Synthesis, Antifungal Activity, and SAR Study of Some New 6-Perfluoropropanyl Quinoline Derivatives

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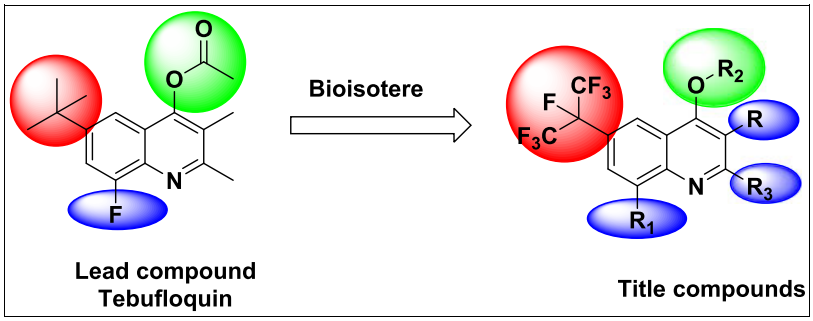

A series of novel quinoline derivatives containing perfluoropropanyl moiety were designed and synthesized. The bioassay results showed that some of them exhibited good control efficacy against *Pyricularia oryae.* The fungicidal activity was affected by the substituted position in the molecule. It was found that the compound **3n** possessed highest control effect against *P. oryae* at different concentration. It is better than that of control Tebufloquin.

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INTRODUCTION

Recent years, the pesticide-resistance problem had become series all over the world [1,2], especially for fungicides. Rice is an oldest and major food crop in asian country. *Pyricularia oryae*, commonly known as fire blast, blast hanging head, and pinch neck blast in China, is the world's important rice disease caused by *P. oryae*. *P. oryae* can decrease the yield of rice. Sometimes, the reduction can reach 40% to 50%, even more. Tricyclazole, an effective fungicide developed by Eli Lilly and Company, is always used to control *P.* oryae for many years. Many references reported that *P. oryae* had resistant when using the fungicide tricyclazole. It is urgent to develop novel environmentally friendly and high active compounds with different mode of action in order to overcome the resistance of fungals [3]. Tebufloquin 1 is a novel structural heterocyclic compound that provides outstanding control over *P. oryae* with novel mode of actions. Meiji Seika Kaisha [4] reported that Tebufloquin is highly active against *P. oryae*.

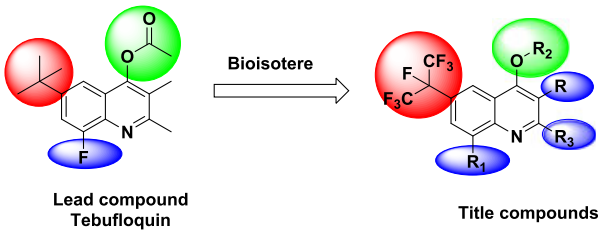
Quinoline derivatives are an important class of heterocyclic aromatic compounds, which name is derived from the anti-malaria drug quinine. In modern synthesis chemistry, quinoline compounds had been applied in many fields [5–7], such as coordination chemistry, organometallic chemistry, asymmetric synthesis, medicinal chemistry, pesticidal chemistry, and materials chemistry. Quinoline is one of the most common skeleton in many natural production and has many important physiological activities, such as anti-tubercular agents [8], anti-cancer [9], antioxidant activity [10], aromatase inhibitors [11], multi-trypanosomatid activity [12], trypanocidal activities [13], and antibacterial activity [14]. Therefore, the synthesis of novel quinolone derivatives has attracted by many organic chemists.

In line with our continued efforts to synthesize novel lead compounds for pesticide discover [15–25], the fungicide Tebufloquin was selected as a lead compound, the *t*-Bu group was replaced by perfluoropropanyl group and the fluorine atom was replaced by methyl group. Then the ether group was replaced by ester carbonate. Our original strategy is depicted in Scheme 1. Surprisingly, the designed compounds not only exhibited excellent control efficacy than the fungicide Tebufloquin against *P. oryae*.

EXPERIMENTAL

Instrument and materials. Melting points were measured on a Taike X-4 apparatus (Beijing, China) and uncorrected. ^{1}H NMR data were determined by Bruker AV-400 instrument (Billerica, MA). The elemental analysis data were measured by a Perkin-Elmer 240C

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



elemental analyzer (Waltham, MA). All the TLC or chemical reagents are purchased (analytical grade).

General procedure. ***Synthesis of intermediate 1.*** To a solution of o-methylaniline (180 g, 1.68 mol) in methyl tert-butyl ether solution (800 mL) and water (800 mL), the mixture of tetrabutylammonium hydrogen sulfate (50.5 g, 1.68 mol), sodium bicarbonate (125.16 g, 1.68 mol), and hydrosulfite (259.42 g, 1.68 mol) was added dropwisely at 25°C. Then the 1,1,1,2,3,3,3-heptafluoro-2-iodopropane (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 water (200 mL); the organic layer was seperated. Then the residue solution was extracted several 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 purified. The 2-ethyl-4-(perfluoropropan-2-yl)aniline was synthesized according to this procedure with the yield 95%.

Synthesis of intermediate 2a. In a 500 mL three-neck bottom, the 2-methyl-4-(perfluoropropan-2-yl)aniline (100 g, 0.364 mol), ethyl 2-substituted-3-oxobutanoate (0.364 mol), and polyphosphoricacid (75.5 g) were stirred at 150°C, TLC monitored. After the reaction is completed, the mixture was poured into the water (400 mL); lots of solid was given and dried, yield 93.1%. The intermediate **2b**, **2c**, and **2d** were synthesized according this method.

Synthesis of target compounds 3a–3p. To a solution of 2,3,8-trimethyl-6-(perfluoropropan-2-yl)quinolin-4-ol (0.5 g, 1.4 mmol) and potassium carbonate (0.084 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 **3a**–**3p**. The synthetic route was shown in Scheme 2.

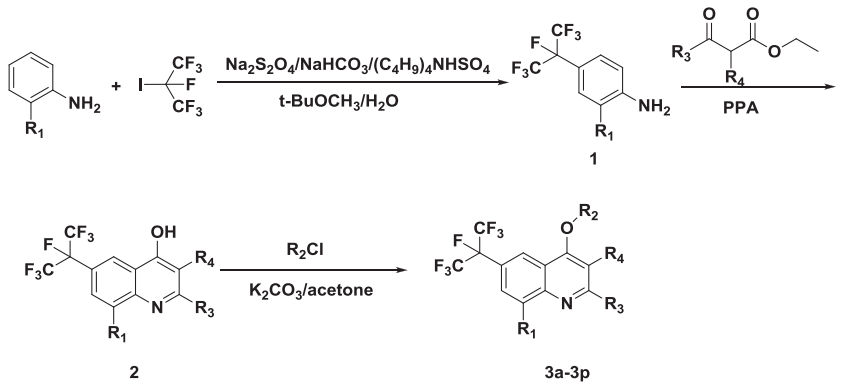
2,3,8-Trimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl acetate 3a. White solid, yield 60.5%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26(s, 3H), 2.50 (s, 3H), 2.75 (s, 3H), 2.82 (s, 3H), 7.61 (s, 1H), 7.82 (s, 1H); ESI–MS: 398 $[M + H]^+$; Elemental *anal.* calculated for $C_{17}H_{14}F_7NO_2$ (%): C, 51.39; H, 3.55; N, 3.53; found: C, 51.44; H, 3.45; N, 3.66.

2,3,8-Trimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl but-3-ynoate 3b. White solid, yield 67.2%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (t, 3H), 1.79–1.88 (m, 2H), 2.35 (s, 3H), 2.78 (s, 3H), 2.85 (s, 3H), 4.32 (t, 2H), 7.66 (s, 1H), 7.95 (s, 1H); ESI–MS: 436 $[M + H]^+$; Elemental *anal.* calculated for $C_{20}H_{16}F_7NO_2$ (%): C, 55.18; H, 3.70; N, 3.22; found: C, 55.23; H, 3.86; N, 3.12.

8-Ethyl-2,3-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl(2-methoxyethyl)carbonate 3c. White solid, yield 54.3%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 2.76 (s, 3H), 2.83 (s, 3H), 3.81 (t, 2H), 4.58 (t, 2H), 7.64 (s, 1H), 7.93 (s, 1H); ESI–MS: 472 $[M + H]^+$; Elemental *anal.* calculated for $C_{20}H_{20}F_7NO_4$ (%): C, 50.96; H, 4.28; N, 2.97; found: C, 51.01; H, 4.32; N, 2.89.

Butyl (8-ethyl-2,3-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl) carbonate 3d. White solid, yield 58.0%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99 (t, 3H), 1.37 (t, 3H), 1.43–1.50 (m, 2H), 1.75–1.79 (m, 2H), 2.33 (s, 3H), 2.75 (s, 3H), 3.31 (q, 2H), 4.35 (t, 2H), 7.70 (s, 1H), 7.92 (s, 1H); ESI–MS: 470 $[M + H]^+$; Elemental *anal.* calculated for $C_{21}H_{22}F_7NO_3$ (%): C, 53.73; H, 4.72; N, 2.98; found: C, 53.98; H, 4.65; N, 3.01.

Scheme 2. The synthetic route of title compounds.



Ethyl (8-ethyl-2,3-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl) carbonate 3e. White solid, yield 61.3%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 (t, 3H), 1.43 (t, 3H), 2.33 (s, 3H), 2.75 (s, 3H), 3.32 (q, 2H), 4.39 (q, 2H), 7.63 (s, 1H), 7.92 (s, 1H); ESI–MS: 442 $[M + H]^+$; Elemental *anal.* calculated for $C_{19}H_{18}F_7NO_3$ (%): C, 51.71; H, 4.11; N, 3.17; found: C, 51.65; H, 4.15; N, 3.24.

8-Ethyl-2,3-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl(trichloromethyl) carbonate 3f. White solid, yield 44.7%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 (t, 3H), 2.56 (s, 3H), 2.76 (s, 3H), 3.32 (q, 2H), 7.65 (s, 1H), 8.32 (s, 1H); ESI–MS: 531 $[M + H]^+$; Elemental *anal.* calculated for $C_{18}H_{13}Cl_3F_7NO_3$ (%): C, 40.74; H, 2.47; N, 2.64; found: C, 40.87; H, 2.45; N, 2.66.

2-Ethyl-3,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-ylisopropylcarbonate 3g. White solid, yield 49.2%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35–1.45 (m, 9H), 2.85 (s, 3H), 3.03 (q, 2H), 4.99–5.06 (m, 1H), 7.64 (s, 1H), 7.91 (s, 1H); ESI–MS: 456 $[M + H]^+$; Elemental *anal.* calculated for $C_{20}H_{20}F_7NO_3$ (%): C, 52.75; H, 4.43; N, 3.08; found: C, 52.67; H, 4.45; N, 3.05.

Allyl(2-ethyl-3,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl)carbonate 3h. White solid, yield 56.0%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (t, 3H), 2.34 (s, 3H), 2.85 (s, 3H), 3.03 (q, 2H), 4.80 (d, 2H), 5.37–5.49 (m, 2H), 5.98–6.07 (m, 1H), 7.64 (s, 1H), 7.93 (s, 1H); ESI–MS: 454 $[M + H]^+$; Elemental *anal.* calculated for $C_{20}H_{18}F_7NO_3$ (%): C, 52.99; H, 4.00; N, 3.09; found: C, 53.06; H, 3.95; N, 3.24.

8-Ethyl-3-methyl-6-(perfluoropropan-2-yl)-2-phenylquinolin-4-ylpropylcarbonate 3i. White solid, yield 51.8%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (t, 3H), 1.39 (t, 3H), 1.80–1.89 (m, 2H), 2.38 (s, 3H), 3.34 (q, 2H), 4.34 (t, 2H), 7.48–8.01 (m, 7H); ESI–MS: 518 $[M + H]^+$; Elemental *anal.* calculated for $C_{25}H_{22}F_7NO_3$ (%): C, 58.03; H, 4.29; N, 2.71; found: C, 58.21; H, 4.44; N, 2.97.

8-Ethyl-3-methyl-6-(perfluoropropan-2-yl)-2-phenylquinolin-4-yl phenyl carbonate 3j. White solid, yield 47.6%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, 3H), 2.48 (s, 3H), 3.36 (q, 2H), 7.28–8.12 (m, 12H); ESI–MS: 552 $[M + H]^+$; Elemental *anal.* calculated for $C_{28}H_{20}F_7NO_3$ (%): C, 60.98; H, 3.66; N, 2.54; found: C, 61.04; H, 3.45; N, 2.49.

Ethyl (8-ethyl-2-isopropyl-3-methyl-6-(perfluoropropan-2-yl) quinolin-4-yl) carbonate 3k. White solid, yield 49.3%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37–1.46 (m, 12H), 2.38 (s, 3H), 3.32 (q, 2H), 3.41–3.47 (m, 1H), 4.39 (q, 2H), 7.62 (s, 1H), 7.91 (s, 1H); ESI–MS: 470 $[M + H]^+$; Elemental *anal.* calculated for $C_{21}H_{22}F_7NO_3$ (%): C, 53.73; H, 4.72; N, 2.98; found: C, 53.98; H, 4.75; N, 3.03.

Allyl (8-ethyl-2-isopropyl-3-methyl-6-(perfluoropropan-2-yl) quinolin-4-yl) carbonate 3l. White solid, yield 47.6%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35–1.39 (m, 9H), 2.38 (s, 3H), 3.30–3.34 (q, 2H), 3.45 (m, 1H), 4.80 (d, 2H), 5.37–5.49 (m, 2H), 6.02 (m, 1H), 7.62 (s, 1H), 7.91 (s, 1H); ESI–MS: 482 $[M + H]^+$; Elemental *anal.* calculated for $C_{22}H_{22}F_7NO_3$ (%): C, 54.89; H, 4.61; N, 2.91; found: C, 54.88; H, 4.58; N, 3.02.

2-Ethyl-3,8-dimethyl-6-(perfluoropropan-2-yl)-4-phenoxyquinoline 3m. White solid, yield 61.5%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (t, 3H), 2.29 (s, 3H), 2.84 (s, 3H), 3.02 (q, 2H), 5.34 (s, 2H), 7.40–7.89 (m, 7H); ESI–MS: 446 $[M + H]^+$; Elemental *anal.* calculated for $C_{22}H_{18}F_7NO$ (%): C, 59.33; H, 4.07; N, 3.14; found: C, 59.44; H, 3.99; N, 3.21.

2-Ethyl-3,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-ylacetate 3n. White solid, yield 42.2%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, 3H), 2.52 (s, 3H), 2.73 (q, 2H), 2.81 (s, 3H), 2.83 (s, 3H), 7.62 (s, 1H), 7.76 (s, 1H); ESI–MS: 412 $[M + H]^+$; Elemental *anal.* calculated for $C_{18}H_{16}F_7NO_2$ (%): C, 52.56; H, 3.92; N, 3.41; found: C, 52.67; H, 3.98; N, 3.66.

2-Chloroethyl (2-ethyl-3,8-dimethyl-6-(perfluoropropan-2-yl) quinolin-4-yl) carbonate 3o. White solid, yield 47.2%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, 3H), 2.78–2.83 (m, 8H), 3.82 (t, 2H), 4.59 (t, 3H), 7.65 (s, 1H), 7.88 (s, 1H); ESI–MS: 476 $[M + H]^+$; Elemental *anal.* calculated for $C_{19}H_{17}ClF_7NO_3$ (%): C, 47.96; H, 3.60; N, 2.94; found: C, 48.04; H, 3.45; N, 2.87.

Butyl(2-ethyl-3,8-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl)carbonate 3p. White solid, yield 61.5%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (t, 3H), 1.23 (t, 3H), 1.78–1.81 (m, 2H), 2.77–2.83 (m, 8H), 4.30 (t, 2H), 7.64 (s, 1H), 7.87 (s, 1H); ESI–MS: 470 $[M + H]^+$; Elemental *anal.* calculated for $C_{19}H_{17}ClF_7NO_3$ (%): C, 53.73; H, 4.72; N, 2.98; found: C, 53.87; H, 4.77; N, 3.01.

***Bioassay for* P. oryae.** The antifungal activity was tested according to our previous work [15]. Greenhouse-grown rice and cucumber seedlings with four leaves were used as the host plants. They were sprayed with the test solution and then placed in a drying hood at room temperature. Three replicates were used for each treatment. Tested compounds and commercial fungicides tebufloquin were sprayed with a hand sprayer on the surface of the leaves (5 mL per plant) at different concentrations. After 24 hr, inoculations of *P. oryae* were carried out by spraying fungal spore suspensions with 2×10^5 spore/mL, homogenized with an IKA T10 basic ULTRA-TURRAX homogenizer (Guangzhou, China). Each kind of inoculum was sprayed at the volume of 5 mL/plant. After inoculation, the plants were maintained at 18–30°C [mean temperature of 24°C and about 80% relative humidity]. The fungicidal activity was evaluated when the nontreated plant (blank) fully developed symptoms. The area of inoculated treated leaves covered by disease symptoms was assessed and compared with that of nontreated ones to determine the average disease index after 7 days. The relative fungicidal efficacy of

compounds compared with the blank assay was calculated via the following equation:

$$\text{relative control efficacy}(\%) = (\text{CK} - \text{PT})/\text{CK} \times 100\%,$$

where CK is the average disease index of the blank assay and PT is the average disease index after treatment during testing. All experiments were replicated three times.

RESULTS AND DISCUSSION

The synthetic route is showed in Scheme 2. Generally, perfluoropropanyl substituted aniline was synthesized using substituted aniline and FITS reagent as starting materials. In this paper, 1,1,1,2,3,3,3-heptafluoro-2-iodopropane was used as FITS reagent due to it can form positive ion easily under the initiator $Na_2S_2O_4$.

Table 1

The *in vivo* protection and curative efficacy against *Pyricularia oryae* at different concentration.

No.	R^1	R^2	R^3	R^4	Concentration (mg/L)	Protection efficacy (%)
3a	CH_3	$COCH_3$	CH_3	CH_3	100	100
					50	65
					10	45
3b	Et	$COCH_2CCH$	CH_3	CH_3	100	100
					50	65
					10	35
3c	Et	$COOCH_2CH_2OCH_3$	CH_3	CH_3	100	95
					50	70
					10	55
3d	Et	$COOCH_2CH_2CH_2CH_3$	CH_3	CH_3	100	90
					50	65
					10	0
3e	Et	$COOCH_2CH_3$	CH_3	CH_3	100	100
					50	75
					10	30
3f	Et	$COOCCl_3$	CH_3	CH_3	100	80
					50	65
					10	30
3g	CH_3	$COOCH(CH_3)_2$	CH_3	Et	100	100
					50	60
					10	25
3h	CH_3	$COOCH_2CH = CH_2$	CH_3	Et	100	90
					50	70
					10	25
3i	Et	$COOCH_2CH_2CH_3$	CH_3	Ph	100	100
					50	85
					10	45
3j	Et	COOAr	CH_3	Ph	100	100
					50	70
					10	35
3k	Et	$COOCH_2CH_3$	CH_3	$CH(CH_3)_2$	100	95
					50	70
					10	50
3l	Et	$COOCH_2CH = CH_2$	CH_3	$CH(CH_3)_2$	100	100
					50	90
					10	75
3m	CH_3	$COOCH_2Ph$	CH_3	Et	100	100
					50	75
					10	45
3n	CH_3	$COCH_3$	CH_3	Et	100	100
					50	99
					10	85
3o	CH_3	$COOCH_2CH_2Cl$	CH_3	Et	100	100
					50	95
					10	80
3p	CH_3	$COOCH_2CH_2\ CH_2CH_3$	CH_3	Et	100	100
					50	85
					10	70
Tebufloquin					100	100
					50	70
					10	0

Table 2

CLogP, total energy, energy gap, and frontier orbital energy.

DFT	**3n**	Tebufloquin
E_{total}/Hartree[b]	−1598.85738245	−1865.96608237
E_{HOMO}/Hartree	−0.22205	−0.22894
E_{LUMO}/Hartree	−0.08253	−0.07096
ΔE[a]/Hartree	0.13952	0.15798
CLogP	5.53	4.81

[a]$\Delta E = E_{LUMO} - E_{HOMO}$.
[b]1 Hartree = $4.35974417 \times 10^{-18}$ J = 27.2113845ev.

Many references reported the synthetic methods about quinolone derivatives, such as Skraup method, Combes method, Camps method, Niementowsld method, Friedlander method, and Pfitzinger method. Comparing these method, Combes method was selected, which cyclized from the starting material 2-methyl-4-(perfluoropropan-2-yl)aniline and ethyl 2-methyl-3-oxobutanoate under acid condition. At first, the target compounds were synthesized using THF as solvent and Et_3N as base, but the yield is low, and the target compound is difficult to purity. Finally, we selected acetone as solvent and K_2CO_3 as base; the yield increased and can purity easily. All the compounds were identified and characterized by ^1H NMR, MS, and elemental analysis. The appearance of signals at about 7.6 and 7.9 ppm are assigned to CH of quinolone ring due to the electronegativity of CF $(CF_3)_2$. Meanwhile, most of the title compounds exhibited the M + H^+ peak in the ESI–MS results.

The results of fungicidal activity against *P. oryae in vivo* were shown in Table 1. Most of the compounds possessed excellent *in vivo* activity (100%) against *P. oryae* at 100 mg/L, except compounds **3c** (95%), **3d** (90%), **3f** (85%), **3h** (95%), and **3k** (95%). On the other hand, all of the compounds held good *in vivo* curative activity (>85%) against *P. oryae* at 100 mg/L. The control Tebufloquin was studied at the same condition with the values of 100% (protection activity).

On the basis of the preliminary *in vivo* fungicidal activity against *P.* oryae results, the title compounds were selected for further bioassay at lower dose for fungicidal activity against *P. oryae*. The subsequent results in Table 1 showed that the most of tested compounds had moderate protection activity against *P. oryae* with the range of 65–85% inhibition at 50 mg/L. But the compound **3l** (90%), **3n** (99%), and **3o** (95%) possessed good efficacy against *P. oryae* at 50 mg/L. The three compounds exhibited higher protection activity than that of control Tebufloquin (70%). At the concentration of 10 mg/L, the control Tebufloquin had no activity. But most of title compounds exhibited good protection activity efficacy, such as compounds **3l** (75%), **3n** (85%), and **3o** (80%), respectively. Among them, only compound **3d** had no inhibitory against *P. oryae* at 10 mg/L.

In order to study their structure–active relationship, we choose a high active compound **3n** and lead compound Tebufloquin as model compounds; the frontier orbital and CLogP was calculated. The CLogP, energy of HOMO and LUMO, total energy, and energy gap are listed in Table 2

According to the frontier molecular orbital theory, HOMO has the priority to provide electrons, while LUMO can accept electrons firstly. As we can see from Figure 1, the LUMO and HOMO are different between the high active compound **3n** and lead compound Tebufloquin, especially in the orient of electron transition

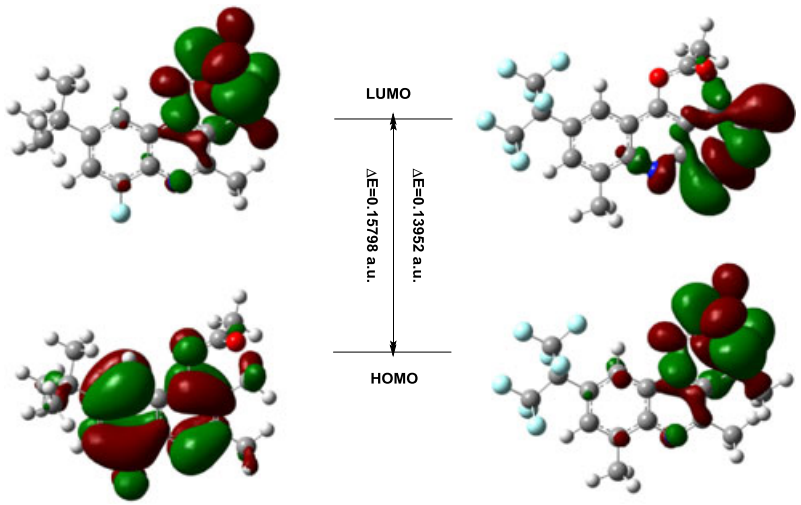


Figure 1. Frontier molecular orbitals of compound **3n** and Tebufloquin. [Color figure can be viewed at wileyonlinelibrary.com]

and energy gap. For the HOMO, the electron of compound **3n** is mainly located on the ester carbonate group and ethyl group and a little on the quinoline ring. On the opposite, the electron of Tebufloquin is mainly located on the quinoline ring and the fluorine atom, a little on the two methyl group and ester carbonate group. For the LUMO, the two compounds still are different. The electron of compound **3n** is evenly distributed among the ethyl group, methyl group, and the quinoline ring. But the electron of Tebufloquin is mainly located on the ester carbonate group, methyl group, and a little quinolone ring. Perhaps the reason of different fungicidal activity between the compound **3n** and Tebufloquin is electron transition direction and energy gap. From the Table 1, we assumed that the compound with higher energy gap and lower total energy exhibited higher fungicidal activity. The other fact is the CLogP. From Table 2, the CLogP is different between the two compounds.

To explore higher active compounds with antifungal activity, some new 6-perfluoropropanyl quinoline derivatives were designed and synthesized via two steps with yields ranging from 42% to 62%. Most of them exhibited excellent *in vivo* antifungal activity against *P. oryzae* at 100 mg/L. Among them, compounds **3n** and **3o** are highly active at 10 mg/L. Furthermore, a density functional theory study established the structure–activity relationships of the synthesized compounds. It can be found that the electron transit orient is different between the high active compound and lead compound Tebufloquin. Quinoline derivatives, which possess good control effective against *P. oryzae*, may become new lead compounds for the development of antifungals with further structure modification.

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