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Synthesis, insecticidal and acaricidal activities of novel 2-arylpyrroles

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To search for novel 2-arylpyrroles with unique biological activities, a series of novel 2-arylpyrrole derivatives were designed and synthesized, and their structures were characterized by ^{1}H and ^{13}C NMR spectroscopy, MS spectrometry, and elemental analysis. Their insecticidal activities against Lepidopteran pests (e.g. *Mythimna separata*) and acaricidal activities against mites (e.g. *Tetranychus urticae*) were evaluated. The results of bioassays indicate that some of these title compounds exhibited excellent insecticidal and acaricidal activities. For example, 4-bromo-1-((chloromethoxy)methyl)-2-(4-chloro phenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile **(6a)**, 4-bromo-2-(4-chlorophenyl)-1-((2-fluoroethoxy)-methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile **(6d)** showed insecticidal activity against *Mythimna separata* and 4-bromo-2-(4-chlorophenyl)-1-((isopropoxymethoxy)methyl)-5-(trifluoro methyl)pyrrole-3-carbonitrile **(7d)** showed acaricidal activity against *Tetranychus urticae*. They were more effective than Chlorfenapyr, which has been the only commercialized member of a new class of chemicals of 2-arylpyrroles.

2-arylpyrroles, Chlorfenapyr, synthesis, insecticidal activity, acaricidal activity

1 Introduction

Dioxapyrrolomycin (**A**, Figure 1), isolated from a Streptomyces strain by American Cyanamid Company in 1987, was found to have moderate activity against a number of insects and mites [1]. Although its acute oral LD_{50} to mice was 14 mg/kg which was too high to become a candidate for further development, its novel structure was simple enough to warrant consideration as a take-off for synthetic modifications. To solve the problem of high toxicity, most of the modifications and optimizations have been focused on the novel 2-arylpyrroles. American Cyanamid Company also found that the compound **B** (Figure 1) exhibited excellent activity against tobacco budworm, two-spotted spider mite, and potato leafhopper. However, 2-arylpyrrole (**B**) was found to have high levels of phytotoxicity [2]. Further optimization on the *N*-hydrogen of compound **B** has been done. In 1988, by substituting the hydrogen on the nitrogen atom with an ethoxymethyl group in compound **B**, American Cyanamid Company found compound **C** which was developed and commercialized as an agricultural insecticide in 2001 under the common name Chlorfenapyr [4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-(trifluoromethyl)-1*H*-pyrrole-3-carbonitrile] [3, 4]. As the only commercialized member of a new class of chemicals, 2-arylpyrroles, Chlorfenapyr is a pro-insecticide activated through oxidative removal of the N-ethoxymethyl group by mixed function oxidases to form the compound **B**, which uncouples oxidative phosphorylation at the mitochondria and results in disruption of ATP production, cellular death, ultimately organism mortality [5]. The acute oral LD_{50} of Chlorfenapyr

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is 55 mg/kg to mice and 626 mg/kg to rats. It has been reported that Chlorfenapyr can induce DNA damage in spleen, liver, renal cells and peripheral blood lymphocytes in mice [6, 7].

To search for novel 2-arylpyrroles with unique biological activities and lower toxicity towards mammalian cells, a series of optimization programs were carried out by replacing the *N*-ethoxymethyl group of Chlorfenapyr with an *N*-alkyloxyoxalyl, an *N*-ester or a *N*-bridged derivative [8–10] based on the principle of prodrug [11]. In our previous work a series of novel sulfur-containing oxime-ethers had shown remarkable insecticidal activity. The compound **D** (Figure 1) showed better insecticidal activity than either of the commercial insecticides Chlorfenapyr and Fenvalerate. We also found another oxime-ethers compound **E** (Figure 1), with acaricidal potency comparable to that of commercial acaricides such as fluacrypyrim, tebufenpyrad and chlorfenapyr [12–15].

Encouraged by these reports, we developed an idea of introducing a sulfur, oxygen and/or halogen-containing substituent into Chlorfenapyr by substituting the ethyl group to improve biological properties and decrease DNA damage. With this goal in mind, a series of novel 2-arylpyrrole derivatives (**6–10**, Figure 2) were designed and synthesized. This paper reports the synthesis, insecticidal and acaricidal activity of these novel 2-arylpyrrole derivatives.

2 Experimental

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Varian INOVA-300 spectrometer using tetramethylsilane (TMS) as the internal standard and deuterochloroform ($CDCl_3$) as the solvent. Mass spectra (MS) were obtained with both Hewlett-Packard 6890-5973 GC/MS and Agilent 1100 Series LC/MSD. Elemental analyses were carried out with a PE CHNS/O 2400 II elemental analyzer. Uncorrected melting points were taken on a WRS-1A digital melting points apparatus.

2.1 Synthesis

The general synthetic schemes for representative compounds (**6a–6e**, **7a–7i**, **8a–8f**, **9** and **10**) are shown in Figure 2. All reactions were carried out under a protective atmos-

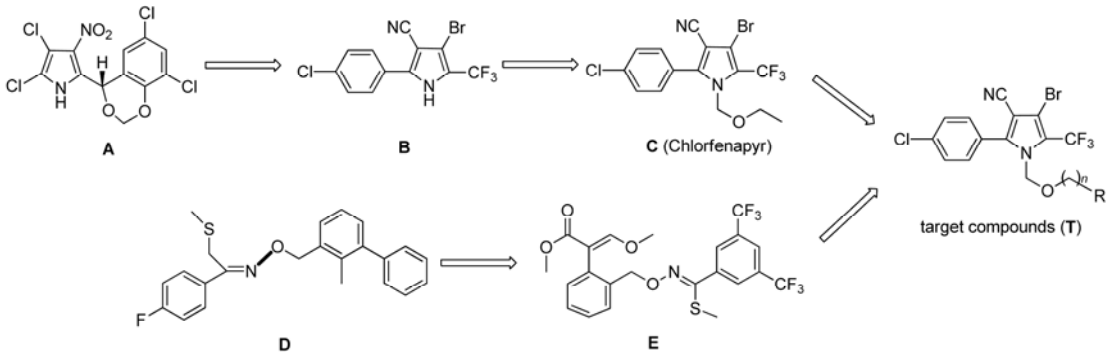


Figure 1 Design strategy for the target compounds.

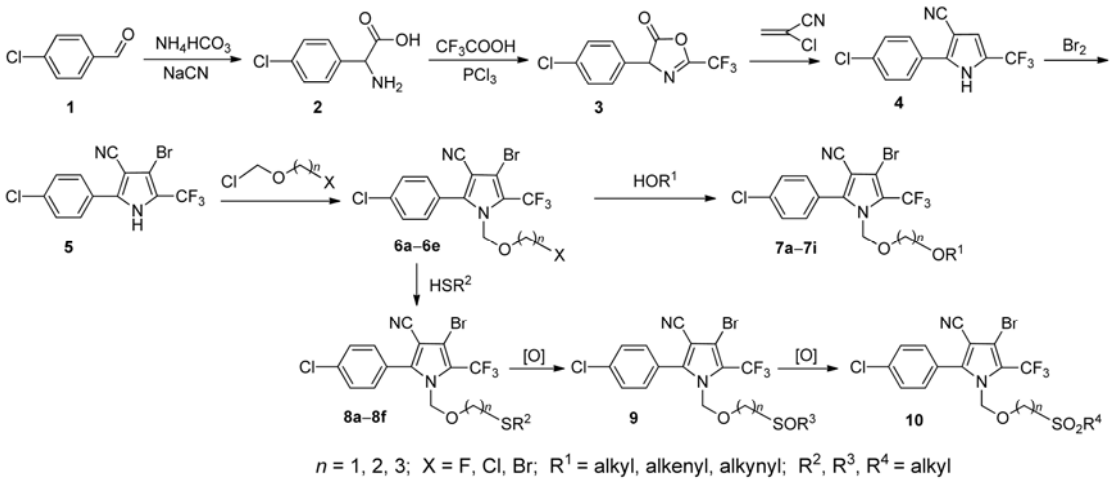


Figure 2 Synthesis schemes of compounds **6a–6e**, **7a–7i**, **8a–8f**, **9** and **10**.

phere of dry nitrogen or utilizing a calcium chloride tube. Reaction yields were not optimized. Representative procedures are given below. Every other compound was synthesized in manners similar to representatives and every new compound was identified and verified by ^{1}H NMR, MS, and elemental analyses.

4-Bromo-2-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrrole-3-carbonitrile (**5**) was prepared according to the literature [16].

4-Bromo-1-((2-chloroethoxy)methyl)-2-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrrole-3-carbonitrile (**6b**) was prepared as follows. A solution of compound **5** (7.10 g, 0.02 mol) in tetrahydrofuran (8 mL) was added dropwise over 15 min to a slurry of sodium hydride (0.96 g, 60 wt.%, 0.024 mol) and THF (20 mL) at 0–5 °C. The mixture was stirred at the same temperature for 0.5 h before a solution of 1-chloro-2-(chloromethoxy)ethane (3.1 g, 0.024 mol) in THF (5 mL) was added dropwise, and the mixture was stirred at room temperature for 4–5 h. The reaction mixture was cooled to room temperature, poured into ice-water and then extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried with anhydrous sodium sulfate, filtered and the solvent was removed. Residue materials were recrystallized from petroleum ether+ethyl acetate (10:1 by volume) to give compound **6b**: 5.80 g (60.70%) of a white solid: m.p. 104.4–106.1 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.57 (t, J = 5.7 Hz, 2H, CH_2), 3.66 (t, J = 5.7 Hz, 2H, CH_2), 5.26 (s, 2H, CH_2), 7.54 (s, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.41, 137.37, 131.21, 129.65, 124.79, 121.71, 118.13, 113.25, 103.73, 99.26, 75.37, 69.11, 42.28; MS (70 eV) *m/z*: Calcd. 440, found 440; Anal. calcd for $C_{15}H_{10}BrCl_2F_3N_2O$: C 40.75, H 2.28, N 6.34; found C 40.82, H 2.25, N 6.30.

Compounds **6a**, **6c–6e** could be synthesized by the method similar to that described in the synthesis of **6b**.

4-Bromo-2-(4-chlorophenyl)-1-((2-(methylthio)ethoxy) methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (**8c**) was prepared as follows. A solution of compound **6b** (94.00%, 4.71 g, 0.01 mol) and sodium methyl mercaptide (20 wt%, 7.0 g, 0.02 mol) in ethanol (20 mL) was stirred at 50–60 °C for 3–4 h. The reaction mixture was cooled to room temperature, poured into ice-water and then extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried with anhydrous sodium sulfate, filtered and the solvent was removed. Residue materials were separated by silica-gel column chromatography using petroleum ether + ethyl acetate (30:1 by volume) as the eluant to give compound **8c**: 2.78 g (57.10%) of a white solid: m.p. 66.0–67.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.10 (s, 3H, CH_3), 2.61 (t, J = 6.3 Hz, 2H, CH_2), 3.52 (t, J = 6.3 Hz, 2H, CH_2), 5.23 (s, 2H, CH_2), 7.53 (s, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.41, 137.37, 131.24, 129.52, 124.79, 121.71, 118.13, 113.25, 103.73, 99.26, 75.85, 69.17, 42.27, 15.07; MS (70 eV) *m/z*: Calcd. 452, found 452; Anal. calcd for $C_{16}H_{13}BrClF_3N_2OS$: C 42.36, H 2.89, N 6.17; found C 42.35, H 2.86, N 6.15.

Compounds **7a–7i**, **8a–8b** and **8d–8f** could be synthesized by the method similar to that described in the synthesis of compound **8c**.

4-Bromo-2-(4-chlorophenyl)-1-((2-(methylsulfinyl)ethoxy) methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**9**) was prepared as follows. A solution of compound **8c** (93.50%, 1.51 g, 3.00 mmol), hydrogen peroxide (30 wt.%, 1.00g, 8.80 mmol), methanol (12 mL) and acetic acid (6 mL) was stirred at room temperature for 5–6 h. The reaction mixture was poured into ice-water and then extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried with anhydrous sodium sulfate, filtered and the solvent was removed. Residue materials were separated by silica-gel column chromatography using petroleum ether + ethyl acetate (10:1 by volume) as the eluant to give compound **9**: 1.08 g (72.90%) of a pale yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.78 (s, 3H, CH_3), 2.81 (t, J = 6.9 Hz, 2H, CH_2), 3.78 (t, J = 6.9 Hz, 2H, CH_2), 5.27 (s, 2H, CH_2), 7.47–7.58 (m, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.37, 137.51, 131.09, 129.81, 124.71, 121.72, 118.13, 113.13, 103.86, 99.40, 75.35, 61.36, 53.89, 39.17; LC-MS (APCI, Pos) (*m/z*) Calcd. 468, found 468; Anal. calcd for $C_{16}H_{13}BrClF_3N_2O_2S$: C 40.91, H 2.79, N 5.96; found C 40.94, H 2.76, N 5.99.

Compound **10** could be synthesized by the method similar to that described in the synthesis of compound **9** at refluxed temperature with hydrogen peroxide (30 wt%, 1.0 g, 16 mmol).

Structures of compounds **6–10** were supported by spectroscopic data shown below.

4-Bromo-1-((chloromethoxy)methyl)-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile **(6a)**. White solid, m.p. 82.8–84.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.40 (s, 4H, $2CH_2$), 7.48–7.57 (m, 4H, Ph H); MS (70 eV) m/z: Calcd. 426, found 426; Anal. calcd for $C_{14}H_8BrCl_2F_3N_2O$: C 39.28, H 1.88, N 6.54; found C 39.15, H 1.91, N 6.44.

4-Bromo-1-((2-chloroethoxy)methyl)-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**6b**). White solid, m.p. 104.4–106.1 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.57 (t, J = 5.7 Hz, 2H, CH_2), 3.66 (t, J = 5.7 Hz, 2H, CH_2), 5.26 (s, 2H, CH_2), 7.54 (s, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.41, 137.37, 131.21, 129.65, 124.79, 121.71, 118.13, 113.25, 103.73, 99.26, 75.37, 69.11, 42.28; MS (70 eV) *m/z*: Calcd. 440, found 440; Anal. calcd for $C_{15}H_{10}BrCl_2F_3N_2O$: C 40.75, H 2.28, N 6.34; found C 40.82, H 2.25, N 6.30.

4-Bromo-1-((3-chloropropoxy)methyl)-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**6c**). viscous liquid, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.95δ2.03 (m, 2H, CH_2), 3.48 (t, J = 5.7 Hz, 2H, CH_2), 3.58 (t, J = 6.3 Hz, 2H, CH_2), 5.21 (s, 2H, CH_2), 7.46–7.57 (m, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 454, found 454; Anal. calcd for $C_{15}H_{10}BrCl_2F_3N_2O$: C 42.14, H 2.65, N 6.14; found C 42.12, H 2.62, N 6.12.

4-Bromo-2-(4-chlorophenyl)-1-((2-fluoroethoxy)-methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**6d**). White solid, m.p. 86.6–88.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.60 (t, J = 4.2 Hz, 2H, CH_2), 4.43 (t, J = 4.2 Hz, 2H, CH_2), 5.27 (s, 2H, CH_2), 7.49–7.55 (m, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 424, found 424; Anal. calcd for $C_{15}H_{10}BrClF_4N_2O$: C 42.33, H 2.37, N 6.58; found C 42.42, H 2.33, N 6.52.

4-Bromo-1-((2-bromoethoxy)methyl)-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**6e**). White solid, m.p. 91.7–94.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.40 (t, J = 5.7 Hz, 2H, CH_2), 3.73 (t, J = 5.7 Hz, 2H, CH_2), 5.26 (s, 2H, CH_2), 7.49–7.55 (m, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.41, 137.40, 131.12, 129.68, 124.77, 121.71, 118.12, 113.25, 103.74, 99.25, 75.18, 68.94, 29.31; MS (70 eV) *m/z*: Calcd. 484, found 484; Anal. calcd for $C_{15}H_{10}Br_2ClF_3N_2O$: C 37.03, H 2.07, N 5.76; found C 37.07, H 2.11, N 5.72.

4-Bromo-2-(4-chlorophenyl)-1-((methoxymethoxy)methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**7a**). White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.29 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 5.29 (s, 2H, CH_2), 7.50–7.52 (m, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 422, found 422; Anal. calcd for $C_{15}H_{11}BrClF_3N_2O_2$: C 42.53, H 2.62, N 6.61; found C 42.54, H 2.50, N 6.67.

4-Bromo-2-(4-chlorophenyl)-1-((ethoxymethoxy)methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**7b**). White solid, m.p. 115.8–116.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.08–1.13 (t, J = 7.2 Hz, 3H, CH_3), 3.46 (q, J = 7.0 Hz, 2H, CH_2), 4.63 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 7.47–7.55 (m, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.48, 137.29, 131.26, 129.51, 125.04, 121.76, 118.18, 113.31, 103.68, 99.28, 93.60, 73.24, 64.28, 14.79; MS (70 eV) *m/z*: Calcd. 436, found 436; Anal. calcd for $C_{16}H_{13}BrClF_3N_2O_2$: C 43.91, H 2.99, N 6.40; found C 43.95, H 3.03, N 6.25.

4-Bromo-2-(4-chlorophenyl)-1-((propoxymethoxy)methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**7c**). White solid, m.p. 109.7–111.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.83 (t, J = 6.6 Hz, 3H, CH_3), 1.43 (m, 2H, CH_2), 3.36 (t, J = 7.5 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 7.46–7.55 (m, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 450, found 450; Anal. calcd for $C_{17}H_{15}BrClF_3N_2O_2$: C 45.21, H 3.35, N 6.20; found C 45.33, H 3.33, N 6.18.

4-Bromo-2-(4-chlorophenyl)-1-((isopropoxymethoxy) methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**7d**). White solid, m.p. 74.9–76.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.04 (d, J = 9.3 Hz, 6H, $2CH_3$), 3.72–3.78 (m, 1H, CH), 4.64 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 7.46–7.54 (m, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 450, found 450; Anal. calcd for $C_{17}H_{15}BrClF_3N_2O_2$: C 45.21, H 3.35, N 6.20; found C 45.09, H 3.30, N 6.29.

1-((2-Allyloxy)methoxy)methyl-4-bromo-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**7e**). White solid, m.p. 116.0–118.1 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.95 (d, J = 5.7 Hz, 2H, CH_2), 4.65 (s, 2H, CH_2), 5.15–5.18 (m, 2H, CH_2), 5.33 (s, 2H, CH_2), 5.70–5.83 (m, 1H, CH), 7.45–7.54 (m, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 448, found 448; Anal. calcd for $C_{17}H_{13}BrClF_3N_2O_2$: C 45.41, H 2.91, N 6.23; found C 45.25, H 2.97, N 6.25.

4-Bromo-2-(4-chlorophenyl)-1-((prop-2-yn-1-yloxy) methoxy)methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (**7f**). White solid, m.p. 139.3–140.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.42 (s, 1H, CH), 4.11 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 5.33 (s, 2H, CH_2), 7.46–7.55 (m, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 446, found 446; Anal. calcd for $C_{17}H_{11}BrClF_3N_2O_2$: C 45.61, H 2.48, N 6.26; found C 45.64, H 2.56, N 6.15.

4-Bromo-2-(4-chlorophenyl)-1-((2-methoxyethoxy) methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**7g**). White solid, m.p. 102.1–103.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.31 (s, 3H, CH_3), 3.49–3.50 (m, 2H, CH_2), 3.51–3.52 (m, 2H, CH_2), 5.26 (s, 2H, CH_2), 7.52 (s, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 436, found 436; Anal. calcd for $C_{16}H_{13}BrClF_3N_2O_2$: C 43.91, H 2.99, N 6.40; found C 43.90, H 2.96, N 6.51.

1-((2-(Allyloxy)ethoxy)methyl-4-bromo-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**7h**). White solid, m.p. 77.3–80.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.52–3.58 (m, 4H, CH_2CH_2), 3.93 (d, J = 8.4 Hz, 2H, CH_2), 5.17 (s, 2H, CH_2), 5.25 (s, 2H, CH_2), 5.78–5.88 (m, 1H, CH), 7.52–7.56 (m, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.34, 137.11, 134.84, 131.21, 129.60, 125.03, 121.70, 118.12, 117.30, 113.36, 103.38, 98.92, 75.83, 72.13, 69.06, 68.33; MS (70 eV) *m/z*: Calcd. 462, found 462; Anal. calcd for $C_{18}H_{15}BrClF_3N_2O_2$: C 46.63, H 3.26, N 6.04; found C 46.69, H 3.43, N 6.09.

4-Bromo-2-(4-chlorophenyl)-1-((2-(prop-2-yn-1-yl)oxy) ethoxy)methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (**7i**). White solid, m.p. 78.1–80.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.08 (s, 1H, CH), 3.56–3.65 (m, 4H, CH_2CH_2), 4.12 (s, 2H, CH_2), 5.26 (s, 2H, CH_2), 7.53 (s, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.39, 137.17, 131.26, 129.55, 125.05, 121.75, 118.17, 113.39, 103.52, 98.83, 78.99, 75.83, 74.90, 68.82, 68.18, 58.39; MS (70 eV) *m/z*: Calcd. 460, found 460; Anal. calcd for $C_{18}H_{13}BrClF_3N_2O_2$: C 46.83, H 2.84, N 6.07; found C 46.83, H 2.93, N 6.00.

4-Bromo-2-(4-chlorophenyl)-1-((methylthio)methoxy) methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (**8a**). Yellow solid, m.p. 145.9–146.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.09 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 7.46–7.56 (m, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 438, found 438; Anal. calcd for $C_{15}H_{11}BrClF_3N_2OS$: C 40.98, H 2.52, N 6.37; found C 40.85, H 2.61, N 6.34.

4-Bromo-2-(4-chlorophenyl)-1-((ethylthio)methoxy) methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (**8b**). White solid, m.p. 97.6–98.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.20 (t, J = 7.2 Hz, 3H, CH_3), 2.49 (q, J = 7.2 Hz, 2H, CH_2), 4.58 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 7.44–7.55 (m, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.49, 137.45, 131.19, 129.62, 124.90, 121.71, 118.13, 113.24, 103.80, 99.27, 72.80, 71.14, 24.89, 14.49; MS (70 eV) *m/z*: Calcd. 452,

found 452; Anal. calcd for $C_{16}H_{13}BrClF_3N_2OS$: C 42.36, H 2.89, N 6.17; found C 42.50, H 2.89, N 6.20.

4-Bromo-2-(4-chlorophenyl)-1-((2-(methylthio)ethoxy) methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**8c**). White solid, m.p. 66.0–67.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.10 (s, 3H, CH_3), 2.61 (t, J = 6.3 Hz, 2H, CH_2), 3.52 (t, J = 6.3 Hz, 2H, CH_2), 5.23 (s, 2H, CH_2), 7.53 (s, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.41, 137.37, 131.24, 129.52, 124.79, 121.71, 118.13, 113.25, 103.73, 99.26, 75.85, 69.17, 42.27, 15.07; MS (70 eV) *m/z*: Calcd. 452, found 452; Anal. calcd for $C_{16}H_{13}BrClF_3N_2OS$: C 42.36, H 2.89, N 6.17; found C 42.35, H 2.86, N 6.15.

4-Bromo-2-(4-chlorophenyl)-1-(2-(ethylthio)ethoxy) methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (**8d**). White solid, m.p. 63.0–64.1 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.21 (t, J = 6.3 Hz, 3H, CH_3), 2.49 (q, J = 7.4 Hz, 2H, CH_2), 2.64 (t, J = 6.6 Hz, 2H, CH_2), 3.51 (t, J = 6.6 Hz, 2H, CH_2), 5.23 (s, 2H, CH_2), 7.53 (s, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 466, found 466; Anal. calcd for $C_{17}H_{15}BrClF_3N_2OS$: C 43.65, H 3.23, N 5.99; found C 43.58, H 3.32, N 6.03.

4-Bromo-2-(4-chlorophenyl)-1-((2-(propylthio)ethoxy) methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**8e**). White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.95 (t, J = 7.2 Hz, 3H, CH_3), 1.54–1.62 (m, 2H, CH_2), 2.45 (t, J = 7.2 Hz, 2H, CH_2), 2.62 (t, J = 6.6 Hz, 2H, CH_2), 3.50 (t, J = 6.6 Hz, 2H, CH_2), 5.23 (s, 2H, CH_2), 7.53 (s, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 480, found 480; Anal. calcd for $C_{17}H_{15}BrClF_3N_2OS$: C 44.88, H 3.56, N 5.81; found C 44.79, H 3.55, N 5.75.

4-Bromo-2-(4-chlorophenyl)-1-(2-(isopropylthio)ethoxy) methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (**8f**). White solid, m.p. 46.5–48.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.23 (d, J = 6.6 Hz, 6H, $2CH_3$), 2.64 (t, J = 6.6 Hz, 2H, CH_2), 2.91–2.98 (m, 1H, CH), 3.50 (t, J = 6.6 Hz, 2H, CH_2), 5.22 (s, 2H, CH_2), 7.53 (s, 4H, Ph H); MS (70 eV) *m/z*: Calcd. 480, found 480; Anal. calcd for $C_{17}H_{15}BrClF_3N_2OS$: C 44.88, H 3.56, N 5.81; found C 44.87, H 3.66, N 5.84.

4-Bromo-2-(4-chlorophenyl)-1-(2-(methylsulfinyl)ethoxy) methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (**9**). Viscous liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.78 (s, 3H, CH_3), 2.81 (t, J = 6.9 Hz, 2H, CH_2), 3.78 (t, J = 6.9 Hz, 2H, CH_2), 5.27 (s, 2H, CH_2), 7.47–7.58 (m, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.37, 137.51, 131.09, 129.81, 124.71, 121.72, 118.13, 113.13, 103.86, 99.40, 75.35, 61.36, 53.89, 39.17; LC-MS(APCI, Pos) *m/z*: Calcd. 468, found 468; Anal. calcd for $C_{16}H_{13}BrClF_3N_2O_2S$: C 40.91, H 2.79, N 5.96; found C 40.94, H 2.76, N 5.99.

4-Bromo-2-(4-chlorophenyl)-1-((2-(methylsulfonyl)ethoxy) methyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**10**). Viscous liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.90 (s, 3H, CH_3), 3.18 (t, J = 5.4 Hz, 2H, CH_2), 3.75 (t, J = 5.4 Hz, 2H, CH_2), 5.30 (s, 2H, CH_2), 7.44–7.59 (m, 4H, Ph H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 144.30, 137.56, 131.09, 129.85, 124.60, 121.68, 118.10, 112.99, 104.10, 99.57, 75.40, 62.59, 54.28, 42.92; LC-MS(APCI, Pos) *m/z*: Calcd. 468, found 468; Calcd. 484, found 484; Anal. calcd for $C_{16}H_{13}BrClF_3N_2O_3S$: C 39.57, H 2.70, N 5.77; found C 39.50, H 2.62, N 5.73.

2.2 Biological assay

Test insects

The entire set of the test insects were reared in a conditioned room maintained at 25 (±1) °C, 65 (±5) % relative humidity and 14:10 h light: dark photoperiod.

Test compounds

Stock solutions of each test compound were prepared in DMF at a concentration of 1.0 g/L, and then diluted to the required test concentrations with water containing Triton X-100 (0.1 ml/L).

Test methods

(i) Insecticidal activity against Lepidopteran pest–*Mythimna separate* [12].

The insecticidal activity against *Mythimna separata* of the title compounds **6–10** and Chlorfenapyr were evaluated using the following procedure. Ten third-instar *Mythimna separata* and five pieces of corn fragments were placed in a Petri dish, and sprayed with test solutions using a Potter sprayer. After air-drying, they were kept in a room for normal cultivation. After 24 h, the numbers of live and dead insects were recorded. Control groups were tested with the solvent (DMF) only. Each assay contained three replications, and results were averaged. Data were subjected to probit analysis and the death rate of each tested compound was calculated. Evaluations were based on a percentage scale of 0–100, where 0 equals no activity and 100 equals total kill, and the median lethal concentration (LC_{50}) value of some compounds was also calculated.

(ii) Acaricidal activity against mite–*Tetranychus urticae* [13, 14].

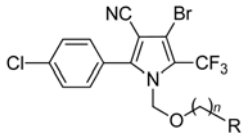
The acaricidal activity against *Tetranychus urticae* of the title compounds **6–10** and Chlorfenapyr was evaluated using the following procedure. Fifty adults of *Tetranychus urticae* were transferred to three horse bean seedlings. After 24 h, the horse bean seedlings with acarids were dipped in the test solutions for 5–10 s, and then allowed to dry with filter paper. After drying they were transferred to a beaker (100 mL) containing water (10 mL) and kept at 25 °C. Each assay contained three replications. Mortality was assessed 24 h after the treatment. Control groups were tested with the solvent (DMF) only. Evaluations were based on a percentage scale of 0–100, where 0 equals no activity and 100 equals total kill.

3 Results and discussion

3.1 Synthesis

The synthesis scheme is shown in Figure 2. Table 1 summarizes the chemical structures of all the title compounds

Table 1 Chemical structures, insecticidal and acaricidal activities of the target compounds (**T**)



target compounds (**T**)

Compd.	Chemical structure		*Mythimna separate*				*Tetranychus urticae*			
	R	*n*	1000 mg/L	100 mg/L	10 mg/L	LC_{50} mg/L	500 mg/L	100 mg/L	10 mg/L	LC_{50} mg/L
6a	Cl	1	100	100	26.47	14.17	100	100	100	1.27
6b	Cl	2	100	100	10.53	25.45	100	100	94.05	2.62
6c	Cl	3	75	no test	no test	no test	19.20	no test	no test	>500
6d	F	2	100	100	13.51	15.80	100	96.55	79.58	1.18
6e	Br	2	100	100	0	no test	95.7	0	0	>100
7a	OCH_3	1	no test	no test	no test	no test	95.0	no test	no test	no test
7b	OCH_2CH_3	1	100	100	16.12	23.95	100	100	98.44	0.86
7c	$OCH_2CH_2CH_3$	1	100	100	0	no test	100	100	36.90	11.65
7d	$OCH(CH_3)_2$	1	100	100	0	no test	100	100	100	0.31
7e	$OCH_2CH{=}CH_2$	1	100	45	0	no test	100	100	68.57	5.19
7f	$OCH_2C{\equiv}CH$	1	100	100	0	no test	83.3	no test	no test	>100
7g	OCH_3	2	NT	no test	no test	no test	0	no test	no test	>500
7h	$OCH_2CH{=}CH_2$	2	100	100	0	no test	58.1	no test	no test	≈500
7i	$OCH_2C{\equiv}CH$	2	NT	no test	no test	no test	0	no test	no test	>500
8a	SCH_3	1	0	no test	no test	>100	0	no test	no test	>500
8b	SCH_2CH_3	1	100	100	0	no test	0	no test	no test	>500
8c	SCH_3	2	100	100	3.45	38.46	37.95	3.70	0	>500
8d	SCH_2CH_3	2	100	100	0	no test	0	no test	no test	>500
8e	$SCH_2CH_2CH_3$	2	64.58	no test	no test	no test	0	no test	no test	>500
8f	$SCH(CH_3)_2$	2	100	100	0	no test	9.50	no test	no test	>500
9	$SOCH_3$	2	90.45	85.91	0	no test	0	no test	no test	>500
10	SO_2CH_3	2	90.91	100	0	no test	0	no test	no test	>500
	Chlorfenapyr		100	100	16.22	21.72	100	100	97.06	0.36

6–10. The observed molecular mass for each compound was as expected in MS analysis, ^{1}H NMR data for each compound of formulas **6–10** and ^{13}C NMR data for **6b**, **6d**, **7b**, **7h–7i**, **8b–8c**, **9** and **10** are listed. Compounds **6** and **8–10** were prepared in >50% yield, but compounds **7** were synthesized with a <50% yield by the procedure shown in Fig. 2 because of the nucleophilicity of the sulfur is stronger than that of oxygen. The yields can be improved by changing the starting materials **6** (X = Cl) to **6** (X = Br) in the synthesis of **7**.

3.2 Insecticidal and acaricidal activities

Table 1 shows the insecticidal and acaricidal activities of the synthesized 2-arylpyrrole derivatives. The activities of Chlorfenapyr, the only commercialized member of a new class of chemicals of 2-arylpyrrols, are also shown in Table 1.

As shown in Table 1, most of the synthesized 2-arylpyrrole derivatives **6–10** exhibit remarkable insecticidal and/or acaricidal activities. Some compounds show high insecticidal and/or acaricidal activities. For example, the insecticidal potency (LC_{50}) against Lepidopteran pest–*Mythimna separate* of compounds **6a** (14.17 mg/L), **6b** (25.45 mg/L), **6d** (15.80 mg/L), **7b** (23.95 mg/L) and the acaricidal potency (LC_{50}) against mite–*Tetranychus urticae* of compounds **7b** (0.86 mg/L), **7d** (0.31 mg/L) are comparable to that of Chlorfenapyr (21.72 mg/L and 0.36 mg/L).

3.3 Apparent structure activity relationship

The activity of the synthesized 2-arylpyrrole derivatives (Figure 1) depended on both *n* and the substituent R. *n* and R have important effects on the activities.

For the same *n* (e.g. *n* = 1), when R = halo (e.g. Cl) or saturated C_2–C_3 alkoxy (e.g. OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$), the compounds (e.g. **6b**, **6d**, **7b**, **7d**) showed the highest activity; when R was changed from halo or alkoxy to alkylthio and alkylsulfinyl or alkylsulfonyl, the activities decreased (e.g. **9** ≈ **10** < **8d** < **6b** < **7b**). The acaricidal activities decreased abruptly when R was changed from halo or alkoxy to alkylthio and alkylsulfinyl or alkylsulfonyl (e.g. **8~9** << **7** ≈ **6**).

For the same R (e.g. R = Cl), when *n* = 1, the compound (e.g. **6a**) showed the highest activity. With the increase of *n*, the activity became lower and lower (e.g. **6c** < **6b** < **6a**).

In general, for the synthesized compounds (Figure 1):

Activity order of *n* is: 1 ≈ 2 > 3

Activity order of R is: halo ≈ alkoxy > alkythio > alkylsulfinyl ≈ alkylsulfonyl; F>Cl>Br; $OCH_2CH_3 \approx OCH(CH_3)_2 > OCH_2CH_2CH_3$; $SCH_3 > SCH_2CH_3 \approx SCH(CH_3)_2 > SCH_2CH_2CH_3 > SOCH_3 \approx SO_2CH_3$.

Further studies on the biological activity and structure-activity relationships of this series of compounds are in progress.

4 Conclusions

A series of novel 2-arylpyrrole derivatives were designed and synthesized; their insecticidal and acaricidal activities were evaluated against Lepidopteran pests (e.g. *Mythimna separata*) and Mites (e.g. *Tetranychus urticae*). The results showed that most compounds exhibited remarkable activity against *Mythimna separate* and *Tetranychus urticae* and the potency of some compounds (e.g. **6a**, **6b 6d**, **7d**) is comparable to that of Chlorfenapyr.

Compound **6b** has demonstrated low acute toxicity to mammals (The acute oral LD_{50} to rats was 4640 mg/kg, much less than that of Chlorfenapyr 626 mg/kg); negative results were observed in the Ames, chromosomal aberration test, mutation assay, and mouse bone marrow micronucleus assay; while compounds **6d** [21.5 (male), 14.7 (female) mg/kg] and **7b** [178 (male), 147 (female) mg/kg] have high acute toxicity to mammals.

When cost, activity and toxicity were taken into account, compound **6b** has been chosen for further development.

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