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Design, Synthesis and Insecticidal Activities of Novel 5-Alkoxyfuran-2(5*H*)-one Derivatives

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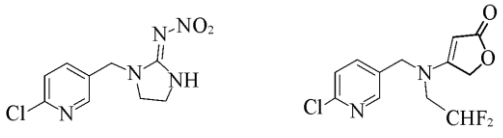
Abstract A series of novel 5-alkoxyfuran-2(5*H*)-one derivatives was synthesized, and characterized by ^{1}H NMR, ^{13}C NMR and HRMS. Biological activities of all the title compounds were evaluated systematically. Preliminary bioassays indicated that most of the compounds exhibited moderate insecticidal activities against *Aphis craccivora* and *Nilaparvata lugens* at 100 mg/L. Compounds **4**h and **4**w exhibited 100% mortality rate against *Aphis craccivora* at 100 mg/L, and compound **4**h exhibited good mortality rate against *Aphis craccivora* and *Nilaparvata lugens (*60% and 75%, respectively) even at 4 mg/L. The results demonstrated the impact of various chemical groups on insecticidal activities and provided a potential clue for further exploring novel high-effective broad-spectrum insecticides.

Keywords Butenolide derivative; Flupyradifurone; Neonicotinoid; Insecticidal activity

1 Introduction

Honeybees, which play an important role in crop pollination and ecological balance, are essential for increasing crop yield and quality[1—5]. However, insecticides are widely used in agricultural production. In particular, neonicotinoid insecticides with a market share of more than 20% of global insecticide sales have been known to have a negative impact on the lifespan and cognition of honeybees[6—10]. Exposure to neonicotinoid insecticides usually reduces the ability of honeybees to survive in winter and the reproductive success rate of wild honeybees. Therefore, it is imperative to develop novel neonicotinoid insecticides that are safe for pollinating insects such as honeybees.

Recently, flupyradifurone(Fig.1) developed by Bayer from the butenolide class is launched in the EU as a novel insecticide. It can be used to control sucking pests, especially whitefly and aphid species[11]. More importantly, flupyradifurone is favorably safe for honeybees on an acute oral exposure basis, and can be foliarly applied even during flowering[12,13]. Owing to their outstanding insecticidal activity, low toxicity to honeybees and mammals, and unique mode of action, neonicotinoid insecticides from the butenolide class have become the frontier of insecticidal research.



Imidacloprid Flupyradifurone

Fig.1 Chemical structures of imidacloprid and flupyradifurone

The design of flupyradifurone was inspired by the structure of stemofoline, the unsubstituted butenolide of its "head group" was selected as the pharmacophore[14,15](Scheme 1). However the intact "head group" of stemofoline exists in many other naturally biologically active molecular structures, such as cepanolide from onion[16], compound **1** from *Aspergillus terreus*[17](LC_{50}=1.25 mol/L against *Artemia*), (+) Strigol and its synthetic strigolactone GR24[18](Fig.2).

Motivated by the above mentioned findings, we systematically replaced the butenolide pharmacophore with 3-halo-5-alkoxybutenolide(halogen as methyl bioisostere) to explore the influence of new pharmacophore on their bioactivities. Through this way, a series of novel 3-halo-5-alkoxyfuran-2(5*H*)-one derivatives(**4**) was designed and synthesized. Their insecticidal activities against *A. craccivora* and *N. lugens* were investigated and correlated with their structures.

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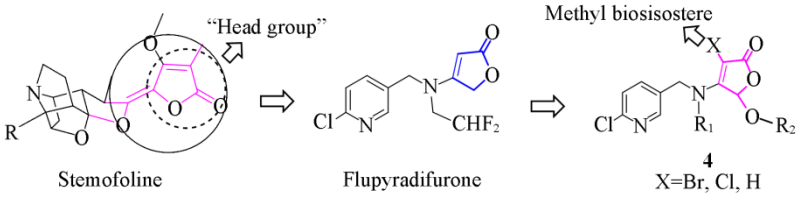


Scheme 1 Design strategy of target compounds 4

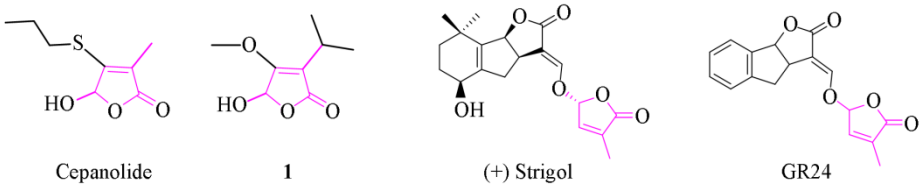


Fig.2 Chemical structures of cepanolide, compound 1, (+)strigol and GR24

2 Experimental

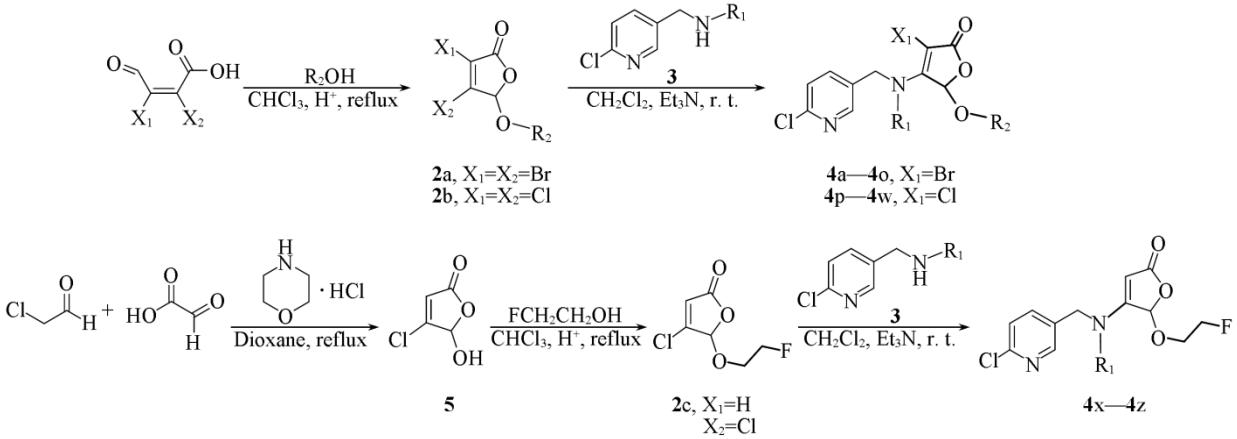
2.1 Materials and Instruments

All the reaction reagents were of analytical grade. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV III 400 MHz NMR spectrometer with tetramethysilane(TMS) as the internal standard. HRMS-ESI data were obtained on an Agilent 6510 spectrometer equipped with an electrospray source. Column chromatography purification was carried out using silica gel(200—300 mesh).

2.2 General Synthetic Procedure for Compounds 4a—4z

The synthetic routes of compounds **4**a—**4**z are shown in Scheme 2.

The preparation of intermediates **2**a, **2**b and **2**c was



Scheme 2 Synthetic routes for compounds 4a—4z

described in refs.[19—21]. The synthetic route of target products **4** was described in ref.[22].

A solution of compounds **2**(5 mmol), compound **3**(5 mmol) and potassium carbonate(5 mmol) in *N*,*N*-dimethylformamide (DMF, 10 mL) was stirred at room temperature. The reaction was monitored by thin-layer chromatography(TLC) and then quenched with water(30 mL). The mixture was extracted into dichloromethane(DCM, 20 mL×3). The organic phase was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, the solvent was removed under reduced pressure. The crude residue was purified by silica flash column chromatography to afford compounds **4**a—**4**z.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](methyl)-amino}-5-methoxyfuran-2(5*H*)-one(**4**a): a yellow solid, yield 83%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.44(d, J=2.4 Hz, 1H, Py—H), 7.65(dd, dd, J=8.1, 2.5 Hz, 1H, Py—H), 7.40(d, J=8.2 Hz, 1H, Py—H), 5.77(s, 1H, O—CH(C)—O), 4.97—4.66(m, 2H, Py—CH_2—N), 3.55(s, 3H, O—CH_3), 3.12(s, 3H, N—CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 168.1, 157.7, 151.5, 148.8, 137.9, 130.5, 124.8, 98.9, 74.2, 55.6, 52.3, 38.4; HRMS(ESI), *m/z* calcd. for $C_{12}H_{12}BrClN_2O_3[M+H]^+$: 348.9798; found: 348.9735.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](ethyl)amino}-5-methoxyfuran-2(5*H*)-one(**4**b): a a yellow oily liquid, yield 80%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.32(s, 1H, Py—H), 7.63(d, J=7.7 Hz, 1H, Py—H), 7.39(d, J=8.1 Hz, 1H, Py—H), 5.76[s, 1H, O—CH(C)—O], 4.66(m, 2H, Py—CH_2—N), 3.54(s, 3H, O—CH_3), 3.51(q, N—C**H**$_2$—CH_3, J=8.1 Hz, 2H), 1.25(t, J=6.8 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 168.2, 157.4, 151.2, 148.5, 137.8, 131.2, 124.6, 98.8, 73.7, 55.6, 49.52, 45.0, 13.9; HRMS(ESI), *m/z* calcd. for $C_{13}H_{14}BrClN_2O_3$ $[M+H]^+$: 360.9955; found: 360.9934.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](propyl)-amino}-5-methoxyfuran-2(5*H*)-one(**4**c): a yellow oily liquid,

yield 77%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.31(d, J=2.4 Hz, 1H, Py—H), 7.61(dd, J=8.2, 2.5 Hz, 1H, Py—H), 7.39(d, J=8.2 Hz, 1H, Py—H), 5.74[s, 1H, O—CH(C)—O], 4.85(d, J=16.4 Hz, 1H, Py—CH_2—N), 4.61(m, 1H, Py—CH_2—N), 3.54(s, 3H, O—CH_3), 3.39(m, 2H), 1.68(m, 2H, —C**H**$_2$—CH_3), 0.93(t, J=7.3 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 168.1, 157.4, 151.3, 148.5, 137.7, 131.1, 124.7, 98.8, 74.0, 55.5, 51.7, 50.2, 21.9, 10.6; HRMS(ESI), *m/z* calcd. for $C_{14}H_{16}BrClN_2O_3$ $[M+H]^+$: 375.0111; found: 375.0156.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](cyclopropyl)-amino}-5-methoxyfuran-2(5*H*)-one(**4**d): a yellow oily liquid, yield 71%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.35(d, J=2.5 Hz, 1H, Py—H), 7.62(dd, J=8.3, 2.5 Hz, 1H, Py—H), 7.38(d, J=8.2 Hz, 1H, Py—H), 5.91(s, 1H, O—CH(C)—O), 5.32(d, J=16.1 Hz, 1H, Py—CH_2—N), 4.44(d, J=16.0 Hz, 1H, Py—CH_2—N), 3.56(s, 3H, O—CH_3), 2.89[m, 1H, N—C**H**(CH_2)—CH_2], 0.92(m, 4H, —CH_2—CH_2—); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.5, 156.7, 151.1, 148.6, 137.8, 131.5, 124.6, 98.6, 90.9, 56.6, 50.3, 33.3, 10.3, 7.8; HRMS(ESI), *m/z* calcd. for $C_{14}H_{14}BrClN_2O_3[M+H]^+$: 372.9955; found: 372.9936.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](methyl)-amino}-5-ethoxyfuran-2(5*H*)-one(**4**e): a yellow solid, yield 80%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.34(d, J=2.4 Hz, 1H, Py—H), 7.65(dd, J=8.3, 2.2 Hz, 1H, Py—H), 7.41(d, J=8.2 Hz, 1H, Py—H), 5.82[s, 1H, O—CH(C)—O], 4.81(s, 2H, Py—CH_2—N), 3.90(m, 1H, O—C**H**$_2$—CH_3), 3.74(q, J=7.0 Hz, 1H, O—C**H**$_2$—CH_3), 3.13(s, 3H, N—CH_3), 1.26(t, J=7.0 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 168.3, 158.1, 151.3, 148.7, 138.0, 130.6, 124.7, 98.1, 73.9, 65.1, 52.4, 38.4, 14.9; HRMS(ESI), *m/z* calcd. for $C_{13}H_{14}BrClN_2O_3[M+H]^+$: 360.9955; found: 360.9950.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](ethyl)amino}-5-ethoxyfuran-2(5*H*)-one(**4**f): a yellow oily liquid, yield 78%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.33(d, J=2.4 Hz, 1H, Py—H), 7.65(dd, J=8.3, 2.4 Hz, 1H, Py—H), 7.39(d, J=8.3 Hz, 1H, Py—H), 5.80[s, 1H, O—CH(C)—O], 4.77(m, 2H, Py—CH_2—N), 3.95(q, J=7.1 Hz, 1H, O—C**H**$_2$—CH_3), 3.74(q, J=7.0 Hz, 1H, O—C**H**$_2$—CH_3), 1.29—1.23(m, 6H, —CH_3, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 168.3, 157.5, 151.33, 148.5, 137.8, 131.1, 124.6, 98.0, 73.9, 65.0, 49.5, 44.8, 14.8, 13.9; HRMS(ESI), *m/z* calcd. for $C_{14}H_{16}BrClN_2O_3[M+H]^+$: 375.0111; found: 375.0134.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](propyl)-amino}-5-ethoxyfuran-2(5*H*)-one(**4**g): a yellow oily liquid, yield 71%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.35(m, 1H, Py—H), 7.67—7.62(m, 1H, Py—H), 7.39(dd, J=8.2, 0.6 Hz, 1H, Py—H), 5.79[s, 1H, O—CH(C)—O], 4.77(m, 2H, Py—CH_2—N), 3.86(m, 2H, O—C**H**$_2$—CH_3), 3.33(m, 2H, N—C**H**$_2$—CH_2), 1.66(m, 2H, —C**H**$_2$—CH_3), 1.23(t, J=7.1 Hz, 3H, —CH_3), 0.92(t, J=7.2 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 168.2, 157.6, 151.4, 148.5, 137.7, 131.1, 124.6, 98.0, 74.1, 65.0, 51.7, 50.29, 22.0, 14.8, 10.6; HRMS(ESI), *m/z* calcd. for $C_{15}H_{18}BrClN_2O_3[M+H]^+$: 389.0268; found: 389.0254.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](methyl)-amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**h): a yellow solid, yield 68%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.34(d, J=2.4 Hz, 1H, Py—H), 7.65(dd, J=8.3, 2.3 Hz, 1H, Py—H), 7.41(d, J=8.2 Hz, 1H, Py—H), 5.90[s, 1H, O—CH(C)—O], 4.84(s, 2H, Py—CH_2—N), 4.70—4.62(m, 1H, F—C**H**$_2$—CH_2), 4.60—4.51 (m, 1H, F—C**H**$_2$—CH_2), 4.18—3.93(m, 2H, O—C**H**$_2$—CH_2F), 3.16(s, 3H, N—CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.9, 157.7, 151.4, 148.7, 137.9, 130.5, 124.7, 98.1, 81.9(d, J=170.5 Hz), 74.1, 67.9(d, J=19.2 Hz), 52.4, 38.5; HRMS(ESI), *m/z* calcd. for $C_{13}H_{13}BrClFN_2O_3[M+H]^+$: 378.9860; found: 378.9820.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](ethyl)amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**i): a yellow oily liquid, yield 61%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.35(d, J=2.1 Hz, 1H, Py—H), 7.63(dd, J=8.3, 2.0 Hz, 1H, Py—H), 7.39(d, J=8.2 Hz, 1H, Py—H), 5.87[s, 1H, O—CH(C)—O], 4.88—4.69(m, 2H, Py—CH_2—N), 4.67—4.58(m, 1H, F—C**H**$_2$—CH_2), 4.52(m, 1H, F—C**H**$_2$—CH_2), 4.21—4.06(m, 1H, O—C**H**$_2$—CH_2F), 4.04—3.92(m, 1H, O—C**H**$_2$—CH_2F), 3.54(q, J=7.3 Hz, 2H, N—C**H**$_2$—CH_3), 1.8(t, J=7.4 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 168.0, 157.2, 151.3, 148.5, 137.8, 131.1, 124.6, 97.9, 81.9(d, J=170.3 Hz), 73.84, 68.04(d, J=19.2 Hz), 49.64, 45.02, 13.91; HRMS(ESI), *m/z* calcd. for $C_{14}H_{15}BrClFN_2O_3[M+H]^+$: 393.0017, found: 393.0023.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](propyl)-amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**j): a yellow oily liquid, yield 58%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.31(d, J=2.5 Hz, 1H, Py—H), 7.62(dd, J=8.3, 2.5 Hz, 1H, Py—H), 7.39(d, J=8.2 Hz, 1H, Py—H), 5.85[s, 1H, O—CH(C)—O], 4.87(d, J=16.5 Hz, 1H, Py—CH_2—N), 4.67(d, J=16.4 Hz, 1H, Py—CH_2—N), 4.64—4.59(m, 1H, F—C**H**$_2$—CH_2), 4.51(d, J=1.1 Hz, 1H, F—C**H**$_2$—CH_2), 4.08(s, 1H, O—C**H**$_2$—CH_2F), 3.99(d, J=2.6 Hz, 1H, O—C**H**$_2$—CH_2F), 3.44(q, J=6.6, 5.9 Hz, 2H, N—C**H**$_2$—CH_2), 1.68(d, J=3.2 Hz, 2H, —CH_2—), 0.93(t, J=7.3 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 168.0, 157.3, 151.3, 148.5, 137.7, 131.0, 124.6, 98.0, 81.9(d, J=170.3 Hz), 74.0, 68.0(d, J=19.1 Hz), 51.8, 50.3, 22.0, 10.5; HRMS(ESI), *m/z* calcd. for $C_{15}H_{17}BrClFN_2O_3$ $[M+H]^+$: 407.0173; found: 207.0134.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](cyclopropyl)-amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**k): a yellow oily liquid, yield 48%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.35(d, J=2.5 Hz, 1H, Py—H), 7.63(dd, J=8.3, 2.6 Hz, 1H, Py—H), 7.37(d, J=8.2 Hz, 1H, Py—H), 6.05[s, 1H, O—CH(C)—O], 5.30(d, J=16.1 Hz, 1H, Py—CH_2—N), 4.64(dd, J=5.3, 2.7 Hz, 1H, F—C**H**$_2$—CH_2), 4.54—4.52(m, 1H, Py—CH_2—N), 4.47(s, 1H, F—C**H**$_2$—CH_2), 4.17—4.04(m, 1H, O—C**H**$_2$—CH_2F), 3.99—3.94(m, 1H, O—C**H**$_2$—CH_2F), 3.01—2.94(m, 1H, N—C**H**(CH_2)—CH_2), 1.37—1.26(m, 1H, —CH_2—), 1.00(d, J=7.5 Hz, 1H, —CH_2—), 0.90—0.83(m, 2H, —CH_2—); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.8, 159.7, 151.1, 148.6, 137.7, 131.5, 124.6, 98.6, 81.9(d, J=170.5 Hz), 77.9, 68.7(d, J=19.4 Hz), 50.5, 33.6, 10.7, 8.0; HRMS(ESI), *m/z* calcd. for $C_{15}H_{15}BrClFN_2O_3[M+H]^+$: 405.0017; found: 405.0035.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](methyl)-amino}-5-(3-fluoropropoxy)furan-2(5*H*)-one(**4**l): a yellow solid, yield 60%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.32(d, J=2.4 Hz, 1H, Py—H), 7.62(dd, J=8.3, 2.3 Hz, 1H, Py—H), 7.40(d, J=8.2 Hz, 1H, Py—H), 5.83[s, 1H, O—CH(C)—O], 4.88(d,

J=16.1 Hz, 1H, Py—CH_2—N), 4.78(d, *J*=16.1 Hz, 1H, Py—CH_2—N), 4.53(qt, *J*=9.3, 5.5 Hz, 1H, F—C**H**$_2$—CH_2), 4.46(qt, *J*=9.3, 5.5 Hz, 1H, F—C**H**$_2$—CH_2), 3.96(dt, *J*=9.5, 5.9 Hz, 1H, O—C**H**$_2$—CH_2), 3.81(dt, *J*=9.4, 6.4 Hz, 1H, O—C**H**$_2$—CH_2), 3.11(s, 3H, N—CH_3), 2.03—1.95(m, 2H, —CH_2—); ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 168.1, 157.9, 151.4, 148.7, 137.8, 130.6, 124.8, 98.2, 80.3(d, *J*=165.3 Hz), 64.8(d, *J*=5.0 Hz), 52.3, 38.5, 30.3(d, *J*=19.9 Hz). 30.4; HRMS(ESI), *m/z* calcd. for $C_{14}H_{15}BrClFN_2O_3[M+H]^+$: 393.0011; found: 393.0019.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](ethyl)amino}-5-(3-fluoropropoxy)furan-2(5*H*)-one(**4**m): a yellow oily liquid, yield 56%; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 8.31(s, 1H, Py—H), 7.61(d, *J*=8.0 Hz, 1H, Py—H), 7.38(d, *J*=7.9 Hz, 1H, Py—H), 5.81[s, 1H, O—CH(C)—O], 4.85(d, *J*=15.4 Hz, 1H, Py—CH_2—N), 4.68(d, *J*=15.9 Hz, 1H, Py—CH_2—N), 4.48(dddd, *J*=47.0, 22.2, 9.6, 4.6 Hz, 2H, F—C**H**$_2$—CH_2), 4.01—3.91(m, 1H, O—C**H**$_2$—CH_2), 3.80(dt, *J*=9.4, 6.2 Hz, 1H, O—C**H**$_2$—CH_2), 3.51(q, *J*=7.4, 6.7 Hz, 2H, N—CH_2—), 2.07—1.92(m, 2H, —CH_2—), 1.31—1.19(m, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 168.2, 157.5, 151.1, 148.4, 137.7, 131.2, 124.6, 98.1, 80.4(d, *J*=165.2 Hz), 73.8, 64.9(d, *J*=5.1 Hz), 49.5, 45.0, 30.3(d, *J*=20.0 Hz), 13.9; HRMS(ESI), *m/z* calcd. for $C_{15}H_{17}BrClFN_2O_3[M+H]^+$: 406.0095; found: 406.0097.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](propyl)-amino}-5-(3-fluoropropoxy)furan-2(5*H*)-one(**4**n): a yellow oily liquid, yield 59%; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 8.30(s, 1H, Py—H), 7.59(d, *J*=8.2 Hz, 1H, Py—H), 7.38(d, *J*=8.1 Hz, 1H, Py—H), 5.79[s, 1H, O—CH(C)—O], 4.88(d, *J*=16.1 Hz, 1H, Py—CH_2—N), 4.61(d, *J*=16.2 Hz, 1H, Py—CH_2—N), 4.55—4.38(m, 2H, F—C**H**$_2$—CH_2), 3.96(dt, *J*=9.3, 5.9 Hz, 1H, O—C**H**$_2$—CH_2), 3.79(dt, *J*=9.4, 6.4 Hz, 1H, O—C**H**$_2$—CH_2), 3.48—3.31(m, 2H, N—CH_2—), 1.98(dp, *J*=26.2, 6.0 Hz, 2H, —CH_2—), 1.67(H, *J*=7.5 Hz, 2H), 0.92(t, *J*=7.3 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 168.1, 157.5, 151.3, 148.4, 137.6, 131.1, 124.6, 98.1, 80.3(d, *J*=165.4 Hz), 74.1, 64.9(d, *J*=5.0 Hz), 51.7, 50.2, 30.3(d, *J*=20.0 Hz), 21.9, 10.57; HRMS(ESI), *m/z* calcd. for $C_{16}H_{19}BrClFN_2O_3[M+H]^+$: 420.0252; found: 420.0256.

3-Bromo-4-{[(6-chloropyridin-3-yl)methyl](cyclopropyl)-amino}-5-(3-fluoropropoxy)furan-2(5*H*)-one(**4**o): a yellow solid, yield 48%; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 8.34(s, 1H, Py—H), 7.67—7.56(m, 1H, Py—H), 7.36(d, *J*=8.1 Hz, 1H, Py—H), 6.00[s, 1H, O—CH(C)—O], 5.38—5.23(m, 1H, Py—CH_2—N), 4.61—4.50(m, 1H, F—C**H**$_2$—CH_2), 4.49—4.44 (m, 1H, Py—CH_2—N), 4.44—4.31(m, 1H, F—C**H**$_2$—CH_2), 3.96(dt, *J*=9.4, 5.6 Hz, 1H, O—C**H**$_2$—CH_2), 3.81(dt, *J*=9.3, 6.4 Hz, 1H, O—C**H**$_2$—CH_2), 2.88(dq, *J*=10.2, 5.2, 4.6 Hz, 1H, N—C**H**(CH_2)—CH_2), 2.07—1.91(m, 2H, —CH_2—), 0.95(dp, *J*=52.9, 5.4, 4.4 Hz, 2H, —CH_2—), 0.83(dt, *J*=13.5, 6.6 Hz, 2H, —CH_2—); ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 167.9, 159.8, 151.1, 148.6, 137.7, 131.4, 124.6, 98.8, 80.3(d, *J*=165.4 Hz), 79.5, 65.5(d, *J*=4.9 Hz), 50.4, 33.5, 30.3(d, *J*=19.9 Hz), 10.7, 7.9; HHRMS(ESI), *m/z* calcd. for $C_{16}H_{17}BrClFN_2O_3[M+H]^+$: 418.0095; found: 418.0092.

3-chloro-4-{[(6-chloropyridin-3-yl)methyl](methyl)-amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**p): a pale yellow oily liquid, yield 48%; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 8.34(d, *J*=2.5 Hz, 1H, Py—H), 7.64(dd, *J*=8.2, 2.5 Hz, 1H, Py—H), 7.40(d, *J*=8.2 Hz, 1H, Py—H), 5.88[s, 1H, O—CH(C)—O], 4.79(s, 2H, Py—CH_2—N), 4.66(m, 1H, F—C**H**$_2$—CH_2), 4.53(m, 1H, F—C**H**$_2$—CH_2), 4.12(m, 2H, O—C**H**$_2$—CH_2F), 3.15(s, 3H, N—CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 167.5, 155.1, 151.5, 148.8, 137.9, 130.5, 124.8, 97.2, 87.9, 81.9(d, *J*=170.4 Hz), 68.0(d, *J*=19.2 Hz), 52.4, 38.2; HRMS(ESI+) calcd for $C_{13}H_{14}Cl_2FN_2O_3$ $[M+H]^+$: 335.0366; found: 335.0360.

3-Chloro-4-{[(6-chloropyridin-3-yl)methyl](ethyl)amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**q): a pale yellow oily liquid, yield 46%; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 8.32(d, *J*=2.4 Hz, 1H, Py—H), 7.64(dd, *J*=8.3, 2.4 Hz, 1H, Py—H), 7.38(d, *J*=8.2 Hz, 1H, Py—H), 5.85[s, 1H, O—CH(C)—O], 4.74(q, *J*=16.4 Hz, 2H, Py—CH_2—N), 4.67—4.60(m, 1H, F—C**H**$_2$—CH_2), 4.57—4.47(m, 1H, F—C**H**$_2$—CH_2), 4.13(d, *J*=7.2 Hz, 1H, O—C**H**$_2$—CH_2F), 4.00(m, 1H, O—C**H**$_2$—CH_2F), 3.61—3.45(m, 2H, N—CH_2—), 1.27(td, *J*=7.1, 3.5 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 167.5, 154.7, 151.3, 148.5, 137.8, 131.1, 124.6, 97.1, 87.5, 81.9(d, *J*=170.3 Hz), 68.1(d, *J*=19.2 Hz), 49.6, 45.0, 13.9; HRMS(ESI), *m/z* calcd. for $C_{14}H_{15}Cl_2FN_2O_3[M+H]^+$: 349.0522; found: 349.0525.

3-Chloro-4-{[(6-chloropyridin-3-yl)methyl](propyl)-amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**r): a yellow solid, yield 43%; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 8.32(d, *J*=2.5 Hz, 1H, Py—H), 7.63(dd, *J*=8.3, 2.4 Hz, 1H, Py—H), 7.39(d, *J*=8.3 Hz, 1H, Py—H), 5.83[s, 1H, O—CH(C)—O], 4.82(d, *J*=16.4 Hz, 1H, F—C**H**$_2$—CH_2), 4.73—4.58(m, 2H, Py—CH_2—N), 4.51(td, *J*=3.8, 1.9 Hz, 1H, F—C**H**$_2$—CH_2), 4.10(m, 2H, O—C**H**$_2$—CH_2), 3.41(m, 2H, N—CH_2—), 1.69(q, *J*=7.4 Hz, 2H, —CH_2—), 0.93(t, *J*=7.4 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.5, 154.8, 151.3, 148.5, 137.7, 131.1, 124.6, 97.1, 87.611, 81.9(d, *J*=170.4 Hz), 68.13(d, *J*=19.2 Hz), 51.8, 50.3, 22.0, 10.6; HRMS(ESI), *m/z* calcd. for $C_{15}H_{17}Cl_2FN_2O_3[M+H]^+$: 363.0679; found: 363.0634.

3-Chloro-4-{[(6-chloropyridin-3-yl)methyl](cyclopropyl)-amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**s): yellow solid, yield 41%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.36(d, *J*=2.5 Hz, 1H, Py—H), 7.64(dd, *J*=8.3, 2.5 Hz, 1H, Py—H), 7.38(d, *J*=8.2 Hz, 1H, Py—H), 6.03[s, 1H, O—CH(C)—O], 5.20(d, *J*=16.1 Hz, 1H, F—CH_2), 4.62(m, 1H, F—C**H**$_2$—CH_2), 4.51(m, 2H, Py—CH_2—N), 4.12(m, 1H, O—C**H**$_2$—CH_2), 4.01(m, 1H, O—C**H**$_2$—CH_2), 3.95[m, 1H, N—C**H**(CH_2)—CH_2], 1.01(m, 4H, —CH_2—CH_2—); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.3, 156.8, 151.1, 148.6, 137.7, 131.5, 124.6, 97.6, 90.9, 81.9(d, *J*=170.4), 68.7(d, *J*=19.3 Hz), 50.5, 33.5, 10.4, 7.8; HRMS(ESI), *m/z* calcd. for $C_{15}H_{15}Cl_2FN_2O_3[M+H]^+$: 361.0522; found: 361.0529.

3-Chloro-4-{[(6-chloropyridin-3-yl)methyl](methyl)-amino}-5-(3-fluoropropoxy)furan-2(5*H*)-one(**4**t): pale yellow oily liquid, yield 55%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.33(d, *J*=2.3 Hz, 1H, Py—H), 7.64(dd, *J*=8.2, 2.1 Hz, 1H, Py—H), 7.41(d, *J*=8.2 Hz, 1H, Py—H), 5.82[s, 1H, O—CH(C)—O], 4.79(d, *J*=14.1 Hz, 2H, Py—CH_2—N), 4.57(td, *J*=5.8, 4.1 Hz, 1H, F—C**H**$_2$—CH_2), 4.51—4.40(m, 1H, F—C**H**$_2$—CH_2), 3.90(ddt, *J*=6.1, 9.4, 6.1 Hz, 2H, O—C**H**$_2$—CH_2), 3.11(s, 3H,

N—CH_3), 2.09—1.95(m, 2H,—CH_2—); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.7, 155.3, 151.3, 148.6, 137.9, 130.6, 124.7, 97.3, 87.6, 80.3(d, *J*=165.1 Hz), 64.88(d, *J*=5.0 Hz), 52.29, 38.19, 30.24(d, *J*=19.9 Hz); HRMS(ESI), *m/z* calcd. For $C_{14}H_{15}Cl_2FN_2O_3[M+H]^+$: 349.0517; found: 349.0513.

3-Chloro-4-{[(6-chloropyridin-3-yl)methyl](ethyl)amino}-5-(3-fluoropropoxy)furan-2(5*H*)-one(**4**u): a yellow oily liquid, yield 47%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.31(d, *J*=2.4 Hz, 1H, Py—H), 7.61(dd, *J*=8.3, 2.3 Hz, 1H, Py—H), 7.38(d, *J*=8.2 Hz, 1H, Py—H), 5.80[s, 1H, O—CH(C)—O], 4.83—4.60(m, 2H, Py—CH_2—N), 4.56—4.31(m, 2H, F—C**H**$_2$—CH_2), 3.88(ddt, *J*=10.4, 9.5, 6.2 Hz, 2H, O—C**H**$_2$—CH_2), 3.49(q, *J*=6.8 Hz, 2H, N—CH_2—), 2.06—1.93(m, 2H,—CH_2—), 1.26(td, *J*=7.1, 5.8 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.7, 154.8, 151.2, 148.4, 137.8, 131.2, 124.6, 97.2, 87.5, 80.4(d, *J*=165.3 Hz), 65.0(d, *J*=5.0 Hz), 49.5, 44.9, 30.3(d, *J*=20.0 Hz), 14.0; HRMS(ESI), *m/z* calcd. for $C_{15}H_{17}Cl_2FN_2O_3[M+H]^+$: 362.0600; found: 362.0604.

3-Chloro-4-{[(6-chloropyridin-3-yl)methyl](propyl)-amino}-5-(3-fluoropropoxy)furan-2(5*H*)-one(**4**v): a yellow solid, yield 43%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.30(d, *J*=2.4 Hz, 1H, Py—H), 7.60(dd, *J*=8.3, 2.3 Hz, 1H, Py—H), 7.38(d, *J*=8.2 Hz, 1H, Py—H), 5.78[s, 1H, O—CH(C)—O], 4.88—4.72(m, 1H, Py—CH_2—N), 4.65—4.55(m, 1H, Py—CH_2—N), 4.54—4.27(m, 2H, F—C**H**$_2$—CH_2), 3.97(dt, *J*=9.5, 5.9 Hz, 1H, O—C**H**$_2$—CH_2), 3.79(dt, *J*=9.5, 6.5 Hz, 1H, O—C**H**$_2$—CH_2), 3.38(tq, *J*=22.3, 13.4, 10.7 Hz, 2H, N—CH_2—), 1.97(dp, *J*=26.3, 5.9 Hz, 2H, —CH_2—), 1.67(H, *J*=7.5 Hz, 2H, —CH_2—), 0.92(t, *J*=7.4 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.7, 154.9, 151.2, 148.4, 137.7, 131.2, 124.6, 97.2, 87.6, 80.3(d, *J*=165.3 Hz), 65.0(d, *J*=5.0 Hz), 51.7, 50.2, 30.3(d, *J*=20.0 Hz), 22.0, 10.7; HRMS(ESI), *m/z* calcd. for $C_{16}H_{19}Cl_2FN_2O_3[M+H]^+$: 376.0757; found: 376.0755.

3-Chloro-4-{[(6-chloropyridin-3-yl)methyl](cyclopropyl)-amino}-5-(3-fluoropropoxy)furan-2(5*H*)-one(**4**w): a yellow solid, yield 57%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.34(d, *J*=2.7 Hz, 1H, Py—H), 7.62(dd, *J*=8.2, 2.3 Hz, 1H, Py—H), 7.36(d, *J*=8.2 Hz, 1H, Py—H), 5.98[s, 1H, O—CH(C)—O], 5.20(d, *J*=16.0 Hz, 1H, Py—CH_2—N), 4.54—4.48(m, 1H, F—C**H**$_2$—CH_2), 4.44(s, 1H, Py—CH_2—N), 4.44—4.36(m, 1H, F—C**H**$_2$—CH_2), 3.96(dt, *J*=9.4, 5.7 Hz, 1H, O—C**H**$_2$—CH_2), 3.81(dt, *J*=9.4, 6.5 Hz, 1H, O—C**H**$_2$—CH_2), 2.90—2.85[m, 1H, N—C**H**(CH_2)—CH_2], 2.03—1.93(m, 2H, —CH_2—), 1.02—0.87(m, 2H, —CH_2—), 0.83(tdd, *J*=7.4, 5.7, 4.8, 2.0 Hz, 2H, —CH_2—); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.5, 156.9, 151.0, 148.5, 137.8, 131.5, 124.6, 97.8, 91.0, 80.3(d, *J*=165.3 Hz), 65.6(d, *J*=4.8 Hz), 50.4, 33.3, 30.3(d, *J*=19.9 Hz), 10.4, 7.7; HRMS(ESI), *m/z* calcd. for $C_{16}H_{17}Cl_2FN_2O_3[M+H]^+$: 374.0600; found: 374.0603.

4-{[(6-Chloropyridin-3-yl)methyl](methyl)amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**x): a yellow solid, yield 53%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.30(d, *J*=2.4 Hz, 1H, Py—H), 7.58(d, *J*=22.1 Hz, 1H, Py—H), 7.38(d, *J*=8.2 Hz, 1H, Py—H), 5.90[s, 1H, O—CH(C)—O], 4.72(s, 1H), 4.68—4.56(m, 2H, Py—CH_2—N), 4.53—4.40(m, 2H, F—C**H**$_2$—CH_2), 4.17—3.90 (m, 2H, O—C**H**$_2$—CH_2), 3.18—2.73(m, 3H, N—CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 171.3, 165.3, 151.4, 148.7, 138.0, 124.7, 97.8, 83.8, 82.0(d, *J*=70.0 Hz), 68.0(d, *J*=19.3 Hz), 51.6, 37.8, 19.2; HRMS(ESI), *m/z* calcd. for $C_{13}H_{14}ClFN_2O_3[M+H]^+$: 301.0755; found: 301.0723.

4-{[(6-Chloropyridin-3-yl)methyl](ethyl)amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**y): a yellow oily liquid, yield 50%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.37(d, *J*=2.5 Hz 1H, Py—H), 7.72(dd, *J*=8.2 Hz, 2.3Hz 1H, Py—H), 7.37(d, *J*=8.2 Hz, 1H, Py—H), 5.88[s, 1H, O—CH(C)—O], 4.63(s, 1H), 4.47(d, *J*=14.8 Hz, 2H, Py—CH_2—N), 4.19(m, 2H, F—C**H**$_2$—CH_2), 4.03(dt, *J*=12.2, 2.9 Hz, 2H, O—C**H**$_2$—CH_2), 3.20(m, 2H, N—CH_2—), 1.36—1.08(m, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 171.5, 164.4, 151.2, 148.5, 138.5, 130.5, 124.5, 97.8, 83.5, 82.1(d, *J*=170.1 Hz), 68.1(d, *J*=19.0 Hz), 60.4, 45.6, 14.2; HRMS(ESI), *m/z* calcd. for $C_{14}H_{16}ClFN_2O_3[M+H]^+$: 315.0912; found: 315.0907.

4-{[(6-Chloropyridin-3-yl)methyl](propyl)amino}-5-(2-fluoroethoxy)furan-2(5*H*)-one(**4**z): a yellow oily liquid, yield 45%; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 8.29(d, *J*=2.4 Hz, 1H, Py-H), 7.60(s, 1H, Py—H), 7.36(d, *J*=8.2 Hz, 1H, Py—H), 5.87[s, 1H, O—CH(C)—O], 4.70(d, *J*=6.1 Hz, 1H, —CH═C), 4.52(m, 4H, Py—CH_2—N, F—C**H**$_2$—CH_2), 4.20—3.90(m, 2H, O—C**H**$_2$—CH_2), 3.15(d, *J*=6.3 Hz, 2H, N—CH_2—), 1.68—1.55(m, 2H, —CH_2—), 0.92(t, *J*=7.4 Hz, 3H, —CH_3); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 171.5, 164.7, 151.2, 148.5, 137.9, 130.7, 124.5, 97.8, 83.7, 82.1(d, *J*=170.1 Hz), 68.0(d, *J*=19.1 Hz), 52.6, 50.4, 18.9, 11.1; HRMS(ESI), *m/z* calcd. for $C_{15}H_{18}ClFN_2O_3[M+H]^+$: 329.1068; found: 329.1056.

3 Results and Discussion

3.1 Synthesis

The general synthetic route is shown in Scheme 2. Intermediates **2**a and **2**b could be obtained from mucobromic acid or mucochloric acid and alcohols by etherification reaction according to literature methods[19]. Derivative **3** was achieved by employing methods similar to our reported procedure[20]. Target products **4**a—**4**w were synthesized from intermediate **2**a or **2**b and **3** under mild reaction conditions. Condensation reaction of glyoxilic acid with chloroacetaldehyde in dioxane afforded intermediate **5** using morpholinium chloride as catalyst[21]. Compounds **4**x—**4**z were synthesized employing the same synthetic method for compounds **4**a—**4**w with intermediate **2**c and derivative **3** as strating materials. The chemical structures of all target compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. Taking compound **4**h as an example, the chemical shifts of three protons in the pyridine ring were observed at δ 8.34(d), 7.65(dd) and 7.41(d), three protons of methyl group were at δ 3.16 as a single peak, single proton of butenolide ring was at δ 5.9 as a single peak in the ^{1}H NMR spectra. In the ^{13}C NMR spectra, the C of CH_2**C**H_2F was observed as a double peak at δ 81.9 and the signal of C of **C**H_2CH_2F was also a double peak at δ 67.9. HRMS spectral data of compound **4**h was in good agreement with the calculated values.

3.2 Insecticidal Activity

Bioassays were performed on representative test

organisms grown in the laboratory. The insecticidal activities of the synthetic compounds against *A. craccivora* and *N. lugens* were tested according to reported procedure[23,24].

The insecticidal activities of the title compounds **4**a—**4**z against *A. craccivora* and *N. lugens* are shown in Table 1. It could be seen form the results that the title compounds exhibited moderate insecticidal activities(mortality rate > 50%) at 100 mg/L for compounds **4**e, **4**h against *A. craccivora* and for **4**a, **4**d, **4**e, **4**h, **4**j, **4**k, **4**l, **4**o against *N. lugens*. However, other compounds exhibited weak or no activities. When X=Br, the biological activities decreased with the alkyl chain length of R_1. Compounds **4**a, **4**e, **4**h, **4**l with methyl groups had the highest insecticidal activities compared with those with longer R_1 chains. It was worth noting that compounds had better insecticidal activities when R_2 were fluoroalkyl groups compared with those with alkyl groups. Compounds **4**h, **4**j, **4**k with fluoroethyl group had over 70% mortality rate against *N. lugens*. When bromine was replaced by chlorine or hydrogen at the 3-position of butenolide, compounds exhibited accepted activities. Compounds **4**w, **4**x exhibited over 70% mortality rate against *A. craccivora*, and **4**p, **4**q, **4**r, **4**t, **4**w, **4**x, **4**y, **4**z showed over 50% mortality against *N. lugens* at 100 mg/L. The insecticidal activities of the title compounds against *N. lugens* were higher than against *A. craccivora*.

Table 1 Insecticidal activities of targeted compounds against *A. craccivora* and *N. lugens*

Compound	R_1	X	R_2	Mortality*(%)(100 mg/L)	
				A. craccivora	*N. lugens*
4a	CH_3	Br	CH_3	+	++
4b	CH_2CH_3	Br	CH_3	—	—
4c	$CH_2CH_2CH_3$	Br	CH_3	—	—
4d	Cyclopropyl	Br	CH_3	+	++
4e	CH_3	Br	CH_2CH_3	++	+++
4f	CH_2CH_3	Br	CH_2CH_3	—	+
4g	$CH_2CH_2CH_3$	Br	CH_2CH_3	—	+
4h	CH_3	Br	CH_2CH_2F	++++	++++
4i	CH_2CH_3	Br	CH_2CH_2F	+	+
4j	$CH_2CH_2CH_3$	Br	CH_2CH_2F	—	+++
4k	Cyclopropyl	Br	CH_2CH_2F	—	+++
4l	CH_3	Br	$CH_2CH_2CH_2F$	—	++
4m	CH_2CH_3	Br	$CH_2CH_2CH_2F$	—	+
4n	$CH_2CH_2CH_3$	Br	$CH_2CH_2CH_2F$	—	+
4o	Cyclopropyl	Br	$CH_2CH_2CH_2F$	—	++
4p	CH_3	Cl	CH_2CH_2F	—	++
4q	CH_2CH_3	Cl	CH_2CH_2F	+	++
4r	$CH_2CH_2CH_3$	Cl	CH_2CH_2F	—	++
4s	Cyclopropyl	Cl	CH_2CH_2F	+	+
4t	CH_3	Cl	$CH_2CH_2CH_2F$	—	++
4u	CH_2CH_3	Cl	$CH_2CH_2CH_2F$	—	+
4v	$CH_2CH_2CH_3$	Cl	$CH_2CH_2CH_2F$	+	+
4w	Cyclopropyl	Cl	$CH_2CH_2CH_2F$	++++	+++
4x	CH_3	H	CH_2CH_2F	+++	++
4y	CH_2CH_3	H	CH_2CH_2F	+	+++
4z	$CH_2CH_2CH_3$	H	CH_2CH_2F	+	++
Imidacloprid				++++	++++
Flupyradifurone				++++	++++

* ++++: 90%—100% mortality; +++: 70%—89% mortality; ++: 50%—69% mortality; +: 30%—50% mortality; —: <30% mortality.

Among the title compounds, **4**h and **4**w exhibited excellent insecticidal activities(100% mortality rate against *A. craccivora*, 100% and 80% against *N. lugens,* respectively) at 100 mg/L(Table 2), which were equal to those of imidacloprid (100%). When the concentrations of compounds **4**h and **4**w were reduced to 4 mg/L, compound **4**h still showed high mortality rate(60% and 75%, respectively against *A. craccivora* and *N. lugens*). Therefore compound **4**h could offer considerable potential for further development as a new lead compound in modern insecticide development. Further study was underway.

Table 2 Insecticidal activity of compounds 4h and 4w against *A. craccivora* and *N. lugens*

Compound	Mortality(%)					
	A. craccivora			*N. lugens*		
	100 mg/L	20 mg/L	4 mg/L	100 mg/L	20 mg/L	4 mg/L
4h	100	100	60	100	92	75
4w	100	60	nt*	80	nt*	nt*
Imidacloprid	100	100	90	100	84	70
Flupyradifurone	100	100	100	100	100	95

* nt: not tested.

4 Conclusions

In summary, a series of 5-alkoxyfuran-2(5*H*)-one analogues was designed and synthesized. Their structures were characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The bioassays indicated that most of the target compounds showed accepted

insecticidal activities against *A. craccivora*(**4**e, **4**h, **4**w, **4**x) and *N. lugens*(**4**a, **4**d, **4**e, **4**h, **4**j, **4**k, **4**l, **4**o, **4**p, **4**q, **4**r, **4**t, **4**w, **4**x, **4**y, **4**z) at 100 mg/L. Despite the activities of most derivatives were moderate at low concentration, compound **4**h was highly active and had high insecticidal activities against *A. craccivora* and *N. lugens* and thus could be used as a lead compound for further development.

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