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Synthesis and fungicidal activities of perfluoropropan-2-yl-based novel quinoline derivatives

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Abstract: A series of novel perfluoropropan-2-yl-based quinoline derivatives was designed and synthesized utilizing tebufloquin as the lead compound. The structures of all the newly synthesized compounds were confirmed by spectroscopic data ^{1}HNMR, MS and elemental analysis. The results of bioassay indicated that these compounds exhibited potent fungicidal activities against *Erysiphe graminis*. Especially, compound **8c** displayed excellent activity with EC_{50} value at 1.48 mg / L, which was better than that of the commercialized fungicide --- tebufloquin. The structure-activity relationship for these new compounds was also discussed.

Keywords: perfluoropropan-2-yl-based quinoline derivatives; synthesis; fungicidal activity; structure-activity relationship

Introduction

Fungicide, with its multiple functions including protecting crops from fungicidal threats and preventing the spread of human infectious diseases, increasingly plays an important role in agriculture. World's fungicide market is dominated by two kinds of compounds---strobilurins and triazoles [1]. However, given the increased application dose and frequency of fungicide, fungi have gradually grown resistance to strobilurins and triazoles, and thus, it is imperative to develop new fungicides. Quinoline derivatives are a group of nitrogen-containing heterocyclic compounds, the spectra of which demonstrate biological activities in weeding [2], fungicidal [3], insecticidal [4-5], antitumor [6-7], antiviral [8-9], anti-tuberculosis [10-11] and antifungal [12-14]. With such an extensive range of biological activities, quinoline derivatives have strong existence in agriculture. For instance, tebufloquin has been being used as a fungicide, in order to further improve the fungicidal activity of tebufloquin, a lot of work has been done for the optimization of it [15-17]. Flometoquin in insecticides, and echinacol in herbicides. Besides a wide application, quinolines are also well known as green pesticides due to their low residue and small harm to the environment. Lastly, quinoline compounds were too worth attention because of the special structure-activity relationship: quinoline's biological activities change as the substituents on the quinoline ring and the number of substituents vary. In order to obtain better new pesticides, fluorine atoms and different substituents were introduced to organic molecules of pesticides is our good idea.

In our optimization program, we used tebufloquin as the lead compound because it has a broad spectrum of fungicidal activity. We also introduced fluorine atom because of its unique properties, such as electronic effect, infiltration effect, simulation effect and hindering effect. A series of perfluoropropan-2-yl-based novel quinoline derivatives were designed and synthesized through analog synthesis and substructure theory. As shown in **Figure 1**, isobutyl was substituted by perfluoropropan-2-yl and side chains of R^1, R^2, R^3 and R^4 were revised until a more effective combination was found. Bioassay results show that compound

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8c has higher fungicidal activity against *Erysiphe graminis* than tebufloquin does.

Results and discussion

The general synthetic method of the target compound is shown in **Scheme 1**. Yields have not been optimized. The synthesis of other compounds is similar to that of the representative compound, and all the reactions were carried out under protective condition by using dry nitrogen or calcium chloride tubes. ^{1}HNMR, MS and elemental analysis were used to identify and verify all synthesized target compounds.

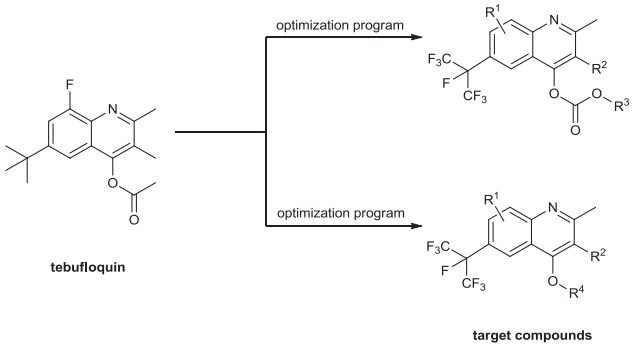
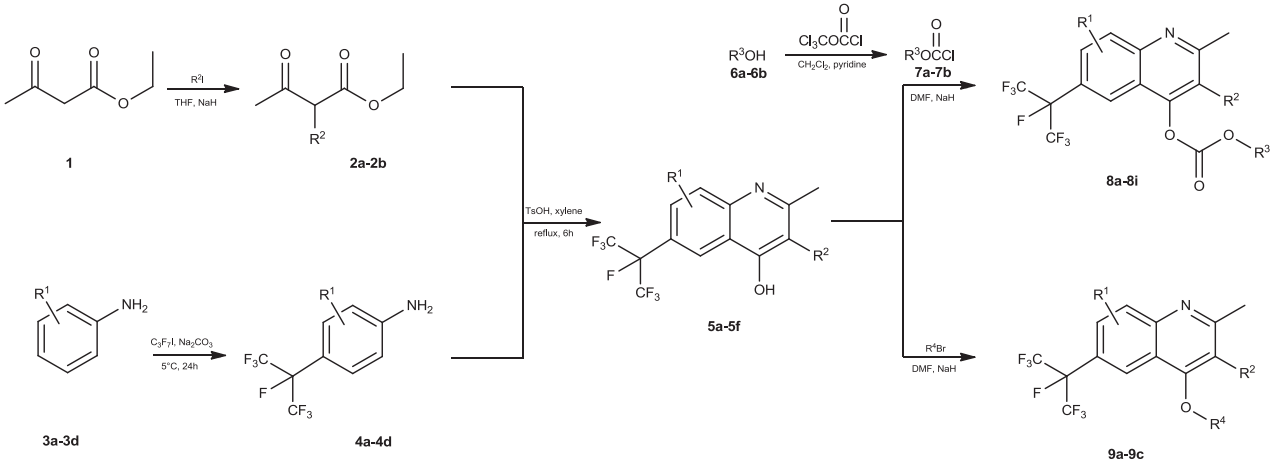


Figure 1 Design strategy of the target compounds.

The fungicidal activities against *Erysiphe graminis* of target compounds are shown in **Table 1.** The datum indicate that most of title compounds has excellent fungicidal activity against *Erysiphe graminis* at 500 mg/L and some even have high fungicidal activity under 50 mg/L. For example, compounds **8b**, **8c**, **8d**, **8e** and **8i** have ≥ 95% fungicidal activity at 100 mg/L, and compounds **8b**, **8c** and **8i** still have > 90% fungicidal activity at 50 mg/L. To further assess the activity level of title compounds, regression equations were calculated by selecting a portion of the compounds with high fungicidal activity. Concentrations of these compounds at their 50% maximal effect (EC_{50}) values are shown in **Table 1**, and activity of tebufloquin is also presented in **Table 1**. As exhibited in **Table 1**, **8b**, **8c**, **8d**, **8e** and **8i** showed a significant control effect against *Erysiphe graminis*, which was superior to tebufloquin. In particular, compound **8c** has EC_{50} values of 1.48 mg/L against *Erysiphe graminis*, which has the most prominent effect.

Although it is hard to draw exact structure-activity relationship from these data, the compounds still follow the rule that fungicidal activities vary as R^1, R^2, R^3 and R^4 moieties of the title compound are optimized. From **Table 1**, the following pattern is observed: When R^1=8-CH_3, R^2=CH_3, R^3=A1, fungicidal activity is the highest; When R^1, R^2 are kept invariant, the activity of R^3 group is A1 > A2;



2a: R^2=CH_3; **2b**: R^2=$CH_2CH_2CH_2CH_3$

3a, **4a**: R^1=H; **3b**, **4b**: R^1=2-CH_3; **3c**, **4c**: R^1=2-CH_2CH_3; **3d**, **4d**: R^1=3-CH_3

5a: R^1=H, R^2=CH_3; **5b**: R^1=H, R^2=$CH_2CH_2CH_2CH_3$; **5c**: R^1=7-CH_3, R^2=CH_3; **5d**: R^1=8-CH_3, R^2=CH_3; **5e**: R^1=8-CH_2CH_3, R^2=CH_3; **5f**: R^1=5-CH_3, R^2=CH_3

6a, **7a**: R^3=A1; **6b**, **7b**: R^3=A2

8a: R^1=H, R^2=$CH_2CH_2CH_2CH_3$, R^3=A1

8b: R^1=H, R^2=CH_3, R^3=A1

8c: R^1=8-CH_3, R^2=CH_3, R^3=A1

8d: R^1=7-CH_3, R^2=CH_3, R^3=A1

8e: R^1=8-CH_2CH_3, R^2=CH_3, R^3=A1

8f: R^1=8-CH_3, R^2=CH_3, R^3=A2

8g: R^1=H, R^2=CH_3, R^3=A2

8h: R^1=H, R^2=$CH_2CH_2CH_2CH_3$, R^3=A2

8i: R^1=7-CH_3, R^2=CH_3, R^3=A2

9a: R^1=H, R^2=CH_3, R^4=A3

9b: R^1=8-CH_3, R^2=CH_3, R^4=A3

9c: R^1=5-CH_3, R^2=CH_3, R^4=A3

Scheme 1 Synthetic pathways for the target compounds.

Table 1 Fungicidal activity against *Erysiphe graminis*, and EC_{50} of title compounds.

Compound	Inhibition of *Erysiphe graminis* (%)				Regression equation	Correlation	EC_{50} mg/L	95% confidence limit (mg/L)
	500 mg/L	200 mg/L	100 mg/L	50 mg/L				
8a	90.00	90.00	70.00	60.00	-	-	-	-
8b	100.00	95.20	100.00	100.00	Y = 3.9621 + 1.5889x	0.9808	4.50	3.04-6.65
8c	95.00	100.00	95.00	94.60	Y = 4.7260 + 1.6045x	0.9953	1.48	1.11-1.98
8d	100.00	99.00	98.40	83.10	Y = 4.3748 + 1.5741x	0.9871	2.50	1.85-3.36
8e	95.00	96.00	96.70	88.90	Y = 4.4587 + 1.3837x	0.9678	2.46	1.85-3.28
8f	85.00	95.10	86.10	50.40	Y = 3.8727 + 1.4010x	0.9458	6.37	4.52-8.99
8g	95.00	100.00	93.10	85.80	Y = 3.7697 + 1.5457x	0.9716	6.25	4.36-8.96
8h	90.00	70.00	60.00	20.00	-	-	-	-
8i	90.00	100.00	95.40	92.40	Y = 4.2558 + 1.8014x	0.9912	2.58	1.82-3.69
9a	60.00	-	-	-	-	-	-	-
9b	95.00	79.10	72.10	74.20	-	-	-	-
9c	90.00	96.10	85.50	76.10	-	-	>20	-
tebufloquin	95.00	89.30	79.30	48.50	Y = 4.1733 + 1.1521x	0.9856	5.22	3.88-7.02

When R^1 and R^3 are kept constant, the activity of R^2 group is CH_3 > $CH_2CH_2CH_2CH_3$. In addition, to keep R^2=CH_3, R^4=A3, the influence of R^1 moiety on improved activity is as follows: 5-CH_3 > 8-CH_3 > H. Therefore, the fungicidal activities may be summarized as follows: **8c** > **8e** ≈ **8d** ≈ **8i** > **8g** > **9c** > **8a** > **8h** > **9a**. Further research on the structure and biological activity of this series of compounds is in progress.

Conclusions

In order to find efficient fungicides, a series of perfluoropropan-2-yl-based new quinoline derivatives were designed and synthesized. Most synthetic compounds showed good fungicidal activity. In particular, EC_{50} of compound **8c** against *Erysiphe graminis* was 1.48 mg/L, which was far superior to tebufloquin. Based on the above results, our research proved that this series of quinolines have great potential in fungicides development and worth further research.

Experimental

Materials and Methods

Unless otherwise noted, solvents and reagents were used as received from commercial suppliers. ^{1}HNMR spectra were acquired with a Varian INOVA-300 spectrometer using TMS as the internal standard and $CDCl_3$ as the solvent. Mass spectra were obtained using a Agilent 5973-6890 gas chromatography-mass spectrometer (GC-MS) and a Agilent 1100 series liquid chromatography-mass spectrometer (LC-MS). Column chromatography was performed using a 200–300 mesh silica gel. Elemental analysis data were obtained with a Vario EL III from Elementar. Uncorrected melting points were taken in the WRS-1B digital melting points apparatus.

Synthesis of Ethyl 2-methyl-3-oxobutanoate (2a) and its analogue (2b).

Sodium hydride (60%, 4.4g, 0.11mol) was added to a solution of ethyl 3-oxobutanoate (13.0 g, 0.10mol) in tetrahydrofuran (150 mL). Methyl iodide (15.6 g, 0.11 mol) was added dropwise at room temperature. The reaction mixture was stirred for 18h at the same temperature until the staring materials was comsumed (monitored by TLC). The reaction mixture was poured into ice water followed by extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate, and solvent was evaporated under reduced pressure to afford 12.5g (82.3% yield, 94.7% purity) of a yellow liquid. **2b** was synthesized in a similar method.

Synthesis of 2-Methyl-4-(perfluoropropan-2-yl)aniline (4b) and its analogue (4a, 4c and 4d)

To the mixture of tetrabutylammonium bromide (3.2g, 0.01mol) and methyl tert-butyl ether (90 mL) in water (100 mL), sodium dithionite (10.4g, 0.06mol),

heptafluoroisopropyl iodide (35.5g, 0.12mol), o-methylaniline (10.7 g, 0.10 mol), anhydrous sodium carbonate (12.7 g, 0.12 mol) was added with stirring below 5°C. The reaction mixture was stirred for 4h in ice-bath. Then sodium dithionite (10.4g, 0.06mol) was added, and the reaction was stirred overninght at the same temperature until the staring materials was comsumed (monitored by TLC). The reaction mixture was poured into ice water followed by extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate, and solvent was evaporated under reduced pressure to afford 25.6g (89.1% yield, 95.6% purity) of a brown liquid. ^{1}H NMR ($CDCl_3$): 2.20 (s, 3H), 3.93 (bs, 2H), 6.71 (d, *J*=6.9 Hz, 1H), 7.06 (d, *J*=7.2 Hz, 1H), 7.25 (s, 1H). LC-MS Pos $[M+1]^+$=276; Anal. Calcd for $C_{10}H_8F_7N$: C, 43.65; H, 2.93; N, 5.09; Found: C, 43.60; H, 2.96; N, 5.11. **4a, 4c** and **4d** were synthesized in a similar method.

Synthesis of 2,3,8-Trimethyl-6-(perfluoropropan-2-yl) quinolin-4-ol (5d) and its analogue (5a-5c and 5e-5f)

The mixture of compound **2a** (8.6 g, 0.060 mol), compound **4b** (8.2 g, 0.030 mol) and p-toluenesulfonic acid (6.2 g, 0.033 mol) in xylene (150 mL) was added to reaction apparatus equipped with a water trap. The reaction was heated under reflux for 6h until the staring materials was comsumed (monitored by TLC). The resulting mixture was cooled to room temperature. Then the resulting mixture was poured into ice water, and the resulted solid was formed. The solid was collected by filtration and dried to give 8.4g (76.8% yield, 92.7% purity) as a white solid. mp 198.5-199.9°C; ^{1}H NMR ($CDCl_3$): 2.15 (s, 3H), 2.53 (s, 3H), 2.59 (s, 3H), 7.58 (s, 1H), 8.17 (s, 1H), 8.56 (s, 1H). LC-MS Pos $[M+1]^+$=356; Anal. Calcd for $C_{15}H_{12}F_7NO$: C, 50.71; H, 3.40; N, 3.94; Found: C, 50.64; H, 3.44; N, 3.97. **5a-5c** and **5e-5f** were synthesized in a similar method.

Tetrahydrofuran-3-yl carbonochloridate (7a) and its analogue (7b)

In 300ml of methylene chloride was dissolved diphosgene (117.6g, 0.60 mol) with stirring below -15°C. The mixture of pyridine (43.5g, 0.55 mol) and tetrahydrofuran-3-ol (44.0g, 0.50 mol) was added dropwise at the same temperature. The reaction mixture was stirred for 3-4h at -15°C. After the reaction was completed, dilute hydrochloric acid (40%, 50 ml) was added to remove the pyridine. Then the reaction mixture was poured into ice water followed by extracted with methylene chloride. The combined organic layer was dried with anhydrous sodium sulfate. Solvent was evaporated under reduced pressure to afford product of a light yellow liquid which was used directly without calculating the yield and purification. **7b** was synthesized in a similar method.

Synthesis of Tetrahydrofuran-3-yl (2,3,8-trimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl) carbonate (8c) and its analogue (8a-8b and 8d-8i)

The sodium hydride (60%, 1.6 g, 0.040 mol) was dissolved in N, N-dimethylformamide (100 mL) at room temperature. After stirring for 20 min, compound **5d** (7.1 g, 0.020 mol) was added, and compound **7a** (3.3 g, 0.022 mol) was added dropwise at the same temperature. The reaction mixture was stirred for 2h at room temperature until the staring materials was comsumed (monitored by TLC). The reaction mixture was poured into ice water followed by extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate, and solvent was evaporated under reduced pressure. The residue material was purified by silica gel column chromatography using petroleum ether and ethyl acetate (25: 1 / 10: 1 by volume) as eluent to afford compound **8c**. Compounds **8a-8b** and **8d-8i** were synthesized by the similar approach.

Synthesis of 2,3,8-trimethyl-6-(perfluoropropan-2-yl)-4-(prop-2-yn-1-yloxy)quinoline (9b) and its analogue (9a and 9c)

The sodium hydride (60%, 1.6 g, 0.04 mol) was dissolved in N, N-dimethylformamide (100 mL) at room temperature. After stirring for 20 min, compound **5d** (7.1 g, 0.02 mol) was added, and 3-bromoprop-1-yne (3.5 g, 0.03 mol) was added dropwise at the same temperature. The reaction mixture was stirred for 2h at room temperature until the staring materials was comsumed (monitored by TLC). The reaction mixture was poured into ice water followed by extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate, and solvent was evaporated under reduced pressure. The residue material was purified by silica gel column chromatography using petroleum ether and ethyl acetate (50: 1 / 30: 1 by volume) as eluent to afford compound **9b**. Compounds **9a** and **9c** were synthesized by the similar method.

All the synthesized intermediates **4** and **5** were confirmed by MS. Due to the structural similarity, only intermediates 4b and 5d were further characterized and confirmed by ^{1}H NMR and elemental analysis respectively.

Structures of the title compounds were supported by spectroscopic data shown below. Due to the structural similarity of the title compounds, only some representative compounds **8c**, **8e**, **9a** and **9b**, were analyzed and confirmed by ^{13}C NMR.

3-Butyl-2-methyl-6-(perfluoropropan-2-yl)quinolin-4-yl (tetrahydrofuran-3-yl) carbonate (8a):

Yield: 43.2%, light brown viscous solid; ^{1}H NMR ($CDCl_3$): 0.97 (t, *J*=2.1 Hz, 3H), 1.30-1.62 (m, 6H), 2.74 (t, *J*=7.8 Hz, 2H), 2.82 (s, 3H), 3.86-4.07 (m, 4H), 5.37-5.42 (m, 1H), 7.82 (d, *J*=9.3 Hz, 1H), 7.99 (d, *J*=1.8 Hz, 1H), 8.15 (d, *J*=9.0 Hz, 1H); GC-MS M^+=497 base peak: 71; Anal. Calcd for $C_{22}H_{22}F_7NO_4$: C, 53.12; H, 4.46; N, 2.82; Found: C, 53.18; H, 4.42; N, 2.79.

2,3-Dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl (tetrahydrofuran-3-yl) carbonate (8b):

Yield: 37.9%, brown viscous liquid; ^{1}H NMR ($CDCl_3$): 2.05-2.25 (m, 2H), 2.36 (s, 3H), 2.82 (s, 3H), 4.94-5.25 (m, 4H), 5.39-5.42 (m, 1H), 7.85 (d, *J*=8.4 Hz, 1H), 8.08 (s, *J*=1.8 Hz, 1H), 8.24 (s, 1H); GC-MS M^+=455 base peak: 71; Anal. Calcd for $C_{19}H_{16}F_7NO_4$: C, 50.12; H, 3.54; N, 3.08; Found: C, 50.16; H, 3.49; N, 3.03.

Tetrahydrofuran-3-yl (2,3,8-trimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl) carbonate (8c):

Yield: 47.7%, light yellow viscous liquid; ^{1}H NMR ($CDCl_3$): 2.23-2.28 (m, 2H), 2.33 (s, 3H), 2.76 (s, 3H), 2.84 (s, 3H), 3.93-4.01(m, 4H), 5.39 (s, 1H), 7.65 (s, 1H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 12.51, 18.32, 24.51, 32.69, 66.90, 72.76, 80.23, 93.96, 114.65 (qd, *J*=286, 28 Hz), 116.94 (d, *J*=12.6 Hz), 120.49 (d, *J*=145 Hz), 122.43, 123.77 (d, *J*=27 Hz), 124.66 (d, *J*=8.0 Hz), 138.55, 146.73, 151.44, 151.91, 161.50. LC-MS Pos $[M+1]^+$=470; Anal. Calcd for $C_{20}H_{18}F_7NO_4$: C, 51.18; H, 3.87; N, 2.98; Found: C, 51.23; H, 3.81; N, 2.94.

Tetrahydrofuran-3-yl (2,3,7-trimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl) carbonate (8d):

Yield: 40.6%, yellow viscous liquid; ^{1}H NMR ($CDCl_3$): 2.15-2.28 (m, 2H), 2.31 (s, 3H), 2.75 (s, 3H), 2.85 (s, 3H), 3.86-4.01 (m, 4H), 5.22-5.24 (m, 1H), 7.69 (s, 1H), 7.98 (d, *J*=1.2 Hz, 1H); LC-MS Pos $[M+1]^+$=470; Anal. Calcd for $C_{20}H_{18}F_7NO_4$: C, 51.18; H, 3.87; N, 2.98; Found: C, 51.21; H, 3.83; N, 2.96.

8-Ethyl-2,3-dimethyl-6-(perfluoropropan-2-yl)quinolin-4-yl(tetrahydrofuran-3-yl) carbonate (8e):

Yield: 36.8%, yellow viscous solid; ^{1}H NMR ($CDCl_3$): 1.35 (t, *J*=7.5 Hz, 3H), 2.22-2.31 (m, 2H), 2.33 (s, 3H), 2.76 (s, 3H), 3.29 (q, *J*=7.5 Hz, 2H), 3.90-4.07 (m, 4H), 5.37-5.40 (m, 1H), 7.64 (s, 1H), 7.89 (d, *J*=1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 12.54, 14.85, 24.54, 24.75, 32.70, 66.93, 72.79, 80.22, 109.68, 114.65 (qd, *J*=286, 28 Hz), 116.81 (d, *J*=12.6 Hz), 120.56 (d, *J*=136 Hz), 122.37, 123.14 (d, *J*=8.6 Hz), 123.95 (d, *J*=20 Hz), 144.17, 146.12, 151.50, 151.94, 161.37; LC-MS Pos $[M+1]^+$=484; Anal. Calcd for $C_{21}H_{20}F_7NO_4$: C, 52.18; H, 4.17; N, 2.90; Found: C, 52.10; H, 4.22; N, 2.83.

Cyclopentyl (2,3,8-trimethyl-6-(perfluoropropan-2-yl) quinolin-4-yl) carbonate (8f):

Yield: 55.6%, light yellow viscous solid; ^{1}H NMR ($CDCl_3$): 1.65-1.97 (m, 8H), 2.32 (s, 3H), 2.33 (s, 3H), 2.76 (s, 3H), 5.22-5.29 (m, 1H), 7.80 (s, 1H), 7.91 (d, *J*=1.5 Hz, 1H); LC-MS Pos $[M+1]^+$=468; Anal. Calcd for $C_{21}H_{20}F_7NO_3$: C, 53.97; H, 4.31; N, 3.00; Found: C, 53.86; H, 4.29; N, 3.07.

Cyclopentyl (2,3-dimethyl-6-(perfluoropropan-2-yl) quinolin-4-yl) carbonate (8g):

Yield: 62.5%, light yellow viscous solid; ^{1}H NMR ($CDCl_3$): 1.65-1.99 (m, 8H), 2.34 (s, 3H), 2.76 (s, 3H), 5.22-5.27 (m, 1H), 7.80 (d, *J*=9.0 Hz, 1H), 8.01 (d, *J*=2.1 Hz, 1H), 8.12 (d, *J*=9.0 Hz, 1H); LC-MS Pos $[M+1]^+$=454; Anal. Calcd for $C_{20}H_{18}F_7NO_3$: C, 52.99; H, 4.00; N, 3.09; Found: C, 52.92; H, 4.03; N, 3.07.

3-Butyl-2-methyl-6-(perfluoropropan-2-yl)quinolin-4-yl cyclopentyl carbonate (8h):

Yield: 39.1%, brown viscous solid; ^{1}H NMR ($CDCl_3$): 0.96 (t, *J*=7.2 Hz, 3H), 1.43-1.98 (m, 12H), 2.75 (t, *J*=5.1 Hz, 2H), 2.81 (s, 3H), 5.23-5.27 (m, 1H), 7.81 (d, *J*=9.0 Hz, 1H), 8.01 (d, *J*=1.8 Hz, 1H), 8.14 (d, *J*=9.0 Hz, 1H). GC-MS M^+=495 base peak: 340; Anal. Calcd for $C_{23}H_{24}F_7NO_3$: C, 55.76; H, 4.88; N, 2.83; Found: C, 55.69; H, 4.92; N, 2.88.

Cyclopentyl (2,3,7-trimethyl-6-(perfluoropropan-2-yl) quinolin-4-yl) carbonate (8i):

Yield: 50.1%, light yellow viscous liquid; ^{1}H NMR ($CDCl_3$): 1.64-1.97 (m, 8H), 2.30 (s, 3H), 2.73 (s, 3H), 2.85 (s, 3H), 5.22-5.25 (m, 1H), 7.64 (d, *J*=9.3 Hz,1H), 7.89 (d, *J*=9.0 Hz, 1H); LC-MS Pos $[M+1]^+$=468; Anal. Calcd for $C_{21}H_{20}F_7NO_3$: C, 53.97; H, 4.31; N, 3.00; Found: C, 53.88; H, 4.37; N, 3.03.

2,3-dimethyl-6-(perfluoropropan-2-yl)-4-(prop-2-yn-1-yloxy)quinoline (9a):

Yield: 55.1%, light yellow solid, mp 117.9-119.5°C; ^{1}H NMR ($CDCl_3$): 2.44 (s, 3H), 2.50 (t, *J*=2.4 Hz, 1H), 2.74 (s, 3H), 4.77 (d, *J*=2.7 Hz, 2H), 7.79 (d, *J*=9.0 Hz, 1H), 8.10 (d, *J*=9.0 Hz, 1H), 8.43 (d, *J*=1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 12.87, 24.30, 61.83, 77.00, 77.65, 114.66 (qd, *J*=286, 28 Hz), 116.35, 121.24 (d, *J*=12.0 Hz), 122.31(d, *J*=102 Hz), 123.08,

123.09 (d, *J*=22 Hz), 124.75 (d, *J*=9.7 Hz), 129.31, 147.77, 159.16, 163.33; LC-MS Pos $[M+1]^+$=380; Anal. Calcd for $C_{17}H_{12}F_7NO$: C, 53.84; H, 3.19; N, 3.69; Found: C, 53.90; H, 3.16; N, 3.67.

2,3,8-trimethyl-6-(perfluoropropan-2-yl)-4-(prop-2-yn-1-yloxy)quinoline (9b):

Yield: 49.2%, light yellow solid, mp 89.0-89.6°C; ^{1}H NMR ($CDCl_3$): 2.43 (s, 3H), 2.51 (s, 1H), 2.73 (s, 3H), 2.82 (s, 3H), 4.74 (d, *J*=2.1 Hz, 2H), 7.62 (s, 1H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 12.79, 18.36, 24.61, 61.74, 76.74, 77.82, 91.66, 114.48 (qd, *J*=286, 26 Hz), 118.90 (d, *J*=11.5 Hz), 119.05, 122.11 (d, *J*=68 Hz), 122.52 (d, *J*=17 Hz), 124.37 (d, *J*=9.1 Hz), 138.04, 147.10, 159.11, 161.94; LC-MS Pos $[M+1]^+$=394; Anal. Calcd for $C_{18}H_{14}F_7NO$: C, 54.97; H, 3.59; N, 3.56; Found: C, 54..91; H, 3.60; N, 3.59.

2,3,5-trimethyl-6-(perfluoropropan-2-yl)-4-(prop-2-yn-1-yloxy)quinoline (9c):

Yield: 53.7%, light yellow solid, mp 118.5-119.9°C; ^{1}H NMR ($CDCl_3$): 2.44 (s, 3H), 2.46 (s, 1H), 2.70 (s, 3H), 2.98 (d, *J*=8.7 Hz, 3H), 4.51 (d, *J*=2.7 Hz, 2H), 7.65 (d, *J*=9.0 Hz, 1H), 7.87 (d, *J*=9.3 Hz, 1H). LC-MS Pos $[M+1]^+$=394; Anal. Calcd for $C_{18}H_{14}F_7NO$: C, 54.97; H, 3.59; N, 3.56; Found: C, 54.93; H, 3.58; N, 3.61.

6-(tert-butyl)-8-fluoro-2,3-dimethylquinolin-4-yl acetate (tebufloquin):

White solid, mp 65.7-67.6°C; ^{1}H NMR ($CDCl_3$): 1.38 (s, 9H), 2.26 (s, 3H), 2.52 (s, 3H), 2.76 (s, 3H), 7.37 (d, *J*=1.8 Hz, 1H), 7.41 (dd, *J*=1.8, 12.6 Hz, 1H). LC-MS Pos $[M+1]^+$=290.

Biological Assay

Test Compounds

Stock solution of every test compound was prepared in DMF at a concentration of 1.0 g/L and then diluted to the required test concentrations (50-500 mg/L) with water containing Tween 80 (0.4 mg/L) [18-21].

Fungicidal activity

The fungicidal activities were tested using our previously reported method [22].

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References

[1] Liu, A.; Wang, X.; Liu, X.; Li, J.; Chen, H.; Hu, L.; Yu, W.; He, L.; Liu, W.; Huang, M. Synthesis and Fungicidal Activity of Novel 2-Heteroatomthiazole-based Carboxanilides. *J. Heterocyclic. Chem.* **2017**, 54(2), 1625-1629.

[2] Hubele, A. Use of quinoline derivatives for the protection of cultivated plants from herbicides. US4902340. 1990.

[3] Kessabi, F.; Beaudegnies, R.; Quaranta, L.; Lamberth, C.; Synthesis of conformationally locked analogs of quinolin-6-yloxyacetamide fungicides. *Tetrahedron. Lett.* **2016**, 57(49), 5511-5513.

[4] Yan, C.; Xu, J.; Weng, Y.; Li, J.; Wang, Y.; Chen, H. A series of ethyl 6-arylmethoxy-7-alkoxy-4-hydroxy-3-quinolinecarboxylates: synthesis and anticoccidial activity against Eimeria tenella. *Chem. Biol. Drug. Des.* **2008**, 72(4), 314–319.

[5] Wang, Y.; Yan, C.; Weng, Y.; Jin, H.; Chen, H. Synthesis and anticoccidial activities of novel ethyl 6-aryloxy-7-bromo-4-hydroxy-3-quinolinecarboxylate against Eimeria tenella. *Pestic. Biochem. Phys.* **2009**, 93(2), 85-90.

[6] Valkó, K. Application of high-performance liquid chromatography based measurements of lipophilicity to model biological distribution. *J. Chromatogr. A.* **2004**, 1037(1-2), 299-310.

[7] Claassen, G.; Brin, E.; Crogangrundy, C.; Vaillancourt, M.; Zhang, H.; Gai, S.; Drewe, J.; Tseng, B.; Kasibhatla, S. Selective activation of apoptosis by a novel set of 4-aryl-3-(3-aryl-1-oxo-2-propenyl)-2(1H)-quinolinones through a Myc-dependent pathway. *Cancer Letters*, **2009**, 274(2), 243-249.

[8] Sato, M.; Motomura, T.; Aramaki, H.; Matsuda, T.; Yamashita, M.; Ito, Y.; Kawakami, H.; Matsuzaki, Y.; Watanabe, W.; Yamataka, K. Ikeda, S.; Kodama, E.; Matsuoka, M.; Shinkai, Hisashi. Novel HIV-1 integrase inhibitors derived from quinolone antibiotics. *J. Med. Chem.* **2006**, 49(5), 1506-1508.

[9] Chen, S.; Chen, R.; He, M.; Pang, R.; Tan, Z.; Yang, M. Design, synthesis, and biological evaluation of novel quinoline derivatives as HIV-1 Tat–TAR interaction inhibitors. *Bioorgan. Med. Chem.* **2009**, 17(5),1948-1956.

[10] Eswaran, S.; Adhikari, A.; Chowdhury, I.; Pal, K.; Thomas, K. New quinoline derivatives: synthesis and investigation of antibacterial and antituberculosis properties. *Eur. J. Med. Chem.* **2010**, 45(8), 3374-3383.

[11] Jain, R.; Vaitilingam, B.; Nayyar, A.; Palde, P. Substituted 4-Methylquinolines as a New Class of anti-Tuberculosis Agents. *Bioorg. Med. Chem. Lett.* **2003**, 13(6), 1051-1054

[12] Solomon, V.; Haq, W.; Srivastava, K.; Sunil, K.; Katti, S. Synthesis and Antimalarial Activity of Side Chain Modified 4-Aminoquinoline Derivatives. *J. Med. Chem.* **2007**, 50(2), 394-398.

[13] Jampilek, J.; Dolezal, M.; Kunes, J.; Buchta, V.; Silva, L.; Kralova, K. Quinaldine derivatives: preparation and biological activity. *Medicinal. Chemistry.* **2005**, 1(6), 591-599.

[14] Giordani, A.; Mandelli, S.; Zanzola, S. Amidine derivatives of 2-heteroaryl-quinazolines and quinolines; potent analgesics and anti-inflammatory agents. US7968558. 2011.

[15] Liu, X.H.; Fang, Y.M.; Xie, F.; Zhang, R.R.; Shen, Z.H.; Tan, C.X.; Weng, J.Q.; Xu, T.M.; Huang, H.Y. Synthesis and in vivo fungicidal activity ofsome new quinoline derivatives against rice blast. *Pest Manag. Sci.* **2017**, 73, 1900-1907.

[16] Fang, Y.M.; Zhang, R.R.; Shen, Z.H.; Wu, H.K.; Tan, C.X.; Weng, J.Q.; Xu, T.M.; Liu, X.H. Synthesis, Antifungal Activity, and SAR Study of Some New 6-Perfluoropropanyl Quinoline Derivatives. *J. Heterocycl. Chem.* **2018**, 55, 240-245.

[17] Fang, Y.M.; Zhang, R.R.; Shen, Z.H.; Tan, C.X.; Weng, J.Q.; Xu, T.M.; Liu, X.H.; Huang, H.Y.; Wu, H.K. Synthesis and Antifungal Activity of Some 6-tert-butyl-8-chloro-2, 3-dimethylquinolin-4-ol Derivatives against Pyricularia oryae. *Lett. Drug Des. Discov.* **2018**, doi: 10.2174/1570180815666180313121735

[18] Huang, D.; Liu, A.; Liu, W.; Liu, X.; Ren, Y.; Zheng, X.; Pei, H.; Xiang, J.; Huang. M.; Wang, X. Synthesis and insecticidal activities of novel 1H-pyrazole-5-carboxylic acid derivatives. *Heterocycl. Commun.* **2017**, 23, 455-460.

[19] Yu, Y.; Wu, D.; Huang, M.; He, L.; Li, J.; Hu, L.; Gao, G.; Liu, A. Synthesis and Fungicidal Activity of N-Biaryl Amides. Fine. Chem. Intermediates. 2013, 43(1), 15-19.

[20] Liu, A.; Wang, X.; Chen, C.; Pei, H.; Mao, C.; Wang, Y.; He, H.; Huang, L.; Liu, X.; Hu, Z.; Ou, X.; Huang, M.; Yao, J. The discovery of HNPC-A3066: a novel strobilurin acaricide. *Pest. Manag. Sci.* **2009**, 65, 229-234.

[21] Liu, A.; Yu, W.; Liu, M.; Bai, J.; Liu, W.; Liu, X.; Pei, H.; Hu, L.; Huang, M.; Wang, X. Synthesis and Insecticidal Activity of Novel Nitropyridyl-Based Dichloropropene Ethers. *J. Agr. Food. Chem.* **2015**, 63(34), 7469-7475.

[22] Liu, A.; Wang, X.; Ou, X.; Huang, M.; Chen, C.; Liu, S.; Huang, L.; Liu, X.; Zhang, C.; Zheng, Y.; Ren, Y.; He, L.; Yao, J. Synthesis and fungicidal activities of novel bis(trifluoromethyl)phenyl-based strobilurins. *J. Agr. Food. Chem.* **2008**, 56(15), 6562-6566.