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Metofluthrin: A Potent New Synthetic Pyrethroid with High Vapor Activity against Mosquitoes

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(1*R*)-*trans*-Norchrysanthemic acid fluorobenzyl esters are synthesized and their structure-activity relationships are discussed. These esters show outstanding insecticidal activity against mosquitoes. In particular, the 2,3,5,6-tetrafluoro-4-methoxymethylbenzyl analog (metofluthrin) exhibits the highest potency, being approximately forty times as potent as *d*-allethrin in a mosquito coil formulation when tested against southern house mosquitoes (*Culex quinquefasciatus*). Metofluthrin also exhibits a significant vapor action at room temperature.

Key words: metofluthrin; norchrysanthemic acid; vapor action; mosquito coil; fan vaporizer

Studies of the structural modification of natural pyrethrins span more than half a century. As a result, a number of synthetic pyrethroids with diverse characteristics have been invented not only for the control of household insect pests, but also for agricultural use. Among these pyrethroids, empenthrin (**2**) (Fig. 1) is noteworthy for having a high vapor action at room temperature, making it suitable for use as a fumigant in closed spaces to control fabric insect pests in closets. Empenthrin does not, however, show satisfactory insecticidal activity against mosquitoes. Much recent attention has been directed at the development of devices to control mosquitoes by using products in ambient-temperature devices because of their increased safety and ease of use, especially during outdoor activities. This development activity has resulted in a variety of fan-powered mosquito vaporizers and associated formulations which are now being marketed. These devices, however, have performance limitations that are imposed by the insecticidal activity of the active ingredient used. In order to overcome some of these limitations, we undertook extensive research to find a new pyrethroid with a higher vapor action that was highly active against mosquitoes.

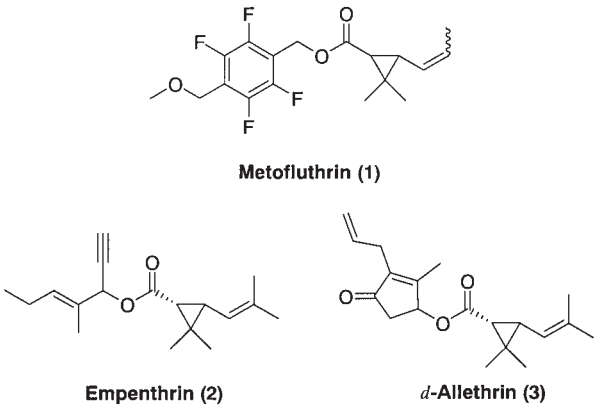

Fig. 1.

As a result of the research, we found that (1*R*)-*trans*-norchrysanthemic acid fluorobenzyl esters showed vapor activity against mosquitoes. In particular, the 2,3,5,6-tetrafluoro-4-methoxymethylbenzyl analog (**1**, metofluthrin) exhibited the highest potency, being approximate forty times as potent as *d*-allethrin (**3**) in a mosquito coil formulation when tested against southern house mosquitoes (*Culex quinquefasciatus*). This paper describes syntheses of the esters and presents their structure-activity relationships.

Materials and Methods

General methods. NMR spectra were recorded with a JEOL JNM-AL400 NMR spectrophotometer, with tetramethylsilane used as an internal standard. The starting materials were prepared by known methods.[1,2)]

Syntheses of the new compounds. Syntheses of the new norchrysanthemates are summarized in Scheme 1.

*(2,3,5,6-Tetrafluorophenyl)methyl (1R,3R)-2,2-dimethyl-3-((1Z)-1-propenyl)cyclopropanecarboxylate (**5**).* Diisopropyl azodicarboxylate (a 40% solution in toluene,

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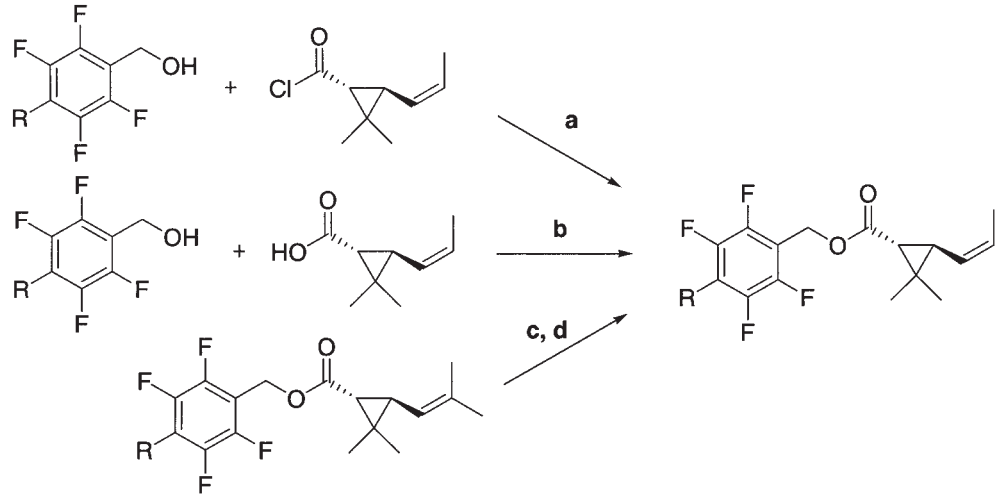


Scheme 1. Synthetic Routes to the Norchrysanthemic Acid Fluorobenzyl Esters.
Reagents and conditions: a) pyridine, THF; b) *i*-PrOCON=NCOO*i*-Pr, PPh_3, THF; c) O_3, MeOH, EtOAc, −78°C; Me_2S; d) $CH_3CH_2PPh_3Br$, *t*-BuOK, THF.

2.0 ml, 4.0 mmol) was added to a mixed solution of (1*R*,3*R*)-2,2-dimethyl-3-((1*Z*)-1-propenyl)cyclopropanecarboxylic acid (0.42 g, 3.0 mmol), (2,3,5,6-tetrafluorophenyl)methanol (0.49 g, 2.7 mmol), triphenylphosphine (0.93 g, 3.5 mmol) and tetrahydrofuran (20 ml). After 16 hours, the reaction solution was concentrated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography with hexane-ethyl acetate (20:1 by volume) as the eluant to give **5** (0.80 g, 93% yield) as a colorless oil. NMR δ_H ($CDCl_3$): 1.15 (3H, s), 1.29 (3H, s), 1.47 (1H, d, $J = 5.3$ Hz), 1.70 (3H, dd, $J = 6.9$ Hz, 1.6 Hz), 2.19 (1H, br dd, $J = 8.1$ Hz, 5.3 Hz), 5.12 (1H, d, $J = 10.6$ Hz, 8.1 Hz, 1.6 Hz), 5.24 (1H, t, $J = 1.6$ Hz), 5.25 (1H, t, $J = 1.6$ Hz), 5.60 (1H, dqd, $J = 10.6$ Hz, 6.9 Hz, 1.1 Hz), 7.10 (1H, tt, $J = 9.7$ Hz, 7.4 Hz).

(2,3,5,6-Tetrafluoro-4-methylphenyl)methyl (1R,3R)-2,2-dimethyl-3-((1Z)-1-propenyl)cyclopropanecarboxylate (7). (1*R*,3*R*)-2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarbonyl chloride (2.06 g, 11.1 mmol) was added to a mixed solution of (2,3,5,6-tetrafluoro-4-methylphenyl)methanol (1.78 g, 9.2 mmol) and pyridine (0.87 g, 11 mmol) in tetrahydrofuran (20 ml) under ice-cooling, and the mixture was stirred for 8 hours at room temperature. The reaction mixture was poured into 100 ml of ice-cooled water and extracted twice with 100 ml each of ethyl acetate. The combined ethyl acetate extracts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was subjected to silica gel column chromatography with hexane-ethyl acetate (20:1 by volume) as eluant to give (2,3,5,6-tetrafluoro-4-methylphenyl)methyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate (2.75 g, 87% yield). Oxygen containing ozone was blown into a mixed solution of this compound (1.27 g, 3.7 mmol), methanol (20 ml) and ethyl acetate (20 ml) at −78°C until the color of the solution had changed to blue. Nitrogen gas was then blown into the solution to remove the excess ozone, 5 ml of dimethylsulfide was added, and the solution was allowed to stand for 12 hours at room temperature. The reaction solution was concentrated under reduced pressure. To the resulting residue were added 20 ml of acetone, 2 ml of water and 0.2 g of *p*-toluenesulfonic acid monohydrate and the mixture was allowed to stand for 2 hours at room temperature. The reaction solution was poured into water and extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with hexane-ethyl acetate (10:1 by volume) as the eluant to give (2,3,5,6-tetrafluoro-4-methylphenyl)methyl (1*R*,3*R*)-3-formyl-2,2-dimethylcyclopropanecarboxylate (0.98 g, 82% yield). Potassium *tert*-butoxide (0.23 g, 2.0 mmol) was added to a stirred mixture of ethyltriphenylphosphonium bromide (1.1 g, 3.0 mmol) in tetrahydrofuran (30 ml) under ice-cooling. After 15 minutes, a tetrahydrofuran (5 ml) solution containing (2,3,5,6-tetrafluoro-4-methylphenyl)methyl (1*R*,3*R*)-3-formyl-2,2-dimethylcyclopropanecarboxylate (0.32 g, 1.0 mmol) was added to the mixture. After 30 minutes more, the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with hexane-ethyl acetate (20:1 by volume) as eluant to give **7** (0.22 g, 67% yield) as a colorless oil. NMR δ_H ($CDCl_3$): 1.14 (3H, s), 1.28 (3H, s), 1.45 (1H, d, $J = 5.3$ Hz), 1.70 (3H, dd, $J = 7.0$ Hz, 1.7 Hz), 2.17 (1H, br dd, $J = 8.4$ Hz, 5.3 Hz), 2.28 (2H, t, $J = 2.1$ Hz), 5.11 (1H, ddq, $J = 10.7$ Hz, 8.4 Hz, 1.7 Hz), 5.20 (1H, t, $J = 1.5$ Hz), 5.21 (1H, t, $J = 1.5$ Hz), 5.59 (1H, dqd, $J = 10.7$ Hz, 7.0 Hz, 1.3 Hz).

*(2,3,5,6-Tetrafluoro-4-methoxymethylphenyl)methyl (1R,3R)-2,2-dimethyl-3-((1Z)-1-propenyl)cyclopropanecarboxylate (**1**, **metofluthrin**).* (1*R*,3*R*)-2,2-dimethyl-3-((1*Z*)-1-propenyl)cyclopropanecarbonyl chloride (1.82 g, 1.05 mmol) was added to a solution of (2,3,5,6-tetrafluoro-4-methoxymethylphenyl)methanol (2.24 g, 10 mmol) and pyridine (0.87 g, 10 mmol) in tetrahydrofuran (20 ml) under ice-cooling, and the mixture was stirred for 8 hours at room temperature. The reaction mixture was poured into 100 ml of ice-cooled water and extracted twice with 100 ml each of ethyl acetate. The combined ethyl acetate extracts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was subjected to silica gel column chromatography with hexane-ethyl acetate (20:1 by volume) as the eluant to give **2** (3.17 g, 88% yield) as a colorless oil. NMR δ_H ($CDCl_3$): 1.15 (3H, s), 1.28 (3H, s), 1.46 (1H, *d*), 1.70 (3H, dd), 2.18 (1H, dd), 3.41 (3H, s), 4.59 (2H, s), 5.08–5.12 (1H, m), 5.24 (2H, s), 5.58–5.62(1H, m).

*(2,3,4,5,6-Pentafluorophenyl)methyl (1R,3R)-2,2-dimethyl-3-((1Z)-1-propenyl)cyclopropanecarboxylate (**6**).* This compound was prepared according to the procedure described for **5**. NMR δ_H ($CDCl_3$): 1.15 (3H, s), 1.28 (3H, s), 1.45 (3H, d, $J = 5.4$ Hz), 1.70 (3H, dd, $J = 6.8$ Hz, 1.7 Hz), 2.18 (1H, br dd, $J = 8.4$ Hz, 5.4 Hz), 5.11 (1H, ddq, $J = 10.6$ Hz, 8.4 Hz, 1.7 Hz), 5.21 (1H, br s), 5.60 (1H, dqd, $J = 10.6$ Hz, 7.0 Hz, 1.2 Hz).

*(4-Ethyl-2,3,5,6-tetrafluorophenyl)methyl (1R,3R)-2,2-dimethyl-3-((1Z)-1-propenyl)cyclopropanecarboxylate (**8**).* This compound was prepared according to the procedure described for **1**. NMR δ_H ($CDCl_3$): 1.14 (3H, s), 1.23 (3H, t, $J = 7.6$ Hz), 1.28 (3H, s), 1.46 (1H, d, $J = 5.4$ Hz), 1.70 (3H, dd, $J = 6.8$ Hz, 1.7 Hz), 2.18 (1H, dd, $J = 8.4$ Hz, 5.4 Hz), 2.77 (2H, q, $J = 7.6$ Hz), 5.10 (1H, ddq, $J = 10.7$ Hz, 8.4 Hz, 1.7 Hz), 5.21 (1H, t, $J = 1.3$ Hz), 5.22 (1H, t, $J = 1.3$ Hz), 5.59 (1H, dqd, $J = 10.7$ Hz, 6.8 Hz, 1.3 Hz).

*(2,3,5,6-Tetrafluoro-4-propylphenyl)methyl (1R,3R)-2,2-dimethyl-3-((1Z)-1-propenyl)cyclopropanecarboxylate (**9**).* This compound was prepared according to the procedure described for **1**. NMR δ_H ($CDCl_3$): 0.97 (3H, t, $J = 7.5$ Hz), 1.13 (3H, s), 1.28 (3H, s), 1.46 (1H, d, $J = 5.4$ Hz), 1.64 (2H, sext, $J = 7.5$ Hz), 1.70 (3H, dd, $J = 6.8$ Hz, 1.7 Hz), 2.18 (1H, dd, $J = 8.4$ Hz, 5.4 Hz), 2.72 (2H, t, $J = 7.5$ Hz), 5.11 (1H, ddq, $J = 10.7$ Hz, 8.4 Hz, 1.7 Hz), 5.21 (1H, t, $J = 1.3$ Hz), 5.22 (1H, t, $J = 1.3$ Hz), 5.59 (1H, dqd, $J = 10.7$ Hz, 6.8 Hz, 1.3 Hz).

*(4-Allyl-2,3,5,6-tetrafluorophenyl)methyl (1R,3R)-2,2-dimethyl-3-((1Z)-1-propenyl)cyclopropanecarboxylate (**10**).* This compound was prepared according to the procedure described for **7**. NMR δ_H ($CDCl_3$): 1.13 (3H, s), 1.24 (3H, s), 1.48 (3H, d, $J = 5.4$ Hz), 1.68 (3H, dd, $J = 6.6$ Hz, 1.4 Hz), 2.03 (1H, br dd, $J = 8.2$ Hz, 5.4 Hz), 3.48 (2H, dt, $J = 6.3$ Hz, 1.3 Hz), 5.07–5.24 (5H, m), 5.62 (1H, dq, $J = 15.1$ Hz, 6.5 Hz), 5.89 (1H, ddt, 16.7 Hz, 10.3 Hz, 6.3 Hz).

*(2,3,5,6-Tetrafluoro-4-methoxyphenyl)methyl (1R,3R)-2,2-dimethyl-3-((1Z)-1-propenyl)cyclopropanecarboxylate (**11**).* This compound was prepared according to the procedure described for **7**. NMR δ_H ($CDCl_3$): 1.14 (3H, s), 1.28 (3H, s), 1.45 (1H, d, $J = 5.4$ Hz), 1.70 (3H, dd, $J = 6.9$ Hz, 1.7 Hz), 2.18 (1H, br dd, $J = 8.4$ Hz, 5.4 Hz), 4.10 (3H, t, $J = 1.4$ Hz), 5.11 (1H, ddq, $J = 10.5$ Hz, 8.4 Hz, 1.7 Hz), 5.18 (1H, t, $J = 1.6$ Hz), 5.19 (1H, t, $J = 1.6$ Hz), 5.60 (1H, dqd, $J = 10.5$ Hz, 7.1 Hz, 1.4 Hz).

Evaluation of the insecticidal effectiveness of the test compounds. Topical application for evaluating the insecticidal efficacy against common house mosquitoes (*Culex pipiens pallens*) complied with the method described by Yamaguchi *et al.*[3]

Evaluation of the vapor action of a non-heated formulation of each test compound at room temperature against common house mosquitoes (Culex pipiens pallens). A test compound (100 mg) was dissolved in 20 ml of acetone and applied onto a sheet of filter paper (20 cm × 50 cm), the acetone then being removed by air-drying. In the center of a 28 m^3 test chamber (4.3 m × 2.65 m × 2.45 m height), the filter paper was hung from the ceiling with the upper end of the filter paper 1.7 m in height from the floor. Four nylon-net cages (cylindrical, 30 cm in diameter and 20 cm in height) each containing 20 female common house mosquitoes (*Culex pipiens pallens*) were hung from the ceiling with the base of each cage 60 cm from the floor. One cage was placed in each corner of the room, 60 cm horizontally from the filter paper. The number of knocked down mosquitoes was counted at designated intervals for 60 minutes. In order to circulate air in the chamber, a fan was positioned under the treated filter paper, and a board was placed between the fan and the filter paper to prevent direct air flow between the two (see Fig. 2).

Evaluation of biological efficacy in a mosquito coil formulation. The preparation of test mosquito coils complied with the method described by Yamaguchi *et al.*[3] The test coil was fitted on a coil holder and placed at the center of the chamber (4.3 m × 2.65 m × 2.45 m height). The coil was ignited and then 100 adult female mosquitoes were released into the chamber. The number of knocked down mosquitoes was counted at designated intervals for 75 minutes.

LD_{50} and KT_{50}. These values were calculated by the probit method.[4]

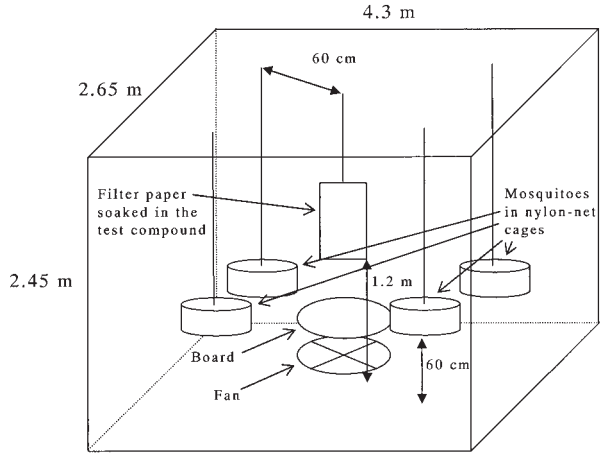


Fig. 2. Method for Evaluating the Vapor Activity of a Formulation at Ambient-temperature.

Fig. 3.

Results and Discussion

Ohno[5] and Elliott[6] independently reported insecticidal norchrysanthemic acid esters in the 1970s (Fig. 3). According to their reports, these norchrysanthemic acid esters showed comparable insecticidal activity to that of the corresponding chrysanthemates.[7] However, further studies were discontinued at that time because they could not find any justification to develop these norchrysanthemic acid esters due to the difficulty of synthesizing norchrysanthemic acid. Despite this, we directed our attention to the norchrysanthemic acid esters because they had a lower molecular weight and showed comparable insecticidal activity to that of the corresponding chrysanthemates. We synthesized various insecticidal norchrysanthemic acid esters and screened them for vapor activity.

As a result of the screening, we found 2,3,5,6-tetrafluorobenzyl norchrysanthemate (**5**) had a faster knockdown activity (KT_{50}, time for 50% knocked-down calculated by the probit method) than the chrysanthemate (**4**)[8] against mosquitoes as shown in Fig. 4. We then synthesized the derivatives with substituents at the 4-position on the phenyl ring of compound **5**.

All analogs had much higher activity against mosquitoes than empenthrin and compound **5** by the standard topical application method as shown in Table 1. The relative toxicity reached the maximum with between two and three carbon atoms at the 4-position (**5**–**9**). Unsaturation (**10**) and incorporation of an oxygen atom (**11**) also showed substantial activity, *inter alia*, the 4-methoxymethyl derivative (**1**, **metofluthrin***) exhibiting the highest lethal potency, being over twenty five times as active as *d*-allethrin. The results presented in Table 2 clearly demonstrate that metofluthrin exhibited a significant level of vapor action against mosquitoes at room temperature. Metofluthrin also exhibited a high levels of knockdown activity in coil formulations when tested against mosquito species as shown in Table 2. In particular, metofluthrin exhibited similar activity to that of *d*-allethrin against southern house mosquitoes (*Culex*

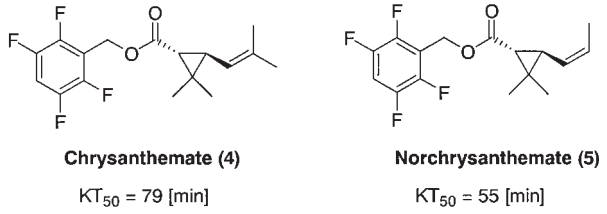
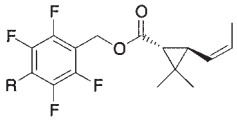


Fig. 4. Effectiveness of 2,3,5,6-Tetrafluorobenzyl Chrysanthemate and Its Norchrysanthemic Analog in an Ambient-temperature Formulation against *Culex pipiens pallens*.

Table 1. Insecticidal Effectiveness of Metofluthrin and Its Analogs against *Culex pipiens pallens*



Compound	R	R.T.[a]
5	H	30
6	F	100
7	Me	200
8	Et	490
9	Pr	250
10	allyl	500
11	OMe	360
metofluthrin (**1**)	CH_2OMe	2500
empenthrin (**2**)		10
d-allethrin (**3**, standard)		100

[a] Relative toxicity (R.T.) against *Culex pipiens pallens* based on LD_{50} by the topical application method.

Table 2. Effectiveness of Metofluthrin in Various Formulations against Mosquito Species

Formulation	Species	Conc. [%]	KT_{50} [min][a] metofluthrin	*d*-allethrin
non-heated	*C. pipiens pallens*		27	>60
mosquito coil	*C. pipiens pallens*	0.013	49	
		0.02	35	
		0.04	22	
		0.2		54
mosquito coil	*C. quinquefasciatus*	0.005	42	
		0.2		58

[a] KT_{50}: time for 50% knocked-down calculated by the probit method.

* ISO 1750 provisionally approved.

quinquefasciatus) at only a fortieth of the active ingredient level.

Metofluthrin will be marketed for environmental health use, having high knockdown activity against mosquitoes and an excellent mammalian safety profile. Metofluthrin is suitable for use in various existing source devices like mosquito coils, and also in the more novel devices such as a fan vaporizers and treated paper strip.

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