin, BPUs are not considered toxic to humans. BPU insecticides have many attractive properties such as high selectivity, high biological activity, rapid degradation in soil and water, and low acute toxicity for animals. Because of the above advantages, BPUs have attracted considerable attention for decades.^{3–10}

The mode of action of the 2,4-diphenyl-1,3-oxazoline insecticides (such as the commercial insecticide Etoxazole) is chitin biosynthesis inhibition, which is similar to the BPUs.^{11,12} The result of the QSAR study of the 2,4-diphenyl-1,3-oxazoline insecticides indicated that they displayed a structure–activity relationship similar to that of BPUs.¹² Aventis Cropscience reported that compound **A** (Figure 1) (oxazoline type) exhibited insecticidal and acaricidal activities.¹³ We have reported that some of compound **B** (Figure 1) (BPU oxime derivative) exhibited excellent larvicidal activities against Oriental armyworm.^{14,15} There were some surprises in discovering new pesticides by cyclization of the chain structure of known pesticide structure.^{16–18} In order to find new pesticides, a series of compound **I** was designed by cyclization of the chain structure of compound **B** and linking of the isoxazoline group of compound **A** to benzoylphenylurea (Figure 1). Similarly, a series of compound **II** was designed by cyclization of the chain structure of Flucycloxuron and analogue synthesis. Because steric and electronic effects influence the bioactivity of pesticide molecules, a series of compound **III** was designed by aromatization of the isoxazoline group in the structure of compound **I**. A total of 22 new benzoylphenylureas containing isoxazoline and isoxazole group were synthesized, and laboratory evaluations of the active compound against different insects were performed.

MATERIALS AND METHODS

Instruments. ^1H 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 or d_6 -DMSO solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in ppm. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. 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 standard techniques prior to use. 2,6-Difluorobenzoyl isocyanate was prepared by the method described in the literature.^{19,20} Commercial insecticide Flucycloxuron and compound **C** were synthesized in our laboratory.

General Synthetic Procedure for the Target Compounds I-1–I-15, II-1, II-2, and III-1–III-5 (Scheme 1). *Synthesis of 5-tert-Butyl-3-(4-nitrophenyl)-4,5-dihydroisoxazole (I-1a).* Freshly prepared *N*-hydroxy-4-nitrobenzimidoyl chloride (1.0 g, 5 mmol) according to the literature¹⁵ was dissolved in dichloromethane (40 mL), and 3,3-dimethylbut-1-ene (0.50 g, 6 mmol) was added. Then the mixture was cooled to -10°C , and triethylamine (0.51 g, 6 mmol) in dichloromethane (10 mL) was added dropwise. The reaction stood overnight at room temperature. When the reaction was completed, the mixture was successively washed by 5% aqueous HCl solution and saturated salt solution. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the crude product. The product was purified by flash column chromatography on silica gel (5:1 petroleum ether/ethyl acetate) to give compound **I-1a** (0.86 g, 85.7%) as a yellow solid; mp $150–154^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 8.25 (d, $J = 8.7$ Hz, 2H, Ar–H), 7.83 (d, $J = 8.7$ Hz, 2H, Ar–H), 4.55 (t, $J = 10.2$ Hz, 1H, OCH), 3.25 (dd, $J = 16.9, 11.3$ Hz, 1H, CH_2), 3.10 (dd, $J = 16.8, 9.3$ Hz, 1H, CH_2), 0.98 (s, 9H, $\text{C}(\text{CH}_3)_3$).

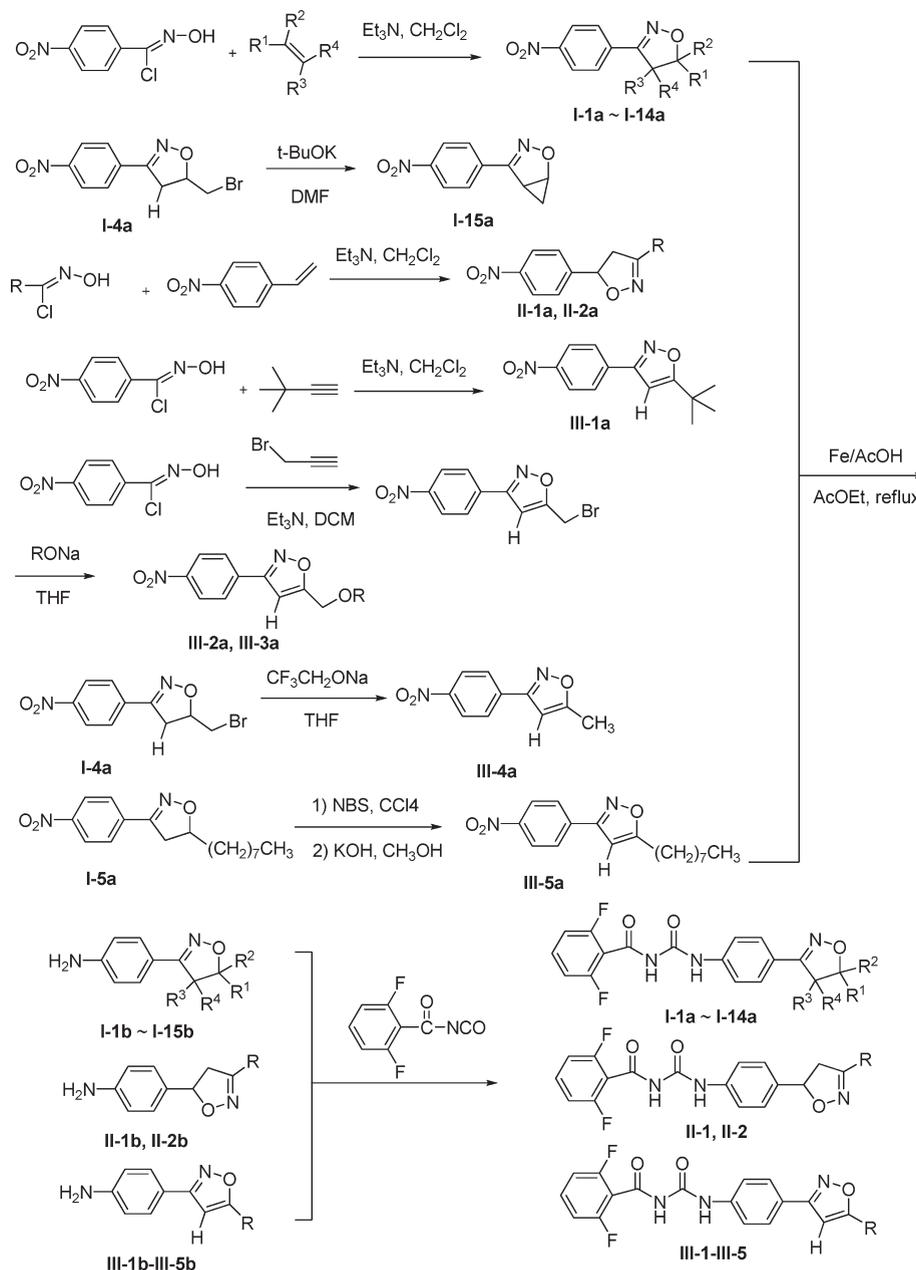
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Scheme 1. General Synthetic Route for Target Compounds I-1–I-15, II-1, II-2, and III-1–III-5



1H, CONHAr), 7.48–7.62 (m, 5H, Ar–H), 7.06 (t, $J = 8.4$ Hz, 2H, Ar–H), 4.70–4.78 (m, 1H, OCH), 3.39 (dd, $J = 16.3, 10.3$ Hz, 1H, $\text{CH}_2\text{C}=\text{N}$), 2.96 (dd, $J = 16.4, 8.2$ Hz, 1H, $\text{CH}_2\text{C}=\text{N}$), 1.77–1.81 (m, 1H, $\text{OCHCH}_2\text{CH}_2$), 1.58–1.68 (m, 1H, $\text{OCHCH}_2\text{CH}_2$), 1.36–1.51 (m, 4H, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 0.93 (t, $J = 6.8$ Hz, 3H, CH_2CH_3). Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{F}_2\text{N}_3\text{O}_3$: C, 62.84; H, 5.22; N, 10.33.

Data for Compound I-4. White solid; yield, 56.1%; mp 230 °C (dec.). ^1H NMR (400 MHz, d_6 -DMSO): δ 11.49 (brs, 1H, CONHCO), 10.31 (brs, 1H, CONHAr), 7.56–7.72 (m, 5H, Ar–H), 7.25 (t, $J = 8.2$ Hz, 2H, Ar–H), 4.97 (dd, $J = 9.7, 4.4$ Hz, 1H, OCH), 3.65–3.76 (m, 2H, CH_2Br), 3.54–3.60 (m, 1H, $\text{CH}_2\text{C}=\text{N}$), 3.19–3.25 (m, 1H, $\text{CH}_2\text{C}=\text{N}$). Anal. Calcd. for $\text{C}_{18}\text{H}_{14}\text{BrF}_2\text{N}_3\text{O}_3$: C, 49.33; H, 3.22; N, 9.59. Found: C, 49.32; H, 3.32; N, 9.39.

Data for Compound I-5. White solid; yield, 80.0%; mp 178–180 °C. ^1H NMR (400 MHz, CDCl_3): δ 10.57 (brs, 1H, CONHCO), 8.58 (brs, 1H, CONHAr), 7.53–7.64 (m, 5H, Ar–H), 7.06 (t, $J = 8.5$ Hz, 2H, Ar–H), 4.70–4.77 (m, 1H, OCH), 3.39 (dd, $J = 16.3, 10.3$ Hz, 1H, $\text{CH}_2\text{C}=\text{N}$), 2.96 (dd, $J = 16.3, 8.2$ Hz, 1H, $\text{CH}_2\text{C}=\text{N}$), 1.76–1.87 (m, 1H, $\text{OCHCH}_2\text{CH}_2$), 1.55–1.64 (m, 1H, $\text{OCHCH}_2\text{CH}_2$), 1.28–1.50 (m, 12H, $\text{CH}_2(\text{CH}_2)_6\text{CH}_3$), 0.88 (t, $J = 6.2$ Hz, 3H, CH_2CH_3). Anal. Calcd. for $\text{C}_{25}\text{H}_{29}\text{F}_2\text{N}_3\text{O}_3$: C, 65.63; H, 6.39; N, 9.18. Found: C, 65.55; H, 6.26; N, 9.32.

Data for Compound I-6. White solid; yield, 63.6%; mp 227–229 °C. ^1H NMR (400 MHz, d_6 -DMSO): δ 11.52 (brs, 1H, CONHCO), 10.34 (brs, 1H, CONHAr), 7.55–7.82 (m, 5H, Ar–H), 7.26 (t, $J = 8.0$ Hz, 2H, Ar–H), 5.81 (dd, $J = 10.1, 5.1$ Hz, 1H, OCH), 3.82–3.97 (m, 2H, CH_2). Anal. Calcd. for $\text{C}_{18}\text{H}_{12}\text{F}_2\text{N}_4\text{O}_3$: C, 58.38; H, 3.27; N, 15.13. Found: C, 58.14; H, 3.24; N, 14.99.

Data for Compound I-7. White solid; yield, 72.7%; mp 196–198 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.60 (brs, 1H, CONHCO), 8.84 (brs, 1H, CONHAr), 7.65 (d, J = 8.6 Hz, 2H, Ar–H), 7.50–7.61 (m, 3H, Ar–H), 7.07 (t, J = 8.6 Hz, 2H, Ar–H), 5.21 (dd, J = 10.3, 7.7 Hz, 1H, OCH), 3.83 (s, 3H, COOCH₃), 3.60–3.74 (m, 2H, CH₂). Anal. Calcd. for C₁₉H₁₅F₂N₃O₅: C, 56.58; H, 3.75; N, 10.42. Found: C, 56.33; H, 3.77; N, 10.48.

Data for Compound I-8. White solid; yield, 82.8%; mp 156–158 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.58 (brs, 1H, CONHCO), 9.10 (brs, 1H, CONHAr), 7.64 (d, J = 8.6 Hz, 2H, Ar–H), 7.53–7.57 (m, 3H, Ar–H), 7.06 (t, J = 8.5 Hz, 2H, Ar–H), 4.87–4.94 (m, 1H, OCH), 3.51–3.66 (m, 4H, CH₂OCH₂CH₂), 3.39 (dd, J = 16.5, 10.7 Hz, 1H, CH₂C=N), 3.24 (dd, J = 16.6, 7.4 Hz, 1H, CH₂C=N), 1.53–1.60 (m, 2H, OCH₂CH₂CH₂CH₃), 1.32–1.41 (m, 2H, CH₂CH₂CH₃), 0.91 (t, J = 7.3 Hz, 3H, CH₂CH₃). Anal. Calcd. for C₂₂H₂₃F₂N₃O₄: C, 61.25; H, 5.37; N, 9.74. Found: C, 61.30; H, 5.33; N, 9.64.

Data for Compound I-9. White solid; yield, 88.5%; mp 175–177 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.57 (brs, 1H, CONHCO), 8.56 (brs, 1H, CONHAr), 7.48–7.73 (m, 5H, Ar–H), 7.07 (t, J = 8.7 Hz, 2H, Ar–H), 4.89–4.97 (m, 1H, OCH), 3.97 (q, J = 8.6 Hz, 2H, OCH₂CF₃), 3.79–3.84 (m, 2H, CH₂O), 3.43 (dd, J = 16.7, 9.2 Hz, 1H, CH₂C=N), 3.43 (dd, J = 16.7, 7.5 Hz, 1H, CH₂C=N). Anal. Calcd. for C₂₀H₁₆F₅N₃O₄: C, 52.52; H, 3.53; N, 9.19. Found: C, 52.34; H, 3.66; N, 9.31.

Data for Compound I-10. White solid; yield, 82.4%; mp 197–199 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.59 (brs, 1H, CONHCO), 9.00 (brs, 1H, CONHAr), 7.66 (d, J = 8.6 Hz, 2H, Ar–H), 7.52–7.59 (m, 3H, Ar–H), 7.32–7.41 (m, 5H, Ar–H), 7.07 (t, J = 8.5 Hz, 2H, Ar–H), 5.75 (dd, J = 10.8, 8.4 Hz, 1H, OCH), 3.79 (dd, J = 16.6, 11.0 Hz, 1H, CH₂), 3.35 (dd, J = 16.6, 8.3 Hz, 1H, CH₂). Anal. Calcd. for C₂₃H₁₇F₂N₃O₃: C, 65.55; H, 4.07; N, 9.97. Found: C, 65.78; H, 3.97; N, 9.71.

Data for Compound I-11. White solid; yield, 72.9%; mp 205–208 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.58 (brs, 1H, CONHCO), 9.34 (brs, 1H, CONHAr), 7.49–7.61 (m, 7H, Ar–H), 7.38 (t, J = 7.6 Hz, 2H, Ar–H), 7.26–7.33 (m, 1H, Ar–H), 7.05 (t, J = 8.4 Hz, 2H, Ar–H), 3.50 (q, J = 16.4, 2H, CH₂C=N), 1.82 (s, 3H, CH₃). Anal. Calcd. for C₂₄H₁₉F₂N₃O₃: C, 66.20; H, 4.40; N, 9.65. Found: C, 65.98; H, 4.49; N, 9.58.

Data for Compound I-12. White solid; yield, 70.4%; mp 187–189 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.57 (brs, 1H, CONHCO), 9.28 (brs, 1H, CONHAr), 7.50–7.62 (m, 5H, Ar–H), 7.06 (t, J = 8.4 Hz, 2H, Ar–H), 3.05 (s, 2H, CH₂C=N), 1.82 (d, J = 5.6 Hz, 4H), 1.63–1.71 (m, 2H), 1.49 (s, 4H). Anal. Calcd. for C₂₂H₂₁F₂N₃O₃: C, 63.91; H, 5.12; N, 10.16. Found: C, 63.67; H, 4.98; N, 10.26.

Data for Compound I-13. White solid; yield, 74.5%; mp 193–195 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.57 (brs, 1H, CONHCO), 9.28 (brs, 1H, CONHAr), 7.47–7.60 (m, 5H, Ar–H), 7.05 (t, J = 8.4 Hz, 2H, Ar–H), 3.26 (s, 2H, CH₂C=N), 2.13–2.21 (m, 2H), 1.74–1.90 (m, 6H). Anal. Calcd. for C₂₁H₁₉F₂N₃O₃: C, 63.15; H, 4.80; N, 10.52. Found: C, 63.11; H, 4.78; N, 10.34.

Data for Compound I-14. White solid; yield, 84.3%; mp 126–128 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.54 (brs, 1H, CONHCO), 8.83 (brs, 1H, CONHAr), 7.67 (d, J = 8.6 Hz, 2H, Ar–H), 7.51–7.59 (m, 3H, Ar–H), 7.06 (t, J = 8.5 Hz, 2H, Ar–H), 5.23 (dd, J = 8.6, 4.6 Hz, 1H, OCH), 4.04 (t, J = 8.3 Hz, 1H, CHC=N), 2.19 (dd, J = 12.0, 5.0 Hz, 1H, OCHCH₂), 1.68–1.96 (m, 4H, CH₂CH₂C=N), 1.48–1.55 (m, 1H, OCHCH₂). HRMS (ESI) *m/z* calcd for C₂₀H₁₇F₂N₃O₃: (M+Na)⁺ 408.1130; found, 408.1138.

Data for Compound I-15. White solid; yield, 81.8%; mp 210 °C (dec.). ¹H NMR (400 MHz, CDCl₃): δ 10.56 (brs, 1H, CONHCO), 8.23 (brs, 1H, CONHAr), 7.79 (d, J = 7.0 Hz, 2H, Ar–H), 7.64 (d, J = 6.9 Hz, 2H, Ar–H), 7.52–7.59 (m, 1H, Ar–H), 7.08 (t, J = 9.1 Hz, 2H, Ar–H), 5.05 (dd, J = 5.3, 3.3 Hz, 1H, OCH), 2.87–2.90 (m, 1H,

CHC=N), 1.08–1.12 (m, 1H, CH₂), 0.45–0.49 (m, 1H, CH₂). HRMS (ESI) *m/z* calcd for C₁₈H₁₃F₂N₃O₃: (M+Na)⁺ 380.0817; found, 380.0820.

Synthesis of 3-(4-Fluorophenyl)-5-(4-nitrophenyl)-4,5-dihydroisoxazole (II-1a). A mixture of 4-fluorobenzaldehyde (1.24 g, 10 mmol), THF (30 mL), hydroxylamine hydrochloride (0.83 g, 12 mmol), and pyridine (0.95 g, 12 mmol) was stirred at room temperature, and the reaction was monitored by TLC. When the reaction was completed, most of the THF was removed by vacuum distillation, and water was added. The mixture was extracted by ethyl acetate (20 mL × 2). The organic layer was successively washed by 5% aqueous HCl solution and saturated salt solution, and dried over anhydrous magnesium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give 4-fluorobenzaldehyde oxime as a pale yellow solid (1.32 g, 95.0%); mp 86–88 °C.

A solution of 4-fluorobenzaldehyde oxime (0.68 g, 4.9 mmol) in propan-2-ol and 1,2-dichloroethane (DCE) (v/v = 1:4, 12 mL) was cooled to –10 °C. Then a solution of butyl hypochlorite (0.63 g, 5.8 mmol) in DCE (5 mL) was slowly added at –10 °C. The mixture was stirred for 1 h at –10 °C. Then the solvent was evaporated off under reduced pressure to give the crude product 4-fluoro-*N*-hydroxybenzimidoyl chloride as a yellow solid (0.83 g, 88.1%), which was used in the next step without purification.

4-Fluoro-*N*-hydroxybenzimidoyl chloride (0.83 g, 4.8 mmol) was dissolved in dichloromethane (40 mL), and freshly prepared 1-nitro-4-vinylbenzene (0.69 g, 4.6 mmol) was added.²¹ Then the mixture was cooled to –10 °C, and triethylamine (0.53 g, 5.3 mmol) in dichloromethane (10 mL) was added dropwise. The reaction stood overnight at room temperature. When the reaction was completed, the mixture was successively washed by 5% aqueous HCl solution and saturated salt solution. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the crude product. The product was purified by flash column chromatography on silica gel (5:1 petroleum ether/ethyl acetate) to give compound II-1a (0.78 g, 59.1%) as a yellow solid; mp 87–90 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.24 (d, J = 8.6 Hz, 2H, Ar–H), 7.67 (dd, J = 8.0, 5.8 Hz, 2H, Ar–H), 7.57 (d, J = 8.5 Hz, 2H, Ar–H), 7.11 (t, J = 8.5 Hz, 2H, Ar–H), 5.84 (dd, J = 11.0, 7.7 Hz, 1H, OCH), 3.87 (dd, J = 16.6, 11.2 Hz, 1H, CH₂), 3.29 (dd, J = 16.6, 7.6 Hz, 1H, CH₂).

Synthesis of 4-(3-(4-Fluorophenyl)-4,5-dihydroisoxazol-5-yl)aniline (II-1b). Intermediate II-1b was obtained as a yellow solid (yield, 97.8%, mp 85–87 °C) by following the same procedure as that for compound I-1b. ¹H NMR (400 MHz, CDCl₃): δ 7.62–7.70 (m, 2H, Ar–H), 7.18 (d, J = 7.8 Hz, 2H, Ar–H), 7.10 (t, J = 8.3 Hz, 2H, Ar–H), 6.68 (d, J = 7.6 Hz, 2H, Ar–H), 5.63 (t, J = 9.7 Hz, 1H, OCH), 3.66 (dd, J = 16.6, 10.6 Hz, 1H, CH₂), 3.30 (dd, J = 16.3, 8.9 Hz, 1H, CH₂).

Synthesis of 2,6-Difluoro-*N*-(4-(3-(4-fluorophenyl)-4,5-dihydroisoxazol-5-yl)phenylcarbamoyl)benzamide (Target Compound II-1). Compound II-1 was obtained as a white solid (yield, 87.2%, mp 192–194 °C) by following the same procedure as that for compound I-1. ¹H NMR (400 MHz, CDCl₃): δ 10.48 (brs, 1H, CONHCO), 9.38 (brs, 1H, CONHAr), 7.69 (dd, J = 8.6, 5.4 Hz, 2H, Ar–H), 7.41–7.58 (m, 3H, Ar–H), 7.32 (d, J = 8.4 Hz, 2H, Ar–H), 7.11 (t, J = 8.6 Hz, 2H, Ar–H), 7.03 (t, J = 8.4 Hz, 2H, Ar–H), 5.70–5.75 (m, 1H, OCH), 3.75 (dd, J = 16.6, 10.9 Hz, 1H, CH₂), 3.30 (dd, J = 16.6, 8.4 Hz, 1H, CH₂). HRMS (ESI) *m/z* calcd for C₂₃H₁₆F₃N₃O₃ (M + Na)⁺ 462.1036; found, 462.1036.

Synthesis of 3-*tert*-Butyl-5-(4-nitrophenyl)-4,5-dihydroisoxazole (II-2a). Intermediate II-2a was obtained as a yellow solid (yield, 90.0%, mp 78–81 °C) by following the same procedure as that for compound II-1a. ¹H NMR (400 MHz, CDCl₃): δ 8.21 (d, J = 9.0 Hz, 2H, Ar–H), 7.50 (d, J = 8.4 Hz, 2H, Ar–H), 5.64 (dd, J = 10.6, 7.4 Hz, 1H, OCH), 3.50 (dd, J = 16.7, 10.9 Hz, 1H, CH₂), 2.89 (dd, J = 16.8, 7.2 Hz, 1H, CH₂), 1.21 (s, 9H, C(CH₃)₃).

Synthesis of 4-(3-tert-Butyl-4,5-dihydroisoxazol-5-yl)aniline (II-2b). Intermediate **II-2b** was obtained as a yellow oil (yield, 93.2%) by following the same procedure as that for compound **I-1b**. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.11 (d, $J = 8.2$ Hz, 2H, Ar-H), 6.66 (d, $J = 8.2$ Hz, 2H, Ar-H), 5.42 (t, $J = 9.6$ Hz, 1H, OCH), 3.68 (brs, 2H, NH_2), 3.30 (dd, $J = 16.8, 10.5$ Hz, 1H, CH_2), 2.90 (dd, $J = 16.8, 8.6$ Hz, 1H, CH_2), 1.22 (s, 9H, $\text{C}(\text{CH}_3)_3$).

Synthesis of 2,6-Difluoro-N-(4-(5-((2,2,2-trifluoroethoxy)methyl)isoxazol-3-yl)phenylcarbamoyl)benzamide (Target Compound II-2). Compound **II-2** was obtained as a white solid (yield, 85.2%, mp 266–268 °C) by following the same procedure as that for compound **I-1**. $^1\text{H NMR}$ (400 MHz, d_6 -DMSO): δ 11.47 (brs, 1H, CONHCO), 10.30 (brs, 1H, CONHAr), 7.52–7.74 (m, 5H, Ar-H), 7.36–7.49 (m, 2H, Ar-H), 7.14–7.31 (m, 4H, Ar-H), 5.71 (t, $J = 9.5$ Hz, 1H, OCH), 3.83 (dd, $J = 17.1, 10.8$ Hz, 1H, CH_2), 3.36 (dd, $J = 17.1, 8.5$ Hz, 1H, CH_2). Anal. Calcd. for $\text{C}_{23}\text{H}_{16}\text{F}_2\text{N}_3\text{O}_3$: C, 62.87; H, 3.67; N, 9.56. Found: C, 62.71; H, 3.79; N, 9.33.

Synthesis of 5-tert-Butyl-3-(4-nitrophenyl)isoxazole (III-1a). Intermediate **III-1a** was obtained as a yellow solid (yield, 30.9%, mp 156–158 °C) by following a procedure similar to that for compound **I-1a**. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.32 (d, $J = 8.7$ Hz, 2H, Ar-H), 7.98 (d, $J = 8.7$ Hz, 2H, Ar-H), 6.33 (s, 1H, Ar-H), 1.42 (s, 9H, $\text{C}(\text{CH}_3)_3$).

Synthesis of 3-(4-nitrophenyl)-5-((2,2,2-trifluoroethoxy)methyl)isoxazole (III-2a). 5-(Bromomethyl)-3-(4-nitrophenyl)isoxazole was obtained as a yellow solid (yield, 53.9%, mp 137–139 °C) by following a procedure similar to that for compound **I-1a**. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.32–8.35 (m, 2H, Ar-H), 7.97–8.01 (m, 2H, Ar-H), 6.72 (s, 1H, Ar-H), 4.52 (s, 2H, CH_2Br).

To a mixture of sodium hydride (0.072 g, 3 mmol) and anhydrous THF (20 mL), 2,2,2-trifluoroethanol (0.30 g, 3 mmol) was added at 0 °C, and the solution was stirred for 30 min. Then a solution of 5-(bromomethyl)-3-(4-nitrophenyl)isoxazole (0.51 g, 2 mmol) in THF (5 mL) was added dropwise, and the mixture was heated to reflux. When the reaction was completed (monitored by TLC), water was added, and the mixture was extracted by ethyl acetate. The organic layer successively washed by 5% aqueous HCl solution and saturated salt solution, and dried over anhydrous magnesium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude product, which was purified by flash column chromatography on silica gel (2:1 petroleum ether/ethyl acetate) to give compound **III-2a** (0.45 g, 81.8%) as a yellow solid; mp 73–75 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.28–8.40 (m, 2H, Ar-H), 7.95–8.05 (m, 2H, Ar-H), 6.72 (s, 1H, Ar-H), 4.86 (s, 2H, CH_2O), 4.00 (q, $J = 8.5$ Hz, 2H, OCH_2CF_3).

Synthesis of 3-(4-Nitrophenyl)-5-((2,2,2-trifluoroethoxy)methyl)isoxazole (III-3a). Intermediate **III-3a** was obtained as a yellow oil (yield, 78.2%) by following a procedure similar to that for compound **III-2a**. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.28–8.38 (m, 2H, Ar-H), 7.94–8.06 (m, 2H, Ar-H), 6.65 (s, 1H, Ar-H), 4.66 (d, $J = 0.5$ Hz, 2H, CH_2O), 3.59 (t, $J = 6.6$ Hz, 2H, OCH_2CH_2), 1.53–1.69 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.36–1.48 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.94 (t, $J = 7.4$ Hz, 3H, CH_2CH_3).

Synthesis of 5-Methyl-3-(4-nitrophenyl)isoxazole (III-4a). To a mixture of sodium hydride (0.072 g, 3 mmol) and anhydrous THF (10 mL), 2,2,2-trifluoroethanol (0.30 g, 3 mmol) was added at 0 °C, and the solution was stirred for 30 min. Then a solution of compound **I-4a** (0.57 g, 2 mmol) in THF (20 mL) was added dropwise, and the mixture was heated to 60 °C. When the reaction was completed (monitored by TLC), most of the THF was removed by vacuum distillation, and water was added. The mixture was extracted by dichloromethane. The organic layer was successively washed by 5% aqueous HCl solution and saturated salt solution, and dried over anhydrous magnesium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash column

chromatography on silica gel (5:1 petroleum ether/ethyl acetate) to give compound **III-4a** (0.32 g, 78.0%) as a yellow solid; mp 153–155 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.31 (d, $J = 8.7$ Hz, 2H, Ar-H), 7.97 (d, $J = 8.7$ Hz, 2H, Ar-H), 6.38 (s, 1H, Ar-H), 2.53 (s, 3H, CH_3).

Synthesis of 3-(4-Nitrophenyl)-5-octylisoxazole (III-5a). A mixture of **I-5a** (0.30 g, 1 mmol), NBS (0.196 g, 1.1 mmol), AIBN (0.05 g), and anhydrous CCl_4 (30 mL) was heated to reflux under nitrogen for 5 h. After the solution was cooled to room temperature, it was filtered, and the solvent was removed. Then methanol (10 mL) and sodium methoxide (0.16 g, 3 mmol) were added and heated to reflux. When the reaction was completed (monitored by TLC), water was added. The mixture was extracted by ethyl acetate. The organic layer was successively washed by 5% aqueous HCl solution and saturated salt solution, and dried over anhydrous magnesium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (5:1 petroleum ether/ethyl acetate) to give compound **III-5a** (0.32 g, 66.7%) as a yellow solid; mp 73–75 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.31 (d, $J = 8.7$ Hz, 2H, Ar-H), 7.98 (d, $J = 8.7$ Hz, 2H, Ar-H), 6.37 (s, 1H, Ar-H), 2.82 (t, $J = 7.6$ Hz, 2H, OCCH_2CH_2), 1.72–1.80 (m, 2H, $\text{OCCH}_2\text{CH}_2\text{CH}_2$), 1.28–1.41 (m, 10H, CH_2 - $(\text{CH}_2)_5\text{CH}_3$), 0.87 (t, $J = 6.5$ Hz, 3H, CH_2CH_3).

Compounds **III-1b–III-5b** and **III-1–III-5** were prepared by following a procedure similar to that for compound **I-1b** and compound **I-1**, respectively.

Data for 4-(5-tert-Butylisoxazol-3-yl)aniline (III-1b). Yellow solid; yield, 96.0%; mp 126–128 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.59 (d, $J = 8.1$ Hz, 2H, Ar-H), 6.71 (d, $J = 8.0$ Hz, 2H, Ar-H), 6.15 (s, 1H, Ar-H), 3.84 (brs, 2H, NH_2), 1.37 (s, 9H, $\text{C}(\text{CH}_3)_3$).

Data for 4-(5-((2,2,2-Trifluoroethoxy)methyl)isoxazol-3-yl)aniline (III-2b). Yellow oil; yield, 92.7%. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.61 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.74 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.54 (s, 1H, Ar-H), 4.79 (s, 2H, CH_2O), 3.95 (q, $J = 8.5$ Hz, 2H, OCH_2CF_3), 3.93 (brs, 2H, NH_2).

Data for 4-(5-(Butoxymethyl)isoxazol-3-yl)aniline (III-3b). Yellow oil; yield, 87.5%. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.61 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.73 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.47 (s, 1H, Ar-H), 4.60 (s, 2H, CH_2O), 3.88 (brs, 2H, NH_2), 3.56 (t, $J = 6.6$ Hz, 2H, OCH_2CH_2), 1.53–1.70 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.35–1.44 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.93 (t, $J = 7.4$ Hz, 3H, CH_2CH_3).

Data for 4-(5-Methylisoxazol-3-yl)aniline (III-4b). Yellow oil; yield, 95.8%. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.59 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.72 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.20 (s, 1H, Ar-H), 3.87 (brs, 2H, NH_2), 2.44 (s, 3H, CH_3).

Data for 4-(5-Octylisoxazol-3-yl)aniline (III-5b). Yellow oil; yield, 83.3%. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.60 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.72 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.19 (s, 1H, Ar-H), 3.85 (brs, 2H, NH_2), 2.75 (t, $J = 7.6$ Hz, 2H, OCCH_2CH_2), 1.68–1.76 (m, 2H, $\text{OCCH}_2\text{CH}_2\text{CH}_2$), 1.27–1.42 (m, 10H, CH_2 - $(\text{CH}_2)_5\text{CH}_3$), 0.88 (t, $J = 6.5$ Hz, 3H, CH_2CH_3).

Data for N-(4-(5-tert-Butylisoxazol-3-yl)phenylcarbamoyl)-2,6-difluorobenzamide (Target Compound III-1). White solid; yield, 85.4%; mp 176–178 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.60 (brs, 1H, CONHCO), 9.93 (brs, 1H, CONHAr), 7.72 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.45–7.58 (m, 3H, Ar-H), 7.05 (t, $J = 8.4$ Hz, 2H, Ar-H), 6.23 (s, 1H, Ar-H), 1.40 (s, 9H, $\text{C}(\text{CH}_3)_3$). HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{19}\text{F}_2\text{N}_3\text{O}_3$: $(\text{M}+\text{Na})^+$ 422.1287, found 422.1296.

Data for 2,6-Difluoro-N-(4-(5-((2,2,2-trifluoroethoxy)methyl)isoxazol-3-yl)phenylcarbamoyl)benzamide (Target Compound III-2). White solid; yield, 83.2%; mp 175–177 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.57 (brs, 1H, CONHCO), 8.18 (brs, 1H, CONHAr), 7.81 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.69 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.52–7.58 (m, 1H, Ar-H), 7.08 (t, $J = 8.6$ Hz, 2H, Ar-H), 6.63 (s, 1H, Ar-H),

Table 1. Larvicidal Activities against Oriental Armyworm, Mosquito, and Diamondback Moth of Compounds I-1–I-15, II-1, II-2, and III-1–III-5, Flucycloxuron, and Compound C

compd	Chemical Structure	Toxicities against Oriental armyworm		Toxicities against mosquito		Toxicities against diamondback moth	
		C ^a (mg L ⁻¹)	P ^a (%)	C ^a (mg L ⁻¹)	P ^a (%)	C ^a (mg L ⁻¹)	P ^a (%)
I-1		50	100	0.25	100	5	100
		25	100	0.1	50	2	80
		10	100			0.2	70
		5	40			0.02	10
I-2		200	10	2	40	20	100
						5	80
						2	30
I-3		200	100	2	30	200	80
		100	100			100	70
		50	0			20	20
I-4		100	100	2	60	200	40
		50	20			20	0
I-5		100	100	2	50	200	0
		50	60				
I-6		100	100	0.25	100	200	0
		50	0	0.1	70		
I-7		100	100	2	60	200	10
		50	0				
I-8		100	100	2	100	200	10
		50	40	1	80		
I-9		100	100	2	40	200	0
		50	60				
I-10		100	100	0.25	100	200	50
		50	0	0.1	90	20	30
I-11		200	100	0.5	100	200	100
		100	100	0.25	100	100	80
		50	60	0.1	80	20	30
I-12		100	100	2	70	200	20
		50	40				
I-13		100	100	2	80	200	10
		50	60				
I-14		100	100	2	50	200	0
		50	0				
I-15		100	100	2	60	200	10
		50	0				

Table 1. Continued

compd	Chemical Structure	Toxicities against Oriental armyworm		Toxicities against mosquito		Toxicities against diamondback moth	
		C ^a (mg L ⁻¹)	P ^a (%)	C ^a (mg L ⁻¹)	P ^a (%)	C ^a (mg L ⁻¹)	P ^a (%)
II-1		50	100	2	100	200	100
		25	100	1	100	20	70
		10	60	0.5	70	5	0
II-2		50	100	2	100	200	100
		25	100	1	80	20	100
		10	40			5	30
III-1		10	100	2	40	5	100
		5	100			2	100
		2.5	0			0.2	60
III-2		200	100	2	40	200	30
		100	100			20	0
		50	20				
III-3		200	100	2	60	200	0
		100	100				
		50	80				
III-4		200	100	2	20	200	10
		100	100				
		50	20				
III-5		200	100	2	40	200	10
		100	100				
		50	20				
C		1.0	100	0.005	100		
		0.5	85	0.001	70		LC ₅₀ = 30.78 mg·L ⁻¹
		0.25	0	0.0005	20		
Flucycloxuron		10	95	0.1	100		
		5	90	0.05	100		
		2.5	50	0.025	15		LC ₅₀ = 72.92 mg·L ⁻¹
		1.0	10				

^a C = concentration; P = larvicidal activity.

4.83 (s, 2H, CH₂O), 3.97 (q, J = 8.5 Hz, 2H, OCH₂CF₃). Anal. Calcd. for C₂₀H₁₄F₃N₃O₄: C, 52.76; H, 3.10; N, 9.23. Found: C, 52.70; H, 3.11; N, 9.28.

Data for *N*-(4-(5-(Butoxymethyl)isoxazol-3-yl)phenylcarbamoyl)-2,6-difluorobenzamide (Target Compound III-3). White solid; yield, 70.0%; mp 156–158 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.60 (brs, 1H, CONHCO), 9.23 (brs, 1H, CONHAr), 7.77 (d, J = 8.5 Hz, 2H, Ar-H), 7.50–7.67 (m, 3H, Ar-H), 7.06 (t, J = 8.4 Hz, 2H, Ar-H), 6.56 (s, 1H, Ar-H), 4.64 (s, 2H, CH₂O), 3.58 (t, J = 6.6 Hz, 2H, OCH₂CH₂), 1.53–1.70 (m, 2H, OCH₂CH₂CH₂), 1.35–1.44 (m, 2H, CH₂CH₂CH₃), 0.94 (t, J = 7.4 Hz, 3H, CH₂CH₃). HRMS (ESI) *m/z* calcd for C₂₂H₂₁F₂N₃O₄: (M + Na)⁺ 452.1392, found 452.1390.

Data for 2,6-Difluoro-*N*-(4-(5-methylisoxazol-3-yl)phenylcarbamoyl)benzamide (Target Compound III-4). White solid; yield, 80.6%; mp 213–216 °C. ¹H NMR (400 MHz, *d*₆-DMSO): δ 11.50 (brs, 1H, CONHCO), 10.32 (brs, 1H, CONHAr), 7.61–7.82 (m, 5H, Ar-H), 7.26 (t, J = 8.2 Hz, 2H, Ar-H), 6.74 (s, 1H, Ar-H), 2.44 (s, 3H, CH₃). Anal. Calcd. for C₁₈H₁₃F₂N₃O₃: C, 60.51; H, 3.67; N, 11.76. Found: C, 60.59; H, 3.48; N, 11.62.

Data for 2,6-Difluoro-*N*-(4-(5-octylisoxazol-3-yl)phenylcarbamoyl)benzamide (Target Compound III-5). White solid; yield, 86.7%; mp 169–171 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.59 (brs, 1H, CONHCO), 9.29 (brs, 1H, CONHAr), 7.75 (d, J = 8.5 Hz, 2H, Ar-H), 7.52–7.58 (m, 3H, Ar-H), 7.06 (t, J = 8.5 Hz, 2H, Ar-H), 6.19 (s, 1H, Ar-H), 2.79 (t, J = 7.5 Hz, 2H, OCCH₂CH₂), 1.71–1.78 (m, 2H, OCCH₂CH₂CH₂), 1.28–1.40 (m, 10H, CH₂(CH₂)₅CH₃), 0.88 (t, J = 6.4 Hz, 3H, CH₂CH₃). Anal. Calcd. for C₂₅H₂₇F₂N₃O₃: C, 65.92; H, 5.97; N, 9.23. Found: C, 65.74; H, 5.81; N, 9.29.

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.²² Evaluations are based on a percentage scale of 0–100 in which 0 = no activity, and 100 = total kill. The standard deviations of the tested biological values were ±5%. LC₅₀ values were calculated by probit analysis.²³

Larvicidal Activities against Oriental Armyworm (*Mythimna separata*). The larvicidal activities of the target compounds I-1–I-15,

II-1, II-2, and III-1–III-5 against Oriental armyworm were evaluated by foliar application using the reported procedure.²⁴ For the foliar armyworm tests, individual corn leaves were placed on moistened pieces of filter 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 three times. The biological data in Table 1 was the average value of the three tested values. For comparative purposes, Flucycloxuron and compound C were tested under the same conditions.

Larvicidal Activities against Mosquito (*Culex pipiens pal-lens*). The larvicidal activities of the target compounds I-1–I-15, II-1, II-2, and III-1–III-5 against mosquito were evaluated by the reported procedure.²⁵ The compounds I-1–I-15, II-1, II-2, and III-1–III-5 were prepared to different concentrations by dissolving compounds I-1–I-15, II-1, II-2, and III-1–III-5 in acetone and adding distilled water. Then 20 fourth-instar mosquito larvae were placed into the 10 mL of test solution and raised for 8 days. Each treatment was performed three times. The biological data in Table 1 was the average value of the three tested values. The results were expressed by death percentage. For comparative purposes, Flucycloxuron and compound C were tested under the same conditions.

Larvicidal Activities against Diamondback Moth (*Plutella xylostella*). The larvicidal activities of the target compounds I-1–I-15, II-1, II-2, and III-1–III-5 against diamondback moth were evaluated by the reported procedure.²⁶ Compounds I-1–I-15, II-1, II-2, and III-1–III-5 were prepared to different concentrations by dissolving compounds I-1–I-15, II-1, II-2, and III-1–III-5 in DMF and by adding distilled water. Leaf discs (5 cm × 3 cm) were cut from fresh cabbage leaves and then were dipped into the test solution for 3 s. After air-drying, the treated leaf discs were placed individually into a vertical tube (or Petri dishes), and the discs were infested with 10 s-instar diamondback moth larvae (or 10 third-instar beet armyworm larvae). Percentage mortalities were evaluated 3 days after treatment. The biological data in Table 1 was the average value of the three tested values. For comparative purposes, Flucycloxuron and compound C were tested under the same conditions.

RESULTS AND DISCUSSION

Synthesis. The target compounds I-1–I-15 were synthesized from 4-nitrobenzaldehyde oxime as shown in Scheme 1. *N*-Hydroxy-4-nitrobenzimidoyl chloride was first produced from 4-nitrobenzaldehyde oxime and butyl hypochlorite, and a subsequent reaction with different olefin yielded compounds I-1a–I-14a, and further reduction using iron powder as a reductant provided compounds I-1b–I-14b, which were combined with 2,6-difluorobenzoyl isocyanate to afford compounds I-1–I-14.

The target compounds II-1 and II-2 were synthesized from 4-fluorobenzaldehyde and pivalaldehyde as shown in Scheme 1. The target compounds III-1–III-5 were synthesized from freshly prepared *N*-hydroxy-4-nitrobenzimidoyl chloride as shown in Scheme 1. When we tried to synthesize III-4a from I-4a using *t*-BuOK as the base in *t*-BuOH, III-4a was obtained smoothly with a little of I-15a as the byproduct. I-15a was obtained from I-4a using CF₃CH₂ONa as the base in THF.

Bioassay. Table 1 shows the larvicidal activities of the target compounds I-1–I-15, II-1, II-2, III-1–III-5, Flucycloxuron, and compound C against Oriental armyworm, mosquito, and diamondback moth. The result indicated that some of the target compounds exhibited higher larvicidal activities against Oriental armyworm and diamondback moth than Flucycloxuron and

compound C, and especially, compound III-1 has 100% morality against diamondback moth at 2 mg L⁻¹. In general, the larvicidal activities of new benzoylureas containing the isoxazole group and target compounds containing the isoxazoline group were at the same level. For example, compound III-3 has 80% morality against Oriental armyworm at 50 mg L⁻¹, and compound I-8 has 40% morality at the same concentration. When R₁, R₃, and R₄ were hydrogen atoms, and R₁ was large alkyl groups in the structure of compound I, new benzoylureas exhibited higher larvicidal activities against Oriental armyworm and diamondback moth, for example, compound I-1 had 100% morality against Oriental armyworm and diamondback moth at 10 mg L⁻¹ and 5 mg L⁻¹, respectively, which had higher insecticidal activities than compounds I-2–I-10. The target compounds displayed different structure–activity relationships (SARs) between mosquito and diamondback moth. For example, compounds I-1 and III-1 have much higher insecticidal activities against diamondback moth than compound I-6, whereas compounds I-6 and I-1 have 100% morality against mosquito at 0.25 mg L⁻¹, and compound III-1 has only 40% morality at 2 mg L⁻¹.

In summary, a series of new benzoylphenylureas containing isoxazoline and the isoxazole group were designed and synthesized. The result of the bioassay showed that most compounds exhibited considerable larvicidal activities against Oriental armyworm and diamondback moth and that some of the target compounds are as effective as Flucycloxuron. Surprisingly, compounds I-1 and III-1 have higher larvicidal activity against diamondback moth than compound C, which was the most effective compound identified in our previous report.¹⁴ Interestingly, compounds I-1, II-2, and III-1 which contain the *tert*-butyl group are the best active compounds in all of the target compounds.

ASSOCIATED CONTENT

S Supporting Information. Physical properties and ¹H NMR data of compounds I-2a–I-14a and I-2b–I-15b. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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REFERENCES

- (1) Berghiche, H.; Houamria, M.; Van de Velde, S.; Soltani, N.; Smaghe, G. Effect of two insect growth regulators on the ecdysteroid contents in eggs of the mealworm. *Belg. J. Zool.* **2008**, *138*, 140–145.
- (2) Merzendorfer, H.; Zimoch, L. Chitin metabolism in insects: structure, function and regulation of chitin synthases and chitinases. *J. Exp. Biol.* **2004**, *206*, 4393–4412.
- (3) Yu, C. C.; Kuhr, R. J. Synthesis and insecticidal activity of substituted 1-phenyl-3-benzoylureas and 1-phenyl-3-benzoyl-2-thioureas. *J. Agric. Food Chem.* **1976**, *24*, 134–137.

- (4) Qian, X. H. Quantitative studies on structure-activity relationship of sulfonylurea and benzoylphenylurea type pesticides and their substituents' bioisosterism using synthons' activity contribution. *J. Agric. Food Chem.* **1999**, *47*, 4415–4418.
- (5) Cao, S.; Lu, D. L.; Zhao, C. M.; Li, L. N.; Huang, Q. C.; Qian, X. H. An efficient and practical method for the synthesis of 1-(2,6-difluorobenzoyl)-3-[2'-alkyl-3'-oxypyridazin-4'-yl]ureas as potential chitin synthesis inhibitors. *Monatsh. Chem.* **2006**, *137*, 779–784.
- (6) Zhao, P. L.; Li, J.; Yang, G. F. Synthesis and insecticidal activity of chromanone and chromone analogues of diacylhydrazines. *Bioorg. Med. Chem.* **2007**, *15*, 1888–1895.
- (7) Gangishetti, U.; Breitenbach, S.; Zander, M.; Saheb, S. K.; Müller, U.; Schwarz, H.; Moussian, B. Effects of benzoylphenylurea on chitin synthesis and orientation in the cuticle of the *Drosophila* larva. *Eur. J. Cell Biol.* **2009**, *88*, 167–180.
- (8) Li, Y.; Li, B. J.; Ling, Y.; Miao, H. J.; Shi, Y. X.; Yang, X. L. Synthesis and fungicidal activity of aryl carbamic acid-5-aryl-2-furan-methyl ester. *J. Agric. Food Chem.* **2010**, *58*, 3037–3042.
- (9) Fan, F.; Cheng, J. G.; Li, Z.; Xu, X. Y.; Qian, X. H. Novel dimer based descriptors with solvational computation for QSAR study of oxadiazoylbenzoyl-ureas as novel insect-growth regulators. *J. Comput. Chem.* **2010**, *31*, 586–591.
- (10) Zhang, J.; Tang, X. H.; Ishaaya, I.; Cao, S.; Wu, J. J.; Yu, J. L.; Li, H.; Qian, X. H. Synthesis and insecticidal activity of heptafluoroisopropyl-containing benzoylphenylurea structures. *J. Agric. Food Chem.* **2010**, *58*, 2736–2740.
- (11) Nauen, R.; Smagghe, G. Mode of action of etoxazole. *Pest Manag. Sci.* **2006**, *62*, 379–382.
- (12) Suzuki, J.; Tanji, I.; Ota, Y.; Toda, K.; Nakagawa, Y. QSAR of 2,4-diphenyl-1,3-oxazolines for ovicidal activity against the two-spotted spider mite *Tetranychus urticae*. *J. Pestic. Sci.* **2006**, *31*, 409–416.
- (13) Ralf, B.; Oswald, O.; Karl-Josef, H.; Matthias, E.; Waltraud, H.; Maria-Theresia, T. Arylisoxazoline derivatives, method for production and use thereof as pesticides. World Patent WO 2002076956, 2002.
- (14) Sun, R. F.; Lü, M. Y.; Chen, L.; Li, Q. S.; Song, H. B.; Bi, F. C.; Huang, R. Q.; Wang, Q. M. Design, synthesis, bioactivity, and structure-activity relationship (SAR) studies of novel benzoylphenylureas containing oxime ether group. *J. Agric. Food Chem.* **2008**, *56*, 11376–11391.
- (15) Sun, R. F.; Li, Y. Q.; Lü, M. Y.; Xiong, L. X.; Wang, Q. M. Synthesis, larvicidal activity, and SAR studies of new benzoylphenylureas containing oxime ether and oxime ester group. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4693–4699.
- (16) McCann, S. F.; Annis, G. D.; Shapiro, R.; Piotrowski, D. W.; Lahm, G. P.; Long, J. K.; Lee, K. C.; Hughes, M. M.; Myers, B. J.; Griswold, S. M.; Reeves, B. M.; March, R. W.; Sharpe, P. L.; Lowder, P.; Barnette, W. E.; Wing, K. D. The discovery of indoxacarb: oxadiazines as a new class of pyrazoline-type insecticides. *Pest. Manag. Sci.* **2005**, *57*, 153–164.
- (17) Takagi, K.; Hamaguchi, H.; Nishimatsu, T.; Konno, T. Discovery of metaflumizone, a novel semicarbazone insecticide. *Vet. Parasitol.* **2007**, *150*, 177–181.
- (18) Ding, N.; Meng, Q. W.; Zhao, W. J.; Miao, W. R. Progress on Indoxacarb as an oxadiazine insecticide. *Chin. J. Pestic. Sci.* **2005**, *7* (2), 97–103.
- (19) Weikert, R. J.; Emanuel, M. A. Synthesis and anthelmintic activity of 3'-benzoylurea derivatives of 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole. *J. Med. Chem.* **1991**, *34*, 1630–1633.
- (20) Meazza, G.; Rama, F.; Bettarini, F. Synthesis and bioactivity of some fluorine-containing benzoyl arylureas. Part I: Insecticidalacaricidal products in which the aryl group bears a trifluoromethyl-substituted alkyl or alkenyl side chain. *Pestic. Sci.* **1992**, *35*, 137.
- (21) Okuma, K.; Sakai, O.; Shioji, K. Wittig reaction by using DBU as a base. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1675–1676.
- (22) Abbott, W. S. A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.* **1925**, *18*, 265–267.
- (23) Raymond, M. Presentation d'un programme basic d'analyse log-probit pour micro-ordinateur. *Cah. ORSTOM Ser. Ent. Med. Parasitol.* **1985**, *23*, 117–121.
- (24) Hsu, A. C.; Murphy, R. A.; Aller, H. E.; Hamp, D. W.; Weinstein, B. Insecticidal N'-substituted-N,N'-disubstitutedhydrazines. U.S. Patent 5117057, 1992.
- (25) Chen, L.; Huang, Z. Q.; Wang, Q. M.; Shang, J.; Huang, R. Q.; Bi, F. C. Insecticidal benzoylphenylurea-S-carbamate: a new propesticide with two effects of both benzoylphenylureas and carbamates. *J. Agric. Food Chem.* **2007**, *55*, 2659–2663.
- (26) Busvine, J. R. *FAO Plant Production and Protection Paper*; Rome, Italy, 1980; No. 21, pp 3–13; 119–122.