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Syntheses of 4-methoxymethylbenzyl permethrinates containing fluorine and their insecticidal activity

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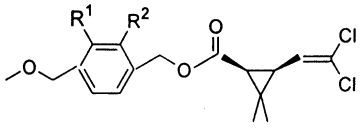
Abstract

In order to investigate the relationship between the position of fluorine atom and insecticidal activity about 4-methoxymethylbenzyl permethrinates containing fluorine, 2 and 3-fluoro-4-methoxymethylbenzyl (±)-*cis*-permethrinate were synthesized. Their insecticidal activities were tested and the fluorine effect of title compounds was discussed.

Keywords: Synthesis; Pyrethroid; 2-Fluoro-4-methoxymethylbenzyl (±)-*cis*-permethrinate; 3-Fluoro-4-methoxymethylbenzyl (±)-*cis*-permethrinate

1. Introduction

4-Methoxymethylbenzyl alcohol containing fluorine is an alcohol moiety having insecticidal activity of pyrethroids [1]. Recently, we found that it's permethrinate have higher insecticidal activities against houseflies, mosquitoes and cockroaches [2–4]. However, the alcohol is a mixture of 2- and 3-fluoro-4-methoxymethylbenzyl alcohol [1]. In order to investigate the relationship between the position of fluorine atom and insectisidal activity, we designed two different routes, synthesized two alcohols and their permethrinates, and tested their biological activity. Herein, we report the preparation of compounds (**1**) and (**2**), their insecticidal activities and discussion about their fluorine effect.



(**1**): R^1=H, R^2=F ; (**2**): R^1=F, R^2=H

2. Results and discussion

In order to obtain the compound (**1**), we contrived a novel synthesis route containing 11 steps showed as Scheme 1, and the key step was the synthesis of 2-fluoro-4-methoxymethylbenzyl alcohol (**12**). We used *p*-toluidine as the starting material. After the amino-group of the *p*-toluidine was protected by acetylation, the nitro-group was introduced selectively in the *ortho* position of the acetamido-group by the nitration. After the compound (**4**) was hydrolyzed by Claisen's base, diazotized it and reacted with cuprous bromide to give the compound (**6**). In the following steps, the reduction and Schiemann reaction were utilized to give 4-bromo-3-fluorotoluene which was transformed into Grignard regent and reacted with carbon dioxide to give the compound (**9**). In the Grignard reaction, we failed to obtain the compound (**9**) by direct method, which was probably due to the benzyne formation because of the *ortho* position between the bromo and fluoro groups [5]. However, we succeeded in obtaining the compound (**9**) by means of low temperature and using ethyl bromide with a not so high yield which was probably due to the same reason as above referred. Afterward, we utilized the bromination and nucleophilic substitution reaction to obtain the 2-fluoro-4-methoxymethylbenzonic acid. During the bromination, we found that the reaction did not proceed thoroughly and the conversion of 2-fluoro-4-methylbenzonic acid was about 50% based on the data of GC–MS of the product. The bromide was confirmed by GC–MS. Because the isolation of the reaction mixture was difficult, it was used directly for next methoxylation. We found that the nucleophilic substitution reaction went almost thoroughly from the GC–MS, the product was not isolated and used for next reaction. The key intermediate (**12**) was obtained by reducing 2-fluoro-4-

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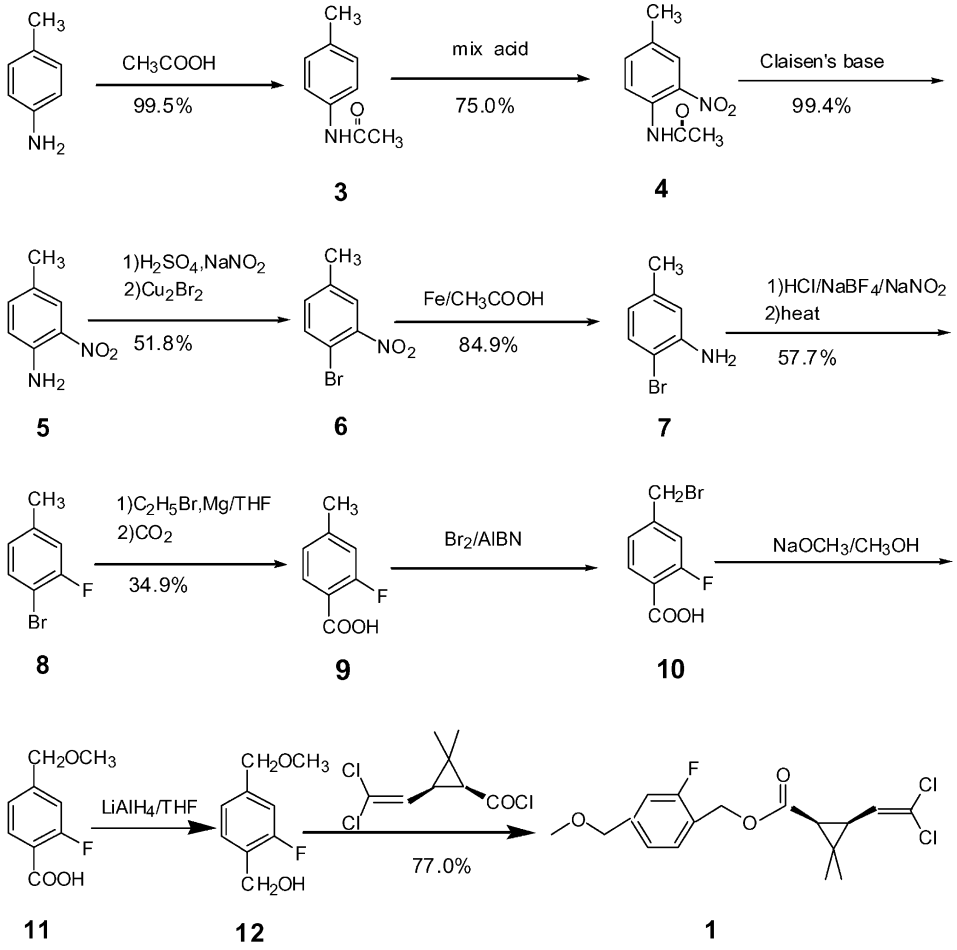
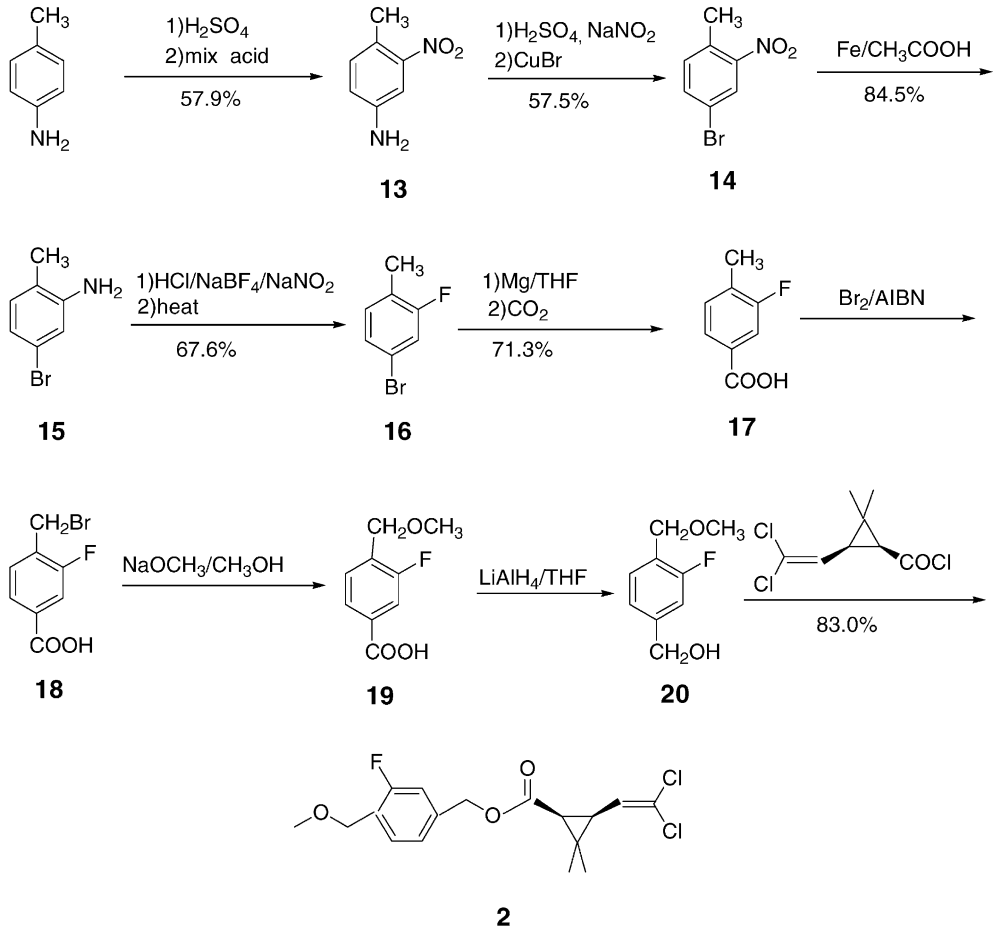


Scheme 1.

methoxymethylbenzonic acid with $LiAlH_4$ and isolation. The ^1H NMR data ($\delta = 3.39$, $–OCH_3$; $\delta = 4.44$, $–OCH_2–$; and $\delta = 4.74$, $–CH_2OH$) of the alcohol all showed single peak which agreed well with the reported data [1] of one of the two isomers as the author had presumed. The single peak ($\delta = -120.5$) of the ^{19}F NMR of the alcohol could be explained as that there was only one substituted fluorine in the aromatic ring and the substituted position was unique. The data of IR, MS and elemental analyses also confirmed the structure of the alcohol. From both the synthesis route and all the spectral data we could draw a conclusion that the compound (**12**) was obtained successfully. The terminal product (**1**) was obtained by the reaction between the alcohol and (±)-*cis*-permethrinic acid halide to give a yield of 77.0%, and it was confirmed by ^1H NMR, MS and IR.

In order to obtain the compound (**2**), we designed a synthetic route containing nine steps showed as Scheme 2. As the starting material, *p*-toluidine was used. In the first step, the concentrated sulfuric acid was used to react with *p*-toluidine to form an anilinium ion, after that, the nitro group was introduced into the *meta* position of the amino group which was coincide to the *ortho* position of the methyl group during the nitration. After the nitration the position of all substituted groups in the aromic ring were fixed. The following Sandmeyer reaction, reduction and Schiemann reaction all proceeded smoothly, and the compound (**17**) could be obtained by the reaction between the Grignard regent and carbon dioxide in a good yield. The bromination of compound (**17**) is similar to the case of 2-fluoro-4-methylbenzoic acid. It is so difficult to obtain (**18**) in high yield, the crude product was used directly for next methoxylation. After reduction of (**19**), a key intermediate (**20**) was obtained and the ^1H NMR data ($\delta = 3.40$, $–OCH_3$; $\delta = 4.51$, $–OCH_2–$, and $\delta = 4.68$, $–CH_2OH–$) agreed well with the reported data [1] of the other isomer. The ^{19}F NMR also showed single peak ($\delta = -119$) and the data of IR, MS and elemental analysis also confirmed the structure of the alcohol. As described above, the alcohol (**20**) was obtained successfully. The terminal product (**2**) was obtained in a yield of 83.0% by the reaction between the alcohol (**20**) and (±)-*cis*-permethrinic acid halide and confirmed by ^1H NMR, MS and IR.

The biological activity of two compounds, (**1**) and (**2**), were tested by the drop method [6]. The insects tested were mosquitoes (*Culex pipiens palles*) and houseflies (*Musca domestica*). The results are summarized in Table 1. The results indicated that compounds, (**1**) and (**2**), all having higher insecticidal activity against houseflies and mosqui-



Scheme 2.

Table 1
The toxicities of the compounds against houseflies and mosquitoes

	Compound (**1**)	Compound (**2**)
Houseflies:		
LD_{50} (μg per insect)	0.0193	0.0204
Relative toxicities	106	100
Mosquitoes:		
LD_{50} (μg per insect)	0.0399	0.0455
Relative toxicities	114	100

toes. The activity of compound (**1**) is a little higher than that of compound (**2**). The introduction of fluorine atom on the aromatic ring increase insecticidal activity [1–3], but the position of fluorine atom seems to be not so much important.

3. Experimental

Boiling points and melting points were uncorrected. The latter were measured on a Yanaco Mp-500 instrument. Infrared spectra were recorded on a PE 580B spectrometer. ^{1}H NMR spectra were obtained at 400 MHz (IMOVA-400), and 60 MHz (JNM-PMX60Si) using Me_4Si as an internal standard, respectively. ^{19}F NMR spectra were obtained using a VARIAN-300 (282 MHz) spectrometer with TFA ($\delta_{CCl_3F} = \delta_{TFA} + 76.8$ ppm, and with upfield positive) as an external standard. GC–MS were measured on a Shimadzu QP-5000 instrument. Combustion analyses for elemental composition were made with an Italian MOD.1106 analyzer. All reactions were monitored by TLC.

3.1. Preparation of 4-methylacetanilide (*3*)

The reaction was carried out as described in [7]. *p*-Toluidine (80 g, 0.75 mol) was used. Compound (**3**): 110 g (yield 99.5%); mp: 152.5–154 °C (lit. 149–151 °C).

3.2. Preparation of 4-methyl-2-nitroacetanilide (*4*)

The reaction was carried out as described in [8]. 4-Methylacetanilide (80 g, 0.534 mol) was used. Compound (**4**): 78.0 g (yield 75.0%); mp: 97–98.5 °C (lit. 96 °C).

3.3. Preparation of 4-methyl-2-nitro-aniline (*5*)

The reaction was carried out as described in [9]. 4-Methyl-2-nitro-aniline (66.1 g, 0.34 mol) was used.

Compound (**5**): 51.5 g (yield 99.4%); mp: 118–20 °C (lit. 115–116 °C); IR (KBr): $\nu = 3347$ and 1567 (NH_2), 1515 and 1378 (NO_2), and 1566, 1461 and 864 cm^{-1} (Ph); ^1H NMR (60 MHz, CCl_4): $\delta = 2.21$ (s, 3H, CH_3), 5.81 (s, br, 2H, NH_2), 6.59 (d, 1H, $^3J_{H,H} = 7.9$ Hz, ArH-6), 7.10 (d, 1H, $^3J_{H,H} = 7.9$ Hz, ArH-5), 7.83 (s, 1H, ArH-3).

3.4. Preparation of 4-bromo-3-nitrotoluene (*6*)

The reaction was carried out as described in [10]. 4-Methyl-2-nitroaniline (36.4 g, 0.24 mol) was used to give a yellow liquid (**6**): 26.8 g (yield 51.8%); bp: 84–100 °C/0.2–0.3 mmHg (lit. 151.5–152.5 °C/14 mmHg); IR (film): $\nu =$ 1535 and 1354 (NO_2), and 1475 and 821 cm^{-1} (Ph); ^1H NMR (60 MHz, CCl_4): $\delta = 2.36$ (s, 3H, CH_3), 7.20–7.66 (m, 3H, ArH).

3.5. Preparation of 2-bromo-5-methylaniline (*7*)

The reaction was carried out as described in [11]. 4-Bromo-3-nitrotoluene (40 g, 0.185 mol) was used to give a colorless liquid (**7**): 29.35 g (yield 84.9%); bp: 72–80 °C/0.22–0.25 mmHg (lit. 129–130 °C/16 mmHg); IR (film): ν = 3471, 3381 and 1614 (NH_2), 1486 and, 858 cm^{-1} (Ph); ^1H NMR (60 MHz, CCl_4): $\delta = 2.17$ (s, 3H, CH_3), 3.80 (s, br, 2H, NH_2), 6.26 (d, 1H, $^3J_{H,H} = 7.9$ Hz, ArH-4), 6.43 (s, 1H, ArH-6), 7.18 (d, 1H, $^3J_{H,H} = 7.9$ Hz, ArH-3).

3.6. Preparation of 4-bromo-3-fluorotoluene (*8*)

The reaction was carried out as described in [12]. 2-Bromo-5-methylaniline (29 g, 0.156 mol) was used to give a colorless liquid (**8**): 17 g (yield 57.7%); bp: 84–86 °C/30 mmHg (lit. 95 °C/50 mmHg); IR (film): $\nu =$ 1582, 1486, 861 and 808 (Ph), and 1158 cm^{-1} (C–F); ^1H NMR (60 MHz, CCl_4): $\delta = 2.33$ (s, 3H, CH_3), 6.89–7.69 (m, 3H, ArH).

3.7. Preparation of 2-fluro-4-methylbenzonic acid (*9*)

The reaction was carried out as described in [13]. Compound (**8**) (6.3 g, 0.058 mol) was used to give a white solid (**9**): 3.1 g (yield 34.9%); mp: 183–186 °C (lit. 181–182 °C); IR (KBr): $\nu =$ 3000–2500, 1689 and 1439 (COOH), 1574, 839, and 774 (Ph), and 1161 cm^{-1} (C–F); ^1H NMR (400 MHz, DMSO-d_6): $\delta =$ 2.363 (s, 3H, CH_3), 7.095–7.132 (m, 2H, ArH-3, -5), 7.752 (t, 1H, $^3J_{H,H} = 8$ Hz, $^4J_{F,H} = 8$ Hz, ArH-6); 12.9 (s, br, 1H, COOH). MS (EI, 70 eV), (*m/e*, %): 154 $[M]^+$ (60.9), 137 $[M - OH]^+$ (100), 109 $[M - COOH]^+$ (48.7).

3.8. Preparation of 4-bromomethyl-2-fluorobenzonic acid (*10*)

A solution of 2-fluoro-4-methylbenzonic acid (3.1 g, 0.02 mol) of in 70 ml of carbon tetrachloride in a 100 ml round-bottomed flask was heated to 80 °C. After added a little AIBN, 1.1 ml (0.02 mol) of bromide was added dropwise in 5 h. After removal of the carbon tetrachloride, 4.1 g of slight yellow solid was obtained, and the purification was not required. MS (EI, 70 eV), (*m/e*, %): 232 $[M]^+$ (5.9), 234 $[M + 2]^+$ (5.9), 153 $[M - Br]^+$ (100), 136 $[M - Br–OH]^+$ (5.9), 125 $[M - 107]^+$ (27.9), 108 $[M - Br–COOH]^+$ (17.6), 107 $[M - 125]^+$ (20.0).

3.9. Preparation of 2-fluoro-4-methoxymethylbenzonic acid (*11*)

To a solution of 4.1 g of crude 4-bromomethyl-2-fluorobenzonic acid in 10 ml methanol, 30 ml of sodium methoxide solution which was prepared from 1.5 g (0.065 mol) of sodium and 30 ml methanol was added dropwise. After the addition, the mixture was heated to reflux for 2 h. After cooled to room temperature, 50 ml of water was added. After removal of the methanol, the mixture was acidified by concentrated hydrochloride acid, and a lot of white solid was precipitated. After filtered and dried, 2.9 g of white solid was obtained, and the purification was also not required. MS (EI, 70 eV), (*m/e*, %): 184 $[M]^+$ (32.4), 183 $[M - 1]^+$ (29.4), 169 $[M - Me]^+$ (48.5), 167 $[M - OH]^+$ (11.8), 153 $[M - OMe]^+$ (55.9), 151 $[M - Me–H_2O]^+$ (61.8), 139 $[M - COOH]^+$ (72.1), 125 $[M - OMe–CO]^+$ (43.5), 107 $[M - OMe–CO–H_2O]^+$ (37.6), 45 $[M - C_6H_3FCOOH]^+$ (100).

3.10. Preparation of 2-fluoro-4-methoxymethylbenzyl alcohol (*12*)

A solution of 2 g (0.048 mol) of lithium aluminum hydride in 20 ml THF was added in a 100 ml three-necked flask equipped with reflux condenser, dropping funnel and mechanical stirrer, and protected from moisture by calcium chloride tube attached to the openings. Through the dropping funnel, a solution of 2.9 g of crude 2-fluoro-4-methoxymethylbenzonic acid in 15 ml THF was added at a rate such as to produce gentle reflux. After the addition, water was added cautiously to decompose excess hydride. Then 50 ml of 10% sulfuric acid was added. After removal of the THF, the mixture was extracted with ether, and the ether layer was washed by saturated sodium hydrogen carbonate and dried. After removal of the ether, 2.3 g of liquid was obtained. The liquid was purified by column chromatography on silica gel. The eluate cyclohexane-ethyl acetate (4:1 v/v) was evaporated in vacuum to give a colorless liquid (**12**): 0.9 g (yield 26.3% based on 2-fluoro-4-methylbenzonic acid); IR (film): $\nu = 3409$ and 1509 (alcohol), 1581, 871 and 829 (Ph), 1194 (C–F), and 1096 cm^{-1} (C–O–C); ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.756 (s, 1H, OH), 3.388 (s, 3H, CH_3), 4.441 (s, 2H, $ROCH_2ph$), 4.743 (s, 2H, $phCH_2OH$), 7.052 (d, 1H, $^3J_{F,H} = 10.4$ Hz, ArH-3), 7.100 (d, 1H, $^3J_{H,H} = 7.6$ Hz, ArH-5) 7.387 (t, 1H, $^3J_{H,H} = 7.6$ Hz, $^4J_{F,H} = 7.6$ Hz, ArH-6); ^{19}F NMR (284 MHz, $CDCl_3$): $\delta = -120.5$ (s, 1F, ArF). MS (EI, 70 eV), (*m/e*, 100%): 170

$[M]^+$ (28.4), 169 $[M-1]^+$ (14.9), 152 $[M-H_2O]^+$ (11.9), 139 $[M-OMe]^+$ (100), 45 $[M-C_6H_3FCH_2OH]^+$ (37.3). Anal. Calc. for $C_9H_{11}FO_2$ (170.18): C, 63.53; H, 6.47%. Found: C, 63.62; H, 6.45%.

3.11. Preparation of 2-fluoro-4-methoxymethylbenzyl-(±)-cis-permethrinate (*1*)

A mixture of 1.56 g (7.46 mmol) of (±)-*cis*-permethrinic acid and 7 g (58.8 mmol) of thionyl chloride was stirred at 50 °C for 4 h and the excess thionyl chloride was evaporated by means of a water pump. The acyl halide in benzene (6 ml) was added dropwise to a stirring solution of 1.25 g (7.35 mmol) of 2-fluoro-4-methoxymethylbenzyl alcohol and 1.05 g (13.3 mmol) of pyridine in 20 ml of benzene. After the addition, the mixture was stirred at 40 °C for 6 h. The mixture was washed by sodium hydroxide (1%, 15 ml), hydrochloric acid (2 M, 15 ml), saturated sodium hydrogencarbonate (15 ml) and saturated sodium chloride (15 ml). The water layer was extracted with benzene, and the organic layer was dried. After removal of the benzene, the residue was purified by column chromatography on silica gel. The eluate cyclohexane-ethyl acetate (19:1 v/v) was evaporated in vacuum to give a slight yellow liquid (**1**): 2.05 g (yield 77.0%); IR (film): ν = 1727 and 1139 (ester), 1582, 865 and 820 (Ph), 1180 (C–F), and 1100 cm^{-1} (C–O–C); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.239 (s, 3H, E_{cycl}-CH_3), 1.254 (s, 3H, Z_{cycl}-CH_3) 1.887 (d, 1H, $^3J_{H,H}$ = 8.8 Hz, cycl-H-1), 2.034 (t, 1H, $^3J_{H,H}$ = 8.8 Hz, cycl-H-3), 3.398 (s, 3H, OCH_3), 4.450 (s, 2H, $ROCH_2$), 5.158 (s, 2H, $COOCH_2$), 6.261 (d, 1H, $^3J_{H,H}$ = 8.8 Hz, = –H), 7.070–7.115 (m, 2H, ArH-3, -5), 7.353 (t, 1H, $^3J_{H,H}$ = 7.6 Hz, $^4J_{F,H}$ = 7.6 Hz, ArH-6). MS (EI, 70 eV), (*m/e*, %): 163 $[M-CH_3OCH_2C_6H_3FCH_2OCO]^+$ (17.6), 165 $[M+2-CH_3OCH_2C_6H_3FCH_2OCO]^+$ (10.9), 153 $[M-C_7H_9Cl_2COO]^+$ (100), 123 $[M-C_7H_9Cl_2COO-CH_2O]^+$ (14.7), 122 $[M-C_7H_9Cl_2COO-OCH_3]^+$ (8.8), 109 $[M-C_7H_9Cl_2COO-C_2H_4O]^+$ (11.8). Anal. Calc. for $C_{17}H_{19}Cl_2FO_3$ (361.22): C, 56.53; H, 5.30%. Found: C, 56.74; H, 5.25%.

3.12. Preparation of 4-methyl-3-nitroaniline (*13*)

The reaction was carried out as described in [14]. *p*-Toluidine (53.5 g, 0.5 mol) was used to give a yellow needle crystal (**13**): 44 g (yield 57.9%); mp:77–78 °C (lit. 74–77 °C); IR (KBr): ν = 3480, 3450 and 1627 (NH_2), 1521 and 1349 (NO_2), and 1584, 886 and 824 cm^{-1} (Ph); ^1H NMR (60 MHz, CCl_4): δ = 2.40 (s, 3H, CH_3), 3.81 (s, br, 2H, NH_2), 6.73–7.23 (m, 3H, ArH).

3.13. Preparation of 4-bromo-2-nitrotoluene (*14*)

The reaction was carried out as described in [15]. 4-Methyl-2-nitroaniline (36.4 g, 0.24 mol) was used to give a yellow liquid (**14**): 29.7 g (yield 57.5%), bp: 75–82 °C/0.2–0.5 mmHg; mp: 43–45 °C (lit. 45–48 °C); IR (KBr): ν = 1530, and 1338 (NO_2), and 1445, 875, and 830 cm^{-1} (Ph); ^1H NMR (60 MHz, CCl_4): δ = 2.59 (s, 3H, CH_3), 7.26–8.20 (m, 3H, ArH).

3.14. Preparation of 5-bromo-2-methylaniline (*15*)

The reaction was carried out as described in [16]. 4-Bromo-2-nitrotoluene (29.6 g, 0.137 mol) was used to give a slight yellow liquid (**15**): 21.5 g (yield 84.5%); bp: 78–88 °C/0.2–0.3 mmHg; mp: 32–33 °C (lit. 33 °C [8]); IR (film): ν = 3500, 3486 and 1626 (NH_2), and 1445, 875, and 831 cm^{-1} (Ph); ^1H NMR (60 MHz, CCl_4): δ = 2.01 (s, 3H, CH_3), 3.41 (s, br, 2H, NH_2), 6.62–6.81 (m, 3H, ArH).

3.15. Preparation of 4-bromo-2-fluorotoluene (*16*)

The reaction was carried out as described in [12]. 5-Bromo-2-methylaniline (21.5 g, 0.116 mol) was used to give a colorless liquid (**16**): 14.8 g (yield 67.6%); bp: 99–100 °C/50 mmHg (lit. 98 °C/50 mmHg); IR (film): ν = 1587, 1468, 879 and 851 (Ph), and 1091 cm^{-1} (C–F); ^1H NMR (60 MHz, CCl_4): δ = 2.17 (s, 3H, CH_3), 6.93–7.17 (m, 3H, ArH).

3.16. Preparation of 3-fluoro-4-methylbenzonic acid (*17*)

The reaction was carried out as described in [17]. 4-Bromo-2-flurotoluene (12 g, 0.063 mol) was used to give a white solid (**17**): 7.0 g (yield 71.3%); mp: 163–166 °C (lit. 160–161 °C); IR (KBr): ν = 3000–2500, 1682 and 1441 (COOH), 1580, 884 and 840 (Ph), and 1087 cm^{-1} (C–F); ^1H NMR (60 MHz, CCl_4): δ = 2.17 (s, 3H, CH_3), 7.23–7.80 (m, 3H, ArH). MS (EI, 70 eV), (*m/e*, %): 154 $[M]^+$ (61.2), 137 $[M-OH]^+$ (50.3), 109 $[M-COOH]^+$ (100).

3.17. Preparation of 4-bromomethyl-3-fluorobenzonic acid (*18*)

A solution of 3-flouro-4-methylbenzonic acid (7.0 g, 0.045 mol) in 130 ml of carbon tetrachloride in a 250 ml round-bottomed flask was heated to 80 °C. After added a little AIBN, 2.4 ml (0.046 mol) of bromide was added dropwise in 5 h. After removal of the carbon tetrachloride, 10.3 g of slight yellow solid was obtained, and the purification was not required. MS (EI, 70 eV), (*m/e*, %): 232 $[M]^+$ (2.9), 234 $[M+2]^+$ (2.9), 153 $[M-Br]^+$ (100), 136 $[M-Br-OH]^+$ (4.4), 125 $[M-107]^+$ (32.4), 108 $[M-Br-COOH]^+$ (19.1), 107 $[M-125]^+$ (19.1).

3.18. Preparation of 3-fluoro-4-methoxymethylbenzonic acid (*19*)

To a solution of 6.9 g of crude 4-bromomethyl-3-flouorobenzonic acid in 20 ml methanol, 40 ml of sodium methoxide solution which was prepared from 2.2 g (0.096 mol) of sodium and 40 ml methanol was added dropwise. After the addition, the mixture was heated to reflux for 2 h. After

cooled to room temperature, 100 ml of water was added. After removal of the methanol, the mixture was acidified by concentrated hydrochloride acid, and a lot of white solid was precipitated, filtered and dried, 5.3 g of white solid was obtained, and the purification was also not required. MS (EI, 70 eV), (*m/e*, %): 184 $[M]^+$ (23.9), 183 $[M-1]^+$ (26.9), 169 $[M-Me]^+$ (97.0), 167 $[M-OH]^+$ (13.4), 153 $[M-OMe]^+$ (100), 151 $[M-Me–H_2O]^+$ (86.6), 139 $[M-COOH]^+$ (56.7), 125 $[M-OMe–CO]^+$ (77.6), 107 $[M-OMe–CO–H_2O]^+$ (37.3), 45 $[M-C_6H_3FCOOH]^+$ (92.5).

3.19. Preparation of 3-fluoro-4-methoxymethylbenzyl alcohol (**20**)

A solution of lithium aluminum hydride (2.3 g, 0.06 mol) in 30 ml THF was added in a 100 ml three-necked flask equipped with reflux condenser, dropping funnel and mechanical stirrer, and protected from moisture by calcium chloride tube attached to the openings. Through the dropping funnel, a solution of 5.3 g of crude 2-fluoro-4-methoxymethylbenzonic acid in 20 ml THF was added at a rate such as to produce gentle reflux. After the addition, water was added cautiously to decompose the excess hydride. Then 100 ml of 10% sulfuric acid was added. After removal of the THF, the mixture was extracted with ether, and the ether layer was washed by saturated sodium hydrogen carbonate and dried. After removal of the ether, 4.7 g of liquid was obtained. The liquid was purified by column chromatography on silica gel. The eluate cyclohexane-ethyl acetate (4:1 v/v) was evaporated in vacuum to give a colorless liquid (**10**): 2.2 g (yield 42% based on 3-fluoro-4-methylbenzonic acid). IR (film): $\nu = 3389$ and 1053 (alcohol), 1582, 865 and 827 (Ph), 1116 (C–F), and 1092 cm^{-1} (C–O–C); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.727$ (s, 1H, OH), 3.403 (s, 3H, CH_3), 4.511 (s, 2H, $ROCH_2$), 4.679 (s, 2H, $HOCH_2$), 7.076 (d, 1H, $^3J_{F,H} = 10.8$ Hz, ArH-2), 7.120 (d, 1H, $^3J_{H,H} = 8$ Hz, ArH-6), 7.378 (t, 1H, $^4J_{F,H} = 8$ Hz, $^3J_{H,H} = 8$ Hz ArH-5); ^{19}F NMR (283 MHz, $CDCl_3$): $\delta = -119.0$ (s, 1F, ArF). MS (EI, 70 eV), (*m/e*, %): 170 $[M]^+$ (22.1), 169 $[M-1]^+$ (11.8), 152 $[M-H_2O]^+$ (11.8), 139 $[M-OMe]^+$ (100), 45 $[M-C_6H_3FCH_2OH]^+$ (52.9). Anal. Calc. for $C_9H_{11}FO_2$ (170.18): C, 63.53; H, 6.47%. Found: C, 63.50; H, 6.54%.

3.20. Preparation of 3-fluoro-4-methoxymethylbenzyl-(±)-cis-permethrinate (**2**)

A mixture of (±)-*cis*-permethrinic acid (2.6 g, 12.36 mmol) and thionyl chloride (11.0 g, 92.44 mmol) was stirred at 50 °C for 4 h and the excess thionyl chloride was evaporated by means of a water pump. The acyl halide in benzene (10 ml) was added dropwise to a stirring solution of 2.1 g (12.35 mmol) of 3-fluoro-4-methoxymethylbenzyl alcohol and 1.75 g (22.15 mmol) of pyridine in 20 ml of benzene. After the addition, the mixture was stirred at 40 °C for 6 h. The mixture was washed by sodium hydroxide (1%, 20 ml), hydrochloric acid (2 M, 20 ml), saturated sodium hydrogencarbonate (20 ml) and saturated sodium chloride (20 ml). The water layer was extracted with benzene, and the organic layer was dried. After removal of the benzene, the residue was purified by column chromatography on silica gel. The eluate cyclohexane-ethyl acetate (19:1 v/v) was evaporated in vacuum to give a slight yellow liquid (**2**): 3.7 g (yield 83.0%). IR (film): $\nu = 1727$ (s) and 1137 (ester), 1582, 856 and 820 (Ph), 1116 (C–F), and 1092 cm^{-1} (C–O–C); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.252$ (s, 3H, E_{cycl}-CH_3), 1.257 (s, 3H, Z_{cycl}-CH_3), 1.895 (d, 1H, $^3J_{H,H} = 8$ Hz, cycl-H-1), 2.053 (t, 1H, $^3J_{H,H} = 8.8$ Hz, cycl-H-3), 3.411 (s, 3H, OCH_3), 4.520 (s, 2H, $ROCH_2$), 5.080 (s, 2H, $COOCH_2$), 6.251 (d, 1H, $^3J_{H,H} = 9.2$ Hz, = –H), 7.060 (dd, 1H, $^3J_{F,H} = 8$ Hz, $^4J_{H,H} = 1.6$ Hz, ArH-3), 7.1260 (dd, 1H, $^3J_{H,H} = 8$ Hz, $^4J_{H,H} = 1.6$ Hz, ArH-5), 7.402 (t, 1H, $^3J_{H,H} = 8$ Hz, $^4J_{F,H} = 8$ Hz, ArH-6). MS (EI, 70 eV), (*m/e*, %): 163 $[M-CH_3OCH_2C_6H_3FCH_2OCO]^+$ (26.5), 165 $[M+2-CH_3OCH_2C_6H_3FCH_2OCO]^+$ (17.6), 167 $[M+4-CH_3OCH_2C_6H_3FCH_2OCO]^+$ (2.9), 153 $[M-C_7H_9Cl_2COO]^+$ (100), 123 $[M-C_7H_9Cl_2COO–CH_2O]^+$ (15.3), 122 $[M-C_7H_9Cl_2COO–OCH_3]^+$ (14.7), 109 $[M-C_7H_9Cl_2COO–C_2H_4O]^+$ (14.7). Anal. Calc. for $C_{17}H_{19}Cl_2F O_3$ (361, 22): C, 56.53; H, 5.30%. Found: C, 56.40; H, 5.10%.

3.21. Biological testing

The insects tested were mosquitoes (*C. pipiens palles*) and houseflies (*M. domestica*). Adult female houseflies and mosquitoes, taken 3–5 days after molting, narcotized by CO_2, were treated on the metathoratic sterna with 0.5 μl drops (mosquitoes), 1 μl drops (houseflies). Thirty mosquitoes and 30 houseflies were treated with each of 5 concentrations of compounds (**1**) and (**2**), then kept by 5% syrup. LD_{50}s were estimated by the probit method from the mortalities 24 h after treatment. Standard errors were less than 10% of the LD_{50} in all tests. The results are summarized in Table 1.

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