Synthesis and Insecticidal Activity of New Quinoline Derivatives Containing Perfluoropropanyl Moiety

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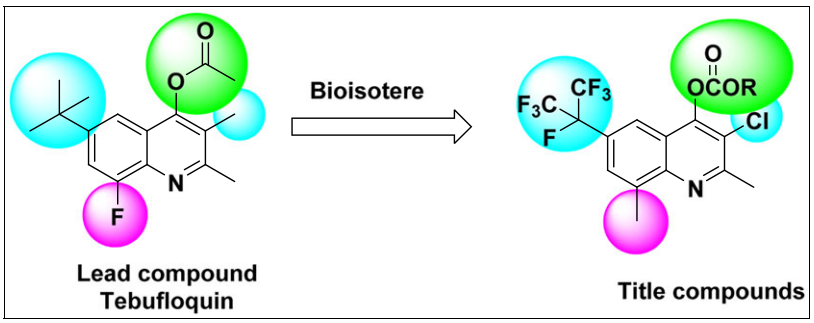
Received August 6, 2018
DOI 10.1002/jhet.3502
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).



A series of new quinoline derivatives containing perfluoropropanyl moiety were designed and synthesized. Their structures were confirmed by ^{1}H-NMR, MS, and elemental analysis. The bioassay results showed that compound **4e** exhibited good insecticidal activity against *Plutella xylostella* and *Mythimna separata* at 100 mg/L.

J. Heterocyclic Chem., **00,** 00 (2019).

INTRODUCTION

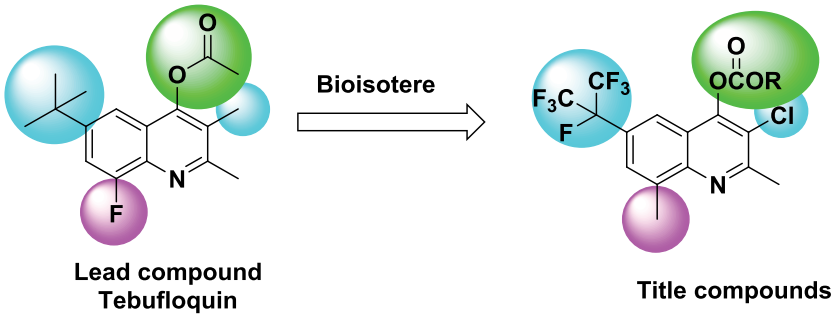
Quinoline heterocycle is an important natural product skeleton, which can be found in many plants. For instance, the famous anti-malaria drug quinine is exacted from the congeneric plants firstly. Neither natural quinoline derivatives nor synthetic quinoline derivatives always displayed diversity activities, such as antioxidant activity [1], antitubercular agents [2], trypanocidal activities [3], anticancer [4], antibacterial activity [5], aromatase inhibitors [6], and multi-trypanosomatid activity [7]. So the synthesis of novel quinoline derivatives has been attracted by many organic chemists. The tebufloquin is a novel quinoline compound with outstanding control effect against *Pyricularia oryae*, which is discovered by Meiji Seika Kaisha, Inc. [8].

In our previous work [9–13], we found that the perfluoropropanyl group on the quinoline ring can increase the fungicidal activity, so in line with our continued efforts to synthesize novel lead compounds for drug discover [14–35], the fungicide tebufloquin was selected as a lead compound, the *t*-Bu group was replaced by perfluoropropanyl group, the methyl group was replaced by chlorine atom, the fluorine atom was replaced by methyl group, and the ether group was replaced by ester carbonate. Our original strategy is depicted in Scheme 1. Surprisingly, the title compounds possessed no *in vivo* fungicidal activity against *P. oryae*, but compound **4e** exhibited good insecticidal activity against *Plutella xylostella* and *Mythimna separata* at 100 mg/L. Even at 20 mg/L, the compound **4e** still exhibited moderate insecticidal activity against *P. xylostella* and *M. separata*. These compounds and their insecticidal activity had been published as patents [36] by us.

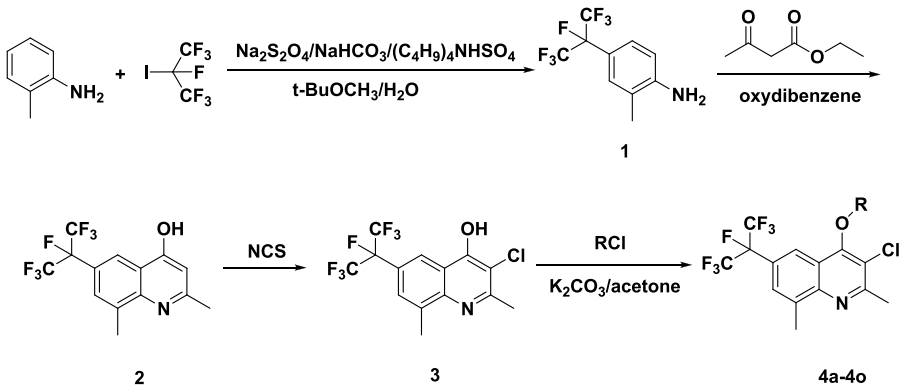
RESULTS AND DISCUSSION

The synthetic route was shown in Scheme 2. Generally, 2-methyl-4-(perfluoropropan-2-yl)aniline was prepared from 2-methyl aniline and 1,1,1,2,3,3,3-heptafluoro-2-iodopropane reagent as starting materials according to our previous work [9–13]. The mechanism [37] of the key intermediate 2-methyl-4-(perfluoropropan-2-yl)aniline was shown in Scheme 3. For the synthesis of quinolone structure, it is reported lots of methods, such as Camps method [38], Skraup method [39], cyclized method [40], Combes method [41], Niementowsld method [42], Friedlander method [43], microwave method [44], Pfitzinger method [45], and one pot method [46]. Among them, Combes method was selected, which cyclized from the starting material 2-methyl-4-(perfluoropropan-2-yl) aniline and ethyl 3-oxobutanoate in the oxydibenzene solution. In our previous work, the quinoline compounds were synthesized under acid condition. For the target

Scheme 1. The design strategy of title compounds. [Color figure can be viewed at wileyonlinelibrary.com]

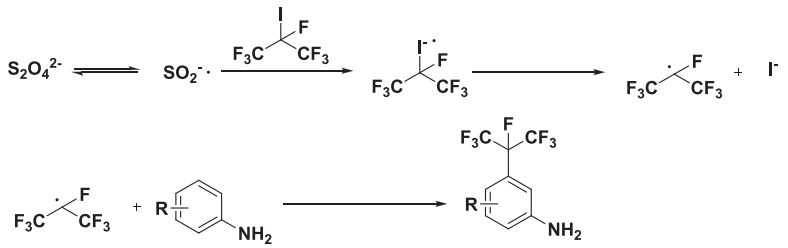


Scheme 2. The synthetic route of title compounds. [Color figure can be viewed at wileyonlinelibrary.com]



4a: R=$COOCCl_3$; **4b**: R=$COOCH_2CH_2CH_2CH_3$; **4c**: R=$COOCH_2CH_2CH_3$; **4d**: R=$CON(CH_3)_2$; **4e**: R=COOPh; **4f**: R=$COOCHClCH_3$; **4g**: R=$COCH(CH_3)_2$; **4h**: R= $COC(CH_3)_3$; **4i**: R= $COCH_3$; **4j**: R=$COOCH_2CH_2Cl$; **4k**: R=$COOCH_2CH_3$; **4l**: R=$COCH_2CH{=}CH_3$; **4m**: R=$COOCH_2Ph$; **4n**: R=$COOCH(CH_3)_2$; **4o**: R=$COOCH_3$

Scheme 3. The mechanism of synthesis intermediate **1**.

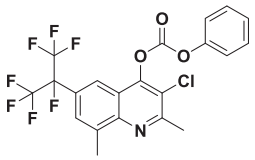


derivatives, the yield is low when tetrahydrofuran was used as solvent and Et_3N used as base. At last, these compounds were synthesized in acetone under K_2CO_3 as base condition, the yield is high and purification is easy. All the target compounds were characterized and identified by ^{1}H-NMR, MS, and ESI-HRMS. The title compounds exhibited the M + H^+ peak in the ESI-MS and ESI-HRMS results.

The *in vivo* fungicidal activity against *P. oryae* was determined. Unfortunately, all of target compounds possessed no activity against *P. oryae* at 200 mg/L. Surprisingly, compound **4e** exhibited good insecticidal activity and result was shown in Table 1. These compounds displayed 100% inhibitory against Lepidoptera pests at 500 and 100 mg/L, but they exhibited no activity against *Aphis craccivora* Koch and

Table 1

The insecticidal activity of some compounds (%, inhibitory).

No.	Structure	Concentration mg/L	*Aphis craccivora* Koch	*Tetranychus cinnabarinus*	*Plutella xylostella*	*Mythimna separata*
4e		500	0	0	100	100
		100	0	0	100	100
		20	0	0	30	60

Tetranychus cinnabarinus. For the *P. xylostella* and *M. separata*, the compound **4e** exhibited 30% and 60% inhibitory at 20 mg/L, respectively.

CONCLUSION

To explore higher active compounds with antifungal activity and insecticidal activity, some new 6-perfluoropropanyl quinoline derivatives were designed and synthesized. Only compound **4e** possessed good insecticidal activity against *P. xylostella* and *M. separata*. The structure can be recognized as new lead insecticidal compounds with further structure modification.

EXPERIMENT

Instrument. Melting points were measured on a Taike X-4 apparatus and uncorrected. ^{1}H-NMR data were determined by Bruker AV-400 instrument. ESI-MS data were determined by LCQ-Advantage Thermofinngen instrument. The elemental analysis data were measured by a Perkin-Elmer 240C elemental analyzer. All the thin-layer chromatography (TLC) or chemical reagents are purchased (analytical grade).

General procedure. ***Synthesis of 2-methyl-4-(perfluoropropan-2-yl)aniline 1.*** To a solution of *o*-methylaniline (180 g, 1.68 mol) in MeOBu-*t* solution (800 mL) and H_2O (800 mL), the mixture of $Bu_4NH_4HSO_4$ (50.5 g, 1.68 mol), Na_2CO_3 (125.16 g, 1.68 mol), and hydrosulfite (259.42 g, 1.68 mol) was added dropwisely at 25°C. Then, the $(CF_3)_2CFI$ (497.28 g, 1.68 mol) was dropwised slowly at 0°C. TLC monitored, after the reaction is completed, subsequently, the reaction mixture was diluted with H_2O (200 mL), and the organic layer was separated. Then, the residue solution was extracted three times with ethyl acetate (200 mL). The combined organic phases were washed with brine, dried over magnesium sulfate and evaporated to afford the red brown oil (328.02 g, yield 71%) without further purification.

Synthesis of 2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-ol 2. In a 500 mL of three neck bottom, the 2-methyl-4-(perfluoropropan-2-yl) aniline (20 g, 0.073 mol), ethyl 3-oxobutanoate (9.49 g, 0.073 mol), and oxydibenzene (100 mL) were stirred at 240°C for 2 h. Then, the mixture was cooled to 70°C; the petroleum ether was added into the mixture; lots of solid were given, filtered, and dried (yield 91.8%). White solid, m.p. 321–323°C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.70 (s, 1H, Py-OH), 8.20 (s, 1H, Ph-H), 6.07 (s, 1H, Py-H), 2.62 (s, 3H, pyridyl-CH_3), 2.43 (s, 3H, Ph-CH_3); ESI-MS: 341 $[M + H]^+$.

Synthesis of 3-chloro-2,8-dimethyl-6-(perfluoropropan-2-yl) quinolin-4-ol 3. In a 250 mL of three neck bottom, the 2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-ol (15 g, 0.044 mol), *N*-chlorosuccinimide (6.38 g, 0.048 mol), and dimethylformamide (50 mL) were stirred at room temperature. TLC monitored, after the reaction is completed, the mixture was poured into water; lots of solid was given, filtered, and dried (yield 90.5%). White solid, m.p. 281–283°C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.84 (s, 1H, Py-OH), 8.27 (s, 1H, Ph-H), 7.77 (s, 1H, Py-H), 2.90 (s, 3H, pyridyl-CH_3), 2.74 (s, 3H, Ph-CH_3); ESI-MS: 375 $[M + H]^+$.

Synthesis of target compounds 4a–4o. To a solution of 3-chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-ol (0.525 g, 1.4 mmol) and K_2CO_3 (0.19 g, 1.4 mmol) in acetone (50 mL), the substituted benzyl carbonochloridate (1.4 mmol) was dropwised. TLC monitored, after the reaction is completed, the mixture was filtered and evaporated. The target compound was purified by chromatography on a silica gel using petroleum ether and ethyl acetate ($V_{(EA)}$:$V_{(PE)}$ = 1:8) as the eluent to afford the compounds **4a**–**4o**.

*3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl (trichloromethyl) carbonate **4a**.* White solid, m.p. 133~134°C, yield 33.1%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.33 (s, 1H, Ph-H), 7.74 (s, 1H, Ph-H), 2.91 (s, 3H,

pyridyl-CH_3), 2.86 (s, 3H, Ph-CH_3); ESI-MS: 535 $[M + H]^+$; Elemental anal. calculated for $C_{16}H_8Cl_4F_7NO_3$ (%): C, 35.78; H, 1.50; N, 2.61; found: C, 35.49; H, 1.24; N, 2.44.

Butyl (3-chloro-2,8-dimethyl-6-(perfluoropropan-2-yl) quinolin-4-yl) carbonate ***4b***. White solid, m.p. 34~35°C, yield 32.2%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.99 (s, 1H, Ph-H), 7.70 (s, 1H, Ph-H), 4.39 (t, 2H, J = 6.4 Hz, -$OCH_2CH_2CH_2CH_3$), 2.88 (s, 3H, pyridyl-CH_3), 2.83 (s, 3H, Ph-CH_3), 1.70~1.81 (m, 2H, -$OCH_2CH_2CH_2CH_3$), 1.39~1.50 (m, 2H, -$OCH_2CH_2CH_2CH_3$), 0.99 (t, 3H, J = 7.6 Hz, -$OCH_2CH_2CH_2CH_3$); ESI-MS: 476 $[M + H]^+$; Elemental anal. calculated for $C_{20}H_{19}ClF_7NO_3$ (%): C, 47.96; H, 3.60; N, 2.94; found: C, 48.06; H, 3.88; N, 3.09.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl propyl carbonate ***4c***. White solid, m.p. 25~26°C, yield 67.3%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.99 (s, 1H, Ph-H), 7.70 (s, 1H, Ph-H), 4.35 (t, 2H, J = 6.8 Hz, -$OCH_2CH_2CH_2CH_3$), 2.88 (s, 3H, pyridyl-CH_3), 2.83 (s, 3H, Ph-CH_3), 1.74~1.89 (m, 2H, -$OCH_2CH_2CH_2CH_3$), 1.04 (t, 3H, J = 7.6 Hz, -$OCH_2CH_2CH_2CH_3$); ESI-MS: 462 $[M + H]^+$; Elemental anal. calculated for $C_{18}H_{15}ClF_7NO_3$ (%): C, 46.82; H, 3.27; N, 3.03; found: C, 46.77; H, 3.24; N, 3.07.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl dimethylcarbamate ***4d***. White solid, m.p. 120~121°C, yield 20.1%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.97 (s, 1H, Ph-H), 7.66 (s, 1H, Ph-H), 3.30 (s, 3H, -CON $(CH_3)_2$), 3.12 (s, 3H, -CON $(CH_3)_2$), 2.86 (s, 3H, pyridyl-CH_3), 2.84 (s, 3H, Ph-CH_3); ESI-MS: 447 $[M + H]^+$; Elemental anal. calculated for $C_{17}H_{14}ClF_7N_2O_2$ (%): C, 45.70; H, 3.16; N, 6.27; found: C, 45.98; H, 3.43; N, 6.23.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl phenyl carbonate ***4e***. White solid, m.p. 93~94°C, yield 39.2%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35~8.11 (m, 7H, Ar-H), 2.92 (s, 3H, pyridyl-CH_3), 2.86 (s, 3H, Ph-CH_3); ESI-MS: 496 $[M + H]^+$; Elemental anal. calculated for $C_{21}H_{13}ClF_7NO_3$ (%): C, 50.88; H, 2.64; N, 2.83; found: C, 50.90; H, 2.54; N, 2.56.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl (1-chloroethyl) carbonate ***4f***. White solid, m.p. 75~76°C, yield 41.3%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.98 (s, 1H, Ph-H), 7.74 (s, 1H, Ph-H), 6.57 (q, 1H, J = 5.6 Hz, -$CHClCH_3$), 2.91 (s, 3H, pyridyl-CH_3), 2.87 (s, 3H, Ph-CH_3), 2.01 (d, 3H, J = 5.6 Hz, -$CHClCH_3$); ESI-MS: 482 $[M + H]^+$; Elemental anal. calculated for $C_{17}H_{12}Cl_2F_7NO_3$ (%): C, 42.35; H, 2.51; N, 2.90; found: C, 42.34; H, 2.87; N, 2.99.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl isobutyrate ***4g***. White solid, m.p. 104~105°C, yield 23.5%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.87 (s, 1H, Ph-H), 7.70 (s, 1H, Ph-H), 2.91~3.12 (m, 1H, -CH $(CH_3)_2$), 2.88 (s, 3H, pyridyl-CH_3), 2.84 (s, 3H, Ph-CH_3), 1.48 (d, 6H, J = 7.2 Hz, -CH $(CH_3)_2$); ESI-MS: 446 $[M + H]^+$; Elemental anal. calculated for $C_{18}H_{15}ClF_7NO_2$ (%): C, 48.50; H, 3.39; N, 3.14; found: C, 48.67; H, 3.65; N, 3.23.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl pivalate ***4h***. White solid, m.p. 108~109°C, yield 40.9%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.88 (s, 1H, Ph-H), 7.72 (s, 1H, Ph-H), 2.89 (s, 3H, pyridyl-CH_3), 2.86 (s, 3H, Ph-CH_3), 1.54 (s, 9H, $-(CH_3)_3$); ESI-MS: 460 $[M + H]^+$; Elemental anal. calculated for $C_{19}H_{17}ClF_7NO_2$ (%): C, 49.63; H, 3.73; N, 3.05; found: C, 49.76; H, 3.87; N, 3.04.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl acetate ***4i***. White solid, m.p. 96~97°C, yield 34.6%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.87 (s, 1H, Ph-H), 7.67 (s, 1H, Ph-H), 2.86 (s, 3H, pyridyl-CH_3), 2.82 (s, 3H, Ph-CH_3), 2.54 (s, 3H, -$COCH_3$); ESI-MS: 418 $[M + H]^+$; Elemental anal. calculated for $C_{16}H_{11}ClF_7NO_2$ (%): C, 46.01; H, 2.65; N, 3.35; found: C, 46.07; H, 2.87; N, 3.43.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl (2-chloroethyl) carbonate ***4j***. White solid, m.p. 47~48°C, yield 35.8%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01 (s, 1H, Ph-H), 7.71 (s, 1H, Ph-H), 4.63 (d, 2H, J = 5.6 Hz, -OCH_2CH_2Cl), 3.84 (d, 2H, J = 5.6 Hz, -OCH_2CH_2Cl), 2.88 (s, 3H, pyridyl-CH_3), 2.84 (s, 3H, Ph-CH_3); ESI-MS: 482 $[M + H]^+$; Elemental anal. calculated for $C_{17}H_{12}Cl_2F_7NO_3$ (%): C, 42.35; H, 2.51; N, 2.90; found: C, 42.35; H, 2.22; N, 3.01.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl ethyl carbonate ***4k***. White solid, m.p. 63~64°C, yield 45.3%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.98 (s, 1H, Ph-H), 7.69 (s, 1H, Ph-H), 4.43 (q, 2H, J = 7.2 Hz, -OCH_2CH_3), 2.87 (s, 3H, pyridyl-CH_3), 2.83 (s, 3H, Ph-CH_3), 1.45 (t, 3H, J = 7.2 Hz, -OCH_2CH_3); ESI-MS: 448 $[M + H]^+$; Elemental anal. calculated for $C_{17}H_{13}ClF_7NO_3$ (%): C, 45.60; H, 2.93; N, 3.13; found: C, 45.77; H, 3.03; N, 3.25.

Allyl (3-chloro-2,8-dimethyl-6-(perfluoropropan-2-yl) quinolin-4-yl) carbonate ***4l***. White solid, m.p. 49~50°C, yield 54.3%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.99 (s, 1H, Ph-H), 7.70 (s, 1H, Ph-H), 4.43 (q, 2H, J = 7.2 Hz, -OCH_2CH_3), 2.87 (s, 3H, pyridyl-CH_3), 2.83 (s, 3H, Ph-CH_3), 1.45 (t, 3H, J = 7.2 Hz, -OCH_2CH_3); ESI-MS: 460 $[M + H]^+$; Elemental anal. calculated for $C_{18}H_{13}ClF_7NO_3$ (%): C, 47.03; H, 2.85; N, 3.05; found: C, 47.23; H, 3.01; N, 3.02.

Benzyl (3-chloro-2,8-dimethyl-6-(perfluoropropan-2-yl) quinolin-4-yl) carbonate ***4m***. White solid, m.p. 83~84°C, yield 67.2%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36~7.95 (m, 7H, Ph-H), 5.38 (s, 2H, -OCH_2Ph), 2.87 (s, 3H, pyridyl-CH_3), 2.83 (s, 3H, Ph-CH_3); ESI-MS: 510 $[M + H]^+$; Elemental anal. calculated for $C_{22}H_{15}ClF_7NO_3$ (%): C, 51.83; H, 2.97; N, 2.75; found: C, 51.98; H, 3.12; N, 2.88.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl isopropyl carbonate ***4n***. White solid, m.p. 72~73°C, yield 77.4%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.98 (s, 3H, Ph-H), 7.70 (s, 3H, Ph-H), 5.02~5.11 (m, 1H, -OCH $(CH_3)_2$), 2.88 (s, 3H, pyridyl-CH_3), 2.83 (s, 3H, Ph-CH_3), 1.44 (d, 6H, J = 6.4 Hz, -OCH $(CH_3)_2$); ESI-MS: 462 $[M + H]^+$; Elemental anal. calculated for $C_{18}H_{15}ClF_7NO_3$ (%): C, 46.82; H, 3.27; N, 3.03; found: C, 46.98; H, 3.33; N, 3.05.

3-Chloro-2,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl methyl carbonate ***4o***. White solid, m.p. 82~84°C, yield 78%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.99 (s, 3H, Ph-H), 7.70 (s, 3H, Ph-H), 4.04 (s, 3H, -OCH_3), 2.88 (s, 3H, pyridyl-CH_3), 2.83 (s, 3H, Ph-CH_3); ESI-MS: 434 $[M + H]^+$; Elemental anal. calculated for $C_{16}H_{11}ClF_7NO_3$ (%): C, 44.31; H, 2.56; N, 3.23; found: C, 44.34; H, 2.81; N, 3.11.

Insecticidal activity. All bioassays were performed on representative test organisms reared in the laboratory, which were repeated at 25 ± 1°C according to the statistical requirements. The detailed procedure was described as follows.

Insecticidal activity against Mythimna separata and Plutella xylostella. The leaf dipping assay method was used for *M. separata* and *P. xylostella* tests, in which the corn leaves were dipped into a test solution for 20 s and allowed to dry. The treated diet was placed in a diameter of 7 cm Petri dish, and 10 fourth-instar oriental armyworm larvae were released into the Petri dish. The symptoms of affected larvae were observed at 24 h after the application, and percentage mortalities were evaluated 72 h after treatment.

Insecticidal activity against Tetranychus cinnabarinus. Sieva bean plants (*Phaseolus vulgaris* L.) with primary leaves expanded to 10 cm were selected and cut back to one plant per pot. A small piece was cut from a leaf taken from the main colony and placed on each leaf of the test plants. This was performed about 2 h before treatment to allow the mites to move to the test plant and to lay eggs. The size of the piece was varied to obtain about 60–100 mites per leaf. At the time of the treatment, the piece of leaf used to transfer the mites was removed and discarded. The mite-infested plants were dipped in the test formulation for 3 s with agitation and set in the hood to dry. Plants were kept for 2 days before the number of alive and dead adults was counted.

Insecticidal activity against Aphis craccivora. Bean aphids were dipped according to a slightly modified Food and Agriculture Organization (FAO) dip test. The tender shoots of soybean with 40–60 healthy apterous adult aphids were dipped in the diluted solutions of the compounds for 5 s, and the superfluous fluid was removed and placed in the conditioned room. Mortality was calculated 48 h after treatment. Each treatment was performed three times. The data for the mortality-regression lines of the compounds were subjected to probit analysis by Finney's method.

Acknowledgments. This work was funded by Zhejiang Provincial Natural Science Foundation of China (LY19C140002) and Research Fund of Department of Education of Zhejiang Province (Y201840646).

CONFLICT OF INTEREST

The authors declare no competing financial interest.

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