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Design, Synthesis, and Biological Evaluation of Various α-Substituted Benzylpyrroles Based on the Structures of Insecticidal Chlorfenapyr and Natural Pyrrolomycins

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ABSTRACT: On the basis of the structures of chlorfenapyr and dioxapyrrolomycin, a series of 2-benzylpyrroles with a hydroxyl, an alkyloxy, an acyloxy, an alkylsulfanyl, or an oxime moiety at the α-position of benzyl were designed and synthesized. Their insecticidal, acaricidal, and fungicidal activities were extensively investigated. The structure−activity relationship showed that benzylpyrroles bearing shorter α-alkyloxy groups gave better activities against most of the insect species; the alkylation of pyrrole usually gave increased activity. Among all compounds, (4-bromo-2-(α-(2,2,2-trifluoroethoxy)-4-chlorobenzyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1*H*-pyrrole-3-carbonitrile) (**5′j**) exhibited the most outstanding insecticidal activities against oriental armyworm (IC_{50} = 10 mg L^{-1}), diamondback moth (0.07 mg L^{-1}), corn borer (50 mg L^{-1}), and mosquito (0.04 mg L^{-1}), which are very close to those of chlorfenapyr (**5**, 0.08, <25, and <0.025 mg L^{-1}, respectively). In addition, some compounds also exhibited a broad or selective fungicidal spectrum.

KEYWORDS: *chlorfenapyr, dioxapyrrolomycin, 2-benzylpyrrole, insecticidal activity, acaricidal activity, fungicidal activity*

INTRODUCTION

Using natural products as lead compounds to develop new pesticides with a novel structure and mechanism is one of the most effective drug design methods.[1,2] Dioxapyrrolomycin (Figure 1), isolated from the metabolites of the microorganism *Streptomyces* by the American Cyanamid Co. in 1987, is the first chiral pyrrole toxin found to have insecticidal, acaricidal, and fungicidal activities.[3] Chlorfenapyr is such a commercial arylpyrrole insecticide/acaricide optimized from dioxapyrrolomycin.[4−7] In fact, after chemical structure modification, chlorfenapyr has obvious changes in the skeleton compared with dioxapyrrolomycin. First, there is a carbon atom between the benzene ring and pyrrole ring in dioxapyrrolomycin, whereas in chlorfenapyr the benzene ring and pyrrole ring are directly connected. Second, the substituents on both the benzene ring and pyrrole ring of the two compounds are significantly different. Third, chlorfenapyr has an ethoxymethyl group on the pyrrole N, which is a necessary structural modification to solve the tough problem that the chlorfenapyr parent compound (**1**) has an intolerable phytotoxicity to the plants applied.[7]

Though dioxapyrrolomycin and chlorfenapyr have some differences in their skeletons, their insecticidal mechanisms are the same. Both dioxapyrrolomycin and the chlorfenapyr parent compound (**1**), acting as uncouplers of oxidative phosphorylation,[8] can uncouple respiratory electron transport in mitochondria and hinder ADP conversion to ATP.[9] Chlorfenapyr, as a precursor pesticide, shows same effect because it could be converted to **1** inside the insect body.[8] Thus, we speculated that when we retain all the substituents on the benzene and pyrrole rings of **1** but insert a methylene group between the two rings (compound **2**, Figure 1), such an alteration in the structure would not change the insecticidal mechanism and insecticidal/acaricidal activity, and the mentioned compound may also likely keep the fungicidal activity. To our delight, compound **2** and its N-alkylation product **3** were synthesized and found to have considerable insecticidal and/or acaricidal activity.[10]

Dioxapyrrolomycin contains a dioxane moiety in the structure; from another point of view, there is an oxygen-containing substituent on the methylene between the benzene ring and pyrrole ring. The presence of oxygen is thought to provide the possibility for the molecule to form a hydrogen bond with the target in the respiratory electron transport chain and therefore to give improved biological activity. Thus, in this paper, choosing compound **2** as the skeleton structure, we designed and synthesized a series of compounds with a hydroxyl group (**4**) and various alkyloxy groups (**5**) on the methylene and investigated the influence of different substituents on the insecticidal, acaricidal, and fungicidal activities; we also synthesized (α-(acyloxy)benzyl)pyrroles **6**, α-sulfanyl compounds **7**, and α-oxime ether compounds **8** to test their bioactivity. For (α-(alkyloxy)benzyl)pyrroles **5** with higher insecticidal activity, we further introduced an ethoxymethyl group onto the nitrogen atom of the pyrrole ring to get **5′** to compare the resulting changes in biological activity (Scheme 1). Herein, we present the synthesis and variety of bioactivities of the compounds mentioned above in detail. The structure−activity relationships are also discussed.

MATERIALS AND METHODS

Instruments. ^{1}H NMR and ^{13}C NMR spectra were obtained at 400 MHz using a Bruker AV400 spectrometer in $CDCl_3$ or DMSO-d_6

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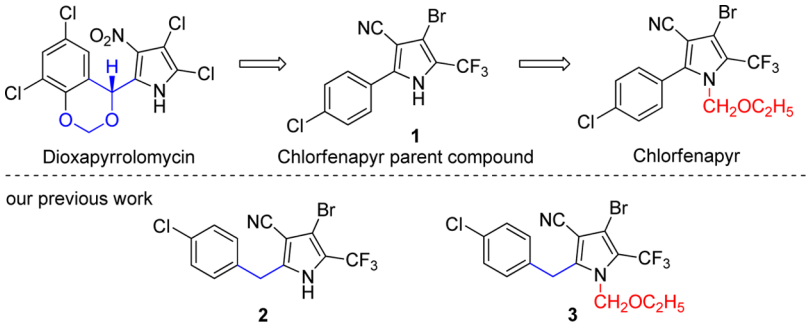
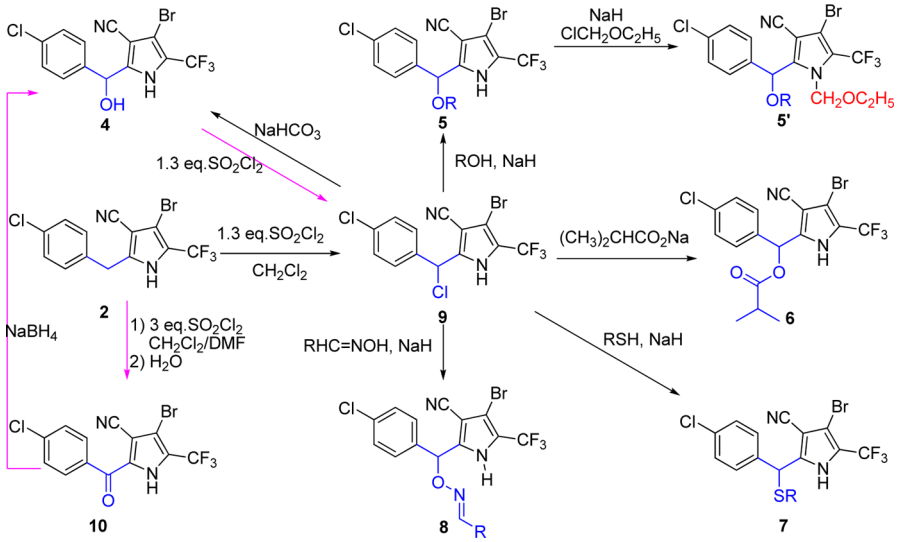


Figure 1. Structures of dioxapyrrolomycin, chlorfenapyr, and designed benzylpyrroles.

Scheme 1. Preparation of Target Compounds



solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. In the ^{13}C NMR data, four peaks in one set of parentheses means that they are assigned to one carbon which is split by three adjacent F atoms. HRMS data were obtained on an FTICR-MS instrument (Ionspec 7.0 T). The melting points were determined on an X-4 binocular microscope melting point apparatus and are uncorrected. The yields were not optimized.

4-Bromo-2-(α-hydroxyl-4-chlorobenzyl)-5-(trifluoromethyl)-1*H*-pyrrole-3-carbonitrile (4). Method 1: A solution of **2** (0.50 g, 1.38 mmol) in dichloromethane (180 mL) was heated to reflux until all solid was dissolved. After this solution was cooled to room temperature, a solution of freshly distilled sulfonyl chloride (0.23 g, 1.70 mmol) in dichloromethane (10 mL) was added, and the reaction mixture was stirred at room temperature for 12 h. Saturated sodium bicarbonate aqueous solution (100 mL) was added, and the mixture was stirred for another 0.5 h. The organic layer was separated and washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to give **4** as a white solid (0.49 g, 90%): mp 158–159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 137.6, 135.6, 129.6, 128.0, (123.6, 120.9, 118.2, 115.6), (119.2, 118.8, 118.4, 118.0), 112.5, 101.7, 95.9, 69.0; HRMS (ESI) m/z calcd for $C_{13}H_6BrClF_3N_2O$ $(M - H)^-$ 376.9315, found 376.9310.

Method 2: To a solution of **2** (0.50 g, 1.38 mmol) in a mixed solvent of dichloromethane (50 mL) and DMF (5 mL) was added freshly distilled sulfonyl chloride (0.46 g, 3.40 mmol) in dichloromethane (10 mL), and the reaction mixture was stirred at room temperature for 12 h. Then water (100 mL) was added to the mixture, and the resulting mixture was stirred for another 0.5 h. The organic layer was separated and washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to give 4-bromo-2-(4-chlorobenzoyl)-5-(trifluoromethyl)-1*H*-pyrrole-3-carbonitrile (**10**) as a white solid (0.49 g, 94%): ^1H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H); HRMS (ESI) m/z calcd for $C_{13}H_3BrClF_3N_2O$ $(M - H)^-$ 374.9153, found 374.9153.

To a solution of **10** (1.0 g, 2.65 mmol) in THF (30 mL) was added $NaBH_4$ (0.15 g, 3.95 mmol), and the reaction mixture was stirred at room temperature for 12 h. The mixture was quenched with water, the solvent evaporated, and then the mixture extracted with dichloromethane. The organic layer was separated, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and then concentrated. The residue was purified by silica gel using petroleum ether/ethyl acetate as the eluent to give **4** as a white solid (0.50 g, 50%).

4-Bromo-2-(α-chloro-4-chlorobenzyl)-5-(trifluoromethyl)-1*H*-pyrrole-3-carbonitrile (9). Method 1: A solution of **2** (0.50 g, 1.38 mmol) in dichloromethane (180 mL) was heated to reflux until all solid was dissolved. After this solution was cooled to room temperature, a solution of freshly distilled sulfonyl chloride (0.23 g, 1.70 mmol) in dichloromethane (10 mL) was added, and the reaction mixture was stirred at room temperature for 12 h. Then the mixture was successively washed with water (3 × 100 mL) and brine, dried over anhydrous magnesium sulfate, an dconcentrated to give **9** as a white solid (0.51 g, 92%): mp 120–122 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.20 (s, 1H).

Method 2: To a solution of **4** (0.50 g, 1.32 mmol) in dichloromethane (40 mL) was added freshly distilled sulfonyl chloride (0.46 g, 3.40 mmol) in dichloromethane (10 mL), and the reaction mixture was refluxed for 8 h. Then the mixture was successively

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washed with water (3 × 100 mL) and brine, dried over anhydrous magnesium sulfate, and concentrated to give **9** (0.47 g, 90%).

Synthesis of (α-Alkoxybenzyl)pyrrole (5). General Procedure. To a solution of the corresponding alcohol (4.5 mmol) in THF (40 mL) was added NaH (0.10 g, 4.1 mmol). After the mixture was refluxed for 1.5 h, crude **9** (0.60 g, 1.51 mmol) was added, and the mixture was refluxed for another 3 h. After the solvent was evaporated, the residue was dissolved in dichloromethane (50 mL), washed with water (3 × 25 mL) and brine, dried over anhydrous magnesium sulfate, and then concentrated. The crude was purified by silica gel using petroleum ether/ethyl acetate (10:1) as the eluent to give **5** as a white solid.

*Data for 4-bromo-2-(α-methoxy-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5a**):* yield 63%; white solid; mp 51−53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.40 (s, 1H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 134.4, 130.1, 128.4, 127.5, (122.6, 119.9, 117.2, 114.5), (118.5, 118.1, 117.7, 117.3), 111.4, 100.3, 95.2, 76.3, 56.2; HRMS (ESI) m/z calcd for $C_{14}H_{13}BrClF_3N_3O$ $(M + NH_4)^+$ 409.9877, found 409.9867.

*Data for 4-bromo-2-(α-ethoxy-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5b**):* yield 80%; white solid; mp 118−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.52 (s, 1H), 3.60−3.48 (m, 2H), 1.28 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 135.0, 134.1, 128.3, 127.4, 111.5, 100.3, 95.1, 74.4, 64.3, 14.0; HRMS (ESI) m/z calcd for $C_{15}H_{15}BrClF_3N_3O$ $(M + NH_4)^+$ 424.0034, found 424.0040.

*Data for 4-bromo-2-(α-propoxy-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5c**):* yield 65%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.50 (s, 1H), 3.45 (t, J = 6.4 Hz, 2H), 1.74−1.55 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{17}BrClF_3N_3O$ $(M + NH_4)^+$ 438.0190, found 438.0193.

*Data for 4-bromo-2-(α-isopropoxy-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5d**):* yield 86%; white solid; mp 62−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.63 (s, 1H), 3.73−3.67 (m, 1H), 1.22 (dd, J = 12.4, 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 136.5, 135.1, 129.4, 128.3, (120.9, 118.3), (119.0, 118.6, 118.2, 117.8), 112.5, 101.5, 96.2, 72.7, 70.9, 22.8, 21.4; HRMS (ESI) m/z calcd for $C_{16}H_{12}BrClF_3N_2O$ $(M - H)^-$ 418.9779, found 418.9786.

*Data for 4-bromo-2-(α-butoxy-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5e**):* yield 74%; white solid; mp 72−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 5.50 (s, 1H), 3.54−3.36 (m, 1H), 1.63 (dt, J = 13.6, 6.8 Hz, 1H), 1.49−1.27 (m, 1H), 0.91 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 135.0, 134.1, 128.3, 127.3, (122.6, 119.9, 117.2, 114.6), (117.9, 117.5, 117.1, 118.3), 100.3, 95.1, 74.6, 68.6, 30.5, 18.2, 12.8; HRMS (ESI) m/z calcd for $C_{17}H_{19}BrClF_3N_3O$ $(M + NH_4)^+$ 452.0347, found 452.0339.

*Data for 4-bromo-2-(α-(hexyloxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5f**):* yield 80%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.50 (s, 1H), 3.54−3.35 (m, 2H), 1.70−1.56 (m, 2H), 1.38−1.21 (m, 6H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 136.6, 136.0, 130.1, 129.1, (121.6, 118.9), (119.5, 119.1), 113.1, 102.1, 97.2, 76.2, 70.7, 32.2, 30.1, 26.4, 23.3, 14.7; HRMS (ESI) m/z calcd for $C_{19}H_{18}BrClF_3N_2O$ $(M - H)^-$ 461.0249, found 461.0245.

*Data for 4-bromo-2-(α-(2-methoxyethoxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5g**):* yield 72%; yellow solid; mp 65−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 5.61 (s, 1H), 4.01−3.89 (m, 1H), 3.80−3.71 (m, 1H), 3.70−3.62 (m, 1H), 3.60−3.54 (m, 1H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 135.0, 134.2, 128.2, 127.7, (122.8, 120.1, 117.4, 114.8), (118.2, 117.8, 117.4, 117.0), 111.6, (100.3, 100.2), 95.1, 75.6, 70.7, 68.3, 58.1; HRMS (ESI) m/z calcd for $C_{16}H_{17}BrClF_3N_3O_2$ $(M + NH_4)^+$ 454.0139, found 454.0131.

*Data for 4-bromo-2-(α-(cyclohexyloxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5h**):* yield 75%; white solid; mp 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 5.71 (s, 1H), 1.97−1.95 (m, 1H), 1.85−1.83 (m, 1H), 1.78−1.75 (m, 2H), 1.60−1.51 (m, 1H), 1.47−1.33 (m, 2H), 1.31−1.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 135.6, 134.0, 128.3, 127.2, (122.6, 119.9, 117.2, 114.5), (118.0, 117.6, 117.2, 116.8), 111.6, 100.4, 95.1, 75.7, 71.3, 31.7, 30.6, 24.4, 23.0, 22.8; HRMS (ESI) m/z calcd for $C_{19}H_{16}BrClF_3N_3O_2$ $(M - H)^-$ 459.0092, found 454.0084.

*Data for 4-bromo-2-(α-(prop-2-ynyloxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5i**):* yield 67%; white solid; mp 127−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.84 (s, 1H), 4.31 (d, J = 16.0 Hz, 1H), 4.06 (d, J = 16.0 Hz, 1H), 2.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 135.8, 134.3, 129.5, 129.0, (123.5, 120.9, 118.2, 115.5), (119.4, 119.0, 118.6, 112.2), (101.62, 101.59, 101.56, 101.54), 96.7, 77.6, 73.8, 56.1; HRMS (ESI) m/z calcd for $C_{16}H_7BrClF_3N_2O$ $(M - H)^-$ 414.9466, found 414.9462.

*Data for 4-bromo-2-(α-(2,2,2-trifluoroethoxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5j**):* yield 70%; yellow solid; mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 5.72 (s, 1H), 3.95−3.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 136.4, 133.6, 129.9, 128.7, (127.5, 124.7, 122.0, 119.2), (123.4, 120.7, 118.1, 115.4), (120.0, 119.6, 119.2, 118.8), 112.0, 101.7, 97.2, 76.7, 66.5, 66.2, 65.8, 65.5; HRMS (ESI) m/z calcd for $C_{15}H_6BrClF_6N_2O$ $(M - H)^-$ 458.9340, found 458.9335.

*Data for 4-bromo-2-(α-(2,2,2-trichloroethoxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5k**):* yield 70%; white solid; mp 112−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 5.90 (s, 1H), 4.15 (d, J = 11.2 Hz, 1H), 4.10 (d, J = 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 136.3, 134.0, 129.8, 128.7, (120.8, 118.1), (119.6, 119.2), 112.0, 101.8, 97.3, 95.8, 80.4, 77.0; HRMS (ESI) m/z calcd for $C_{15}H_7BrCl_4F_3N_2O$ $(M - H)^-$ 506.8453, found 506.8450.

*Data for 4-bromo-2-(α-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5l**):* yield 76%; white solid; mp 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 5.96 (s, 1H), 4.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.2, 130.8, 129.0, 128.3, (124.5, 121.7, 118.9, 116.1), (123.8, 121.0, 118.2, 115.4), (122.2, 119.6, 116.9, 114.2), (119.7, 119.3, 118.9, 118.5), 110.4, (100.91, 100.88, 100.85, 100.82), 97.4, 77.1, (72.8, 72.6, 72.2, 71.9, 71.6, 71.2, 70.9); HRMS (ESI) m/z calcd for $C_{16}H_6BrClF_9N_2O$ $(M - H)^-$ 526.9214, found 526.9215.

*Data for 4-bromo-2-(α-(3-chloropropoxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5m**):* yield 40%; white solid; mp 71−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.54 (s, 1H), 3.73−3.60 (m, 4H), 2.19−2.03 (m, 2H); HRMS (ESI) m/z calcd for $C_{16}H_{11}BrCl_2F_3N_2O$ $(M - H)^-$ 452.9389, found 452.9385.

*Data for 2-(α-(benzyloxy)-4-chlorobenzyl)-4-bromo-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5n**):* yield 71%; white solid; mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.43−7.37 (m, 5H), 7.34−7.28 (m, 4H), 5.58 (s, 1H), 4.62 (d, J = 11.2 Hz, 1H), 4.45 (d, J = 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 135.0, 134.5, 134.3, 128.4, 127.8, 127.62, 127.58, 127.3, (122.5, 119.8, 117.2, 114.5), (118.4, 118.0, 117.6, 117.2), 111.4, (100.43, 100.40, 100.38, 100.35), 95.4, 73.4, 70.2; HRMS (ESI) m/z calcd for $C_{20}H_{11}BrClF_3N_2O$ $(M - H)^-$ 466.9779, found 466.9778.

*Data for 4-bromo-2-(α-((diethylamino)oxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**5o**):* yield 60%; white solid; mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 5.85 (s, 1H), 2.88−2.76 (m, 4H), 1.00 (t, J = 7.2 Hz, 6H); HRMS (ESI) m/z calcd for $C_{17}H_{18}BrClF_3N_3O$ $(M + H)^+$ 450.0190, found 450.0198.

Alternative Method for 5b. To a solution of **9** (0.55 g, 1.38 mmol) in ethanol (40 mL) was added sodium bicarbonate (0.35 g, 4.15 mmol), and the mixture was refluxed for 1 h. After the solvent was evaporated, the residue was dissolved in ethyl acetate (50 mL),

washed with water (3 × 25 mL) and brine, dried over anhydrous magnesium sulfate, and concentrated to give **5b** as a white solid (0.52 g, 93%).

4-Bromo-2-(α-ethoxy-4-chlorobenzyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1*H*-pyrrole-3-carbonitrile (5′b). To a stirred solution of **5b** (0.40 g, 1.24 mmol) in THF (20 mL) under an ice−salt bath was added sodium hydride (0.12 g, 6.19 mmol) in batches. After the mixture was stirred at room temperature for 10 min, chloromethyl ethyl ether (0.35 g, 3.71 mmol) was added, and the mixture was refluxed for 2.5 h. Then the solvent was removed by evaporation, and the residue was redissolved in ethyl acetate, successively washed with water and brine, dried over sodium sulfate, and concentrated give **5′b** as a white solid (0.50 g, 85%): mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.77 (s, 1H), 5.27 (d, J = 10.4 Hz, 1H), 5.18 (d, J = 10.4 Hz, 1H), 3.63 (q, J = 6.8 Hz, 2H), 3.25 (hept, J = 6.8 Hz, 2H), 1.32 (t, J = 6.8 Hz, 3H), 1.06 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 135.3, 133.5, 128.0, 126.6, (122.8, 120.7, 117.4, 114.7), (120.7, 120.4, 120.0, 119.6), 111.9, 101.9, 101.9, 99.0, 74.8, 73.9, 65.0, 63.4, 13.9, 13.5; HRMS (ESI) m/z calcd for $C_{18}H_{21}BrClF_3N_3O_2$ $(M + NH_4)^+$ 482.0452, found 482.0448.

4-Bromo-1-(ethoxymethyl)-2-(α-(2,2,2-trifluoroethoxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1*H*-pyrrole-3-carbonitrile (5′j). The synthetic procedure was according to that of **5′b** using **5j** as the starting material: yield 90%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.89 (s, 1H), 5.21 (d, J = 10.4 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 3.87 (q, J = 8.4 Hz, 2H), 3.25 (q, J = 6.8 Hz, 2H), 1.00 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 134.5, 133.2, 128.4, 127.1, (126.7, 123.9, 121.1, 118.3), (122.7, 120.0, 117.4, 114.7), (121.2, 120.8, 120.5, 120.1), 111.4, 102.2, 99.4, 75.2, 74.9, (66.2, 65.9, 65.5, 65.2), 63.7, 13.4; HRMS (ESI) m/z calcd for $C_{18}H_{18}BrClF_6N_3O_2$ $(M + NH_4)^+$ 536.0170, found 536.0163.

(4-Bromo-3-cyano-5-(trifluoromethyl)-1*H*-pyrrol-2-yl)(4-chlorophenyl)methyl Isobutyrate (6). To a solution of sodium isobutyrate (0.28 g, 2.51 mmol) in dichloromethane (40 mL) was added the appropriate amount of molecular sieves, and the mixture was refluxed for 0.5 h. After compound **9** (0.50 g, 1.26 mmol) was added, the mixture was refluxed for another 1.5 h. Then the molecular sieves were filtrated, and the filtrate was washed with water (3 × 25 mL) and brine, dried over anhydrous magnesium sulfate, and then concentrated. The crude was purified by silica gel using petroleum ether/ethyl acetate (5:1) as the eluent to give **6** as a white solid: yield 71%; mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 6.89 (s, 1H), 2.76 (hept, J = 7.0 Hz, 1H), 1.25 (d, J = 4.0 Hz, 3H), 1.23 (d, J = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 139.3, 135.7, 133.9, 129.6, 128.1, (123.4, 120.7, 118.0, 115.4), (120.2, 119.8, 119.4, 119.0), 112.1, 102.1, 97.7, 69.1, 34.1, 18.9, 18.6; HRMS (ESI) m/z calcd for $C_{17}H_{17}BrClF_3N_3O_2$ $(M + NH_4)^+$ 466.0139, found 466.0147.

Synthesis of (α-(Alkylsulfanyl)benzyl)pyrroles 7 and Benzylpyrrole α-Oxime Ethers 8. The synthetic procedures were according to that of **5** using compound **9** and 1.5−2 equiv of the corresponding alkanethiol or oxime as the starting material.

*Data for 4-bromo-2-(α-(ethylthio)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**7a**):* yield 90%; pale yellow solid; mp 46−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 5.32 (s, 1H), 2.64−2.28 (m, 2H), 1.28 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 134.5, 133.6, 128.5, 127.9, (122.4, 119.8, 117.1, 114.4), (118.7, 118.3, 117.9, 117.5), 111.4, 100.3, 100.3, 97.1, 44.0, 25.9, 13.2; HRMS (ESI) m/z calcd for $C_{15}H_{10}BrClF_3N_2S$ $(M - H)^-$ 420.9394, found 420.9395.

*Data for 4-bromo-2-(α-(tert-butylthio)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**7b**):* yield 62%; pale yellow solid; mp 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 5.27 (s, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 135.9, 133.3, 128.5, 127.8, (122.5, 119.8, 117.2, 114.5), (118.1, 117.7, 117.3, 116.9), 111.4, 100.6, 96.2, 45.1, 41.8, 29.9; HRMS (ESI) m/z calcd for $C_{17}H_{19}BrClF_3N_3S$ $(M + NH_4)^+$ 468.0118, found 468.0127.

*Data for (E)-4-bromo-2-(α-(((4-nitrobenzylidene)amino)oxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**8a**):* yield 53%; yellow solid; mp 211−213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.94 (s, 1H), 8.67 (s, 1H), 8.28 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 6.54 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.1, 148.3, 142.2, 137.3, 135.9, 133.6, 129.0, 128.9, 128.3, 124.1, (124.0, 121.3, 118.6, 115.9), (118.8, 118.4), 113.3, 100.7, 95.3, 79.0; HRMS (ESI) m/z calcd for $C_{20}H_{15}BrClF_3N_5O_3$ $(M + NH_4)^+$ 543.9993, found 543.9972.

*Data for (E)-4-bromo-2-(α-((((4-(dimethylamino)benzylidene)-amino)oxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**8b**):* yield 50%; white solid; mp 86−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.15 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 6.34 (s, 1H), 3.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 141.4, 140.5, 135.3, 135.1, 129.3, 128.9, 128.8, (120.9, 118.2), (119.8, 119.4, 119.0, 118.6), 112.4, 112.1, 101.4, 97.9, 40.3; HRMS (ESI) m/z calcd for $C_{22}H_{18}BrClF_3N_4O$ $(M + H)^+$ 525.0299, found 525.0299.

*Data for (E)-4-bromo-2-(α-(((3,3-dimethylbutan-2-ylidene)-amino)oxy)-4-chlorobenzyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile (**8c**):* yield 68%; white solid; mp 97−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.22 (s, 1H), 1.91 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 140.6, 134.4, 134.0, 128.1, 127.7, (125.6, 119.9, 117.2, 114.5), (118.8, 118.4, 118.0, 117.6), 111.3, (100.03, 100.00), 97.0, 75.8, 36.6, 26.4, 10.2; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrClF_3N_3O$ $(M + H)^+$ 476.0347, found 476.0353.

4-Bromo-2-(α-(2,2,2-trifluoroethoxy)-4-chlorobenzyl))-5-(tris(2,2,2-trifluoroethoxy)methyl)-1*H*-pyrrole-3-carbonitrile (11). To a solution of **9** (0.05 g, 0.13 mmol) in trifluoroethanol (15 mL) was added sodium bicarbonate (0.10 g, 0.94 mmol), and the mixture was refluxed for 5 h. After the solvent was evaporated, the residue was dissolved in dichloromethane (25 mL), washed with water (3 × 25 mL) and brine, dried over anhydrous magnesium sulfate, and then concentrated to give **11** as a white solid (0.08 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.4 Hz,2H), 7.26 (d, J = 8.4 Hz, 2H), 5.60 (s, 1H), 3.93 (q, J = 8.0 Hz, 6H), 3.80 (q, J = 8.0 Hz, 2H).

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. Each bioassay was replicated three times at 25 ± 1 °C for the statistical requirements. Mortalities were evaluated according to a percentage scale of 0−100%, in which 0% indicates no activity and 100% indicates total kill. When the mortality of the blank control was less than 5%, the test result was directly used. However, if the mortality of the blank control was less than 20%, the test result was corrected by means of $V = ((X - Y)/X) \times 100$ (V = value of the corrected mortality, X = livability of the blank control, and Y = livability of the treated organisms). To calculate IC_{50}, at least two mortalities at different concentrations had to be lower than 50%. The IC_{50} was taken from a graph plotting mortality (y-axis) against compound concentration (x-axis); the IC_{50} value is the concentration where the mortality crosses 50%.

Stock solutions of each test compound were prepared in dimethylformamide at a concentration of 600 or 200 mg L^{-1} and then diluted to the required concentration (100, 50, 25, 10, 5, 2, 1, 0.5, 0.25, 0.1, 0.05, 0.025, and 0.01 mg L^{-1}) with water containing 0.1% TW-20 (a type of emulsifier).

Insecticidal Activity. *Insecticidal Activities against Oriental Armyworm (Mythimna separata), Diamondback Moth (Plutella xylostella), Cotton Bollworm (Helicoverpa armigera), Corn Borer (Ostrinia nubilalis), Beet Armyworm (Spodoptera exigua), and Bean Aphid (Aphis craccivora).* The leaf-dip method was used. Leaf disks (5 cm × 3 cm) were cut from fresh cabbage leaves (or other leaves) and then dipped into the test solution for 3 s. After air-drying, the treated leaf disks were placed individually into vertical tubes (or Petri dishes), and the disks were infested with 10 larvae (for example, 2nd-instar diamondback moth larvae). The mortalities were evaluated 3 days after treatment.

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Scheme 2. Unexpected Reactions of 9 in Ethanol and Trifluoroethanol

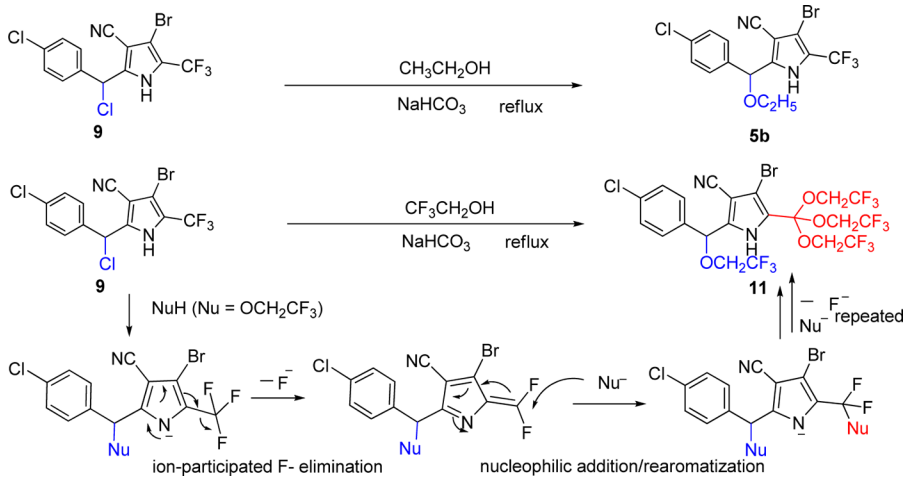

Table 1. Insecticidal Activity (Mortality Rates, %) against Different Insects' Larvae

Compd.	oriental armyworm	diamondback moth	cotton bollworm	corn borer	beet armyworm	bean aphid	mosquito larvae
	600[a]	600[a]	600[a]	600[a]	200[a]	200[a]	5[a]
2	100	100	45	45	-[b]	0	-
3	100	100	55	55	0	0	100
4	100	100	100	60	0	0	20
9	100	-	35	50	-	-	10
5a	100	100	100	100	40	0	100
5b	100	100	35	90	40	30	60
5'b	100	100	100	100	-	0	100
5c	100	100	100	100	0	0	100
5d	100	-	100	100	0	0	100
5e	50	100	65	85	0	0	100
5f	10	100	70	80	0	0	100
5g	100	100	-	-	0	0	100
5h	100	100	35	35	0	0	60
5i	100	100	45	85	60	-	40
5j	100	100	55	85	40	-	100
5'j	100	100	100	100	-	-	100
5k	100	100	80	70	-	0	100
5l	40	50	15	10	-	0	20
5m	100	100	100	100	-	-	100
5n	100	100	15	55	0	0	60
5o	100	100	100	40	0	0	35
6	40	100	30	25	0	0	30
7a	20	100	5	15	-	-	15
7b	100	100	70	60	0[c]	70[c]	100
8a	100	100	100	50	40[c]	30[c]	100
8b	100	100	100	50	0[c]	0[c]	100
8c	100	100	100	60	0[c]	0[c]	100
chlorfenapyr	100	100	100	100	100	0	100

[a]Concentration of the tested compounds. The units are milligrams per liter. [b]A dash means not tested. [c]The assay was conducted at a concentration of 600 mg L^{-1}.

Insecticidal Activities against Mosquito (Culex pipiens pallens). Twenty 4th-instar mosquito larvae were put into 10 mL of the test solution. The mortalities were evaluated 8 days after treatment.

Acaricidal Activity Assay. The detailed assay method against the eggs, larvae, and adults of the spider mite (*Tetranychus cinnabarinus*) was described in the literature.[10]

Fungicidal Activity Assay. In vitro assay: The compounds were evaluated in mycelial growth tests in artificial media against 10 phytopathogens, *Fusarium oxysporium*, *Cercospora arachidicola* Hori, *Physalospora piricola*, *Alternaria solani*, *Fusarium graminearum*, *Phytophthora infestans*, *Sclerotinia sclerotiorum*, *Botrytis cinerea*, *Rhizoctonia solani*, and *Phytophthora capsici*, at rate of 50 mg L^{-1}.

In vivo assay: The compounds were evaluated in leaf-piece assays at a rate of 200 mg L^{-1} for *Corynespora cassiicola* and *B. cinerea* on cucumber, *Blumeria graminis* f. sp. *tritici* on wheat, *S. sclerotiorum* on oilseed rape, *R. solani* on rice, and *Phytophthora* on pepper.

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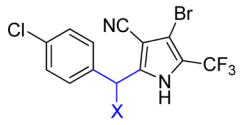
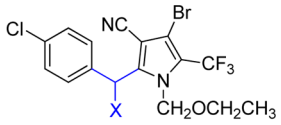
Table 2. IC_{50} (mg L^{-1}) of Compounds against Insects' Larvae[a]



2, 4, 5, 6, 7, 8, 9



3, 5'

Compd.	X	oriental armyworm[b]	diamondback moth[c]	Cotton Bollworm[b]	Corn Borer[b]	Mosquito[d]
2	H	30	0.9	>600	>600	-
3	H	25	0.3	<600	<600	0.17
4	OH	75	2	180	60	>5.0
9	Cl	80	-	>600	600	>5.0
5a	OMe	13	<1	50	140	1.2
5b	OEt	10	<0.01	>600	<600	4.0
5'b	OEt	20	<10	130	<100	0.07
5c	OPr-*n*	8	<1	<100	<100	0.8
5d	OPr-*i*	13	-	140	120	1.6
5e	OBu-*n*	>600	90	<600	<600	2.5
5f	OHex-*n*	>600	110	<600	<600	1.6
5g	$OCH_2CH_2OCH_3$	10	4	-	-	1.6
5h	OHex-c	>200	125	>600	>600	4.0
5i	$OCH_2C{\equiv}CH$	13	0.05	>600	<600	>5.0
5j	OCH_2CF_3	6	0.04	<600	<600	0.15
5'j	OCH_2CF_3	10	0.07	60	50	0.04
5k	OCH_2CCl_3	8	0.07	<600	<600	0.15
5l	$OCH(CF_3)_2$	>600	600	>600	>600	>5.0
5m	$O(CH_2)_3Cl$	30	<10	200	<200	3.0
5n	OBn	80	0.2	>600	<600	4.0
5o	$ONEt_2$	115	2	350	>600	>5.0
6	OC(=O)Pr-*i*	>600	40	>600	>600	>5.0
7a	SEt	>600	35	>600	>600	>5.0
7b	SBu-*t*	13	4	<600	<600	1.2
8a	$4\text{-}NO_2C_6H_4CH{=}NO$	60	20	270	600	0.3
8b	$4\text{-}Me_2NC_6H_4CH{=}NO$	>200	180	180	600	1.2
8c	Me(t-Bu)C=NO	>200	180	200	<600	1.4
chlorfenapyr		5	0.08	<0.1	<25	0.025

[a]The data in blue mean good to excellent activity, and the data in pink mean moderate activity. [b]The concentrations were set as 600, 200, 100, 50, 25, 10, and 5 mg L^{-1} for calculation of IC_{50}. In the rectangular coordinate system, a line was drawn with concentration as the abscissa and mortality rate as the ordinate. The IC_{50} value was roughly read from the straight line that connected the two concentrations that gave mortality rates of just more and just less than 50%. Other IC_{50} values were calculated in the same way. [c]The concentrations were set as 600, 200, 100, 10, 1, 0.1, and 0.01 mg L^{-1} for calculation of IC_{50}. [d]The concentrations were set as 5, 2, 1, 0.5, 0.25, 0.1, 0.05, 0.025, and 0.01 mg L^{-1} for calculation of IC_{50}.

The detailed assay method was described in the literature.[10]

RESULTS AND DISCUSSION

Synthesis. Benzylpyrrole **2**, prepared according to our previous method,[10] was reacted with 1.3 equiv of sulfonyl dichloride to obtain *α*-monochlorinated benzylpyrrole **9**. As a key intermediate, **9** was treated with different nucleophiles such as sodium bicarbonate aqueous solution, sodium alkoxide, sodium carboxylate, thiol sodium salt, or oxime sodium salt to afford **4**, **5**, **6**, 7, or **8**, respectively (Scheme 1). **5** was further allowed to react with chloromethyl ethyl ether to obtain N-substituted compound **5'**. (*α*-(Aryloxy)benzyl)pyrroles or more (*α*-(acyloxy)benzyl)pyrroles were to be synthesized, but they were too unstable during the workup.

Note that, due to the poor solubility of **2** in dichloromethane, the preparation of intermediate **9** required a lot of solvent (0.50 g of **2** requires about 180 mL of warm dichloromethane), and adding dimethylformamide to increase the solubility was only to find an increased amount of *α*,*α*-dichlorinated benzylpyrrole. During the multiple repeated tests, it was also found that the amount of sulfonyl dichloride had to be changed depending on the degree of solvent dryness and even the humidity of the air because insufficient sulfonyl dichloride resulted in incomplete reaction, while excess sulfonyl dichloride produced more *α*,*α*-dichlorinated benzylpyrrole, and both circumstances made the reaction systems complicated. Therefore, preparing **9** directly from **2** was not always the quickest and the most convenient method. The preparation of **9** was then adopted as an alternative route (Scheme 1, route with purple arrows). **2** was first transformed to dichlorinated benzylpyrrole by using excess sulfonyl dichloride (3 equiv) in a mixed solvent of dichloromethane and dimethylformamide (0.5 g of **2** in 50 mL of dichloromethane and 5 mL of DMF) and after hydrolysis gave benzoylpyrrole **10**. Then **10** was reduced by $NaBH_4$ to (*α*-hydroxybenzyl)pyrrole **4**. Finally, **4** was treated with 1.3 equiv of sulfonyl dichloride to obtain *α*-monochlorinated benzylpyrrole **9**. This route needs three steps from compound **2**, **4** had much better solubility than **2**, and the chlorination step was not

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Table 3. Acarcidal Activity (Mortality Rates, %) against Spider Mite (*T. cinnabarinus* Boisduval)

Compd.	adults			larvae			eggs		
	600[a]	200[a]	100[a]	600[a]	200[a]	100[a]	600[a]	200[a]	100[a]
2	0	-[b]	-	0	-	-	0	-	-
3	100	90	70	97	85	70	100	100	70
4	0	-	-	85	-	-	90	-	-
9	85	0	0	95	90	60	95	70	0
5a	80	-	-	70	-	-	80	-	-
5b	100	90	60	90	80	0	100	95	70
5'b	70	0	-	0	-	-	0	-	-
5c	70	-	-	80	-	-	95	-	-
5e	0	-	-	0	-	-	30	-	-
5f	0	-	-	50	-	-	90	-	-
5g	0	-	-	0	-	-	0	-	-
5h	70	0	0	85	75	0	90	85	0
5i	95	50	0	90	90	50	90	80	50
5j	100	100	90	95	78	0	95	90	65
5'j	0	-	-	0	-	-	70	-	-
5k	0	-	-	0	-	-	50	-	-
5l	0	-	-	0	-	-	0	-	-
5m	85	0	-	65	-	-	70	-	-
5n	90	0	0	70	60	0	85	70	40
5o	0	-	-	75	-	-	70	-	-
6	40	-	-	0	-	-	0	-	-
7a	80	-	-	40	-	-	50	-	-
7b	40	-	-	70	-	-	70	-	-
8a	60	-	-	50	-	-	0	-	-
8b	60	-	-	88	-	-	85	-	-
8c	50	-	-	60	-	-	70	-	-
chlorfenapyr	100	100	100	100	100	100	100	100	100

[a]The data in blue mean good to excellent activity. Concentration of tested compounds. The units are milligrams per liter. [b]A dash means not tested.

so uncontrollable; thus, the purity of crude **9** prepared from **4** was better than that from **2**, which made the following nucleophilic substitution step clearer and the product easier to purify. Another thing to remember is that compound **9** is sensitive to alkaline aqueous solution, so whether it was prepared from **2** or **4**, during the workup the reaction mixture should be washed with sufficient water to remove excess sulfonyl dichloride but not with sodium bicarbonate aqueous solution.

Here we also mention some other experimental phenomena we encountered. (α-Alkoxybenzyl)pyrroles **5** were generally prepared from **9** and the corresponding sodium alkoxide, which were prepared in advance. Accidentally, we found (α-ethoxybenzyl)pyrrole **5b** also formed when **9** was refluxed in ethanol in the presence of sodium bicarbonate. The simpler procedure was then expected to be applied to other alcohols. However, when **9** was refluxed in trifluoroethanol, orthoester **11** was unexpectedly separated in high yield. In the structure of **11** not only the α-chloro atom but also the three fluorine atoms in the trifluoromethyl group on the pyrrole ring were replaced by trifluoroethoxyl (Scheme 2). The formation of the orthoester was thought to be via the repeated ion-participating F^- elimination and nucleophilic addition/rearomatization courses, which had been elucidated in detail in our previously published paper.[11] It seemed that an alcoholic solvent, a high reaction temperature (at least higher than the boiling point of dichloromethane), and a large excess amount of sodium bicarbonate jointly promoted the formation of the orthoester.

Bioactivity. The α-substituted benzylpyrroles were designed from insecticidal/acaricidal chlorfenapyr and dioxapyrrolomycin, so their insecticidal, acaricidal, and fungicidal activities were all assayed.

Insecticidal Activity. Table 1 shows the data of insecticidal activity against the larvae of oriental armyworm (*M. separata*), diamondback moth (*P. xylostella*), cotton bollworm (*H. armigera*), corn borer (*O. nubilalis*), beet armyworm (*Sp. exigua*), bean aphid (*A. craccivora*), and mosquito. Chlorfenapyr is included as a control.

As shown in Table 1, at 600 mg L^{-1}, most of the compounds exhibited 100% mortality against oriental armyworm, diamondback moth, and mosquito, and half of them gave 100% mortality against cotton bollworm and corn borer. However, for beet armyworm and bean aphid, no compounds gave the desired activity. Therefore, against those five species, the insecticidal activities at lower concentrations were determined, and the IC_{50} (the concentration of compounds resulting in 50% mortality) values of each species were roughly calculated (Table 2).

Table 2 shows clear structure−activity relationships for each insect species. For oriental armyworm, α-H-substituted (**2**), α-hydroxy-substituted (**4**), α-chloro-substituted (**9**), and most α-alkyloxy-substituted (**5a−n**) benzyl pyrroles gave moderate to

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Table 4. In Vitro Fungicidal Activity against Phytopathogens[a]

Compd.	inhibitory rate (%) at 50 mg L^{-1} in vitro									
	FO	CH	PP	AS	FG	PI	SS	BC	RS	PC
2	-[b]	-	-	50	35	15	55	60	35	30
3	20	15	30	25	25	10	40	35	35	40
4	-	-	-	81	65	65	87	87	50	92
9	45	65	75	60	55	45	81	70	80	85
5a	55	85	96	89	70	83	97	96	90	89
5b	70	88	97	88	50	75	85	83	88	75
5'b	25	60	65	40	20	20	80	80	40	60
5d	45	70	98	83	60	75	97	86	90	86
5e	45	0	95	80	65	75	87	75	80	70
5f	40	75	97	50	75	50	87	91	65	89
5g	45	75	97	70	55	70	94	70	60	83
5h	40	65	95	65	55	65	75	50	65	45
5i	65	70	98	70	55	60	85	65	85	75
5j	65	83	98	94	50	65	96	70	98	75
5'j	20	0	70	55	25	15	35	0	30	15
5k	65	92	96	89	55	83	92	65	84	75
5l	40	85	92	55	40	45	89	70	55	86
5m	55	75	96	83	40	83	94	65	80	83
5n	60	70	95	65	50	65	70	45	70	45
5o	25	85	96	60	45	65	83	70	55	70
6	45	70	65	55	25	35	83	65	60	89
7a	45	75	96	65	65	83	97	86	80	75
7b	40	75	92	65	55	70	83	65	70	80
8a	20	40	65	30	25	40	55	55	55	30
8b	30	60	50	30	35	20	70	65	50	65
8c	40	75	92	45	35	60	70	55	55	40

[a]The data in blue mean good to excellent activity. FO = *F. oxysporium*, CH = *C. arachidicola* Hori, PP = *Phys. piricola*, AS = *Al. solani*, FG = *F. graminearum*, PI = *Phyt. infestans*, SS = *S. sclerotiorum*, BC = *B. cinerea*, RS = *R. solani*, and PC = *Phyt. capsici*. [b]A dash means not tested.

excellent activity, except those bearing long or hindered alkyl groups such as **5e** (X = OBu-*n*), **5f** (X = OHex-*n*), **5h** (X = OHex-*c*), and **5l** (X = $OCH(CF_3)_2$). Compound **6** bearing an isobutyryloxy group at the α-position of benzylpyrrole also gave poor activity due to both steric and stereoelectronic effects. The α-alkylsulfanyl compounds **7a** and **7b** had structure−activity relationships different from those of α-alkyloxy compounds, as **7b** (X = SBu-*t*) had a more hindered substituent than **7a** (X = SEt) but exhibited much higher activity. Data for oxime ethers **8a−c** showed that an electron-withdrawing group played a significant role in the activity, as **8a** (4-$NO_2C_6H_4CH{=}NO$) gave much better activity than **8b** (X = 4-$Me_2NC_6H_4CH{=}$NO). In comparing *N*-ethoxymethyl compounds **3**, **5′b**, and **5′j** with corresponding NH compounds **2**, **5b**, and **5j**, the two types of structures did not show significant differences in the activity against oriental armyworm.

For diamondback moth, the compounds showed structure−activity relationships very similar to those for oriental armyworm. Benzylpyrroles with a shorter alkyloxy group at the α-position also gave better activity, with **5b** (X = OEt), **5i** (X = $OCH_2C{\equiv}CH$), **5j** (X = OCH_2CF_3), **5′j** (X = OCH_2CF_3), and **5k** (X = OCH_2CCl_3) having the lowest IC_{50} values (<0.1 mg L^{-1}), close to that of chlorfenapyr (0.08 mg L^{-1}).

The structure−activity relationships for cotton bollworm and corn borer were very similar to each other. However, neither of them had insecticidal ability comparable to that of chlorfenapyr.

For mosquito, most of the benzylpyrroles bearing shorter or longer α-alkyloxy groups (**5**) gave moderate to excellent activity, but the activity rule was not so distinct. The compounds with an oxime ether moiety (**8a−c**) also showed good activity. Notably, compounds **3**, **5′b**, and **5′j** with an ethoxymethyl group at the nitrogen of pyrrole all exhibited higher activity than their corresponding parent compounds **2**, **5b**, and **5j**, and the IC_{50} values for **5′b** and **5′j** (0.07 and 0.04 mg L^{-1}, respectively) were close to that of chlorfenapyr (0.025 mg L^{-1}).

Overall, benzylpyrroles bearing shorter α-alkyloxy groups gave better activities against most of the insect species. The alkylation of pyrrole usually gave increased activity. Among all the compounds, **5b** (X = OEt), **5i** (X = $OCH_2C{\equiv}CH$), **5j** (X = OCH_2CF_3), **5′j** (X = OCH_2CF_3), and **5k** (X = OCH_2CCl_3)

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Table 5. In Vivo Fungicidal Activity against Phytopathogens[a]

Compd.	inhibitory rate (%) at 200 mg L^{-1} in vivo					
	SS	RS	BG	CC	PH	BC
3	-[b]	-	85	-	-	-
4	-	-	60	50	83	30
5a	50	50	20	15	80	60
5b	-	-	50	-	-	-
5b'	40	25	-	40	25	45
5d	50	50	60	15	80	40
5e	40	50	0	55	25	35
5f	-	-	-	50	40	55
5g	65	40	80	40	80	40
5h	-	-	30	-	-	-
5i	-	-	30	-	-	-
5j	-	-	60	-	-	-
5j'	-	-	70	15	65	0
5k	45	45	70	15	80	15
5l	40	40	0	15	40	25
5m	35	40	40	15	87	20
5n	-	-	40	-	-	-
5o	30	30	75	50	60	30
6	45	65	70	40	55	40
7a	50	60	20	20	83	45
7b	30	45	60	20	80	40
8a	-	-	0	20	50	20
8b	30	45	0	55	55	35
8c	20	40	0	15	40	35
azoxystrobin	90	92	-	-	-	92
carbendazim	-	-	100	-	-	-
thiram	-	-	-	87	-	-
dimethomorph	-	-	-	-	92	-

[a]The data in blue mean good to excellent activity. SS = *S. sclerotiorum*, RS = *R. solani*, BG = *Bl. graminis*; CC: *Co. cassiicola*; PH: *Phytophthora*; BC = *B. cinerea*. [b]A dash means not tested.

exhibited excellent insecticidal activity against both oriental armyworm and diamondback moth; **5′j** also showed an eminent insecticidal effect against corn borer and mosquito.

Acaricidal Activity. Table 3 shows that few compounds exhibited satisfactory acarcidal activity; only compounds **3**, **9**, **5b**, **5i**, **5j**, and **5n** maintained certain mortality at a concentration of 100 mg L^{-1} against spider mite adults, larvae, and/or eggs, and none of them were comparable to chlorfenapyr. An interesting discovery is that though **5′b** and **5′j** had much lower activity than their parent products **5b** and **5j**, compound **3** gave much higher acarcidal activity than its parent product **2**.

Another thing to note is that no serious phytotoxicity was observed during the insecticidal and acaricidal assays; even those compounds without an ethoxymethyl group on the pyrrole N, such as compounds **2** and **5**, did not cause distinct harm to the leaves of the test plants at different concentrations.

Fungicidal Activity. The compounds were designed according to the structure of fungicidal dioxapyrrolomycin, so their fungicidal activities were also assayed to see if they could maintain fungicidal activity. The compounds were first evaluated in mycelial growth tests in artificial media against 10 species of phytopathogens at a rate of 50 mg L^{-1}. As shown in Table 4, most of the designed (α-(alkyloxy)benzyl)pyrroles **5** and α-alkylsulfanyl compounds **7** gave more than 80% inhibition against *Phys. piricola* (PP) and *S. sclerotiorum* (SS). **5a** (X = OMe) had the broadest fungicidal spectrum, with more than 80% inhibition against eight kinds of fungi. **5b** (X = OEt), **5d** (X = OPr-*i*), **5j** (X = OCH_2CF_3), **5k** (X = OCH_2CCl_3), and **5m** (X = $O(CH_2)_3Cl$) also gave broad fungicidal activity against at least five kinds of fungi.

Selected compounds were also tested for their fungicidal activity in vivo at 200 mg L^{-1}. Azoxystrobin, carbendazim, thiram, and dimethomorph were respectively used as contrast compounds for different fungi (Table 5). At the test concentration, most compounds exhibit certain fungicidal activity; especially **5a**, **5d**, **5g**, **6**, and **7a** gave better and broader fungicidal activity against at least three kinds of fungi. In contrast, **5m** showed some selectivity; it inhibited 87% of *Phytophthora*, which was very close to the value for dimethomorph. Thus, this kind of compound can be used as a lead compound for further fungicide research and development.

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In summary, on the basis of the structures of chlorfenapyr and dioxapyrrolomycin, a series of 2-benzylpyrroles with a hydroxyl, an alkyloxy, an acyloxy, an alkylsulfanyl, or an oxime moiety at the α-position of benzyl were designed and synthesized. The structure−activity relationships showed that benzylpyrroles bearing shorter α-alkyloxy groups gave better activities against most of the insect species; the alkylation of pyrrole usually gave increased activity. Several compounds were identified with excellent insecticidal and/or fungicidal activities, and the structure−activity relationship should be useful for future new active compound design and development.

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Notes

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