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

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Supporting Information

ABSTRACT: Twenty-two new benzoylphenylureas containing isoxazoline and the isoxazole group were designed and synthesized, and their structures were characterized by ^{1}H 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. ^{1}H 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 synthezied 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 literature[15] was dissolved in dichloromethane (40 mL), and 3,3-dimethyl-but-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 °C. ^{1}H 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, OC*H*), 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, C(CH_3)$_3$).

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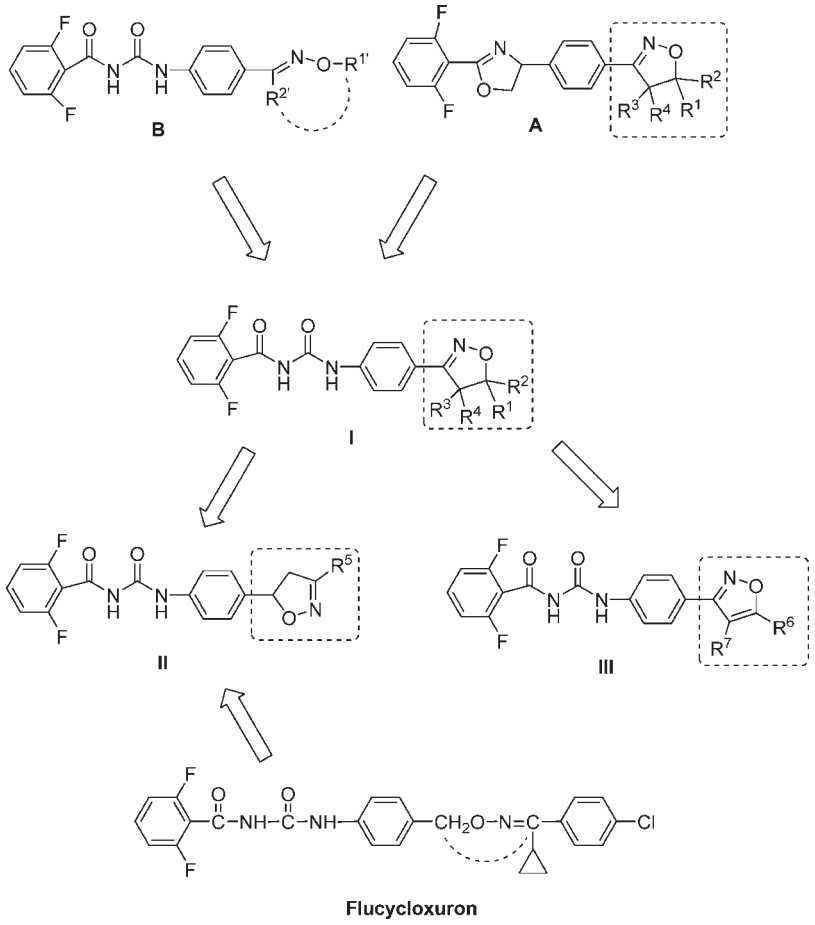


Figure 1. Design of compounds **I**, **II**, and **III**.

*Synthesis of 4-(5-tert-Butyl-4,5-dihydroisoxazol-3-yl)aniline (**I-1b**).* A mixture of **I-1a** (0.50 g, 2.0 mmol), ethyl acetate (30 mL), acetic acid (2 mL), and water (1 mL) was heated to 70 °C, then reduced iron powder (0.45 g, 8 mmol) was added, and the solution cooled to room temperature until the reaction was completed (monitored by TLC). The mixture was filtered, and the filtrate was successively washed by saturated sodium bicarbonate 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 compound **I-1b** (0.40 g, 90.9%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.5 Hz, 2H, Ar−H), 6.66 (d, J = 8.6 Hz, 2H, Ar−H), 4.38 (t, J = 10.0 Hz, 1H, OC*H*), 3.86 (brs, 2H, NH_2), 3.17 (dd, J = 16.7, 11.1 Hz, 1H, CH_2), 3.02 (dd, J = 16.7, 9.0 Hz, 1H, CH_2), 0.95 (s, 9H, C(CH_3)$_3$).

*Synthesis of N-(4-(5-tert-Butyl-4,5-dihydroisoxazol-3-yl)phenyl-carbamoyl)-2,6-difluorobenzamide (Target Compound **I-1**).* A solution of 2,6-difluorobenzoyl isocyanates (0.32 g, 1.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of **I-1b** (0.38 g, 1.7 mmol) in dichloromethane (10 mL) at room temperature. The reaction was monitored by TLC. After the reaction was completed, the solvent was evaporated off under reduced pressure, and the product was purified by flash column chromatography on silica gel (3:1 petroleum ether/ethyl acetate) to give compound **I-1** (0.43 g, 61.4%) as a white solid, mp 197−199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.54 (brs, 1H, CONHCO), 8.80 (brs, 1H, CONHAr), 7.63 (d, J = 8.4 Hz, 2H, Ar−H), 7.51−7.58 (m, 3H, Ar−H), 7.06 (t, J = 8.5 Hz, 2H, Ar−H), 4.45 (t, J = 10.1 Hz, 1H, OC*H*), 3.17 (dd, J = 16.8, 11.4 Hz, 1H, CH_2), 3.07 (dd, J = 16.6, 9.2 Hz, 1H, CH_2), 0.98 (s, 9H, C(CH_3)$_3$). Anal. Calcd. for $C_{21}H_{21}F_2N_3O_3$: C, 62.84; H, 5.27; N, 10.47. Found: C, 62.72; H, 5.33; N, 10.62.

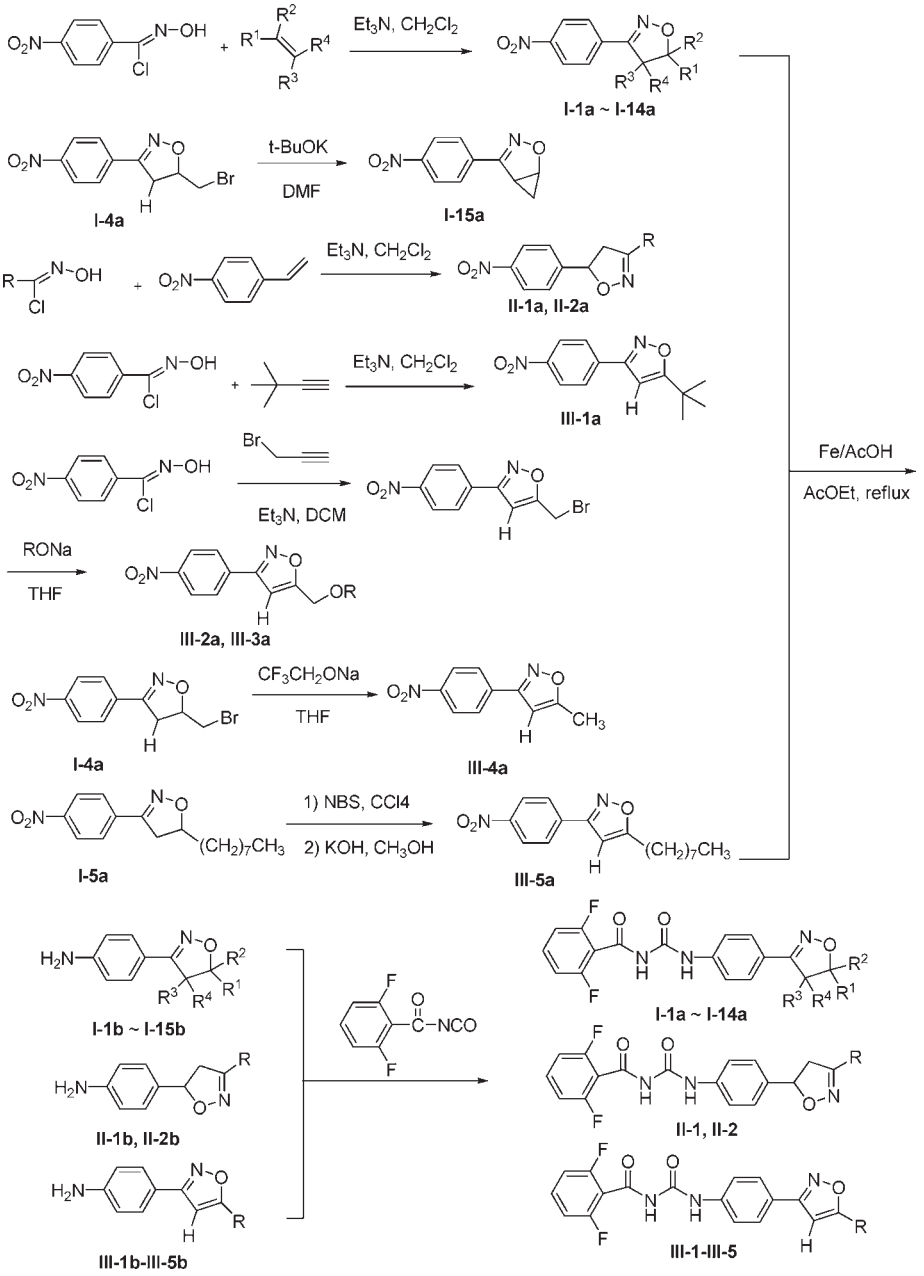
*Synthesis of 4-(4-Nitrophenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**I-15a**).* **I-4a** (0.44 g, 1.0 mmol) was dissolved in DMF (10 mL), and potassium *tert*-butoxide (0.22 g, 2 mmol) was added. The mixture was heated to 80 °C and was left for 2 h. Then the solution was cooled to room temperature, and water (50 mL) was added and 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 (3:1 petroleum ether/ethyl acetate) to give compound **I-15a** (0.13 g, 65.0%) as a yellow solid; mp 164−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 8.6 Hz, 2H, Ar−H), 7.97 (d, J = 8.6 Hz, 2H, Ar−H), 5.16 (dd, J = 5.1, 3.3 Hz, 1H, OC*H*), 2.87−2.97 (m, 1H, C*H*C═N), 1.17 (dt, J = 9.3, 5.8 Hz, 1H, CH_2), 0.50 (s, 1H, CH_2).

Compounds **I-2a**−**I-14a**, **I-2b**−**I-15b**, and **I-2**−**I-15** were prepared by a method similar to that used for compounds **I-1a**, **I-1b**, and **I-1**. The physical properties and ^{1}H NMR data of compounds **I-2a**−**I-15a** and **I-2b**−**I-15b** are listed in Table S1 in Supporting Information.

*Data for Compound **I-2**.* White solid; yield, 54.3%; mp 266−268 °C. ^{1}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, OC*H*), 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 $C_{23}H_{16}F_3N_3O_3$: C, 62.87; H, 3.67; N, 9.56. Found: C, 62.71; H, 3.79; N, 9.33.

*Data for Compound **I-3**.* White solid; yield, 73.6%; mp 175−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (brs, 1H, CONHCO), 9.54 (brs,

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, OC*H*), 3.39 (dd, J = 16.3, 10.3 Hz, 1H, CH_2C═N), 2.96 (dd, J = 16.4, 8.2 Hz, 1H, CH_2C═N), 1.77−1.81 (m, 1H, OCH$CH_2$$CH_2$), 1.58−1.68 (m, 1H, OCH$CH_2$$CH_2$), 1.36−1.51 (m, 4H, CH_2(CH_2)$_2$$CH_3$), 0.93 (t, J = 6.8 Hz, 3H, $CH_2$$CH_3$). Anal. Calcd. for $C_{21}H_{21}F_2N_3O_3$: C, 62.84; H, 5.27; N, 10.47. Found: C, 62.84; H, 5.22; N, 10.33.

Data for Compound ***I-4***. White solid; yield, 56.1%; mp 230 °C (dec.). ^{1}H 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, OC*H*), 3.65−3.76 (m, 2H, CH_2Br), 3.54 − 3.60 (m, 1H, CH_2C═N), 3.19 − 3.25 (m, 1H, CH_2C═N). Anal. Calcd. for $C_{18}H_{14}BrF_2N_3O_3$: 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. ^{1}H 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, OC*H*), 3.39 (dd, J = 16.3, 10.3 Hz, 1H, CH_2C═N), 2.96 (dd, J = 16.3, 8.2 Hz, 1H, CH_2C═N), 1.76−1.87 (m, 1H, OCH$CH_2$$CH_2$), 1.55−1.64 (m, 1H, OCH$CH_2$$CH_2$), 1.28−1.50 (m, 12H, CH_2-(CH_2)$_6$$CH_3$), 0.88 (t, J = 6.2 Hz, 3H, $CH_2$$CH_3$). Anal. Calcd. for $C_{25}H_{29}F_2N_3O_3$: 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. ^{1}H 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, OC*H*), 3.82−3.97 (m, 2H, CH_2). Anal. Calcd. for $C_{18}H_{12}F_2N_4O_3$: C, 58.38; H, 3.27; N, 15.13. Found: C, 58.14; H, 3.24; N, 14.99.

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Data for Compound ***I-7***. White solid; yield, 72.7%; mp 196−198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 3.83 (s, 3H, COOCH_3), 3.60−3.74 (m, 2H, CH_2). Anal. Calcd. for $C_{19}H_{15}F_2N_3O_5$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 3.51−3.66 (m, 4H, $CH_2OCH_2CH_2$), 3.39 (dd, J = 16.5, 10.7 Hz, 1H, CH_2C═N), 3.24 (dd, J = 16.6, 7.4 Hz, 1H, CH_2C═N), 1.53−1.60 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.32−1.41 (m, 2H, $CH_2CH_2CH_3$), 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_3). Anal. Calcd. for $C_{22}H_{23}F_2N_3O_4$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 3.97 (q, J = 8.6 Hz, 2H, OCH_2CF_3), 3.79−3.84 (m, 2H, CH_2O), 3.43 (dd, J = 16.7, 9.2 Hz, 1H, CH_2C═N), 3.43 (dd, J = 16.7, 7.5 Hz, 1H, CH_2C═N). Anal. Calcd. for $C_{20}H_{16}F_5N_3O_4$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 3.79 (dd, J = 16.6, 11.0 Hz, 1H, CH_2), 3.35 (dd, J = 16.6, 8.3 Hz, 1H, CH_2). Anal. Calcd. for $C_{23}H_{17}F_2N_3O_3$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, CH_2C═N), 1.82 (s, 3H, CH_3). Anal. Calcd. for $C_{24}H_{19}F_2N_3O_3$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, CH_2C═N), 1.82 (d, J = 5.6 Hz, 4H), 1.63−1.71 (m, 2H), 1.49 (s, 4H). Anal. Calcd. for $C_{22}H_{21}F_2N_3O_3$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, CH_2C═N), 2.13−2.21 (m, 2H), 1.74−1.90 (m, 6H). Anal. Calcd. for $C_{21}H_{19}F_2N_3O_3$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 4.04 (t, J = 8.3 Hz, 1H, C*H*C═N), 2.19 (dd, J = 12.0, 5.0 Hz, 1H, OCHCH_2), 1.68−1.96 (m, 4H, CH_2CH_2CHC═N), 1.48−1.55 (m, 1H, OCHCH_2). HRMS (ESI) m/z calcd for $C_{20}H_{17}F_2N_3O_3$: $(M+Na)^+$ 408.1130; found, 408.1138.

Data for Compound ***I-15***. White solid; yield, 81.8%; mp 210 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 2.87−2.90 (m, 1H, C*H*C═N), 1.08−1.12 (m, 1H, CH_2), 0.45−0.49 (m, 1H, CH_2). HRMS (ESI) m/z calcd for $C_{18}H_{13}F_2N_3O_3$: $(M+Na)^+$ 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 3.87 (dd, J = 16.6, 11.2 Hz, 1H, CH_2), 3.29 (dd, J = 16.6, 7.6 Hz, 1H, CH_2).

*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**. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 3.66 (dd, J = 16.6, 10.6 Hz, 1H, CH_2), 3.30 (dd, J = 16.3, 8.9 Hz, 1H, CH_2).

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**. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 3.75 (dd, J = 16.6, 10.9 Hz, 1H, CH_2), 3.30 (dd, J = 16.6, 8.4 Hz, 1H, CH_2). HRMS (ESI) m/z calcd for $C_{23}H_{16}F_3N_3O_3$ $(M + Na)^+$ 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**. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OC*H*), 3.50 (dd, J = 16.7, 10.9 Hz, 1H, CH_2), 2.89 (dd, J = 16.8, 7.2 Hz, 1H, CH_2), 1.21 (s, 9H, C(CH_3)$_3$).

*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}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, OC*H*), 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, C(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}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, OC*H*), 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 $C_{23}H_{16}F_3N_3O_3$: 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}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, C(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}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}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}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, OCH$_2CH_2$CH$_2$) 1.36−1.48 (m, 2H, CH$_2CH_2$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}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}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, OCCH$_2CH_2$CH$_2$), 1.28−1.41 (m, 10H, CH$_2$-(CH_2)$_5$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}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, C(CH_3)$_3$).

*Data for 4-(5-((2,2,2-Trifluoroethoxy)methyl)isoxazol-3-yl)aniline (**III-2b**).* Yellow oil; yield, 92.7%. ^{1}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}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, OCH$_2CH_2$CH$_2$), 1.35−1.44 (m, 2H, CH$_2CH_2$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}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}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, OCCH$_2CH_2$CH$_2$), 1.27−1.42 (m, 10H, CH$_2$(CH_2)$_5$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}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, C(CH_3)$_3$). HRMS (ESI) m/z calcd for $C_{21}H_{19}F_2N_3O_3$: $(M+Na)^+$ 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}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

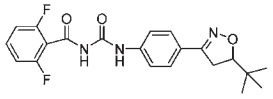
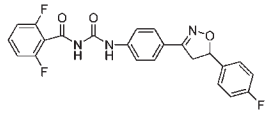
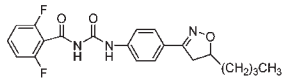
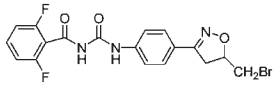
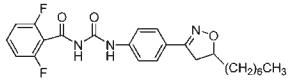
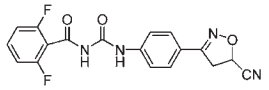
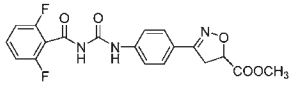
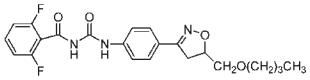
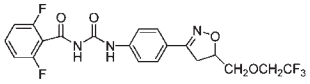
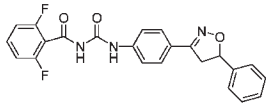
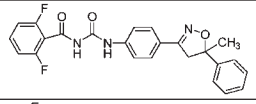
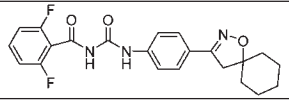
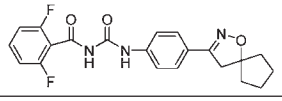
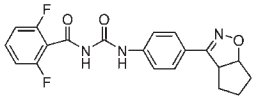
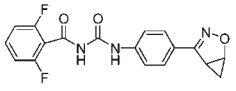
compd	Chemical Structure	Toxicities against Oriental armyworm		Toxicities against mosquito		Toxicities against diamondback moth	
		C[a] (mg L^{-1})	P[a] (%)	C[a] (mg L^{-1})	P[a] (%)	C[a] (mg L^{-1})	P[a] (%)
I-1		50	100	0.25	100	5	100
		25	100	0.1	50	2	80
		10	100			0.2	70
		5	40			0.02	10
I-2		200	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				

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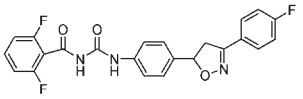
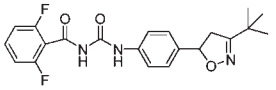
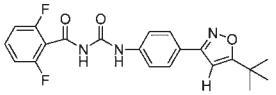
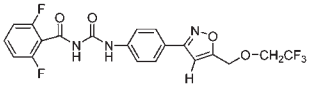
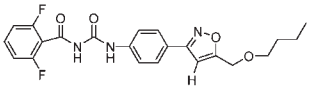
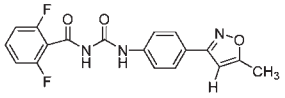
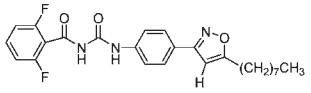
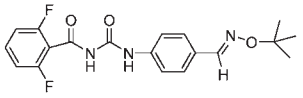
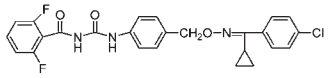
Table 1. Continued

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
						0.02	30
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	LC_{50} = 72.92 mg·L^{-1}	
		2.5	50	0.025	15		
		1.0	10				

[a] C = concentration; P = larvicidal activity.

4.83 (s, 2H, CH_2O), 3.97 (q, J = 8.5 Hz, 2H, OCH_2CF_3). Anal. Calcd. for $C_{20}H_{14}F_5N_3O_4$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, CH_2O), 3.58 (t, J = 6.6 Hz, 2H, OCH_2CH_2), 1.53−1.70 (m, 2H, $OCH_2CH_2CH_2$) 1.35−1.44 (m, 2H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.4 Hz, 3H, CH_2CH_3). HRMS (ESI) m/z calcd for $C_{22}H_{21}F_2N_3O_4$: $(M + Na)^+$ 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. ^{1}H 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, CH_3). Anal. Calcd. for $C_{18}H_{13}F_2N_3O_3$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, $OCCH_2CH_2$), 1.71−1.78 (m, 2H, $OCCH_2CH_2CH_2$), 1.28−1.40 (m, 10H, $CH_2(CH_2)_5CH_3$), 0.88 (t, J = 6.4 Hz, 3H, CH_2CH_3). Anal. Calcd. for $C_{25}H_{27}F_2N_3O_3$: 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%. LC_{50} 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**,

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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 pallens*). 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 CF_3CH_2ONa 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 R_1, R_3, and R_4 were hydrogen atoms, and R_1 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

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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