ARTICLE

Design and Synthesis of Benzoylphenylureas with Fluorinated Substituents on the Aniline Ring as Insect Growth Regulators

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ABSTRACT: Enormous numbers of synthetic fluorine-containing compounds have been widely used in a variety of fields, especially in drug and pesticide design. To find novel insect growth regulators, a series of benzoylphenylureas with fluorinated substituents were designed and synthesized. The results of larvicidal activities of those novel fluoro-substituted benzoylphenylureas against oriental armyworm and mosquito revealed that most compounds exhibited excellent activities. It is worth mentioning that compounds **3** and **6** exhibited higher activities against oriental armyworm and mosquito than commercial Hexaflumuron. It can be further seen that the insecticidal activities would increase significantly by introducing fluorinated substituents into the structure of the designed benzoylphenylureas.

KEYWORDS: benzoylphenylureas (BPUs), structure−activity relationship, larvicidal activity, insect growth regulator

INTRODUCTION

Food production capacity is faced with an ever-growing number of challenges. Some 20−40% of the world's potential crop production is already lost annually because of the effects of weeds, pests, and diseases (according to the Food and Agriculture Organization of the United Nations or FAO). These crop losses would be doubled if existing pesticide uses were abandoned, significantly raising food prices.[1] The use of pesticides brings numerous benefits and makes a significant contribution to the lifestyles we have come to expect, but pollution and the emergence of pesticide resistance push researchers to develop novel pesticides. The extraordinary potential of fluorine-containing molecules in medicinal chemistry and chemical biology has been recognized. The special nature of fluorine (mimic effect, block effect, steric effect, and inductive effect) imparts a variety of properties to certain pesticides, including enhanced binding interactions, metabolic stability, changes in physical properties, and selective reactivities.[2−4] It is reported that 30−40% of commercial pesticides contain fluorine atoms.[5]

Insect growth regulators (IGRs), which interrupt or inhibit the life cycle of pests, are low-toxicity pesticides and widely used in integrated pest management (IPM). Benzoylphenylureas (BPUs) are a familiar type of IGRs, which have attracted considerable attention for decades because of their unique mode of action and low toxicity to nontarget organisms (including many beneficial arthropods).[6−10] More than 20 benzoylphenylureas have been developed as IGRs since Dimilin (diflubenzuron) was introduced to the market in 1972. Most of the commercial BPUs contain fluorine atoms because QSAR studies of BPUs showed that benzoylurea derivatives with a 2,6-difluoro substitution in the benzoyl moiety exhibited much higher larvicidal activity than other substitutions.[11,12] The substituent changes of aniline ring have been the focus of research on benzoylurea insecticides.[13−18] Structural comparison of commercial benzoylphenylureas revealed that fluorinated substituents at an anilide moiety could increase the insecticidal activities and minor structural changes at the anilide moiety could discover novel insecticides as insect growth regulators (Figure 1). Recently, Cao et al. have designed and synthesized a series of novel benzoylphenylurea derivatives (compound **1**) by introducing a heptafluoroisopropyl group into the structure of benzoylphenylurea (Figure 2). They found that compound **2** had better solubility than chlorfluazuron and exhibited similar efficacy comparable with that of hexaflumuron against diamondback moth.[19] In view of the above statement, introducing fluorinated substituents into the structure of benzoylphenylureas would improve the insecticidal activities and solubility. To find novel benzoylurea derivatives, compounds **3−8** were designed and synthesized by introducing fluorinated substituents into the structure of benzoylphenylureas according to substructure linking (Figure 3). Then the larvicidal activities of these novel fluoro-substituted benzoylphenylureas **3−8** against oriental armyworm (*Mythimna separata*) and mosquito (*Culex pipiens pallens*) were evaluated.

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 CDCl₃ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in parts per million (δ). Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. 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.
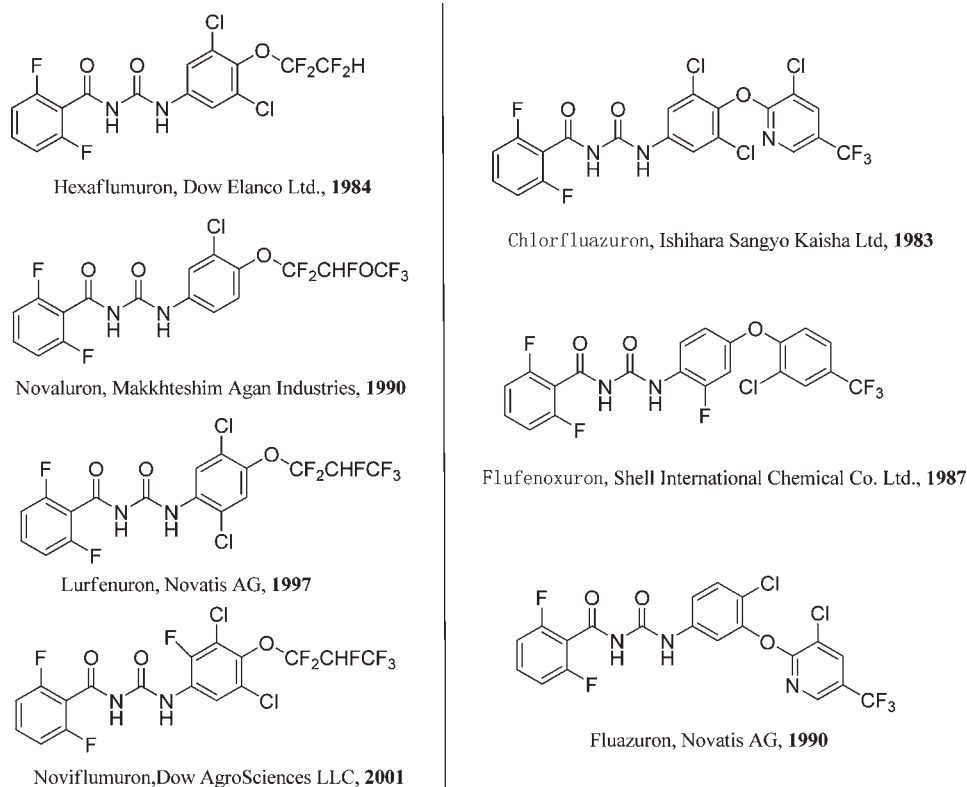
Figure 1. Structures of commercial benzoylphenylureas as insect growth regulators.
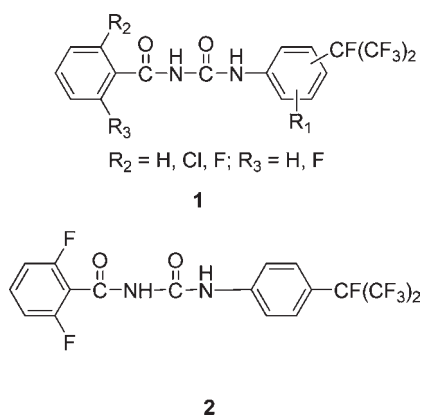

Figure 2. Structures of benzoylphenylureas containing a heptafluoroisopropyl group.

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 according to the method of the literature.[20]

Synthesis of 3,5-Dichloro-4-(1,1,2,2-tetrafluoroethoxy)-phenol (3b). To a mixture of water (70 mL) and concentrated sulfuric acid (98%, 15 mL) was added dropwise 3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)aniline (3a, 3.5 g, 12.59 mmol) at 75−80 °C. When 3a was dissolved completely, the mixture was cooled to 0 °C, and a solution of NaNO$_2$ (0.96 g, 13.91 mmol) in water (5 mL) was slowly dropwise added at this temperature. Then the reaction stood at 0 °C for 0.5 h and at 25 °C for another 0.5 h. After the mixture was slowly added to a solution of CuSO$_4$ (10.0 g, 62.89 mmol) in water (150 mL) at boiling point, the solution was distilled until no oil was produced. The fraction was extracted by ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give compound 3b as a brown oil (1.02 g, 29.0%): ^{1}H NMR (400 M, CDCl$_3$) δ 5.30 (br s, 1H, Ar-OH), 6.03 (tt, $^3J_{HF}$ = 3.4 Hz, $^2J_{HF}$ = 53.0 Hz, 1H, CF$_2$CF$_2$H), 6.84 (s, 2H, Ar−H).

Synthesis of 1,3-Dichloro-5-(4-nitrophenoxy)-2-(1,1,2,2-tetrafluoroethoxy)benzene (3c). Compound 3b (0.30 g, 1.08 mmol) and NaOH (0.043 g, 1.08 mmol) were dissolved in DMF (8 mL) and toluene (10 mL), and the mixture was heated to remove moisture by distillation as an azeotrope with toluene. Then 1-chloro-4-nitrobenzene (0.16 g, 1.02 mmol) was added and refluxed for 7 h. When the reaction was complete, DMF was removed and saturated brine water (5 mL) was added. The mixture was extracted by ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by flash column chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (v/v = 20:1) as the eluent to obtain compound 3c (0.20 g, 49.0%) as a yellow solid: mp 81−82 °C; ^{1}H NMR (400 M, CDCl$_3$) δ 6.06 (tt, $^3J_{HF}$ = 3.3 Hz, $^2J_{HF}$ = 52.9 Hz, 1H, CF$_2$CF$_2$H), 7.10 (s, 2H, Ar−H), 7.12 (d, $^3J_{HH}$ = 9.2 Hz, 2H, Ar−H), 8.28 (d, $^3J_{HH}$ = 9.2 Hz, 2H, Ar−H).

Synthesis of 4-(3,5-Dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenoxy)aniline (3d). To a solution of CuCl$_2$·2H$_2$O (0.04 g, 0.23 mmol) in 1.2% hydrochloric acid (10 mL) was added zinc powder; the solution was removed until bubbles no longer appeared. Then the Zn−Cu couple was washed with distilled water one time and directly used in the next step.

Freshly prepared Zn−Cu couple was added to a mixture of compound 3c (0.19 g, 0.48 mmol) in diethyl ether (15 mL) and saturated aqueous NH$_4$Cl (15 mL) and then stirred for 5 h at room temperature. When the reaction was complete (monitored by TLC), the organic layer was washed successively with saturated sodium carbonate solution and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed to give a crude product,
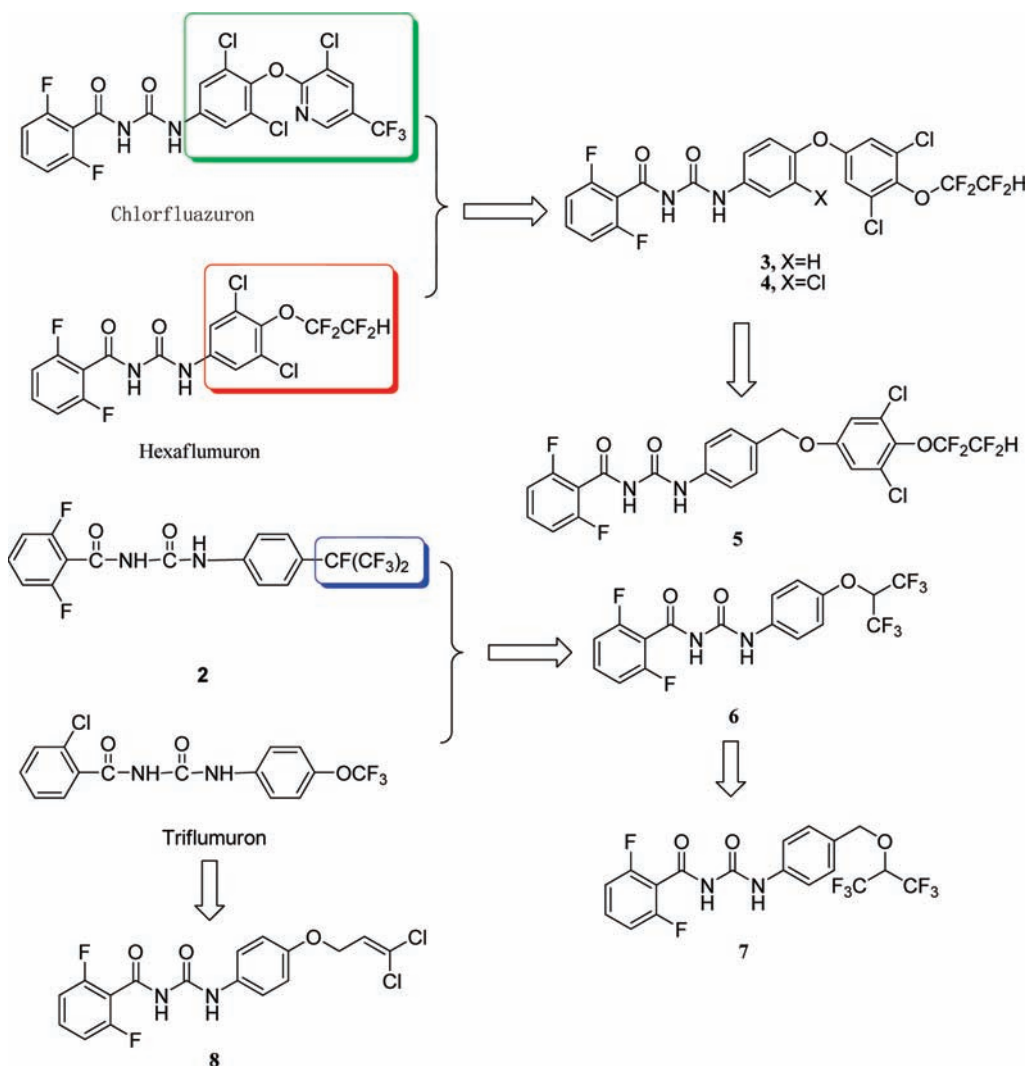
Figure 3. Design of novel fluoro-substituted benzoylphenylureas **3**−**8**.

which was purified by flash column chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (v/v = 3:1) as the eluent to give compound **3d** as a brown oil (0.16 g, 91.0%): ^{1}H NMR (400 M, CDCl$_3$) δ 3.70 (br s, 2H, Ar-NH_2), 6.02 (tt, [3]J_{HF} = 3.3 Hz, [2]J_{HF} = 52.9 Hz, 1H, CF$_2$CF$_2$H), 6.70 (d, [3]J_{HH} = 8.7 Hz, 2H, Ar−H), 6.86 (d, [3]J_{HH} = 8.7 Hz, 2H, Ar−H), 6.89 (s, 2H, Ar−H).

Synthesis of *N*-(4-(3,5-Dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenoxy)phenylcarbamoyl)-2,6-difluorobenzamide (3). A solution of 2,6-difluorobenzoyl isocyanates (0.08 g, 0.44 mmol) in dry dichloromethane (5 mL) was added dropwise to a solution of compound **3d** (0.16 g, 0.43 mmol) in dry dichloromethane (10 mL) at room temperature. The reaction stood for 2 h, and the solvent was evaporated off under reduced pressure. Then the product was purified by recrystallization from a mixture of ethyl acetate and petroleum ether (60−90 °C) (v/v = 2:1), giving target compound **3** as a white solid (0.16 g, 89.4%): mp 199−201 °C; ^{1}H NMR (400 M, CDCl$_3$) δ 6.04 (tt, [3]J_{HF} = 3.3 Hz, [2]J_{HF} = 52.9 Hz, 1H, CF$_2$CF$_2$H), 6.96 (s, 2H, Ar−H), 7.01−7.10 (m, 4H, Ar−H), 7.49−7.60 (m, 3H, Ar−H), 8.57 (br s, 1H, CON*H*Ar), 10.45 (br s, 1H, ArCON*HC*O). Anal. Calcd for C$_{22}$H$_{12}$Cl$_2$F$_6$N$_2$O$_4$: C, 47.76; H, 2.19; N, 5.06. Found: C, 47.60; H, 2.17; N, 4.91.

Synthesis of 1,3-Dichloro-5-(2-chloro-4-nitrophenoxy)-2-(1,1,2,2-tetrafluoroethoxy)benzene (4c). Intermediate **4c** was obtained as a yellow viscous liquid (yield, 87.0%) by following the same procedure as for compound **3c**: ^{1}H NMR (300 M, CDCl$_3$) δ 6.03 (tt, [3]J_{HF} = 3.4 Hz, [2]J_{HF} = 52.9 Hz, 1H, CF$_2$CF$_2$H), 6.86 (s, 2H, Ar−H),

6.96 (d, [4]J_{HH} = 2.6 Hz, 1H, Ar−H), 7.55 (dd, [4]J_{HH} = 2.6 Hz, [3]J_{HH} = 8.7 Hz, 1H, Ar−H), 7.85 (d, [3]J_{HH} = 8.7 Hz, 1H, Ar−H).

Synthesis of 3-Chloro-4-(3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenoxy)aniline (4d). Compound **4d** was obtained as a pale yellow viscous liquid (yield, 98.5%) by following the same procedure as for compound **3d**: ^{1}H NMR (300 M, CDCl$_3$) δ 3.76 (br s, 2H, Ar-NH_2), 6.03 (tt, [3]J_{HF} = 3.4 Hz, [2]J_{HF} = 52.9 Hz, 1H, CF$_2$CF$_2$H), 6.60 (dd, [4]J_{HH} = 2.6 Hz, [3]J_{HH} = 8.6 Hz, 1H, Ar−H), 6.79 (d, [4]J_{HH} = 2.6 Hz, 1H, Ar−H), 6.86 (s, 2H, Ar−H), 6.93 (d, [3]J_{HH} = 8.6 Hz, 1H, Ar−H).

Synthesis of *N*-(3-Chloro-4-(3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenoxy)phenylcarbamoyl)-2,6-difluorobenzamide (4). Target compound **4** was obtained as a white solid (yield, 89.2%, mp 185−187 °C) by following the same procedure as for compound **3**: ^{1}H NMR (400 M, CDCl$_3$) δ 6.05 (tt, [3]J_{HF} = 3.3 Hz, [2]J_{HF} = 52.8 Hz, 1H, CF$_2$CF$_2$H), 6.91 (s, 2H, Ar−H), 7.05−7.11 (m, 3H, Ar−H), 7.36 (dd, [4]J_{HH} = 2.5 Hz, [3]J_{HH} = 8.7 Hz, 1H, Ar−H), 7.49−7.57 (m, 1H, Ar−H), 7.84 (d, [4]J_{HH} = 2.5 Hz, 1H, Ar−H), 9.13 (br s, 1H, CON*H*Ar), 10.60 (br s, 1H, ArCON*HC*O). Anal. Calcd for C$_{22}$H$_{11}$Cl$_3$F$_6$N$_2$O$_4$: C, 44.96; H, 1.89; N, 4.77. Found: C, 45.08; H, 1.97; N, 4.89.

Synthesis of 1,3-Dichloro-5-(4-nitrobenzyloxy)-2-(1,1,2,2-tetrafluoroethoxy)benzene (5c). Intermediate **3b** (0.35 g, 1.25 mmol) and NaOH (0.05 g, 1.25 mmol) were dissolved in ethanol (5 mL), and the ethanol was removed under reduced pressure. Then the solid was dissolved in DMF (10 mL) and 1-(bromomethyl)-4-nitrobenzene

Scheme 1. General Synthetic Route for Compounds 3 and 4[a]
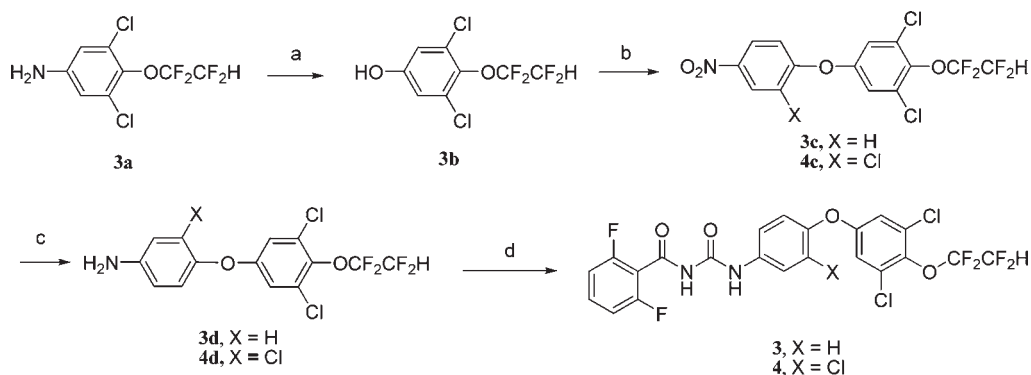
[a] Reagents and conditions: (a) NaNO$_2$, H$_2$SO$_4$; CuSO$_4$; (b) 1-chloro-4-nitrobenzene for compound **3c**, 1,2-dichloro-4-nitrobenzene for compound **4c**, NaOH, DMF/toluene, reflux, 7 h; (c) Zn/Cu/NH$_4$Cl, Et$_2$O, 25 °C; (d) 2,6-difluorobenzoyl isocyanates, CH$_2$Cl$_2$, 25 °C.

Scheme 2. Synthetic Route for Compound 5[a]
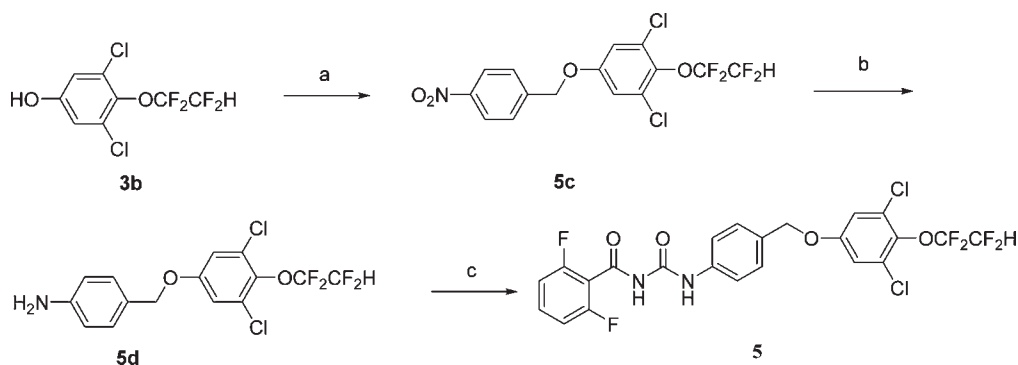
[a] Reagents and conditions: (a) 1-(bromomethyl)-4-nitrobenzene, NaOH, DMF, 25 °C, 1 h; (b) Zn/Cu/NH$_4$Cl, Et$_2$O, 25 °C; (c) 2,6-difluorobenzoyl isocyanates, CH$_2$Cl$_2$, 25 °C.

(0.27 g, 1.25 mmol) was added to the solution. The mixture was stirred for 1 h, and the solvent was evaporated off under reduced pressure. Afterward, saturated brine water (10 mL) was added, and the mixture was extracted by ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by recrystallization from a mixture of ethyl acetate and petroleum ether to give compound **5c** as a pale yellow solid (0.44 g, 85.3%): mp 117−118 °C; ^{1}H NMR (400 M, CDCl$_3$) δ 5.15 (s, 2H, Ar−CH$_2$O), 6.04 (tt, $^3J_{HF}$ = 3.4 Hz, $^2J_{HF}$ = 53.0 Hz, 1H, CF$_2$CF$_2$H), 7.00 (s, 2H, Ar−H), 7.58 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar−H), 8.28 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar−H).

Synthesis of 4-((3,5-Dichloro-4-(1,1,2,2-tetrafluoroethoxy)-phenoxy)methyl)aniline (5d). Compound **5d** was obtained as a pale yellow viscous liquid (yield, 98.5%) by following the same procedure as for compound **3d**: ^{1}H NMR (400 M, CDCl$_3$) δ 3.75 (br s$_2$, 2H, CF$_2$CF$_2$H), 4.88 (s, 2H, Ar−CH$_2$O), 6.02 (tt, $^3J_{HF}$ = 3.4 Hz, $^2J_{HF}$ = 53.0 Hz, 1H, CF$_2$CF$_2$H), 6.69 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ar−H), 6.96 (s, 2H, Ar−H), 7.17 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ar−H).

Synthesis of N-(4-((3,5-Dichloro-4-(1,1,2,2-tetrafluoroeth-oxy)phenoxy)methyl)phenylcarbamoyl)-2,6-difluoroben-zamide (5). Target compound **5** was obtained as a white solid (yield, 72.5%, mp 211−212 °C) by following the same procedure as for compound **3**: ^{1}H NMR (400 M, CDCl$_3$) δ 5.00 (s, 2H, Ar−CH$_2$O), 6.03 (tt, $^3J_{HF}$ = 3.3 Hz, $^2J_{HF}$ = 53.0 Hz, 1H, CF$_2$CF$_2$H), 6.98 (s, 2H, Ar−H), 7.06 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.7 Hz, 2H, Ar−H), 7.37 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.49−7.57 (m, 1H, Ar−H), 7.59 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H),

8.23 (br s, 1H, CONHAr), 10.45 (br s, 1H, ArCONHCO). Anal. Calcd for C$_{23}$H$_{14}$Cl$_2$F$_6$N$_2$O$_4$: C, 48.70; H, 2.49; N, 4.94. Found: C, 48.53; H, 2.57; N, 4.85.

Synthesis of 1-(1,1,1,3,3,3-Hexafluoropropan-2-yloxy)-4-nitrobenzene (6c) [21]**.** To a solution of 1,1,1,3,3,3-hexafluoro-2-propanol (0.50 g, 2.98 mmol) and N(Bu)$_4$F·3H$_2$O (1.53 g, 4.85 mmol) in DMF (45 mL) was added 1,4-dinitrobenzene (0.17 g, 1.01 mmol), and the mixture was stirred for 24 h at room temperature. Then 1.2% hydrochloric acid (30 mL) was added, and the mixture was extracted by diethyl ether. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by flash column chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (v/v = 10:1) as the eluent to give compound **6c** as a pale yellow solid (0.10 g, 34.5%): mp 52−53 °C; ^{1}H NMR (400 M, CDCl$_3$) δ 4.92−5.00 (m, 1H, OCH(CF$_3$)$_2$), 7.19 (d, $^3J_{HH}$ = 9.2 Hz, 2H, Ar−H), 8.29 (d, $^3J_{HH}$ = 9.2 Hz, 2H, Ar−H).

Synthesis of 4-(1,1,1,3,3,3-Hexafluoropropan-2-yloxy)-aniline (6d). Compound **6d** was obtained as a pale yellow oil (yield, 89.0%) by following the same procedure as for compound **3d**: ^{1}H NMR (400 M, CDCl$_3$) δ 3.59 (br s, 2H, Ar−NH$_2$), 4.52−4.61 (m, 1H, OCH(CF$_3$)$_2$), 6.30 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 6.90 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H).

Synthesis of 2,6-Difluoro-N-(4-(1,1,1,3,3,3-hexafluoropro-pan-2-yloxy)phenylcarbamoyl)benzamide (6). Target compound **6** was obtained as a white solid (yield, 67.2%, mp 197−198 °C) by following

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Scheme 3. Synthetic Route for Compound 6[a]
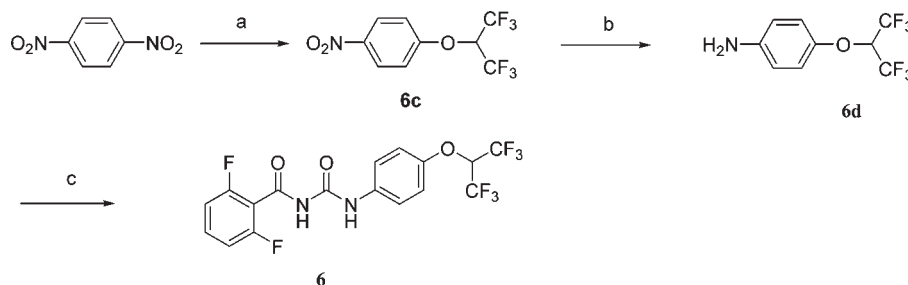
[a] Reagents and conditions: (a) tetra-*n*-butylammoniumfluoridetrihydrate (TBAF), DMF, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), 25 °C, 24 h; (b) Zn/Cu/NH$_4$Cl, Et$_2$O, 25 °C; (c) 2,6-difluorobenzoyl isocyanates, CH$_2$Cl$_2$, 25 °C.

the same procedure as for compound **3**: ^{1}H NMR (400 M, CDCl$_3$) δ 4.71–4.77 (m, 1H, OC*H*(CF$_3$)$_2$), 7.04–7.09 (m, 4H, Ar—H), 7.50–7.56 (m, 3H, Ar—H), 8.18 (br s, 1H, CON*H*Ar), 10.39 (br s, 1H, ArCON*H*CO). Anal. Calcd for C$_{17}$H$_{10}$F$_8$N$_2$O$_3$: C, 46.17; H, 2.28; N, 6.33. Found: C, 46.07; H, 2.33; N, 6.33.

Synthesis of 1-((1,1,1,3,3,3-Hexafluoropropan-2-yloxy)-methyl)-4-nitrobenzene (7c). Metal sodium (0.09 g, 3.91 mmol) was added to 1 1,1,1,3,3,3-hexafluoro-2-propanol (5 mL), and then DMF (5 mL) and 1-(bromomethyl)-4-nitrobenzene (0.43 g, 1.99 mmol) were added and refluxed for 2 h. The solvent was removed, and water (10 mL) was added. Afterward, the mixture was extracted by ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give compound **7c** as a brown oil (yield, 98.8%): ^{1}H NMR (400 M, CDCl$_3$) δ 4.15–4.23 (m, 1H, OC*H*(CF$_3$)$_2$), 4.99 (s, 2H, ArC*H*$_2$O), 7.54 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar—H), 8.26 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar—H).

Synthesis of 4-((1,1,1,3,3,3-Hexafluoropropan-2-yloxy)-methyl)aniline (7d). Compound **7d** was obtained as a yellow oil (yield, 90.0%) by following the same procedure as for compound **3d**: ^{1}H NMR (400 M, CDCl$_3$) δ 3.75 (br s, 2H), 4.04–4.12 (m, 1H, OC*H*-(CF$_3$)$_2$), 4.74 (s, 2H, ArC*H*$_2$O), 6.68 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar—H), 7.14 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar—H).

Synthesis of 2,6-Difluoro-*N*-(4-((1,1,1,3,3,3-hexafluoro-propan-2-yloxy)methyl)phenylcarbamoyl)benzamide (7). Target compound **7** was obtained as a white solid (yield, 27.6%, mp 174–175 °C) by following the same procedure as for compound **3**: ^{1}H NMR (400 M, CDCl$_3$) δ 4.07–4.16 (m, 1H, OC*H*(CF$_3$)$_2$), 4.84 (s, 2H, ArC*H*$_2$O), 7.06 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.4 Hz, 2H, Ar—H), 7.34 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar—H), 7.49–7.57 (m, 1H, Ar—H), 7.57 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar—H), 8.54 (br s, 1H, CON*H*Ar), 10.49 (br s, 1H, ArCON*H*CO). Anal. Calcd for C$_{18}$H$_{12}$F$_8$N$_2$O$_3$: C, 47.38; H, 2.65; N, 6.14. Found: C, 46.90; H, 3.09; N, 6.23.

Synthesis of 1-(3,3-Dichloroallyloxy)-4-nitrobenzene (8c). 4-Nitrophenol (0.28 g, 2.01 mmol) and NaOH (0.08 g, 2.00 mmol) were dissolved in ethanol (10 mL), and the ethanol was removed under reduced pressure. Then the solid was dissolved in DMF (10 mL), and 1,1,3-trichloroprop-1-ene (0.50 g, 3.45 mmol) was added to the solution. The mixture was heated to 70 °C and stirred for 2 h at this temperature. Then the solvent was evaporated off under reduced pressure, and saturated brine water (10 mL) was added. Afterward, the mixture was extracted by ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by flash column chromatography on silica gel using a mixture of petroleum ether (60–90 °C) and ethyl acetate (v/v = 8:1) as the eluent to give compound **6c** as a pale yellow solid (0.29 g, 58.5%): mp 55–56 °C; ^{1}H NMR (400 M, CDCl$_3$) δ 4.74 (d, $^3J_{HH}$ = 6.3, 2H, OC*H*$_2$CHCCl$_2$), 6.15 (t, $^3J_{HH}$ = 6.3, 1H, OCH$_2$C*H*CCl$_2$), 6.93 (d, $^3J_{HH}$ = 9.2 Hz, 2H, Ar—H), 8.21 (d, $^3J_{HH}$ = 9.2 Hz, 2H, Ar—H).

**Scheme 4. Synthetic Route for Compound 7[a]**
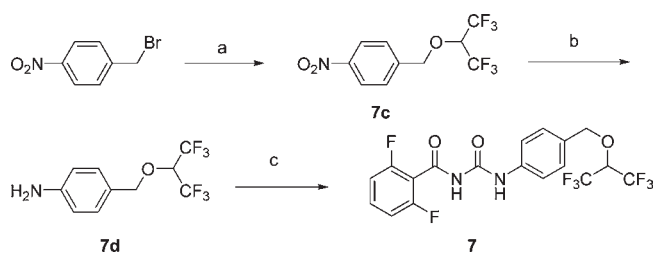
[a] Reagents and conditions: (a) 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), Na, DMF, 25 °C, 24 h; (b) Zn/Cu/NH$_4$Cl, Et$_2$O, 25 °C; (c) 2,6-difluorobenzoyl isocyanates, CH$_2$Cl$_2$, 25 °C.

Synthesis of 4-(3,3-Dichloroallyloxy)aniline (8d). Compound **8d** was obtained as a yellow viscous liquid (yield, 99.5%) by following the same procedure as for compound **3d**: ^{1}H NMR (400 M, CDCl$_3$) δ 4.35 (br s, 2H, Ar—N*H*$_2$), 4.57 (d, $^3J_{HH}$ = 6.1 Hz, 2H, OC*H*$_2$CHCCl$_2$), 6.14 (t, $^3J_{HH}$ = 6.1 Hz, 1H, OCH$_2$C*H*CCl$_2$), 6.64 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar—H), 6.73 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar—H).

Synthesis of *N*-(4-(3,3-Dichloroallyloxy)phenylcarbamo-yl)-2,6-difluorobenzamide (8). Target compound **8** was obtained as a white solid (yield, 80.2%, mp 187–188 °C) by following the same procedure as for compound **3**: ^{1}H NMR (400 M, CDCl$_3$) δ 4.66 (d, $^3J_{HH}$ = 6.2 Hz, 2H, OC*H*$_2$CHCCl$_2$), 6.16 (t, $^3J_{HH}$ = 6.2 Hz, 1H, OCH$_2$C*H*CCl$_2$), 6.85 (d, $^3J_{HH}$ = 9.0 Hz, 2H, Ar—H), 7.04 (t, $^3J_{HF}$ = 8.3 Hz, 2H, Ar—H), 7.41 (d, $^3J_{HH}$ = 9.0 Hz, 2H, Ar—H), 7.47–7.57 (m, 1H, Ar—H), 9.01 (br s, 1H, CON*H*Ar), 10.29 (br s, 1H, ArCON*H*CO). Anal. Calcd for C$_{17}$H$_{12}$Cl$_2$F$_2$N$_2$O$_3$: C, 50.89; H, 3.01; N, 6.98. Found: C, 51.03; H, 3.04; N, 7.03.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was carried out in standard conditions (temperature, 25 ± 1 °C; humidity, 60–80%; light cycle, L/D = 16:8). 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 relative standard deviations of the test biological values were ±5%.

Larvicidal Activity against Oriental armyworm. The larvicidal activities of the target compounds **3**–**8** against oriental armyworm were evaluated by foliar application using the reported procedure.[23] 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

Scheme 5. Synthetic Route for Compound 8[a]
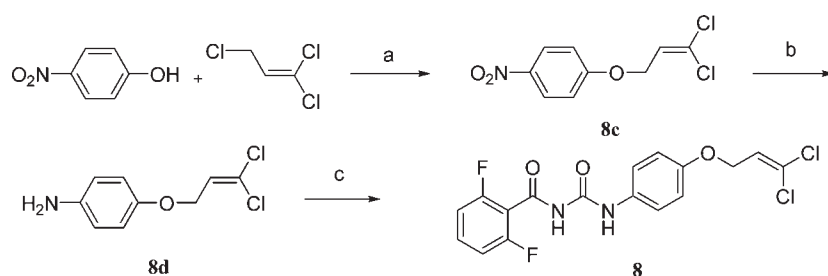
[a] Reagents and conditions: (a) NaOH, DMF, 70 °C, 2 h; (b) Zn/Cu/NH₄Cl, Et₂O, 25 °C; (c) 2,6-difluorobenzoyl isocyanates, CH₂Cl₂, 25 °C.

treatment was performed three times. For comparative purposes, compound **2** and Hexaflumuron were tested under the same conditions.

Larvicidal Activity against Mosquito. The larvicidal activities of the target compounds **3**−**8** against mosquito were evaluated by using the reported procedure.[24] The compounds **3**−**8** were prepared to different concentrations by dissolving **3**−**8** 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. For comparative purposes, compound **2** and Hexaflumuron were tested under the same conditions.

■ RESULTS AND DISCUSSION

Synthesis. Diazotization and hydrolysis of fluorine-containing intermediate **3a** gave 3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenol (**3b**) in 34% yield (Scheme 1). Then nucleophilic substitution of 1-chloro-4-nitrobenzene, 1,2-dichloro-4-nitrobenzene, or 1-(bromomethyl)-4-nitrobenzene with intermediate **3b** gave intermediates **3c**, **4c**, and **5c**, respectively (Schemes 1 and 2).[25] However, commonly used methods of reduction of aromatic nitro group to amino (Fe/HCl, Fe/AcOH, SnCl₂/AcOH, Na₂S, N₂H₄/Pd−C) were not suitable for the synthesis of intermediate **5d** from **5c**, which was decomposed in these conditions. After continuous attempts, intermediate **5d** was obtained in excellent yield using a Zn/Cu couple for the reduction of the nitro-aromatics **5c** in saturated aqueous NH₄Cl−Et₂O solution according to the literature.[26] Afterward, intermediate **5d** was combined with 2,6-difluorobenzoyl isocyanate to afford target compound **5** (see Scheme 2). Intermediates **3d** and **4d** were obtained according to the same method used to obtain intermediate **5d** and then were combined with 2,6-difluorobenzoyl isocyanate to afford target compounds **3** and **4** (see Scheme 1). Target compounds **6**−**8** were synthesized (see Schemes 3, 4, and 5, respectively) using methodologies similar to those employed for the preparation of compound **5**.

Biological Assay. *Larvicidal Activities against Oriental Armyworm and Mosquito.* The larvicidal activities of novel fluoro-substituted benzoylphenylureas **3**−**8**, Cao's compound **2**, and commercial Hexaflumuron against oriental armyworm and mosquito were evaluated. The results (seen in Table 1) indicate that most compounds have excellent larvicidal activities against oriental armyworm and mosquito, and it was found that phenoxyl or alkoxyl benzoylphenylureas exhibited better larvicidal activities than phenoxymethyl or alkoxymethyl benzoylphenylureas, respectively,. For example, compound **3** has 100% morality at a concentration of 2.5 mg L⁻¹, whereas compound **5** has only 10% morality at a concentration of 5 mg L⁻¹. Furthermore, compounds **3** and **6**,

Table 1. Larvicidal Activities against Oriental Armyworm and Mosquito of Compounds 2−8 and Hexaflumuron

compd	toxicity against oriental armyworm		toxicity against mosquito	
	concn (mg L⁻¹)	activity (%)	concn (mg L⁻¹)	activity (%)
3	2.5	100	0.005	100
	1.0	0	0.0025	50
4	50	100	0.025	100
	25	90	0.01	80
	10	60	0.005	30
5	25	100	2	0
	10	40		
	5	10		
6	5	90	0.1	100
	2.5	80	0.05	80
	1.0	0	0.025	70
7	200	40	0.25	100
	100	10	0.1	80
	50	0	0.05	30
8	200	90	0.1	100
	100	80	0.05	70
	50	60	0.025	60
Hexaflumuron	10	80	0.25	100
2	5	100	0.01	100
	2.5	90	0.005	90
	1.0	0	0.0025	80

which are different types of BPUs, exhibited higher activity than commercial Hexaflumuron. In particular, compound **3** displayed larvicidal activities against oriental armyworm and mosquito similar to thost of compound **2**, which was reported by Cao et al.[19] At the same time, compound **4** exhibited lower activity than compound **3** with a 3-chlorine substituent at the aniline ring of compound **3**.

In summary, a group of benzoylphenylureas with fluorinated substituents at the anilide moiety were designed and synthesized,

and their structures were characterized by ^{1}H NMR and elemental analysis. The larvicidal activities against oriental armyworm and mosquito of these novel fluoro-substituted benzoylphenylureas were evaluated. The result shows that most compounds exhibited excellent larvicidal activities against oriental armyworm and mosquito. Surprisingly, compounds **3** and **6** exhibited higher activities against oriental armyworm and mosquito than commercial Hexaflumuron. It can be further seen that the insecticidal activities would increase significantly by the introduction of fluorinated substituents into the structure of the designed benzoylphenylureas.

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