Chem. Res. Chin. Univ., 2016, 32(4), 600—606 doi: 10.1007/s40242-016-6041-6

Synthesis and Antifungal Activities of Novel Strobilurin Derivatives Containing Quinolin-2(1*H*)-one Moiety

LIU Ming, LIU Yang, ZHOU Sha, ZHANG Xiao, YU Shujing and LI Zhengming*

State Key Laboratory of Elemento-organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering(Tianjin), Nankai University, Tianjin 300071, P. R. China

Abstract To discover novel lead compounds with better antifungal activities, a series of novel strobilurin derivatives containing quinolin-2(1*H*)-one moiety was designed and synthesized *via* intermediate derivatization method. Their structures were characterized by means of ^{1}H nuclear magnetic resonance(^{1}H NMR), ^{13}C NMR and high resolution mass spectrometry(HRMS). The biological assay results indicate that most target compounds exhibit good to excellent fungicidal activities against 10 plant pathogens. Compounds **4**d, **5**b and **5**c possess 94.1%, 83.8% and 80.9% *in vitro* inhibition respectively against *Rhizotonia cereals* at the concentration of 50 μg/mL, which are better than that of the control agents. Especially, the inhibition activities of compound **4**d against all of the tested fungi approach or exceed those of the controls. The structure-activity relationship was also discussed.

Keywords Strobilurin; Fungicidal activity; Quinolinone; Intermediate derivatization method

1 Introduction

The strobilurin, one of the most important classes of agricultural fungicides and inhibitors, can bind at the ubiquinol oxidation center(Q_o site) of the cytochrome bc_1-enzyme complex(complex III) and exhibits wide spectrum of antifungal activities and low toxicity toward mammal cells[1—8]. Many strobilurin fungicides have been commercially available since 1996[1]. However, significant resistances were observed in some important plant pathogens after a period of field applications of strobilurin class fungicides[8,9]. Therefore, developing new strobilurin derivatives to coordinate the increasing demand for the treatment of resistant pathogens has attracted much attention in recent years.

Intermediate derivatization method(IDM) is a new approach to discovering and developing novel agrochemicals. Many innovative patentable leads and target compounds have been developed[10—12]. For example, the replacement of 2-methylphenyl terminal group of strobilurin fungicide Kresoxim-methyl by key intermediate coumarins led to the discovery of Coumoxystrobin[10]. Quinolinone derivatives always show potent biological activities, including antifungal[13], anticancer[14] and insecticidal[15] effects and are considered to be bioisosteres of coumarins. Thus, we envisioned that the replacement of coumarins module in Coumoxystrobin by quinolinone derivatives could provide novel lead compounds with better antifungal activities(Fig.1). Herein, a series of strobilurin derivatives containing quinolin-2(1*H*)-one moiety was designed and synthesized. Furthermore, the antifungal activities of these products against 10 plant pathogens were assessed accordingly.

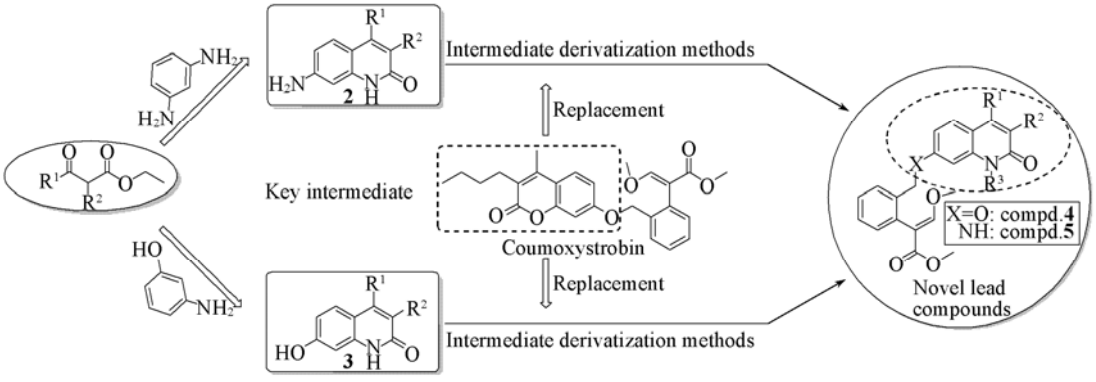


Fig.1 Design strategy for strobilurin derivatives containing quinolin-2(1*H*)-one moiety

*Corresponding author. E-mail: nkzml@vip.163.com

Received January 28, 2016; accepted March 3, 2016.

Supported by the "111" Project of the Ministry of Education of China(No.B06005), the Project of the State Key Laboratory of Elemento-organic Chemistry and Collaborative Innovation Center of Chemical Science and Engineering(Tianjin), China.

2 Experimental

2.1 Materials and Instruments

All solvents were purified according to standard procedures and all chemicals were reagent grade and used as purchased. Reactions were monitored by thin layer chromatography(TLC) on silica gel precoated glass plates. Flash column chromatography was performed on flash silica gel(200—300 mesh) from Qingdao Haiyang Company. ^{1}H nuclear magnetic resonance(^{1}H NMR) and ^{13}C NMR spectra were recorded on a Bruker spectrometer using tetramethylsilane as internal standard. Coupling constants were given in hertz. The following abbreviations were used to indicate the multiplicity: s, singlet; d, double; t, triplet; m, multiplet. The melting points were determined on an X-4 binocular microscope melting point apparatus(Beijing Tech Instruments Co., China) and were uncorrected. High resolution mass spectra(HRMS) were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource.

2.2 General Synthetic Procedure

*2.2.1 Syntheses of Compounds **2** and **3***

Compounds **2** and **3** were prepared according to the previously reported method[15—18].

7-Amino-4-methylquinolin-2(1*H*)-one(**2**a): a yellow solid. Yield 68%; m. p. 271—272 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 11.28(s, 1H), 7.36(d, *J*=8.6 Hz, 1H), 6.49(dd, *J*=8.6, 1.9 Hz, 1H), 6.42(d, *J*=1.8 Hz, 1H), 5.99(s, 1H), 5.80(s, 2H), 2.30(s, 3H).

7-Amino-3-ethyl-4-methylquinolin-2(1*H*)-one(**2**b): a yellow solid. Yield 50%; m. p. 282—283 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 11.17(s, 1H), 7.37(d, *J*=8.7 Hz, 1H), 6.45(dd, *J*=8.7, 2.1 Hz, 1H), 6.36(d, *J*=2.1 Hz, 1H), 5.59(s, 2H), 2.55(q, *J*=7.6 Hz, 2H), 2.29(s, 3H), 0.99(t, *J*=7.4 Hz, 3H).

7-Amino-3-butyl-4-methylquinolin-2(1*H*)-one(**2**c): a yellow solid. Yield 53%; m. p. 199—200 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 11.17(s, 1H), 7.36(d, *J*=8.6 Hz, 1H), 6.44(d, *J*=8.7 Hz, 1H), 6.35(s, 1H), 5.60(s, 2H), 2.56—2.50(m, 2H), 2.28(s, 3H), 1.39—1.29(m, 4H), 0.90(t, *J*=6.0 Hz, 3H).

7-Amino-4-methyl-3-pentylquinolin-2(1*H*)-one(**2**d): a yellow solid. Yield 51%; m. p. 195—196 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 11.16(s, 1H), 7.36(d, *J*=8.7 Hz, 1H), 6.44(d, *J*=8.6 Hz, 1H), 6.35(s, 1H), 5.60(s, 2H), 2.56—2.51(m, 2H), 2.28(s, 2H), 1.43—1.25(m, 6H), 0.87(t, *J*=6.1 Hz, 3H).

7-Amino-3-hexyl-4-methylquinolin-2(1*H*)-one(**2**e): a white solid. Yield 75%; m. p. 234—235 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 11.13(s, 1H), 7.36(d, *J*=8.7 Hz, 1H), 6.44(dd, *J*=8.7, 1.8 Hz, 1H), 6.35(d, *J*=1.8 Hz, 1H), 5.58(s, 2H), 2.55—2.51(m, 2H), 2.28(s, 3H), 1.41—1.24(m, 8H), 0.86(t, *J*=6.2 Hz, 3H).

7-Amino-4-(trifluoromethyl)quinolin-2(1*H*)-one(**2**f): a white solid. Yield 73%; m. p. 274—275 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 10.12(s, 1H), 7.16(d, *J*=8.4 Hz, 1H), 6.58(s, 1H), 6.25(dd, *J*=8.4, 2.2 Hz, 1H), 6.11(d, *J*=2.1 Hz, 1H), 5.38(s, 2H).

7-Amino-1,4-dimethylquinolin-2(1*H*)-one(**2**g): a yellow solid. Yield 41%; m. p. 173—174 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 7.43(d, *J*=9.1 Hz, 1H), 6.56—6.52(m, 2H), 6.09(s, 1H), 5.87(s, 2H), 3.46(s, 3H), 2.30(s, 3H).

7-Amino-1-ethyl-4-methylquinolin-2(1*H*)-one(**2**h): a yellow solid. Yield 40%; m. p. 170—171 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.35(d, *J*=8.3 Hz, 1H), 6.54(d, *J*=9.0 Hz, 2H), 6.26(s, 1H), 5.34(s, 2H), 4.17(q, *J*=6.9 Hz, 2H), 2.25(s, 3H), 1.20(t, *J*=7.1 Hz, 3H).

1-Allyl-7-amino-4-methylquinolin-2(1*H*)-one(**2**i): a yellow solid. Yield 38%; m. p. 136—137 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 7.43(d, *J*=8.6 Hz, 1H), 6.52(dd, *J*=8.6, 1.8 Hz, 1H), 6.47(d, *J*=1.7 Hz, 1H), 6.11(s, 1H), 5.97—5.76(m, 3H), 5.14(dd, *J*=10.4, 1.3 Hz, 1H), 4.97(dd, *J*=17.3, 1.3 Hz, 1H), 4.72(d, *J*=4.4 Hz, 2H), 2.31(s, 3H).

7-Hydroxy-4-methylquinolin-2(1*H*)-one(**3**a): a yellow solid. Yield 76%; m. p. 299—300 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 11.37(s, 1H), 10.07(s, 1H), 7.51(d, *J*=8.7 Hz, 1H), 6.69(d, *J*=1.7 Hz, 1H), 6.65(d, *J*=8.7 Hz, 1H), 6.14(s, 1H), 2.34(s, 3H).

3-Hexyl-7-hydroxy-4-methylquinolin-2(1*H*)-one(**3**b): a yellow solid. Yield 72%; m. p. 203—204 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 11.38(s, 1H), 9.91(s, 1H), 7.52(d, *J*=8.6 Hz, 1H), 6.72—6.53(m, 2H), 2.60—2.52(m, 2H), 2.33(s, 3H), 1.28(s, 8H), 0.86(s, 3H).

7-Hydroxy-4-(trifluoromethyl)quinolin-2(1*H*)-one(**3**c): a yellow solid. Yield 72%; m. p. 297—298 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 12.11(s, 1H), 10.55(s, 1H), 7.54(dd, *J*=8.9, 1.8 Hz, 1H), 6.83(d, *J*=2.3 Hz, 1H), 6.79(dd, *J*=8.9, 2.4 Hz, 1H), 6.69(s, 1H).

2.2.2 Synthesis of (E)-Methyl 2-(2-Formyl phenyl)-3-methoxyacrylate

(*E*)-methyl 2-(2-formylphenyl)-3-methoxyacrylate was prepared according to the previously reported method[19] in a yield of 66% as a white solid. m. p. 70—71 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 10.0(s, 1H), 7.90—7.93(m, 1H), 7.72(s, 1H), 7.31—7.67(m, 3H), 3.86(s, 3H), 3.75(s, 3H).

*2.2.3 General Synthetic Procedure for Compounds **4**a—**4**c*

A solution of 7-hydroxyquinolin-2(1*H*)-ones(**3**a, **3**b or **3**c, 2 mmol) in DMF(30 mL) was treated with anhydrous potassium carbonate(3 mmol). Then (*E*)-methyl 2-[2-(bromomethyl)phenyl]-3-methoxyacrylate(2 mmol) was added and the reaction system was stirred at room temperature for 2 h. After the reaction completed, water(60 mL) was added and the solution was extracted with EtOAc(3×20 mL). The combined organics were washed with brine(20 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography[*V*(petroleum ether)/*V*(ethyl acetate)=1:1] to afford compounds **4**a—**4**c.

(*E*)-Methyl 3-methoxy-2-(2-{[(4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy]methyl}phenyl)acrylate(**4**a): a white solid. Yield 73%. m. p. 251—252 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 11.46(s, 1H), 7.65(s, 1H), 7.60(d, *J*=8.9 Hz, 1H), 7.54—7.47(m, 1H), 7.37—7.29(m, 2H), 7.16—7.10(m, 1H), 6.84(d, *J*=2.3 Hz, 1H), 6.77(dd, *J*=8.9, 2.3 Hz, 1H), 6.22(s, 1H),

4.93(s, 2H), 3.82(s, 3H), 3.61(s, 3H), 2.37(s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 166.96, 162.05, 160.68, 159.96, 147.91, 140.27, 135.21, 132.30, 131.17, 127.95, 127.71, 127.54, 126.18, 117.90, 113.91, 110.31, 108.72, 99.30, 67.69, 61.84, 51.28, 18.47. HRMS(ESI), *m/z*, calcd.([M+H]$^+$) 380.1498, found 380.1498.

(*E*)-Methyl 2-(2-{[(3-hexyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy]methyl}phenyl)-3-methoxyacrylate(**4**b): a yellow solid. Yield 72%. m. p. 44—45 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 12.30(s, 1H), 7.60(s, 1H), 7.54(dd, *J*=11.4, 7.0 Hz, 2H), 7.32(dd, *J*=5.3, 3.5 Hz, 2H), 7.20(dd, *J*=10.4, 5.4 Hz, 1H), 6.93(d, *J*=1.7 Hz, 1H), 6.77(dd, *J*=8.9, 1.8 Hz, 1H), 5.04(s, 2H), 3.79(s, 3H), 3.71(s, 3H), 2.83—2.70(m, 2H), 2.41(s, 3H), 1.66—1.48(m, 2H), 1.46—1.36(m, 2H), 1.33—1.21(m, 4H), 0.84(t, *J*=6.7 Hz, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.95, 164.40, 160.19, 159.75, 143.09, 138.48, 135.60, 131.95, 131.24, 128.70, 128.21, 128.12, 127.93, 125.55, 115.44, 111.42, 110.14, 100.02, 68.50, 62.07, 51.76, 31.93, 29.59, 29.33, 26.82, 22.74, 15.13, 14.17. HRMS(ESI), *m/z*, calcd.([M+H]$^+$) 464.2437, found 464.2439.

(*E*)-Methyl 3-methoxy-2-[2-({[2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-7-yl]oxy}methyl)phenyl]acrylate(**4**c): a white solid. Yield 73%. m. p. 243—244 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 12.19(s, 1H), 7.66(s, 1H), 7.61(d, *J*=8.1 Hz, 1H), 7.55—7.48(m, 1H), 7.38—7.30(m, 2H), 7.18—7.11(m, 1H), 6.98—6.89(m, 2H), 6.78(s, 1H), 4.97(s, 2H), 3.83(s, 3H), 3.61(s, 3H). ^{13}C NMR(100 MHz, DMSO-d_6), δ: 167.41, 161.21, 160.86, 142.16, 136.88(q, *J*=31.1 Hz), 135.32, 132.93, 131.71, 128.62, 128.35, 128.05, 126.19, 124.41, 121.68, 118.80(q, *J*=4.3 Hz), 112.50, 109.16, 107.66, 100.36, 68.44, 62.33, 51.77. HRMS(ESI), *m/z*, calcd.([M+H]$^+$) 434.1215, found 434.1212.

2.2.4 General Synthetic Procedure for Compounds 4d and 4e

To a solution of compound **4**a or **4**b(1 mmol) in DMF(10 mL) were added sodium hydride(1.5 mmol) and iodoethane(1 mmol). The reaction mixture was stirred for 10 h at room temperature. After the reaction completed, water(30 mL) was added and the solution was extracted with EtOAc(3×10 mL). The combined organics were washed with brine(10 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography[*V*(petroleum ether)/*V*(ethyl acetate)=1:1] to afford the compounds **4**d or **4**e.

(*E*)-Methyl 2-(2-{[(1-ethyl-4-methyl-2-oxo-1,2-dihydroquinoin-7-yl)oxy]methyl}phenyl)-3-methoxyacrylate(**4**d): a yellow solid. Yield 72%. m. p. 49—50 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.64—7.54(m, 2H), 7.53—7.47(m, 1H), 7.34(dd, *J*=5.4, 3.3 Hz, 2H), 7.25—7.17(m, 1H), 6.87—6.79(m, 2H), 6.42(s, 1H), 5.10(s, 2H), 4.24(dd, *J*=13.8, 6.8 Hz, 2H), 3.83(s, 3H), 3.72(s, 3H), 2.39(s, 3H), 1.19(t, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 167.75, 162.16, 160.62, 160.19, 146.21, 140.25, 135.34, 131.34, 131.10, 128.20, 127.78, 127.22, 126.67, 118.40, 115.92, 109.94, 109.70, 100.29, 68.52, 62.09, 51.76, 36.96, 19.02, 12.50. HRMS(ESI), *m/z*, calcd.([M+H]$^+$) 408.1811, found 408.1811.

(*E*)-Methyl 2-(2-{[(1-ethyl-3-hexyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy]methyl}phenyl)-3-methoxyacrylate (**4**e): a yellow solid. Yield 78%. m. p. 110—111 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.52(d, *J*=7.3 Hz, 2H), 7.45—7.38(m, 1H), 7.23(dd, *J*=5.6, 3.4 Hz, 2H), 7.15—7.08(m, 1H), 6.76—6.66(m, 2H), 5.00(s, 2H), 4.18(dd, *J*=13.8, 6.7 Hz, 2H), 3.72(s, 3H), 3.62(s, 3H), 2.71—2.57(m, 2H), 2.31(s, 3H), 1.45—1.35(m, *J*=6.6 Hz, 2H), 1.34—1.27(m, 2H), 1.25—1.19 (m, 4H), 1.11(t, *J*=7.0 Hz, 3H), 0.79(t, *J*=6.6 Hz, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 167.75, 161.94, 160.15, 159.64, 140.48, 138.71, 135.54, 131.30, 131.12, 129.04, 128.15, 127.69, 127.24, 126.36, 116.17, 109.98, 109.51, 99.95, 68.47, 62.04, 51.72, 37.55, 31.80, 29.69, 29.16, 27.81, 22.73, 15.15, 14.17, 12.48. HRMS(ESI), *m/z*, calcd.([M+H]$^+$) 492.2750, found 492.2741.

2.2.5 General Synthetic Procedure for Compounds 5a—5e

To a solution of compound **2**(2 mmol) and (*E*)-methyl 2-(2-formylphenyl)-3-methoxy acrylate(2 mmol) in methanol(20 mL) were added $NaBH_3CN$(6 mmol) and AcOH(0.5 mL). The reaction was allowed to continue for 12 h at room temperature and then quenched with water(60 mL) and extracted with EtOAc(3×20 mL). The combined organics were washed with brine(20 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography[*V*(petroleum ether)/*V*(ethyl acetate)= 2:1] to afford compounds **5**a—**5**e.

(*E*)-Methyl 3-methoxy-2-(2-{[(4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino]methyl}phenyl)acrylate(**5**a): a white solid. Yield 52%. m. p. 211—212 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 10.62(s, 1H), 7.57(s, 1H), 7.47—7.38(m, 2H), 7.36—7.29(m, 2H), 7.21—7.13(m, 1H), 6.45(dd, *J*=8.8, 1.8 Hz, 1H), 6.34(s, 1H), 6.23(s, 1H), 4.49(s, 1H), 4.23(d, *J*=4.4 Hz, 2H), 3.86(s, 3H), 3.71(s, 3H), 2.39(s, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 168.06, 160.13, 150.19, 149.18, 141.87, 140.28, 137.21, 132.10, 131.27, 128.41, 128.33, 127.57, 125.60, 115.48, 112.32, 110.46, 110.14, 96.01, 62.13, 51.82, 46.17, 19.03. HRMS(ESI), *m/z*, calcd.([M+H]$^+$) 379.1658, found 379.1659.

(*E*)-Methyl 2-(2-{[(3-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino]methyl}phenyl)-3-methoxyacrylate(**5**b): a yellow solid. Yield 50%. m. p. 91—92 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 11.42(s, 1H), 7.57(s, 1H), 7.43(m, 2H), 7.34—7.27(m, 2H), 7.20—7.14(m, 1H), 6.44(d, *J*=10.5 Hz, 2H), 4.44(s, 1H), 4.21(s, 2H), 3.84(s, 3H), 3.70(s, 3H), 2.73(q, *J*=7.4 Hz, 2H), 2.38(s, 3H), 1.12(t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 168.13, 164.05, 160.12, 149.28, 143.28, 138.73, 137.50, 132.19, 131.24, 128.59, 128.35, 127.51, 127.43, 125.33, 112.94, 110.50, 109.98, 96.15, 62.11, 51.80, 46.30, 19.94, 14.64, 13.69. HRMS(ESI), *m/z*, calcd.([M+H]$^+$) 407.1971, found 407.1967.

(*E*)-Methyl 2-(2-{[(3-butyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino]methyl}phenyl)-3-methoxyacrylate(**5**c): a yellow solid. Yield 51%. m. p. 41—42 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 10.20(s, 1H), 7.58(s, 1H), 7.43—1.34(m, 2H), 7.26(s, 2H), 7.16—7.11(m, 1H), 6.46(d, *J*=8.8 Hz, 1H), 6.17(s,

1H), 4.55(s, 1H), 4.16(s, 2H), 3.81(s, 3H), 3.69(s, 3H), 2.57(t, *J*=6.8 Hz, 2H), 2.31(s, 3H), 1.40—1.32(m, 2H), 1.28—1.23(m, 2H), 0.81(t, *J*=6.7 Hz, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 211.70, 168.40, 163.66, 160.46, 149.46, 138.02, 137.31, 131.93, 131.25, 128.33, 128.08, 127.42, 125.54, 113.01, 110.80, 110.23, 99.99, 95.61, 62.15, 51.86, 45.98, 31.47, 26.35, 22.81, 14.97, 14.00. HRMS(ESI), *m/z*, calcd.($[M+H]^+$) 435.2284, found 435.2281.

(*E*)-Methyl 3-methoxy-2-(2-{[(4-methyl-2-oxo-3-pentyl-1,2-dihydroquinolin-7-yl)amino]methyl}phenyl)acrylate(**5**d): a yellow solid. Yield 41%. m. p. 55—56 °C; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 10.99(s, 1H), 7.56(s, 1H), 7.43(d, *J*=8.8 Hz, 2H), 7.35—7.27(m, 2H), 7.19—7.13(m, 1H), 6.46(d, *J*=8.7 Hz, 1H), 6.34(s, 1H), 4.42(s, 1H), 4.21(s, 2H), 3.84(s, 3H), 3.70(s, 3H), 2.73—2.62(m, 2H), 2.38(s, 3H), 1.55—1.43(m, 2H), 1.40—1.31(m, 4H), 0.87(t, *J*=6.5 Hz, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 168.13, 164.06, 160.12, 149.29, 143.88, 138.45, 137.39, 132.15, 131.26, 128.51, 128.37, 127.54, 126.17, 125.43, 113.01, 110.48, 110.27, 95.88, 62.12, 51.81, 46.30, 32.02, 29.02, 26.63, 22.69, 14.97, 14.13. HRMS(ESI), *m/z*, calcd.($[M+H]^+$) 449.2440, found 449.2438.

(*E*)-Methyl 2-(2-{[(3-hexyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino]methyl}phenyl)-3-methoxyacrylate(**5**e): a yellow solid. Yield 43%. m. p. 58—59 °C; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 11.55(s, 1H), 7.56(s, 1H), 7.42(d, *J*=7.8 Hz, 2H), 7.34—7.26(m, 2H), 7.19—7.12(m, 1H), 6.45(d, *J*=8.8 Hz, 1H), 6.39(s, 1H), 4.46(s, 1H), 4.20(s, 2H), 3.83(s, 3H), 3.69(s, 3H), 2.73—2.62(m, 2H), 2.38(s, 3H), 1.55—1.44(m, 2H), 1.37(s, 2H), 1.31—1.26(m, 4H), 0.86(t, *J*=5.5 Hz, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 168.15, 164.37, 160.16, 149.39, 144.10, 138.46, 137.45, 132.20, 131.27, 128.55, 128.33, 127.51, 125.92, 125.41, 113.03, 110.46, 110.35, 95.95, 62.10, 51.79, 46.28, 31.89, 29.58, 29.34, 26.67, 22.73, 14.97, 14.17. HRMS(ESI), *m/z*, calcd.($[M+H]^+$) 463.2597, found 463.2591.

*2.2.6 General Synthetic Procedure for Compounds **6**a—**6**e*

(*E*)-Methyl 2-(2-formylphenyl)-3-methoxyacrylate(2 mmol), silica(900 mg), AcOH(0.5 mL) and compound **2**(2 mmol) were mixed in methanol(20 mL) and irradiated in the water bath of the ultrasonic cleaner at room temperature for 30 min. Then $NaBH_3CN$(6 mmol) was added, and the reaction system was stirred for 12 h at room temperature. After the completion of the reaction, the mixture was filtered, washed with methanol. Then the cake was purified by silica gel column chromatography[$V(CH_2Cl_2)/V$(MeOH)=50:1] to afford compounds **6**a—**6**e.

(*E*)-7-[4-(Methoxymethylene)-3-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl]-4-methyl quinolin-2(1*H*)-one(**6**a): a yellow solid. Yield 73%. m. p. 277—278 °C; ^{1}H NMR(400 MHz, DMSO-d_6), *δ*: 11.50(s, 1H), 8.16(d, *J*=7.8 Hz, 1H), 7.94(s, 1H), 7.75(d, *J*=8.8 Hz, 1H), 7.27(t, *J*=7.6 Hz, 1H), 7.24—7.14(m, 3H), 7.12(d, *J*=1.9 Hz, 1H), 6.32(s, 1H), 4.98(s, 2H), 3.76(s, 3H), 2.41(s, 3H). ^{13}C NMR(100 MHz, DMSO-d_6), *δ*: 166.28, 162.31, 148.10, 145.36, 142.63, 140.26, 129.62, 128.12, 127.48, 126.79, 126.69, 126.55, 123.62, 119.87, 116.45, 112.15, 104.02, 103.22, 51.44, 49.79, 18.91. HRMS(ESI), *m/z*, calcd.($[M+H]^+$) 347.1396, found 347.1391.

(*E*)-7-[4-(Methoxymethylene)-3-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl]-1,4-dimethyl quinolin-2(1*H*)-one(**6**b): a yellow solid. Yield 78%. m. p. 213—214 °C; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 8.28(d, *J*=8.0 Hz, 1H), 7.98(s, 1H), 7.71(d, *J*=8.7 Hz, 1H), 7.31(t, *J*=7.6 Hz, 1H), 7.20(t, *J*=7.4 Hz, 1H), 7.08(dd, *J*=15.6, 8.1 Hz, 2H), 6.95(s, 1H), 6.53(s, 1H), 4.96(s, 2H), 3.86(s, 3H), 3.73(s, 3H), 2.46(s, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 166.78, 162.42, 146.03, 145.99, 142.14, 141.10, 129.47, 128.22, 126.62, 126.59, 126.56, 125.60, 124.25, 119.71, 117.63, 111.75, 105.79, 102.48, 51.28, 50.67, 29.45, 18.96. HRMS(ESI), *m/z*, calcd.($[M+H]^+$) 361.1552, found 361.1548.

(*E*)-1-Ethyl-7-[4-(methoxymethylene)-3-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl]-4-methylquinolin-2(1*H*)-one(**6**c): a yellow solid. Yield 80%. m. p. 168—169 °C; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 8.29(d, *J*=7.5 Hz, 1H), 7.97(s, 1H), 7.72(d, *J*=8.7 Hz, 1H), 7.35—7.28(m, 1H), 7.20(td, *J*=7.4, 1.1 Hz, 1H), 7.11(d, *J*=7.3 Hz, 1H), 7.06(dd, *J*=8.7, 2.2 Hz, 1H), 6.98(d, *J*=2.1 Hz, 1H), 6.52(d, *J*=0.8 Hz, 1H), 4.95(s, 2H), 4.38(q, *J*=7.1 Hz, 2H), 3.86(s, 3H), 2.45(d, *J*=0.9 Hz, 3H), 1.38(t, *J*=7.1 Hz, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 166.76, 161.94, 146.06, 145.92, 142.35, 139.95, 129.51, 128.22, 126.80, 126.56, 126.49, 125.62, 124.20, 119.90, 117.98, 111.73, 105.62, 102.43, 51.26, 50.70, 37.14, 19.01, 12.75. HRMS(ESI), *m/z*, calcd.($[M+H]^+$) 375.1709, found 375.1706.

(*E*)-1-Allyl-7-[4-(methoxymethylene)-3-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl]-4-methylquinolin-2(1*H*)-one(**6**d): a yellow solid. Yield 76%. m. p. 143—144 °C; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 8.28(d, *J*=8.0 Hz, 1H), 7.96(s, 1H), 7.71(d, *J*=8.7 Hz, 1H), 7.31(t, *J*=7.7 Hz, 1H), 7.19(t, *J*=7.4 Hz, 1H), 7.07(dd, *J*=15.8, 8.1 Hz, 2H), 6.97(s, 1H), 6.55(s, 1H), 5.96(ddd, *J*=15.6, 10.2, 4.9 Hz, 1H), 5.29(d, *J*=10.3 Hz, 1H), 5.18(d, *J*=17.3 Hz, 1H), 4.99(d, *J*=3.8 Hz, 2H), 4.92(s, 2H), 3.85(s, 3H), 2.47(s, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 166.73, 162.05, 146.44, 145.80, 142.12, 140.33, 132.23, 129.47, 128.22, 126.61, 126.56, 126.51, 125.61, 124.23, 119.62, 117.76, 117.29, 111.64, 105.59, 103.36, 51.22, 50.50, 44.60, 19.03. HRMS(ESI), *m/z*, calcd.($[M+H]^+$) 387.1709, found 387.1711.

(*E*)-3-Hexyl-7-[4-(methoxymethylene)-3-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl]-4-methylquinolin-2(1*H*)-one(**6**e): a yellow solid. Yield 83%. m. p. 192—193 °C; ^{1}H NMR(400 MHz, $CDCl_3$), *δ*: 12.35(s, 1H), 8.30(d, *J*=7.5 Hz, 1H), 8.01(s, 1H), 7.69(d, *J*=8.9 Hz, 1H), 7.30(dd, *J*=11.2, 4.2 Hz, 1H), 7.18(td, *J*=7.4, 1.0 Hz, 1H), 7.12—7.06(m, 2H), 7.03(dd, *J*=8.9, 2.3 Hz, 1H), 4.95(s, 2H), 3.85(s, 3H), 2.85—2.74(m, 2H), 2.48(s, 3H), 1.63—1.52(m, 2H), 1.47—1.38(m, 2H), 1.33—1.23(m, 4H), 0.82(t, *J*=7.0 Hz, 3H). ^{13}C NMR(100 MHz, $CDCl_3$), *δ*: 166.82, 164.36, 144.65, 142.92, 142.18, 137.96, 130.38, 129.55, 128.10, 126.63, 126.38, 125.75, 125.58, 124.14, 117.41, 112.26, 104.83, 103.17, 51.16, 50.34, 31.84, 29.71, 29.19, 27.05, 22.71, 15.12, 14.09. HRMS(ESI), *m/z*, calcd.($[M+H]^+$) 431.2335, found 431.2326.

2.3 *In vitro* Fungicidal Activity Assay

The *in vitro* fungicidal activities of the target compounds against *Fusarium oxysporum*, *Cercospora arachidicola Hori*,

Physalospora piricola, *Rhizotonia cerealis*, *Colletotrichum orbiculare*, *Gibberella fujikuroi*, *Sclerotinia sclerotiorum*, *Phytophthora infestans, Alternaria solani* and *Fusarium graminearum* were tested *via* the mycelium growth rate method[20—22]. Their relative inhibition ratio was calculated according to the following formula:

$$\text{Relative inhibition rate}(\%)=(D_1-D_2)/D_1\times 100\%$$

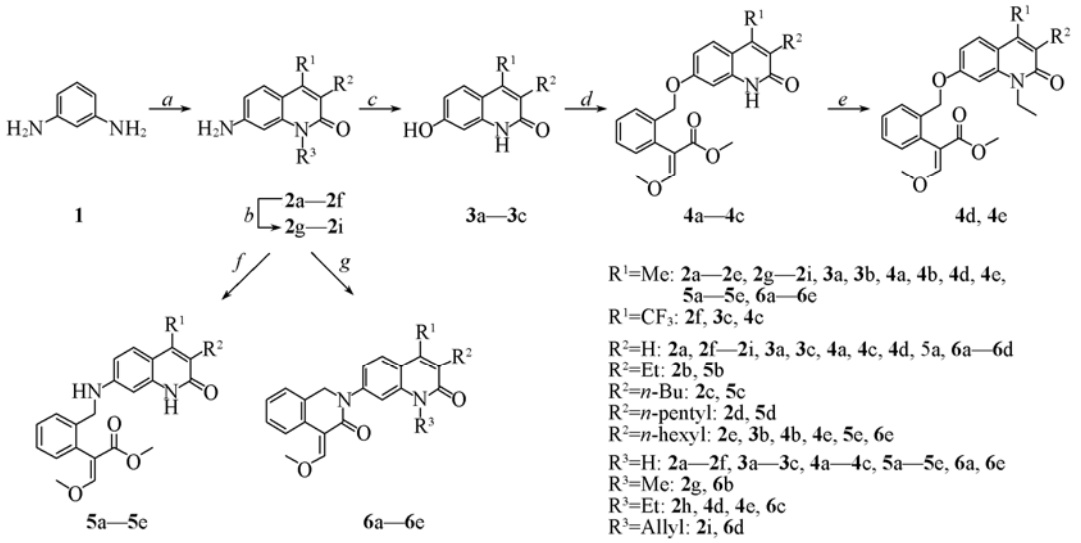
where D_1 is the average diameter of the circle mycelia during the blank assay and D_2 is the average diameter of the circle mycelia in the presence of target compounds. Coumoxystrobin, ZJ0712{*E*-2-[2-(2,5-dimethyl-phenoxy)-phenylmethyl]-3-methoxyacrylic acid methyl ester} and Azoxystrobin were used as the controls. All the strains were conserved in the Biological Test Center, Nankai University, Tianjin, China.

3 Results and Discussion

3.1 Chemistry

The general synthetic routes of the target compounds are depicted in Scheme 1. Compounds **2**a—**2**f were prepared with 1,3-diaminobenzene and substituted ethyl acetoacetates as initiators referring to the literature[15,17]. Then compounds **2**g—**2**i could be obtained by the alkylation on the lactam of compound **2**a. In this reaction, excess alkyl halide and reaction time will lead to the alkylation on the amino group at C7 position of products. Initially, compounds **3** were prepared with 3-aminophenol as initiator[18], but it is difficult to separate three isomers of this reaction. To our surprise, the diazotization and hydrolysis of compounds **2** could generate compounds **3** in good yields without chromatographic separation. Subsequently, compounds **3** were allowed to react with (*E*)-methyl 2-[2-(bromomethyl)phenyl]-3-methoxyacrylate in the presence of K_2CO_3 to produce the target compounds **4**a—**4**c in good yields. And target compounds **4**d and **4**e could be obtained *via* the reaction of corresponding compounds **4**a and **4**b with iodoethane in the presence of NaH.

The yields of compounds **5** were very low when compounds **2** reacted with (*E*)-methyl 2-[2-(bromomethyl)-phenyl]-3-methoxyacrylate according to the similar method reported in the literature[7,23]. And changes in the reaction temperature and the amount of base did not improve the yields. Attempt of using microwave irradiation failed to enhance the yields either[24]. Finally, compounds **5** were obtained in moderate yields *via* the reaction of corresponding compounds **2**a—**2**f with (*E*)-methyl 2-(2-formyl phenyl)-3-methoxyacrylate in the presence of $NaBH_3CN$ and AcOH. But there was no product when compounds **2**g—**2**i were used as the raw material. A reduction process of intermediate imine was considered to be included in this reaction. With the purpose of synthesizing the corresponding product from compounds **2**g—**2i,** we firstly tried to synthesize the intermediate imine using ultrasound irradiation in the presence of SiO_2[25]. To our surprise, a series of cyclized products **6** was accidentally obtained after $NaBH_3CN$ was added.



Scheme 1 Synthetic route of the target compounds

Reagents and conditions: *a*. substituted ethyl acetoacetates, 130 °C for 48 h; *b.* NaH, DMF, alkyl halide, r. t., 4 h; *c*. $NaNO_2$, 10 mol/L H_2SO_4, 0 °C to reflux; *d*. K_2CO_3, (*E*)-methyl 2-[2-(bromomethyl)phenyl]-3-methoxyacrylate, DMF, r. t., 2 h; *e*. NaH, DMF, EtI, r. t., 4 h; *f.* $NaBH_3CN$, AcOH, MeOH, (*E*)-methyl 2-(2-formylphenyl)-3-methoxyacrylate, r. t.; *g*. SiO_2, AcOH, MeOH, (*E*)-methyl 2-(2-formylphenyl)-3-methoxyacrylate, ultrasound irradiation, then $NaBH_3CN$, r. t.

3.2 Fungicidal Activity

The *in vitro* fungicide activities of compounds **4—6** against the typical plant pathogens occurring in the Chinese agro-ecosystems are summarized in Table 1 and Table 2. From Table 1 it can be observed that all the title compounds **4—6** exhibit moderate to good inhibitory activities against all the tested fungi at a concentration of 50 μg/mL. It is noted that some of the title compounds exhibit excellent fungicidal activities against *Physalospora piricola*, *Rhizotonia cerealis* and *Sclerotinia sclerotiorum.* For example, compounds **4**d, **5**b and **5**c possess 94.1%, 83.8% and 80.9% inhibition respectively against *Rhizotonia cereals,* which are better than control agents(Coumoxystrobin and ZJ0712). Especially, compound **4**d shows 46.9%—94.1% inhibition activities against all the tested fungi, which approach or exceed those of the controls. We

further tested the EC_{50} values of compounds **4**d, **5**b and **5**c against *Rhizotonia cerealis*(Table 2). The results indicate that the fungicidal activity of compound **4**d is 4.17-, 5.19- and 5.07-fold more toxic than Coumoxystrobin, ZJ0712 and Azoxystrobin against *Rhizotonia cerealis*, respectively. The EC_{50} values of compounds **5**b and **5**c are also smaller than those of the controls, which are in accordance with the results in Table 1.

Table 1 Fungicidal activity of target compounds against typical plant pathogen at 50 μg/mL *in vitro*[a]

Compd.	Fungicidal activity(%)									
	FO	*CA*	*PP*	*RC*	*CO*	*GF*	*SS*	*PI*	*AS*	*FG*
4a	17.6	26.1	43.1	76.5	18.8	18.8	26.8	11.8	16.1	19.7
4b	38.2	47.8	64.7	75.0	50.0	34.4	53.6	29.4	38.7	41.0
4c	23.5	39.1	51.0	75.0	21.9	34.4	42.9	23.5	25.8	27.9
4d	**52.9**	**52.2**	**88.2**	**94.1**	**50.0**	**46.9**	**91.1**	**47.1**	**54.8**	**57.4**
5a	11.8	30.4	56.9	64.7	21.9	28.1	46.4	11.8	22.6	32.8
5b	44.1	52.2	68.6	**83.8**	43.8	50.0	55.4	41.2	48.4	47.5
5c	41.2	47.8	52.9	**80.9**	56.3	56.3	51.8	35.3	41.9	42.6
5d	44.1	43.5	47.1	76.5	46.9	46.9	53.6	35.3	51.6	52.5
5e	29.4	39.1	43.1	76.5	37.5	43.8	57.1	35.3	45.2	57.4
6a	14.7	30.4	43.1	45.6	18.8	18.8	44.6	11.8	16.1	32.8
6b	11.8	39.1	52.9	64.7	25.0	25.0	35.7	11.8	22.6	37.7
6c	23.5	30.4	58.8	61.8	28.1	18.8	51.8	5.9	38.7	52.5
6d	23.5	30.4	52.9	42.6	28.1	18.8	51.8	5.9	29.0	37.7
6e	20.6	17.4	47.1	55.9	21.9	21.9	41.1	23.5	16.1	8.2
C-1[b]	29.4	60.9	68.6	79.4	62.5	46.9	82.1	47.1	48.4	50.8
C-2[c]	38.2	52.2	68.6	76.5	53.1	46.9	80.4	41.2	41.9	57.4

a. *FO*: *Fusarium oxysporum; CA*: *Cercospora arachidicola Hori; PP*: *Physalospora piricola; RC*: *Rhizotonia cerealis; CO*: *Colletotrichum orbiculare; GF*: *Gibberella fujikuroi; SS*: *Sclerotinia sclerotiorum; PI*: *Phytophthora infestans; AS*: *Alternaria solani; FG*: *Fusarium graminearum*; *b*. Coumoxystrobin; *c*. ZJ0712.

Table 2 EC_{50} values of compounds 4d, 4e, 5b and 5c against *Rhizotonia cerealis*

Compd.	$y=a+bx$	R	EC_{50}/(μg·mL^{-1})
4d	y=1.5755x+4.1498	0.9886	3.4646
4e	y=1.5580x+2.9467	0.9865	20.7947
5b	y=1.1572x+3.9005	0.9972	8.9148
5c	y=1.5724x+3.2291	0.9940	13.3718
C-1[a]	y=1.7164x+3.0088	0.9949	14.4593
C-2[b]	y=1.3732x+3.2790	0.9961	17.9715
C-3[c]	y=1.6208x+2.9821	0.9928	17.5804

a. Coumoxystrobin; *b*. ZJ0712; *c*. Azoxystrobin.

The fungicidal results can provide useful information for studying the structure-activity relationship for these new strobilurin derivatives. It is worth mentioning that the fungicidal activities of compounds **5** were better than those of compounds **6**(**5**a *vs.* **6**a, **5**e *vs.* **6**e), indicating that the cyclized strobilurin structure was detrimental to the fungicidal activities of compounds containing a quinolinone moiety. The amino group at C7 position of quinolinone moiety displayed better antifungal activity against *Gibberella fujikuroi*, *Sclerotinia sclerotiorum*, *Phytophthora infestans*, *Alternaria solani* and *Fusarium graminearum* than an ether linkage which was beneficial to the antifungal activity against *Fusarium oxysporum* and *Rhizotonia cerealis*(**4**a *vs.* **5**a, **4**b *vs.* **5**e). The length of alkyl chain at C3 position of quinolinone moiety was unfavorable for the antifungal activity of compounds **5** against *Cercospora arachidicola Hori*, *Physalospora piricola*, *Rhizotonia cerealis* and *Phytophthora infestans*(**5**b>**5**c>**5**d>**5**e). *n*-Hexyl moiety at C3 also had a negative effect on the fungicidal activity against *Rhizotonia cerealis*(**4**a>**4**b). We further synthesized compound **4**e to explore the effect of *n*-hexyl at C3 position. The EC_{50} values of compounds **4**d and **4**e(Table 2) also indicate that *n*-hexyl group is a "bad" substituent for the fungicidal activity against *Rhizotonia cerealis*. Lactam moiety is the special structure of these novel strobilurin compounds compared to coumarin structure in Coumoxystrobin, which provides a site to be modified. And the results in Table 1 show that the modification of lactam is very important for the fungicidal activity. When the hydrogen at N1 position was replaced by an ethyl group, the fungicidal activity against all the test fungi could be significantly enhanced(**4**d>**4**a).

4 Conclusions

In summary, a series of novel strobilurin derivatives containing quinolin-2(1*H*)-one moiety was designed and synthesized *via* intermediate derivatization methods. The biological assay results indicated that most target compounds exhibited good to excellent fungicidal activities, especially against *Physalospora piricola*, *Rhizotonia cerealis* and *Sclerotinia sclerotiorum*. Among these compounds, the fungicidal activity of compound **4**d against all the tested fungi approached or exceeded those of Coumoxystrobin, ZJ0712 and Azoxystrobin.

References

[1] Bartlett D. W., Clough J. M., Godwin J. R., Hall A. A., Hamer M., Parr-Dobrzanski B., *Pest Manag. Sci*., **2002**, *58*, 649

[2] Zhang X., Liu H., Gao Y., Wang H., Guo B., Li J., *Chin. J. Chem.,* **2012**, *30*, 1517

[3] Lu G. H., Chu H. B., Chen M., Yang C. L., *Chin. Chem. Lett.*, **2014**, *25*, 61

[4] Li Y., Zhang H. Q., Liu J., Yang X. P., Liu Z. J., *J. Agric. Food Chem.*, **2006**, *54*, 3636

[5] Wood P. M., Hollomon D. W., *Pest Manag. Sci.*, **2003**, *59*, 499

[6] Hao G. F., Wang F., Li H., Zhu X. L., Yang W. C., Huang L. S., Wu J. W., Berry E. A., Yang G. F., *J. Am. Chem. Soc.*, **2012**, *134*, 11168

[7] Zhu X., Wang F., Li H., Yang W., Chen Q., Yang G., *Chin. J. Chem.*, **2012**, *30*, 1999
[8] Fisher N., Meunier B., *Pest Manag. Sci.*, **2005**, *61*, 973
[9] Huang W., Zhao P. L., Liu C. L., Chen Q., Liu Z. M., Yang G. F., *J. Agric. Food Chem.*, **2007**, *55*, 3004
[10] Guan A., Liu C., Yang X., Dekeyser M., *Chem. Rev.*, **2014**, *114*, 7079
[11] Chai B. S., Liu C. L., Li H. C., Zhang H., Liu S. W., Huang G., Chang J. B., *Pest Manag. Sci.*, **2011**, *67*, 1141
[12] Guan A. Y., Liu C. L., Huang G., Li H. C., Hao S. L., Xu Y., Li Z. N., *J. Agric. Food Chem.*, **2013**, *61*, 11929
[13] Kalkhambkar R. G., Aridoss G., Kulkarni G. M., Bapset R. M., Kadakol J. C., Premkumar N., Jeong Y. T., *Monatsh. Chem.*, **2012**, *143*, 1075
[14] Shiro T., Fukaya T., Tobe M., *Eur. J. Med. Chem.*, **2015**, *97*, 397
[15] Liu M., Liu Y., Hua X., Wu C., Zhou S., Wang B., Li Z., *Chin. J. Chem.*, **2015**, *33*, 1353
[16] Yamada S., Ohsawa F., Fujii S., Shinozaki R., Makishima M., Naitou H., Enomoto S., Tai A., Kakuta H., *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 5143
[17] Kathuria A., Priya N., Chand K., Singh P., Gupta A., Jalal S., Gupta S., Raj H. G., Sharma S. K., *Bioorg. Med. Chem.*, **2012**, *20*, 1624
[18] Chilin A., Rodighiero P., Pastorini G., Guiotto A., *J. Org. Chem.*, **1991**, *56*, 980
[19] Clough J. M., Godfrey C. R., de Fraine P. J., Hutchings M. G., Anthony V. M., *Fungicides*, US5021581, **1991**
[20] Zhu H., Wang B., Zhang X., Xiong L., Yu S., Li Z., *Chem. Res. Chinese Universities*, **2014**, *30*(3), 409
[21] Chen W., Li Y., Shi Y., Wei W., Chen Y., Li Y., Liu J., Li B., Li Z., *Chem. Res. Chinese Universities*, **2015**, *31*(2), 218
[22] Liu J., Li Y., Chen Y., Wu C., Wan Y., Wei W., Xiong L., Zhang X., Yu S., Li Z., *Chem. Res. Chinese Universities*, **2016**, *32*(1), 41
[23] Maillard M. C., Perlman M. E., Amitay O., Baxter D., Berlove D., Connaughton S., Fischer J. B., Guo J. Q., Hu L. Y., McBurney R. N., Nagy P. I., Subbarao K., Yost E. A., Zhang L., Durant G. J., *J. Med. Chem.*, **1998**, *41*, 3048
[24] Romera J. L., Cid J. M., Trabanco A. A., *Tetrahedron Lett.*, **2004**, *45*, 8797
[25] Guzen K. P., Guarezemini A. S., Orfao A. T. G., Cella R., Pereira C. M. P., Stefani H. A., *Tetrahedron Lett.*, **2007**, *48*, 1845