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Letter

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Synthesis and Insecticidal Activity of Novel Nitropyridyl-based Dichloropropene Ethers

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KEYWORDS: nitropyridyl-based dichloropropene ethers; synthesis; insecticide; structure-activity relationship

ABSTRACT: Dihalopropene ether insecticides are known for good features such as no cross-resistance to other insecticide classes, safe for mammals, etc. Pyridalyl is the only currently commercialized dichloropropene ether insecticide, however it contains a trifluoromethyl group whose synthesis requires harsh reagents and reaction conditions. In order to search for novel dihalopropene ethers with unique biological activities but without trifluoromethyl groups, a series of nitropyridyl-based dichloropropene ether analogues were synthesized by reacting nitro-based halopyridine with 2,6-dichloro-4-(3,3-dichloroallyloxy)phenol or 2,6-dichloro-4-(3,3-dichloroallyloxy)phenyl 3-hydroxypropyl ether. Bioassay showed that the compounds exhibited potent insecticidal activities against various lepidopteran pests. Particularly, 2,6-dichloro-4-(3,3-dichloroallyloxy)phenyl 3-(5-nitro-2-pyridyloxy)propyl ether (**8e**) was active against major agricultural pests and its insecticidal potency was comparable to that of Pyridalyl. Besides the trifluoromethyl group in Pyridalyl, a nitro group on the 5-position of the pyridyl ring is also viable for the development of optimal insecticidal activity.

■

■ INTRODUCTION

The insecticide market has been dominated by organophosphates, carbamates, synthetic pyrethroids and neonicotinoids since the 1970s, and consequently insect resistance to these insecticides has become a serious problem. The development of resistance to current treatments, along with newly evolving pest problems, the changing regulatory landscape and market environment, gives rise to an emerging demand of new insecticides that are not only active to resistance strains but also safe to humans and the environment.

Dihalopropene ethers are active against a wide range of pests *(1-4)*. However only one member of this group, 2,6-dichloro-4-(3,3-dichloroallyoxy)phenyl 3-[5-(trifluoromethyl)-2-pyridyloxy]propyl ether (S-1812) (*5-8*), has been developed as an agricultural insecticide under the trade name 'Pyridalyl' by Sumitomo Chemical Co Ltd., Japan (**Figure 1**). Although the mechanism of Pyridalyl is yet unknown or undetermined, it exhibits diverse characteristics, such as long residual activity, excellent rain fastness, no cross-resistance to other insecticide classes, and great safety to non-target beneficial organisms especially honey bees and bumble bees. Thus, Pyridalyl is expected to be a key component for pest control in Integrated Pest Management (IPM) and insecticide resistance management.

Sakamoto et al. pioneered in the research of Pyridalyl analogues. He pointed out that a trifluoromethyl group on the 5-position of the pyridyl ring was required for the development of optimal insecticidal activity. More specifically, although both the nitro group and the trifluoromethyl group are electron-withdrawing, introducing different group on the 5-position of the pyridyl ring yields distinctively different results. For the nitro product **1a** [2-(2,6-dichloro-4-((3,3-dichloroallyl)oxy)phenoxy)-5-nitropyridine], insecticidal activity against *Spodoptera litura* dropped considerably to LC_{50} > 200 mg/L as opposed to that of the trifluoromethyl product **2a** [2-(2,6-dichloro-4-((3,3-dichloroallyl)oxy)phenoxy)-5-(trifluoromethyl)pyridine] with LC_{50} = 1.25-5.00 mg/L (**Figure 1**) *(6)*. This also makes sense theoretically because the trifluoromethyl group confers increased metabolic stability and lipophilicity in addition to its high

electronegativity (*9-10*). However, the current processes for trifluoromethyl compounds require harsh reagents and reaction conditions, and the degradation products of trifluoromethyl-substituted compounds is usually environmental unfriendly. It is thus meaningful to develop new dihalopropene ether insecticides that have insecticidal activities comparable to that of Pyridalyl but are more readily to be produced and more environmentally friendly.

In our previous work (3), we derived **3a** [2,6-dichloro-4-(3,3-dichloroallyloxy)phenyl 3-[6-trifluoromethyl-2-ethoxy-4-pyrimidyloxy] propyl ether] from Pyridalyl and Fluacrypyrim, a commercial acaricide, and **3a s**howed remarkable insecticidal activity against *Mythimna separate* (LC_{50} = 23.72 mg/L). In order to obtain novel dihalopropene ethers without trifluoromethyl groups, **3a** was optimized first by removing the trifluoromethyl group. Because both the nitro group and the nitrogen atom in the pyrimidyl ring are strongly electron-withdrawing, **3a** was then optimized by replacing the nitrogen atom next to the trifluoromethyl group in the pyrimidyl ring with C-NO_2. This led to **8a-2** [2,6-dichloro-4-(3,3-dichloroallyloxy)phenyl 3-[5-nitro-6-ethoxy-2-pyridyloxy]propyl ether]. **8a-2** was synthesized starting from 2,6-dichloro-3-nitropyridine, and **8a'-2**, the 3-NO_2 compound, was obtained as a by-product of **8a-2**, the 5-NO_2 compound. However, the insecticidal activity against *M. separate* of 5-NO_2 compound (LC_{50} = 7.45 mg/L) was relatively stronger than that of the 3-NO_2 compound (LC_{50} > 40 mg/L). In addition, bioassay showed that biological activities of **8a-2** against the larvae of some important pests such as *M. separate* (LC_{50} = 7.45 mg/L) and *Plutella xylostella* (LC_{50} = 7.07 mg/L) were comparable to that of Pyridalyl (LC_{50} = 4.81 mg/L and 4.29 mg/L respectively). However, **8a-2** (LC_{50} = 54.92 mg/L) was less active against *Prodenia litura* compared to Pyridalyl (LC_{50} = 10.07 mg/L).

In fact, we did not discover any compound whose insecticidal activity against *P. litura* was comparable to that of Pyridalyl until we replaced 6-ethoxy in **8a-2** with hydrogen, which led to our final product **8e** [2,6-dichloro-4-(3,3-dichloroallyloxy)phenyl 3-[5-nitro-2-pyridyloxy]propyl ether]. Although Sakamoto et al. suggested that trifluoromethyl group on the 5-position was required, our other works on nitropyridyl-based compounds indicated that hydrogen exhibited similar or stronger insecticidal activities than 6-alkoxy.

Therefore, **8a-2** was optimized by replacing the ethoxy with hydrogen to give **8e**. Bioassay results indicated that **8e** exhibited insecticidal activities against major agricultural pests such as *M. separate*, *P. xylostella*, *P. litura*, and etc at levels similar to that of Pyridalyl. The design strategies of all compounds are shown in **Figure 2**.

■ MATERIALS AND METHODS

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. NMR spectra were obtained with a Varian INOVA-300 spectrometer using tetramethylsilane (TMS) as the internal standard and deuteriochloroform ($CDCl_3$) as the solvent. LC-MS were recorded with an Agilent 1260/6120 Series and GC-MS with an Agilent 7890-5975C Series. Uncorrected melting points were taken in a WRS-1A digital melting points apparatus. Elemental analyses were obtained with a Vario EL III from Elementar.

Synthesis. The general synthetic methods for the target compounds **8** are shown in **Figure 3**. Representative procedures are given below. Yields were not optimized. All reactions were carried out under a protective atmosphere of dry nitrogen or utilizing a calcium chloride tube.

2,6-Dichloro-4-(3,3-dichloroallyloxy)phenol ***(4a).*** 1,1,3-Trichloropropene (27.6 g, 190 mmol) in *N,N*-dimethyl formamide (DMF; 30 mL) was added dropwise to a solution of hydroquinone (23.1 g, 210 mmol) and potassium carbonate (30.4 g, 220 mmol) in DMF (100 mL) at room temperature. After stirred for 6-8 h, the reaction was poured into ice-water (500 mL) and extracted with ethyl acetate (2*250 mL). The combined ethyl acetate extracts were washed with water and dried with anhydrous sodium sulfate. Then the solvent was removed using rotary evaporator. The residue was separated by silica-gel column chromatography with petroleum ether and ethyl acetate (10:1 by volume) as eluant to give 99.5% (GC) 4-((3,3-dichloroallyl)oxy)phenol 26.2 g (63.0%). Sulfuryl dichloride (35.0 g, 260 mmol) was added dropwise to the solution of 4-((3,3-dichloroallyl)oxy)phenol (26.2 g, 120 mmol) and triethylamine (0.70 g, 7.0 mmol) in toluene (150 mL) at 90-100℃. The reaction was stirred for 8-10 h. After the extra sulfuryl dichloride was removed, the resulting solution was poured into ice-water (500 mL), washed with saturated sodium hydrogencarbonate solution and then water, and dried with anhydrous sodium sulfate. The solvent was removed to give 95.5% (GC) **4a** 26.6 g (73.7%).

2,6-Dichloro-4-(3,3-dichloroallyloxy)phenyl 3-hydroxypropyl ether ***(5a).*** 3-Bromopropanol (2.02 g, 14.5 mmol) in DMF (20 mL) was added dropwise to a solution of **4a** (2.88 g, 10 mmol) and potassium carbonate (2.00 g, 14.5 mmol) in DMF (60 mL) at room temperature. The reaction mixture was stirred for 26-28 h, after which the reaction was poured into ice-water (150 mL) and extracted with ethyl acetate (2*100 mL). The

combined ethyl acetate extracts were washed with water and dried with anhydrous sodium sulfate. Then the solvent was removed using rotary evaporator. The residue was separated by silica-gel column chromatography with petroleum ether and ethyl acetate (10:1 by volume) as eluant to give 96.0% (GC) **5a** 2.14 g (59.4%).

6-Chloro-2-ethoxy-3-nitropyridine ***(6a-2).*** Ethanol (2.40 g, 52.0 mmol) in toluene (10 mL) was added dropwise to a solution of 60% sodium hydride (4.48 g, 112 mmol) in toluene (80 mL) at 0 ℃ and stirred for 30-45 min. 2,6-Dichloro-3-nitropyridine (10.0 g, 52.0 mmol) in toluene (40 mL) was added dropwise to the reaction mixture. After stirred for 2-4 h at room temperature, the reaction was poured into ice-water (250 mL) and extracted with toluene (2*150 mL). The combined toluene extracts were washed with water and dried with anhydrous sodium sulfate. The solvent was removed to give a residue 9.80 g. After separated by silica-gel column chromatography with petroleum ether and ethyl acetate (100:1~50:1 by volume) as eluant to give 95.2% (GC) **6a-2** 7.92 g (71.7%); GC-MS (EI, 70Ev) (m/z) 202 (50% M^+), 174 (70% M^+-28), 158 (100% M^+-44), 117 (60% M^+-85); ^{1}H NMR δ($CDCl_3$) 1.45 (3H, t, *J*=7.2 Hz, CH_3), 4.55 (2H, q, *J*=7.2 Hz, CH_2), 7.01 (1H, d, *J*=8.1 Hz, Py H), 8.24 (1H, d, *J*=8.1 Hz, Py H).

2-Chloro-6-ethoxy-3-nitropyridine ***(6a'-2).*** Sodium ethanolate (4.10 g, 60 mmol) in ethanol (20 mL) was added dropwise to a solution of 2,6-dichloro-3-nitropyridine (11.6 g, 60 mmol) in ethanol (40 mL) at 0℃. After stirred for 4-5 h at room temperature, the reaction was poured into ice-water (350 mL) and extracted with ethyl acetate (2*100 mL). The combined ethyl acetate extracts were washed with water and dried with anhydrous sodium sulfate. Then the solvent was removed using rotary evaporator to give a residue which was then recrystallized from petroleum ether and ethyl acetate to give 97.0% (GC) **6a'-2** 5.62 g (44.7%). GC-MS (EI, 70Ev) (m/z) 202 (30% M^+), 187 (100% M^+-15), 174 (60% M^+-28), 158 (60% M^+-44), 117 (30% M^+-85); ^{1}H NMR δ($CDCl_3$) 1.40 (3H, t, *J*=7.2 Hz, CH_3), 4.44 (2H, q, *J*=7.2 Hz, CH_2), 6.74 (1H, d, *J*=8.7 Hz, Py H), 8.24 (1H, d, *J*=8.7 Hz, Py H).

2-(3-Bromopropoxy)-6-ethoxy-3-nitropyridine ***(7a'-2).*** **6a'-2** (2.02 g, 10 mmol) in tetrahydrofuran (THF; 20 mL) was added dropwise to a solution of 60% sodium hydride (0.52 g, 13 mmol) in THF (30 mL) at 0℃ and stirred for 15-30 min. 3-Bromopropanol (1.39 g, 10.0 mmol) in THF (15 mL) was then added

dropwise. The reaction mixture was stirred at room temperature for 2-3 h, after which the reaction was treated as described in the synthesis of **5a**. The residue was separated by silica-gel column chromatography with petroleum ether and ethyl acetate (50:1 by volume) as eluant to give 98.9% (GC) **7a'-2** 2.00 g (64.9%). GC-MS (EI, 70Ev) (m/z) 304 (60% M^+), 289 (15% M^+-15), 169 (100% M^+-135), 156 (75% M^+-148), 140 (65% M^+-164); ^{1}H NMR δ($CDCl_3$) 1.40 (3H, t, *J*=7.05 Hz, CH_3), 2.36-2.42 (2H, m, CH_2), 3.67 (2H, t, *J*=6.15 Hz, CH_2), 4.43 (2H, q, *J*=7.1 Hz, CH_2), 4.62 (2H, t, *J*=6.0 Hz, CH_2), 6.35 (1H, d, *J*=8.7 Hz, Py H), 8.32 (1H, d, *J*=8.7 Hz, Py H).

2,6-Dichloro-4-(3,3-dichloroallyloxy)phenyl 3-[6-ethoxy-5-nitro-2-pyridyloxy] propyl ether ***(8a-2).*** **5a** (0.88 g, 2.54 mmol) in THF (10 mL) was added dropwise to a solution of **6a-2** (0.52 g, 2.54 mmol) and 60% sodium hydride (0.12 g, 3.00 mmol) in THF (20 mL) at 0℃, then stirred for 8-10 h at 20-30℃. The reaction mixture was poured into ice-water (120 mL) and extracted with ethyl acetate (2*50 mL). The combined ethyl acetate extracts were washed with water and dried with anhydrous sodium sulfate. After the solvent was removed, the crude product was separated by silica-gel column chromatography using petroleum ether and ethyl acetate (200:1 to 100:1 by volume) as eluant to give 95.7% (HPLC) **8a-2** as an oil 0.38 g, yield 28.0%. LC-MS (APCI, Pos)(m/z) 511 (M^++1); calc for $C_{19}H_{18}Cl_4N_2O_6$: C 44.56, H 3.54, N 5.47; found: C 44.65, H 3.59, N 5.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.45 (3H, t, *J* =7.1 Hz), 2.26～2.34 (2H, m), 4.10 (2H, t, *J*=5.9 Hz), 4.54 (2H, q, *J* =7.1 Hz), 4.56 (2H, t, *J*=6.3 Hz), 4.57 (2H, d, *J*=6.6 Hz), 6.09 (1H, t, *J*=6.2 Hz), 6.34 (1H, d, *J*=8.7 Hz), 6.84 (2H, s), 8.31 (1H, d, *J*=9.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.39, 29.34, 63.76, 64.15, 65.41, 69.66, 126.53, 115.19, 120.55, 124.43, 124.93, 129.58, 138.61, 145.53, 154.00, 157.03, 164.93.

2,6-Dichloro-4-(3,3-dichloroallyloxy)phenyl 3-[6-ethoxy-3-nitro-2-pyridyloxy]propyl ether ***(8a'-2).*** **7a'-2** (1.62 g, 5.30 mmol) in THF (10 mL) was added dropwise to a solution of 60% sodium hydride (0.26 g, 6.50 mmol) and **4a** (1.53 g, 5.30 mmol) in THF (20 mL) at 0℃. The reaction mixture was stirred for 25-30 min at 0℃, then for 10-12 h at 20-30 ℃. The reaction was then treated as described in the synthesis of **8a-2** to give 96.6% (HPLC) **8a'-2** as an oil 1.05 g, yield 37.6%. LC-MS (APCI, Pos)(m/z) 511 (M^++1); calc for $C_{19}H_{18}Cl_4N_2O_6$: C 44.56, H 3.54, N 5.47; found: C 44.59, H 3.50, N 5.52; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.39 (3H, t, *J* =7.1

Hz), 2.31～2.39 (2H, m), 4.17 (2H, t, *J*=5.9 Hz), 4.41 (2H, q, *J* =7.1 Hz), 4.56 (2H, d, *J*=6.3 Hz), 4.75 (2H, t, *J*=6.3 Hz), 6.09 (1H, t, *J*=6.2 Hz), 6.32 (1H, d, *J*=8.7 Hz), 6.82 (2H, s), 8.31 (1H, d, *J*=8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.36, 29.37, 63.45, 64.27, 65.44, 69.73, 102.56, 115.18, 124.50, 124.90, 126.26, 129.58, 138.54, 145.54, 154.00, 157.03, 165.05.

The synthesis of **8a'-1, 8a-3 – 8a-10, 8b-1 – 8b-10, 8c'-1, 8c-2 – 8c-4, 8d-1 – 8d-4, 8e'** and **8e** with ≥95.0% purity (HPLC) were similar to that of **8a-2** or **8a'-2** and their structures were supported by spectroscopic data in **Table 1** - **Table 2.**

Biological assay (*11-14*)

Test insects. Stock colonies of test insects were reared in a conditioned room maintained at 25(±1)℃, 60(±5)% relative humidity and 14:10 h / light:dark.

Test compounds. Stock solution of every test compound was prepared in DMF or acetone at a concentration of 1.0 g litre^{-1}, and then diluted to the required test concentrations (1～500 mg litre^{-1}) with water containing 0.2% Tween 80.

Activity against *M. separate*. Ten third-instar of *M. separata* and 5 pieces of corn fragments were placed in a Petri dish, and sprayed with test solutions using a potter sprayer. After air-drying, kept in a room for normal cultivation. Mortality was determined 72 h after treatment. A control group was tested with the solvent only. Test was run 3 times, and results were averaged. Data were subjected to probit analysis and the medium lethal concentration (LC_{50}) value of tested compounds were calculated (95% FL) (*15*).

Activity against *Plutella xylostella* or *Prodenia litura*. Cabbage leaves were dipped into test solutions for 10 s. After air-drying, five leaves were put into a Petri dish with ten third-instar of test insects, kept in a room for normal cultivation. Mortality was assessed 72 h after treatment. A control group was tested with the solvent only. Test was run 4 times. Data were treated as described in *M. separate*.

■ RESULTS AND DISCUSSION

Chemistry. The synthesis scheme shown in **Figure 3** provides moderate yields of the test compounds. The structures of all synthesized compounds were analyzed and confirmed by ^{1}H NMR and MS. Due to the structural similarity of compounds **8**, only some representative compounds, such as **8a'-1**, **8a-2**, **8a'-2**, **8b-2**, **8e** and **8e'**, were analyzed and confirmed by ^{13}C NMR and **8a-2**, **8a'-**2 and **8e** by elemental analysis. **Table 1** summarizes the chemical

structures, MS data and physical characteristics of compounds **8.** NMR and elemental analysis data are listed in **Table 2**.

Due to the presence of the nitro group on the pyridyl ring, we expected to observe positional isomers on compounds **8**. Selective synthesis of positional isomers of **6** can be achieved by selecting different solvents. In aprotic solvent, the reaction of 2,6-dichloro-3-nitropyridine and nucleophilic alcohol yields mostly 3-NO_2 product **6a'**; in protic solvent, however, the same reaction gives mainly 5-NO_2 product **6a**. Also in protic solvent, the reaction of 2,6-dichloro-3-nitropyridine and nucleophilie amine or thiol gives 3-NO_2 product **6b'** or **6c'**.

Positional isomers may be differentiated with ^{1}H NMR data. Because NO_2 is a strongly electron-withdrawing group, when NO_2 is on the ortho position of -$OCH_2CH_2CH_2O$- (defined as 3-NO_2), the maximum value of δ_H in -$OCH_2CH_2CH_2O$- is usually $\geq$ 4.75 ppm; however when NO_2 is on the para position of -$OCH_2CH_2CH_2O$- (defined as 5-NO_2), the maximum value of δ_H in -$OCH_2CH_2CH_2O$- is often < 4.75 ppm. For example, δ_H = 4.56 ppm for **8a-2** and δ_H = 4.75 ppm for **8a'-2**.

Another way to identify positional isomers of compounds **8** is to study the ^{1}H NMR or GC-MS of their corresponding intermediate **6** and **7.** In ^{1}H NMR, the hydrogen on the ortho position of chlorine on the pyridyl ring has lower chemical shift value than the hydrogen on the ortho position of alkoxy, alkylthio or alkylamino on the pyridyl ring. For example, δ_H = 7.01 ppm for **6a-2** and δ_H = 6.74 ppm for **6a'-2**. In GC-MS, when alkoxy locates between the nitro group and the nitrogen atom in the pyridyl ring, the base peak is usually M^+ - alkoxy + 1 or M^+ - alkyl + 1 because alkoxy or alkyl can be removed easily. For example, the base peak of **6a-2** is 158 (202 - OCH_2CH_3 + 1), but the base peak of **6a'-2** is 187 (202 - CH_3).

Insecticidal activity. All compounds prepared were evaluated for initial activity against *M. separate* at 100 mg/L by typical assay above, and LC_{50} was calculated through further assay in which five to six different concentrations were used and listed in **Table 1**. A few representative compounds were evaluated against *P. xylostella* and *P. litura*, and LC_{50} values of **8a-2** and **8e** were listed in **Table 3**. The activities of Pyridalyl were also shown in **Table 1** and **Table 3**.

As shown in **Table 1,** all compounds **8** except **8a-9**, **8a-10**, **8d-2**, **8d-4** and **8'** exhibit 100% insecticidal activity against *M. separate* at 100 mg/L, and some compounds have shown potent insecticidal activities when compared with commercial insecticides. For example, **8a-2**,

8a-4, **8a-5**, **8b-2**, **8d-1** and **8e** have LC_{50} (mg L^{-1}) values of 7.45, 5.58, 8.58, 7.13, 8.37 and 4.09 respectively. Particularly, LC_{50} value of **8e** is at the same level with that of Pyridalyl.

Apparent Structure-activity Relationship. The general structure of compounds **8** (**Figure 3**) was optimized through R moiety and the position of the nitro group. Different choices of R and position of NO_2 can greatly affect insecticidal activity (**Table 1**).

When the nitro group was kept on the 5-position, the insecticidal activity against *M. separata* was influenced by the nature of the R group. Changing the R group from 6-alkoxy to 6-alkylamino or 6-alkylthio maintained or slightly reduced the insecticidal activity. For example, the insecticidal activities were correlated as following: **8c-2** < **8b-2** ≈ **8a-2**, **8b-3** < **8c-3** < **8a-3**, **8c-4** < **8b-4** < **8a-4**. For 6-substituted analogues, the results in **Table 1** showed that a C_2-C_3 saturated chain alkyl was required for the development of optimal insecticidal activity, and there was no obvious relationship between activity and the number of carbon atoms in alkyl; for 3-substituted analogues, the insecticidal activities of the corresponding compounds increased. For example, the insecticidal activities of **8d-1** and **8d-3** were stronger than that of **8d-2** and **8d-4** respectively; for R=H, the resulting compound **8e** showed the highest activity among compounds **8** and it possessed levels of insecticidal activity comparable to that of Pyridalyl. When the position of the nitro group was changed from 5-NO_2 to 3-NO_2 and R was kept constant, the insecticidal activity of the corresponding compound decreased as illustrated by the orders **8a'-2** << **8a-2**, and **8e'** << **8e**.

In general, for compounds **8**:

Activity order of NO_2: 5-NO_2 >> 3-NO_2.

Activity order of R: H > 6-$OCH(CH_3)_2$ > 6-OCH_2CH_3, 6-$NHCH_2CH_3$ > 6-$O(CH_2)_3CH_3$, 3-Cl > 6-$O(CH_2)_2CH_3$, 6-$NHCH(CH_3)_2$, 6-SCH_2CH_3 > 6-$NHCH_3$, 6-$S(CH_2)_2CH_3$ > 3-NH_2, 6-$NHCH_2CH \equiv CH$, 6-$NH(CH_2)_2CH_3$, 6-$NHCH_2CH{=}CH_2$, 6-$NHCH_2C_6H_5$.

The above results demonstrate that besides the trifluoromethyl group in Pyridalyl (*6*), a nitro group on the 5-position of the pyridyl ring is also viable for the development of optimal insecticidal activity when the chain between the phenyl ring and the pyridyl ring is -$OCH_2CH_2CH_2O$-. Further studies on the biological activity and structure-activity relationships of this series of compounds are in progress.

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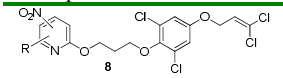
608 **Table 1**. Chemical Structures, MS, Physical Characteristics, Insecticidal Activity against *M. separate* at 100 mg/L and LC_{50} (3d)
609 of compounds **8.**



No.	NO_2	R	formula	MS	mp (^oC)	100 mg/L	20 mg/L	regression equation	r	LC_{50} mg/L
8a'-1	3-NO_2	6-OCH_3	$C_{18}H_{16}Cl_4N_2O_6$	496	oil	0[a]	0	-[c]	-	> 40
8a-2	5-NO_2	6-OCH_2CH_3	$C_{19}H_{18}Cl_4N_2O_6$	510	oil	100	100	Y=2.6262+2.77x	0.993	7.45
8a'-2	3-NO_2	6-OCH_2CH_3	$C_{19}H_{18}Cl_4N_2O_6$	510	oil	0[a]	0	-	-	> 40
8a-3	5-NO_2	6-$OCH_2CH_2CH_3$	$C_{20}H_{20}Cl_4N_2O_6$	524	oil	100	100	Y=-0.9779+4.5542x	0.9439	9.78
8a-4	5-NO_2	6-$OCH(CH_3)_2$	$C_{20}H_{20}Cl_4N_2O_6$	524	oil	100	100	Y=0.1333+6.5171x	0.9528	5.58
8a-5	5-NO_2	6-$O(CH_2)_3CH_3$	$C_{21}H_{22}Cl_4N_2O_6$	538	viscous solid	100	100	Y=1.5059+3.7473x	0.9974	8.58
8a-6	5-NO_2	6-$OCHCH_3CH_2CH_3$	$C_{21}H_{22}Cl_4N_2O_6$	538	oil	100	9[a]	-	-	> 20
8a-7	5-NO_2	6-$OC(CH_3)_3$	$C_{21}H_{22}Cl_4N_2O_6$	538	viscous solid	100	11	-	-	> 20
8a-8	5-NO_2	6-$O(CH_2)_4CH_3$	$C_{22}H_{24}Cl_4N_2O_6$	552	viscous solid	100	45	Y=1.4715+2.4428x	0.9988	27.83
8a-9	5-NO_2		$C_{22}H_{22}Cl_4N_2O_6$	550	oil	30	0	-	-	> 100
8a-10	5-NO_2		$C_{23}H_{24}Cl_4N_2O_6$	564	oil	80	17[b]	-	-	> 20
8b-1	5-NO_2	6-$NHCH_3$	$C_{18}H_{17}Cl_4N_3O_5$	495	81.7-83.2	100	100	Y=-0.0586+4.901x	0.9721	10.77
8b-2	5-NO_2	6-$NHCH_2CH_3$	$C_{19}H_{19}Cl_4N_3O_5$	509	36.0-36.9	100	100	Y=1.0031+4.6838x	0.9629	7.13
8b-3	5-NO_2	6-$NH(CH_2)_2CH_3$	$C_{20}H_{21}Cl_4N_3O_5$	523	63.2-64.5	100	27	Y=0.7600+3.4073x	1.0000	17.48
8b-4	5-NO_2	6-$NHCH(CH_3)_2$	$C_{20}H_{21}Cl_4N_3O_5$	523	62.4-66.1	100	100	Y=1.3962+3.7704x	0.9270	9.03
8b-5	5-NO_2	6-$NH(CH_2)_3CH_3$	$C_{21}H_{23}Cl_4N_3O_5$	537	61.6-64.1	100	30	Y=-2.8521+5.5649x	0.9738	25.76
8b-6	5-NO_2	6-$NHCH_2CH{=}CH_2$	$C_{20}H_{19}Cl_4N_3O_5$	521	52.6-55.0	100	43	Y=-2.5045+5.9926x	0.9534	17.88
8b-7	5-NO_2	6-$NHCH_2C{\equiv}CH$	$C_{20}H_{17}Cl_4N_3O_5$	519	76.4-97.4	100	53	Y=-1.9984+5.7114x	0.9699	16.80
8b-8	5-NO_2	6-NHC_6H_5	$C_{23}H_{19}Cl_4N_3O_5$	557	74.9-76.2	0[a]	0	-	-	> 40
8b-9	5-NO_2	6-$NHCH_2C_6H_5$	$C_{24}H_{21}Cl_4N_3O_5$	571	oil	100	37	Y=1.8561+2.5131x	0.9869	17.82
8b-10	5-NO_2	6-NH_2	$C_{17}H_{15}Cl_4N_3O_5$	481	yellow solid	100	< 50	Y=-1.0132+4.3627x	0.9037	16.47
8c'-1	3-NO_2	6-SCH_3	$C_{18}H_{16}Cl_4N_2O_5S$	512	89.9-91.1	20	0	-	-	> 100
8c-2	5-NO_2	6-SCH_2CH_3	$C_{19}H_{18}Cl_4N_2O_5S$	526	viscous solid	100	87	Y=2.9291+2.144x	0.9081	9.24
8c-3	5-NO_2	6-$S(CH_2)_2CH_3$	$C_{20}H_{20}Cl_4N_2O_5S$	540	viscous solid	100	73	Y=2.2714+2.6178x	0.9854	11.02
8c-4	5-NO_2	6-$SCH(CH_3)_2$	$C_{20}H_{20}Cl_4N_2O_5S$	540	oil	100	3.3	-	-	> 20
8d-1	5-NO_2	3-Cl	$C_{17}H_{13}Cl_5N_2O_5$	500	oil	100	100	Y=2.3223+2.9004x	0.9826	8.37
8d-2	5-NO_2	6-Cl	$C_{17}H_{13}Cl_5N_2O_5$	500	oil	0	0	-	-	> 100
8d-3	5-NO_2	3-Br	$C_{17}H_{13}BrCl_4N_2O_5$	544	viscous solid	100	-	Y=0.9814+2.8266x	0.9586	26.41
8d-4	5-NO_2	6-Br	$C_{17}H_{13}BrCl_4N_2O_5$	544	oil	0	0			> 500
8e	5-NO_2	H	$C_{17}H_{14}Cl_4N_2O_5$	466	oil	100	100	Y=3.2727+2.8259x	0.9888	4.09
8e'	3-NO_2	H	$C_{17}H_{14}Cl_4N_2O_5$	466	oil	-	-	Y=-0.5573+2.7648x	0.9657	102.3
Pyridalyl						100	100	Y=2.8967+3.0826x	0.9948	4.81

610 [a]:40 mg/L; [b]:12.5 mg/L; [c]:no test;
611

612 **Table 2**. ^{1}H NMR data of the synthesized nitropyridyl-based dichloropropene ethers

No.	^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) , δ ppm; elemental analysis
8a'-1	^{1}H NMR: 2.34～2.40 (2H, m), 4.01 (3H, s), 4.12 (2H, t, *J* =6.0 Hz), 4.56 (2H, d, *J* =6.6 Hz), 4.79 (2H, t, *J* =6.0 Hz), 6.09 (1H, t, *J* =6.3 Hz), 6.35 (1H, d, *J* =9.0 Hz), 6.82 (2H, s), 8.32 (1H, d, *J* =9.0 Hz); ^{13}C NMR: 29.40, 54.63, 64.35, 65.48, 69.74, 102.67, 115.25, 124.50, 124.90, 126.26, 129.69, 138.63, 145.69, 154.00, 157.05,165.35
8a-3	^{1}H NMR: 1.04 (3H, t, *J* =7.5 Hz), 1.84～1.91 (2H, m), 2.28～2.34 (2H, m), 4.12 (2H, t, *J* =6.15 Hz), 4.46 (2H, t, *J* =6.6 Hz), 4.58 (2H, d, *J* =6.6 Hz), 4.67 (2H, t, *J* =6.3 Hz), 6.11 (1H, t, *J* =6.0 Hz), 6.34 (1H, d, *J* =9.0 Hz), 6.82 (2H, s), 8.33 (1H, d, *J* =8.7 Hz).
8a-4	^{1}H NMR: 1.44 (6H, d, *J* =6.3 Hz), 2.26～2.34 (2H, m), 4.11 (2H, t, *J* =5.85 Hz), 4.60 (2H, d, *J* =6.3 Hz), 4.65 (2H, t, *J* =4.2 Hz), 5.44～5.52 (1H, m), 6.11 (1H, t, *J* =6.3 Hz), 6.32 (1H, d, *J* =8.7 Hz), 6.81 (2H, s), 8.31 (1H, d, *J* =8.7 Hz).
8a-5	^{1}H NMR: 0.95 (3H, t, *J* =7.5Hz), 1.48～1.55 (2H, m), 1.80～1.85 (2H, m), 2.28～2.32 (2H, m), 4.12 (2H, t, *J* =6.0 Hz), 4.50 (2H, t, *J* =6.6 Hz), 4.58 (2H, d, *J* =6.3 Hz), 4.65 (2H, t, *J* =6.3 Hz), 6.11 (1H, t, *J* =6.3 Hz), 6.34 (1H, d, *J* =8.7 Hz), 6.84 (2H, s), 8.32 (1H, d, *J* =8.7 Hz).
8a-6	^{1}H NMR: 1.00 (3H, t, *J* =7.5 Hz), 1.40 (3H, d, *J* =6.6 Hz), 1.70～1.89 (2H, m), 2.26～2.34 (2H, m), 4.12 (2H, t, *J* =6.0 Hz),4.58 (2H, d, *J* =6.3 Hz), 4.65 (2H, t, *J* =6.3 Hz), 5.22～5.34 (1H, m), 6.11 (1H, t, *J* =6.3 Hz), 6.32 (1H, d, *J* =9.0 Hz), 6.84 (2H, s), 8.31 (1H, d, *J* =8.7 Hz).
8a-7	^{1}H NMR: 1.68 (9H, s), 2.30～2.32 (2H, m), 4.13 (2H, t, *J* =5.85 Hz), 4.57 (2H, d, *J* =6.3 Hz), 4.62 (2H, t, *J* =6.6 Hz), 6.11 (1H, t, *J* =6.3 Hz), 6.31 (1H, d, *J* =9.0 Hz), 6.84 (2H, s), 8.24 (1H, d, *J* =8.7 Hz).
8a-8	^{1}H NMR: 0.92 (3H, t, *J* =6.9 Hz), 1.39～1.59 (4H, m), 1.82～1.87 (2H, m), 2.28～2.32 (2H, m), 4.12 (2H, t, *J* =6.0 Hz), 4.49 (2H, t, *J* =6.6 Hz), 4.58 (2H, d, *J* =6.6 Hz), 4.67 (2H, t, *J* =6.3 Hz), 6.11 (1H, t, *J* =6.3 Hz), 6.34 (1H, d, *J* =8.7 Hz), 6.84 (2H, s), 8.32 (1H, d, *J* =8.7 Hz).
8a-9	^{1}H NMR: 1.60～2.05 (8H, m), 2.26～2.36 (2H, m), 4.12 (2H, t, *J* =5.85 Hz), 4.58 (2H, d, *J* =6.0 Hz), 4.67 (2H, t, *J* =6.45 Hz), 5.54～5.59 (1H, m), 6.11 (1H, t, *J* =6.3 Hz), 6.31 (1H, d, *J* =8.7 Hz), 6.84 (2H, s), 8.29 (1H, d, *J* =9.0 Hz).
8a-10	^{1}H NMR:1.40～1.97 (10H, m), 2.25～2.33 (2H, m), 4.12 (2H, t, *J* =5.85 Hz), 4.58 (2H, d, *J* =5.7 Hz), 4.64 (2H, t, *J* =6.45 Hz), 5.26～5.28 (1H, m), 6.11 (2H, t, *J* =6.15 Hz), 6.31 (1H, d, *J* =9.0 Hz), 6.84 (2H, s), 8.30 (1H, d, *J* =8.7 Hz).
8b-1	^{1}H NMR: 2.22～2.34 (2H, m), 3.15(3H, d, *J* =5.1 Hz), 4.12 (2H, t, *J* =5.85 Hz), 4.58 (2H, d, *J* =6.3 Hz), 4.69 (2H, t, *J* =6.3 Hz), 6.05 (1H, t, *J* =9.0 Hz), 6.12 (1H, t, *J* =6.0 Hz), 6.84 (2H, s), 8.30 (1H, d, *J*=9.0 Hz), 8.640 (1H, s).
8b-2	^{1}H NMR: 1.29 (3H, t, *J* =7.2 Hz), 2.25～2.33 (2H, m), 3.60～3.69 (2H, m), 4.10 (2H, t, *J* =6.0 Hz), 4.57 (2H, d, *J* =6.3 Hz), 4.64 (2H, t, *J* =6.3 Hz), 6.02 (1H, t, *J* =9.3 Hz), 6.09 (1H, t, *J* =6.3 Hz), 6.82 (2H, s), 8.27 (1H, d, *J* =9.3 Hz), 8.65 (1H, s); ^{13}C NMR: 14.65, 36.14, 29.31, 63.75, 65.39, 69.82, 100.40, 115.14, 121.64, 124.44, 124.85, 129.59, 138.88, 153.93, 145.56, 153.16, 166.52; Anal. Calcd. for $C_{19}H_{19}Cl_4N_3O_5$: C 44.64, H 3.75, N 8.22; found: C 44.64, H 3.82, N 8.16.
8b-3	^{1}H NMR: 1.00 (3H, t, *J* =7.5 Hz), 1.65～1.75 (2H, m), 2.25～2.33 (2H m), 3.55～3.61 (2H, m), 4.13 (2H, t, *J* =5.85 Hz), 4.57 (2H, d, *J* =6.3 Hz), 4.64 (2H, t, *J* =5.55 Hz), 6.03(1H, d, *J* =9.3 Hz), 6.11(1H, t, *J* =6.15 Hz), 6.84 (2H, s), 8.29 (1H, d, *J* =9.3 Hz) , 8.73 (1H, s).
8b-4	^{1}H NMR: 1.25 (6H, d), 2.25～2.34 (2H, m), 4.12 (2H, t, *J* =6.0 Hz), 4.43～4.48 (1H, m), 4.58 (2H, d, *J* =6.0 Hz), 4.66 (2H, t, *J* =6.0 Hz), 6.03 (1H, d, *J* =9.0 Hz), 6.12 (1H, t, *J*=6.3 Hz), 6.84 (2H, s), 8.29 (1H, d, *J* =9.3 Hz), 8.60 (1H, s).
8b-5	^{1}H NMR: 0.97 (3H, t, *J* =7.2 Hz), 1.37～1.49 (2H, m), 1.62～1.72 (2H, m), 2.25～2.36 (2H, m), 3.57～3.65 (2H, m), 4.10 (2H, t, *J* =6.0 Hz), 4.58 (2H, d, *J* =6.0 Hz), 4.68 (2H, t, *J* =6.0 Hz), 6.03 (1H, d, *J* =9.3 Hz), 6.11 (1H, t, *J* =6.15 Hz), 6.84 (2H, s), 8.29 (1H, d, *J* =9.3 Hz) , 8.72 (1H, s).
8b-6	^{1}H NMR: 2.26～2.32 (2H, m), 4.11 (2H, t, *J* =5.85 Hz), 4.23～4.28 (2H, m), 4.57 (2H, d, *J*=6.6 Hz), 4.65 (2H, t, *J* =6.3 Hz), 5.16～5.31 (2H, m), 5.91～5.99 (1H, m), 6.06 (1H, d, *J* =9.0 Hz), 6.11 (1H, t, *J* =6.3 Hz), 6.84 (2H, s), 8.30 (1H, d, *J*=9.0 Hz) , 8.75 (1H, s).
8b-7	^{1}H NMR: 2.24 (1H, t, *J* =2.4 Hz), 2.29～2.38 (2H, m), 4.12 (2H, t, *J* =6.0 Hz), 4.38～4.40 (2H, m), 4.58 (2H, d, *J* =6.0 Hz), 4.71 (2H, t, *J* =6.3 Hz), 6.11 (1H, t, *J* =6.3 Hz)., 6.12 (1H, d, *J* =9.0 Hz), 6.84(2H, s), 8.32 (1H, d, *J* =9.0 Hz), 8.65 (1H, s).
8b-8	^{1}H NMR: 2.25～2.39 (2H, m), 4.09 (2H, t, *J* =5.85 Hz), 4.58 (2H, d, *J* =6.3 Hz), 4.63 (2H, t, *J* =6.45 Hz), 6.11 (1H, t, *J* =6.15 Hz), 6.22 (1H, d, *J* =9.0 Hz), 6.83 (2H, s), 7.23～7.67 (5H, m), 8.42 (1H, d, *J* =9.0 Hz) , 10.64 (1H, s).
8b-9	^{1}H NMR: 2.18～2.26 (2H, m), 4.07 (2H, t, *J* =5.85 Hz), 4.57 (2H, t, *J* =6.0 Hz), 4.58 (2H, d, *J* =6.3 Hz), 4.81 (2H, d, *J* =5.7 Hz), 6.09 (1H, d, *J* =9.0 Hz), 6.10 (1H, t, *J* =6.15 Hz), 6.84 (2H, s), 7.28～7.37 (5H, m), 8.30 (1H, d, *J* =9.0 Hz), 9.02(1H, s).
8b-10	^{1}H NMR: 2.25～2.33 (2H, m), 4.11 (2H, t, *J* =5.7 Hz), 4.58 (2H, d, *J* =6.6 Hz), 4.60 (2H, t, *J* =5.7 Hz), 6.12 (1H, t, *J* =6.6 Hz), 6.16 (1H, d, *J* =9.3 Hz), 6.84 (2H, s), 8.30 (1H, d, *J* =9.3 Hz).
8c'-1	^{1}H NMR: 2.34～2.38 (2H, m), 2.62 (3H, s), 4.19 (2H, t, *J* =5.85 Hz), 4.59 (2H, d, *J* =6.3 Hz), 4.85 (2H, t, *J* =6.3 Hz), 6.11(1H, t, *J* =6.3 Hz), 6.83 (2H, s), 6.88 (1H, d, *J* =8.7 Hz), 8.17(1H, d, *J* =8.7 Hz).
8c-2	^{1}H NMR: 1.38 (3H, t, *J* =7.2 Hz), 2.30～2.36 (2H, m), 3.22 (2H, q, *J* =7.2 Hz), 4.13 (2H, t, *J* =5.85 Hz), 4.59 (2H, d, *J* =6.3 Hz), 4.73 (2H, t, *J* =6.3 Hz), 6.11 (1H, t, *J* =6.3 Hz), 6.54 (1H, d, *J* =9.0 Hz), 6.84 (2H, s,), 8.41 (1H, d, *J* =9.0 Hz).
8c-3	^{1}H NMR: 1.07 (3H, t, *J* =7.5 Hz), 1.72～1.85 (2H, m), 2.28～2.36 (2H, m), 3.18 (2H, t, *J* =7.2 Hz), 4.14 (2H, t, *J* =6.3 Hz), 4.58 (2H, d, *J* =6.0 Hz), 4.72 (2H, t, *J* =6.3 Hz), 6.11 (2H, t, *J* =6.3 Hz), 6.45 (1H, d, *J* =9.0 Hz), 6.84 (2H, s), 8.40 (1H, d, *J* =9.0 Hz).
8c-4	^{1}H NMR: 1.43 (6H, d, *J* =6.9 Hz), 2.28～2.36 (2H, m,), 4.07～4.17 (1H, m,), 4.13 (2H, t, *J* =5.7 Hz), 4.58 (2H, d, *J* =6.6 Hz,), 4.72 (2H, t, *J* =6.45 Hz), 6.11 (2H, t, *J* =6.3 Hz), 6.50 (1H, d, *J* =9.0 Hz), 6.85 (2H, s), 8.40 (1H, d, *J* =9.0 Hz).
8d-1	^{1}H NMR: 2.36～2.41 (2H, m), 4.18 (2H, t, *J* =6.0 Hz), 4.68 (2H, d, *J* =6.3 Hz), 4.82 (2H, t, *J* =6.0 Hz), 6.17 (1H, t, *J* =6.3 Hz), 6.84 (2H, s), 8.45 (1H, d, *J* =2.7 Hz), 8.99 (1H, d, *J* =2.4 Hz).
8d-2	^{1}H NMR: 2.30～2.38 (2H, m), 4.18 (2H, t, *J* =6.0 Hz), 4.57 (2H, d, *J* =6.0 Hz), 4.80 (2H, t, *J* =6.3 Hz), 6.11 (1H, t, *J* =6.3Hz), 6.83 (2H, s), 7.02 (1H, d, J=8.1 Hz), 8.26 (1H, d, *J* =8.1 Hz).
8d-3	^{1}H NMR: 2.27～2.35 (2H, m), 4.13 (2H, t, *J* =6.0 Hz), 4.61 (2H, d, *J* =6.3 Hz), 4.69 (2H, t, *J* =6.3 Hz), 6.14 (1H, t, *J* =6.2 Hz), 6.82 (2H, s), 8.61 (1H, d, *J* =2.7 Hz), 8.99 (1H, d, *J* =2.7 Hz).
8d-4	^{1}H NMR: 2.30～2.40 (2H, m), 4.18 (2H, t, *J*=6.0 Hz), 4.57 (2H, d, *J* =6.3 Hz), 4.80 (2H, t, *J* =6.0 Hz), 6.11 (1H, t, *J* =6.0 Hz), 6.82 (2H, s), 7.22 (1H, d, *J* =8.4 Hz), 8.13 (1H, d, *J* =8.1 Hz).
8e'	^{1}H NMR: 2.30-2.38 (2H, m), 4.18 (2H, t, *J*=6.0 Hz), 4.57 (2H, d, *J*=6.3 Hz), 4.81(2H, t, *J*=6.0 Hz), 6.09 (1H, t, *J*=6.3 Hz), 6.82 (2H, s), 7.01(1H, dd, *J*=8.1 Hz, 4.8 Hz), 8.25(1H, dd, *J*=8.1 Hz, 1.8 Hz), 8.39(1H, dd, *J*=4.8 Hz, 1.8 Hz); ^{13}C NMR: 29.41, 64.15, 65.45, 69.74, 115.18, 116.34, 124.51, 124.89, 129.70, 133.95, 134.91, 145.74, 153.43, 153.93,156.28.
8e	^{1}H NMR: 2.28-2.36 (2H, m), 4.12 (2H, t, *J*=6.0 Hz), 4.57 (2H, d, *J*=6.3 Hz), 4.70 (2H, t, *J*=6.3 Hz), 6.09 (1H, t, *J*=6.3 Hz), 6.82 (1H, d, *J*=9.0

	Hz), 6.83 (2H, s), 8.34 (1H, dd, *J*=9.0 Hz, 2.7 Hz), 9.09 (1H, d, *J*=2.7 Hz); ^{13}C NMR: 29.39, 64.29, 65.40, 69.74, 111.22, 115.16, 124.43, 124.96, 129.66, 133.85, 139.30, 144.88, 145.62, 153.97,167.05; Anal. Calcd. for $C_{17}H_{14}Cl_4N_2O_5$: C 43.62, H 3.01, N 5.98; found: C 43.64, H 3.00, N 6.00.

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Table 3. LC_{50} against *P. xylostella* and *P. litura* of 8a-2, 8e and Pyridalyl (3d)

No.	Y=a+bx	r	LC_{50}(mg/L)	test insect
8a-2	Y=2.6262+2.77x	0.993	7.07	*P. xylostella*
8e	Y=4.0618+1.4006x	0.9964	4.68	
Pyridyl	Y=3.9255+1.6996x	0.9880	4.29	
8a-2	Y=-3.1505+4.6849x	0.9659	54.92	*P. litura*
8e	Y=2.8096+2.0033x	0.9734	11.66	
Pyridyl	Y=2.8738+2.1177x	0.9942	10.07	

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Figure captation

Figure 1: Pyridalyl and NO_2, CF_3 analogues quantitative structure-activity profiles

Figure 2: Design strategies of the target compounds containing nitropyridyl

Figure 3: Synthetic pathways for the novel nitropyridyl-based dichloropropene ethers

Figure 1

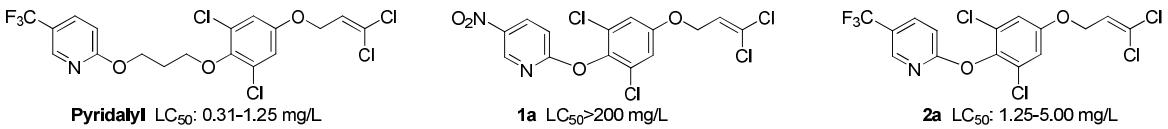


Figure 2

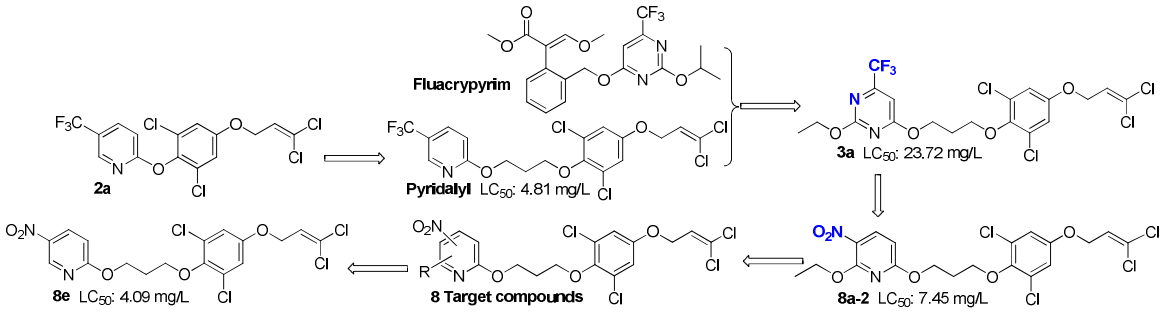
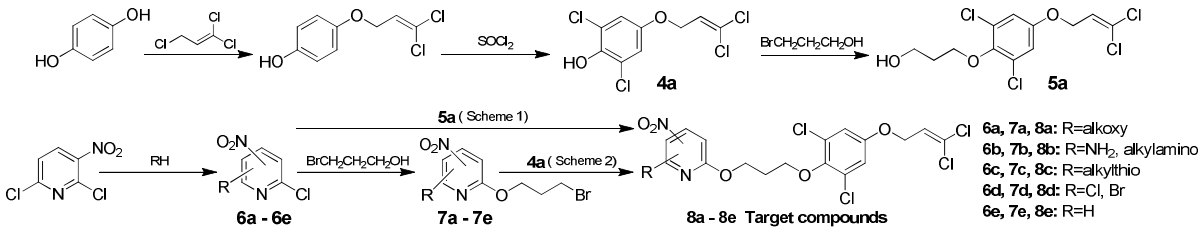


Figure 3



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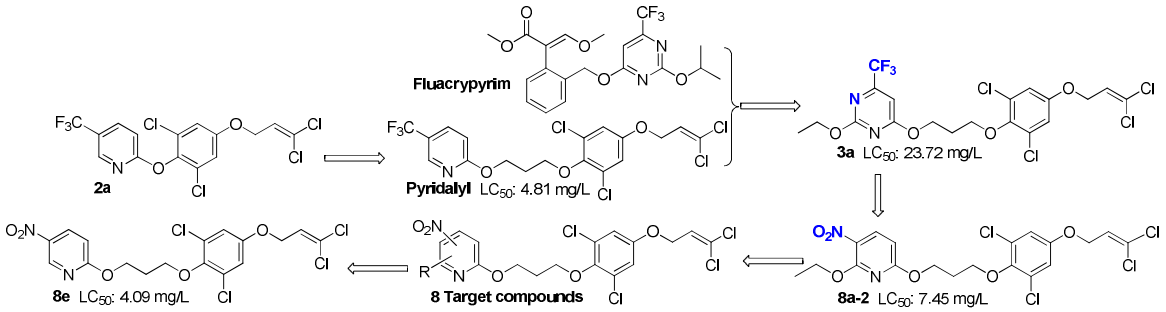
648 **TOC Graphic**



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