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Design, Synthesis, and Fungicidal Activities of New Strobilurin Derivatives

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Strobilurins are one of the most important classes of agricultural fungicides. To discover new strobilurin analogues with high activity against resistant pathogens, a series of new strobilurin derivatives bearing structurally diverse heterocycle side chains **3a**−**m** and **4a**−**g** were designed and synthesized via a microwave-assisted procedure. The advantages, such as good to excellent yields, shorter reaction times, mild reaction conditions, and simple purification procedures, distinguish the present synthetic protocol as a highly efficient method for the preparation of strobilurin thioether derivatives. Bioassays indicated that most of the compounds showed broad-spectrum fungicidal activity in vitro. Interestingly, as compared to the control of a commercial strobilurin fungicide, Kresoxim-methyl, compounds **3b**, **3g**, **4c**, and **4d** possessed remarkably higher in vitro fungicidal activity against six kinds of tested fungi. Exhilaratingly, compound **3g** exhibited higher in vivo activity against *Sphaerotheca fuliginea* and *Pseudoperoniospora cubensis* than Kresoxim-methyl, and the in vivo fungicidal activities of compound **4d** and Kresoxim-methyl against *S. fuliginea* and *P. cubensis* are at the same level. The present work demonstrated that strobilurin analogues containing benzothiazole side chains could be used as a lead structure for further developing novel fungicides.

KEYWORDS: Strobilurin; fungicide; benzothiazole; microwave irradiation

INTRODUCTION

Strobilurins have been identified as one of the most important classes of agricultural fungicides since being launched first in 1996 (*1*, *2*). These compounds exhibited fungicidal activity by blocking the electron transfer between cytochrome *b* and cytochrome c_1 by binding at the so-called Q_0 site of cytochrome *b*. By 2005, over 10 strobilurin fungicides were commercially available (*1*−*3*); however, significant increases in resistance were observed in a range of important plant pathogens for the strobilurin class fungicides after a short period of field applications (*4*, *5*). Therefore, developing new strobilurin analogues for the increasing demand for the treatment of resistant pathogens has attracted much attention from agricultural chemists in recent years.

The general structure of strobilurin fungicides consists of three parts: pharmacophore, brige ring, and side chain (**Scheme 1**). It has been demonstrated (*6*−*8*) that all highly active analogues have an (*E*)-methyl-*β*-methoxyacrylate group or (*E*)-methyl-methoxyiminoacetate as a common pharmacophore, and many examples have proved that modification of the side chain is the most effective way to obtain new analogues with a higher activity (*9*−*13*). Because various N- or S-containing heterocyclic derivatives, such as pyridine, pyrazole, imidazole, triazinane, oxazinane, pyrimidine, thiadiazole, benzothiazole, and oxodiazole, always display broad-spectrum biological activities, screening strobilurin derivatives bearing various heterocyclic side chains might produce new lead compounds with a more potent fungicidal activity against resistant pathogens. Keeping these considerations in mind, we herein designed and synthesized a series of strobilurin derivatives containing structurally diverse heterocyclic side chains. Fortunately, we found that some compounds displayed higher fungicidal activities against

Scheme 1. General Structure of Fungicidal Strobilurins

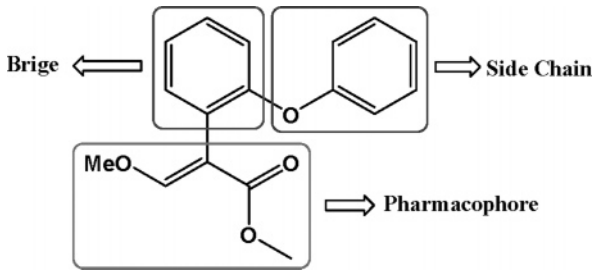

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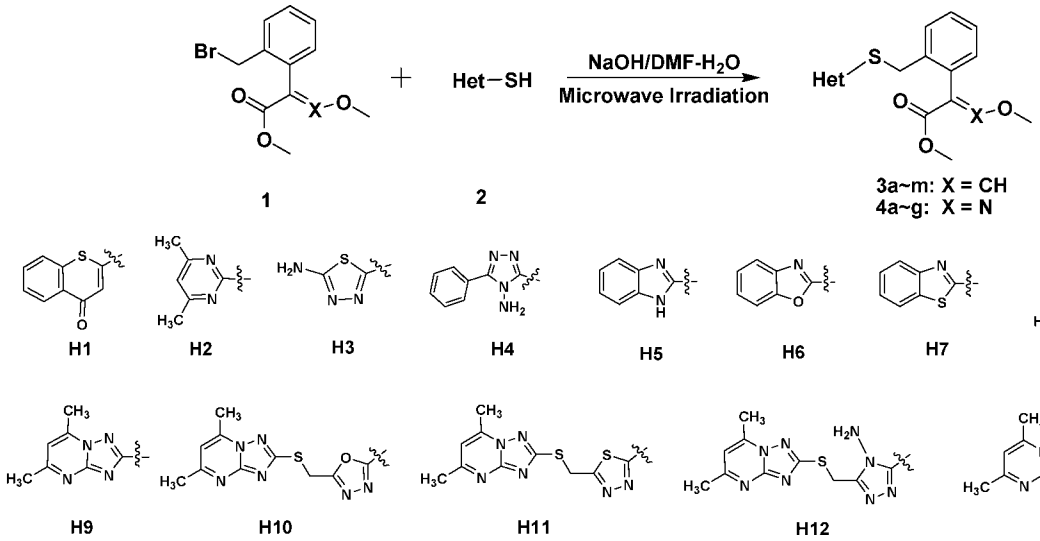
Table 1. Synthetic Results of Compounds **3** and **4**



			traditional heating		microwave irradiation	
compound	Het	X	time (h)[a]	yield (%)[b]	time (min)[a]	yield (%)[b]
3a	H1	CH	3.0	61	10	78
3b	H2	CH	2.5	72	8	81
3c	H3	CH	3.0	67	10	75
3d	H4	CH	3.0	70	10	78
3e	H5	CH	2.0	78	6	87
3f	H6	CH	2.0	75	6	85
3g	H7	CH	2.0	72	6	81
3h	H8	CH	2.5	72	8	85
3i	H9	CH	2.5	78	8	90
3j	H10	CH	3.0	75	10	87
3k	H11	CH	4.0	72	10	83
3l	H12	CH	3.0	68	10	81
3m	H13	CH	2.5	78	10	90
4a	H1	N	3.0	64	10	80
4b	H2	N	2.5	70	8	78
4c	H5	N	2.0	76	6	87
4d	H7	N	2.0	70	6	81
4e	H9	N	2.5	75	8	87
4f	H10	N	3.0	72	10	85
4g	H11	N	4.0	70	10	81

[a] Time to finish the reaction monitored by TLC. [b] Isolated yields.

Sphaerotheca fuliginea and *Pseudoperoniospora cubensis* in vivo than the control, Kresoxim-methyl.

MATERIALS AND METHODS

Unless otherwise noted, all materials were commercially available and were used directly without further purification. All solvents were redistilled before use. *Fusarium oxysporium*, *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberella zeae*, *Dothiorella gregaria*, *Bipolaris mayclis*, and *Colletotrichum gossypii* were provided through the courtesy of the Center for Bioassay, Central China Normal University. *S. fuliginea* and *P. cubensis* were provided through the courtesy of the Center for Bioassay, Zhejiang Chemical Industry Research Institute. ^{1}H NMR spectra were recorded on a Mercury-Plus 400 spectrometer in $CDCl_3$ with TMS as the internal reference. MS spectra were determined using a TraceMS 2000 organic mass spectrometer. Elemental analyses were performed on a Vario EL III elemental analysis instrument. Melting points were taken on a Buchi B-545 melting point apparatus and uncorrected. Conventional heating was carried out on Corning stirrer/hotplates in oil baths. Microwave syntheses were carried out on a Smith synthesizer. 2-Mercapto-benzimidazole, 2-mercapto-benzoxazole, and 2-mercapto-benzothiazole were purchased from commercial suppliers. All other heterocyclic thiols and bromomethyl intermediate **1** were prepared according to the reported methods (*14*−*19*).

General Procedure for the Microwave-Assisted Synthesis of Target Compounds 3 or 4. A solution of thiol **2** (1 mmol) in 1% aqueous NaOH (5 mL) was added dropwise into a solution of methyl 2-(2-bromomethylphenyl)-3-methoxyacrylate (1 mmol) or methyl (2-bromomethylphenyl)-methoxyiminoacetate **1** (1 mmol) in DMF (1 mL). The mixture was sealed in a microwave tube, synthesized, and irradiated at 90 °C for 6−10 min. Completion of the reaction was checked by TLC. The resulted mixture was cooled and diluted with 10 mL of ice water. Solid products were filtrated and recrystallized from acetone/petroleum ether (30−60 °C) to afford desired thioether **3** or **4**.

General Procedure for the Conventional Synthesis of Target Compounds 3 or 4. A solution of thiol **2** (1 mmol) in 1% aqueous NaOH (5 mL) was added dropwise into a solution of methyl 2-(2-bromomethylphenyl)-3-methoxyacrylate (1 mmol) or methyl (2-bromomethylphenyl)- methoxyiminoacetate **1** (1 mmol) in DMF (1 mL). The resulting solution was heated by an oil bath at 90 °C for 2−4 h. After the reaction was completed and checked by TLC, the resulting mixture was cooled and diluted with 10 mL of ice water. Solid products

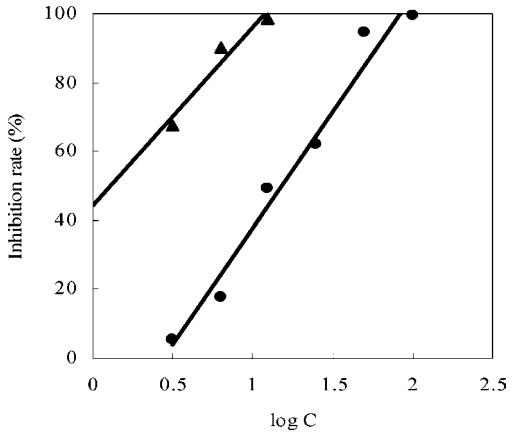


Figure 1. Preventive activities of compound **3g** against cucumber *S. fuliginea* (▲, $y = 51.11x + 49.49'$ $EC_{90} = 6.17$ μg mL^{-1}) and *P. cubensis* (●, $y = 67.62x - 22.65'$ $EC_{90} = 46.32$ μg mL^{-1}).

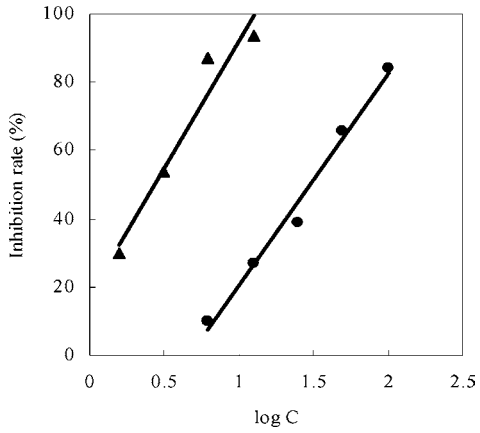


Figure 2. Preventive activities of compound **4d** against cucumber *S. fuliginea* (▲, $y = 74.61x + 16.85'$ $EC_{90} = 9.60$ μg mL^{-1}) and *P. cubensis* (●, $y = 62.318x - 45.658'$ $EC_{90} = 150.32$ μg mL^{-1}).

were filtrated and recrystallized from acetone/petroleum ether (30−60 °C) to afford the desired thioether **3** or **4**.

The experimental results under microwave irradiation and conventional heating were summarized in **Table 1**. The data of **3a**−**m** and **4a**−**g** are shown as follows.

3-Methoxy-2-[2-(4-oxo-4H-thiochromen-2-ylsulfanylmethyl)phenyl]acrylic Acid Methyl Ester 3a. Yield 78% (61%) [microwave irradiation (conventional heating)] mp, 139−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H, =CH−OCH_3), 3.85 (s, 3H, $COOCH_3$), 4.41 (s, 2H, -CH_2-), 6.93 (s, 1H, 3-HetCH), 7.16 (d, J = 4.4 Hz, 1H, 3-ArH), 7.26 (t, J = 4.4 Hz, 2H, 4,5-ArH), 7.46−7.55 (m, 3H, 6-ArH, 6′,7′-ArH), 7.56 (d, J = 8.4 Hz, 1H, 8′-ArH), 7.62 (s, 1H, CH-OCH_3), 8.45 (d, J = 8.4 Hz, 1H, 5′-ArH). EI MS: m/z (%) 398 (M^+, 7), 366 (20), 352 (6), 231 (7), 192 (8), 163 (40), 159 (100), 134 (45). Anal. Calcd for $C_{21}H_{18}O_4S_2$: C, 63.29; H, 4.55; Found: C, 63.06; H, 4.70.

2-[2-(4,6-Dimethyl-pyrimidin-2-ylsulfanylmethyl)-phenyl]-3-methoxyacrylic Acid Methyl Ester 3b. Yield 81% (72%) mp, 109−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 6H, 2×$HetCH_3$), 3.71 (s, 3H, =CH−OCH_3), 3.86 (s, 3H, $COOCH_3$), 4.41 (s, 2H, -CH_2-), 6.72 (s, 1H, 6-HetCH), 7.12 (d, J = 5.6. Hz, 1H, 3-ArH), 7.26 (t, J = 5.6 Hz, 2H, 4,5-ArH), 7.56 (d, J = 5.6. Hz, 1H, 6-ArH), 7.59 (s, 1H, CH-OCH_3). EI MS: m/z (%) 344 (M^+, 4), 312 (12), 252 (39), 209 (100), 145 (22), 115 (40). Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13; Found: C, 62.58; H, 5.99; N, 8.01.

2-[2-(5-Amino-(1,3,4)thiadiazol-2-ylsulfanylmethyl)phenyl]-3-methoxyacrylic Acid Methyl Ester 3c. Yield 75% (67%) mp, 144−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 3H, =CH−OCH_3), 3.86 (s, 3H, $COOCH_3$), 4.27 (s, 2H, -CH_2-), 5.45 (broad, 2H, $HetNH_2$), 7.13 (d, J = 6.0 Hz, 1H, 3-ArH), 7.29 (m, 2H, 4,5-ArH), 7.42 (d, J = 5.6. Hz, 1H, 6-ArH), 7.58 (s, 1H, CH-OCH_3). EI MS: m/z (%) 337 (M^+, 6), 305 (32), 260 (79), 205 (81), 173 (30), 145 (100), 115 (84). Anal. Calcd for $C_{14}H_{15}N_3O_3S_2$: C, 49.83; H, 4.48; N, 12.45; Found: C, 49.68; H, 4.52; N, 12.26.

2-[2-(4-Amino-5-phenyl-4H-[1,2,4]triazol-3-ylsulfanylmethyl)phenyl]-3-methoxyacrylic Acid Methyl Ester 3d. Yield 78% (70%) mp, 98−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (s, 3H, =CH−OCH_3), 3.88 (s, 3H, $COOCH_3$), 4.08 (broad, 2H, $HetNH_2$), 4.49 (s, 2H, -CH_2-), 6.85 (d, J = 7.6 Hz, 1H, 3-ArH), 7.10 (t, J = 6.4 Hz, 1H, 4′-ArH), 7.30−7.40 (m, 4H, 4,5-ArH, 3′,5′-ArH), 7.62 (d, J = 5.6 Hz, 2H, 2′,6′-ArH), 7.92 (d, J = 7.6 Hz, 1H, 5-ArH), 8.04 (s, 1H, CH-OCH_3). EI MS: m/z (%) 396 (M^+, 8), 339 (19), 293 (11), 225 (19), 205 (20), 145 (100), 103 (36) Anal. Calcd for $C_{20}H_{20}N_4O_3S$: C, 60.59; H, 5.08; N, 14.13; Found: C, 60.33; H, 5.19; N, 14.01.

2-[2-(1H-Benzoimidazol-2-ylsulfanylmethyl)-phenyl]-3-methoxyacrylic Acid Methyl Ester 3e. Yield 87% (78%) mp, 151−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H, =CH−OCH_3), 3.83 (s, 3H, $COOCH_3$), 4.28 (s, 2H, -CH_2-), 7.09−7.18 (m, 4H, 3,6-ArH, 5′,6′-ArH), 7.21−7.29 (m, 2H, 4,5-ArH), 7.46−7.48 (broad, 2H, 4′,7′-ArH), 7.60 (s, 1H, CH-OCH_3). EI MS: m/z (%) 354 (M^+, 95), 321 (21), 277 (43), 219 (60), 145 (100), 103 (10). Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90; Found: C, 64.25; H, 5.40; N, 7.74.

2-[2-(Benzooxazol-2-ylsulfanylmethyl)-phenyl]-3-methoxyacrylic Acid Methyl Ester 3f. Yield 85% (75%) mp, 47−49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H, =CH−OCH_3), 3.84 (s, 3H, $COOCH_3$), 4.41 (s, 2H, -CH_2-), 7.10−7.17 (m, 2H, 3-ArH, 4′-ArH), 7.26−7.32 (m, 4H, 4,5-ArH, 5′,6′-ArH), 7.40−7.48 (m, 2H, 6-ArH, 7′-ArH), 7.60 (s, 1H, CH-OCH_3). EI MS: m/z (%) 355 (M^+, 9), 321 (31), 240 (27), 208 (100), 145 (47), 128 (87), 103 (13). Anal. Calcd for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94; Found: C, 64.05; H, 4.97; N, 3.78.

2-[2-(Benzothiazol-2-ylsulfanylmethyl)-phenyl]-3-methoxyacrylic Acid Methyl Ester 3g. Yield 80% (64%) mp, 59−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H, =CH−OCH_3), 3.85 (s, 3H, $COOCH_3$), 4.55 (s, 2H, -CH_2-), 7.16 (d, J = 4.4 Hz, 1H, 3-ArH), 7.16 (t, J = 4.4 Hz, 1H, 4-ArH), 7.27−7.31 (m, 3H, 3,6-ArH, 6′-ArH), 7.41 (t, J = 8.0 Hz, 1H, 5′-ArH), 7.56 (t, J = 4.4 Hz, 1H, 5-ArH), 7.60 (s, 1H, CH−OCH_3), 7.73 (d, J = 8.0 Hz, 1H, 4′-ArH), 7.88 (d, J = 8.0 Hz, 1H, 7′-ArH). EI MS: m/z (%) 371 (M^+, 4), 339 (13), 294 (28), 235 (70), 205 (7), 165 (12), 144 (100), 101 (24). Anal. Calcd for $C_{19}H_{17}NO_3S_2$: C, 61.43; H, 4.61; N, 3.77; Found: C, 61.25; H, 4.80; N, 3.64.

3-Methoxy-2-[2-(3-methyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylsulfanylmethyl)-phenyl]acrylic Acid Methyl Ester 3h. Yield 85% (72%) mp, 128−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (s, 3H, $HetCH_3$), 3.68 (s, 3H, =CH−OCH_3), 3.85 (s, 3H, $COOCH_3$), 4.42 (s, 2H, -CH_2-), 7.17 (d, J = 6.4. Hz, 1H, 3-ArH), 7.33 (t, J = 6.4 Hz, 2H, 4,5-ArH), 7.49 (d, J = 5.6. Hz, 1H, 6-ArH), 7.62 (s, 1H, CH−OCH_3). EI MS: m/z (%) 376 (M^+, 11), 345 (15), 261 (28), 237 (46), 205 (26), 171 (36), 144 (100), 128 (32). Anal. Calcd for $C_{16}H_{16}N_4O_3S_2$: C, 51.05; H, 4.28; N, 14.88; Found: C, 50.91; H, 4.50; N, 14.77.

2-[2-(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylsulfanylmethyl)phenyl]-3-methoxyacrylic Acid Methyl Ester 3i. Yield 90% (78%) mp, 132−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, 5-$HetCH_3$), 2.72 (s, 3H, 7-$HetCH_3$), 3.71 (s, 3H, =CH−OCH_3), 3.86 (s, 3H, $COOCH_3$), 4.48 (s, 2H, -CH_2-), 6.71 (s, 1H, HetCH), 7.14 (d, J = 5.6 Hz, 1H, 3-ArH), 7.28 (m, 2H, 4,5-ArH), 7.60 (s, 1H, CH−OCH_3), 7.63 (d, J = 5.6. Hz, 1H, 6-ArH). EI MS: m/z (%) 384 (M^+, 8), 352 (38), 319 (19), 248 (100), 203 (12), 179 (25), 144 (42), 101 (17). Anal. Calcd for $C_{19}H_{20}N_4O_3S$: C, 59.36; H, 5.24; N, 14.57 Found: C, 59.16; H, 5.40; N, 14.35.

2-{2-[5-(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylsulfanylmethyl)-[1,3,4]-oxadiazol-2-ylsulfanylmethyl]phenyl}-3-methoxyacrylic Acid Methyl Ester 3j. Yield 87% (75%) mp, 145−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, 5-$HetCH_3$), 2.72 (s, 3H, 7-$HetCH_3$), 3.69 (s, 3H, =CH−OCH_3), 3.84 (s, 3H, $COOCH_3$), 4.36 (s, 2H, -CH_2-), 4.70 (s, 2H, -Het-CH_2-), 6.76 (s, 1H, 6-HetCH), 7.13 (d, J = 6.4. Hz, 1H, 3-ArH), 7.28 (t, J = 6.4 Hz, 2H, 4,5-ArH), 7.48 (d, J = 5.6. Hz, 1H, 6-ArH), 7.58 (s, 1H, HetCH), 7.63 (s, 1H, CH−OCH_3). EI MS: m/z (%) 498 (M^+, 7), 305 (12), 252 (80), 242 (20),

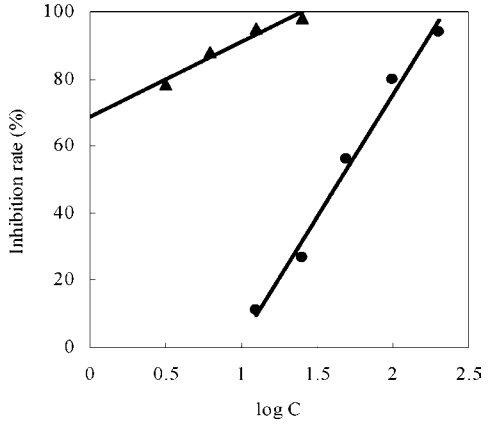


Figure 3. Preventive activities of Kresoxim-methyl against cucumber *S. fuliginea* (▲, $y = 22.18x + 70.85$, $EC_{90} = 7.30$ μg mL^{-1}) and *P. cubensis* (●, $y = 72.64x - 69.08$, $EC_{90} = 154.92$ μg mL^{-1}).

208 (73), 180 (57), 147 (100), 116 (53). Anal. Calcd for $C_{22}H_{22}N_6O_4S_2$: C, 53.00; H, 4.45; N, 16.86; Found: C, 52.81; H, 4.67; N, 16.71.

2-{2-[5-(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylsulfanylmethyl)-[1,3,4]-thiadiazol-2-ylsulfanylmethyl]phenyl}-3-methoxyacrylic Acid Methyl Ester 3k. Yield 83% (72%) mp, 155−157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H, 5-HetCH$_3$), 2.73 (s, 3H, 7-HetCH$_3$), 3.66 (s, 3H, =CH−OCH$_3$), 3.83 (s, 3H, COOCH$_3$), 4.40 (s, 2H, -CH$_2$-), 4.84 (s, 2H, -Het-CH$_2$-), 6.78 (s, 1H, 6-Het-CH), 7.13 (d, $J = 4.8$. Hz, 1H, 3-ArH), 7.25 (t, $J = 4.8$ Hz, 1H, 5-ArH), 7.31 (t, $J = 4.8$ Hz, 1H, 4-ArH), 7.46 (d, $J = 4.8$ Hz, 1H, 6-ArH), 7.57 (s, 1H, HetCH), 7.64 (s, 1H, CH−OCH$_3$). EI MS: *m*/*z* (%) 514 (M$^+$, 2), 482 (2), 437 (18), 379 (7), 323 (6), 293 (12), 204 (37), 179 (28), 144 (100), 130 (35), 107 (36). Anal. Calcd for $C_{22}H_{22}N_6O_3S_3$: C, 51.34; H, 4.31; N, 16.33; Found: C, 51.18; H, 4.52; N, 16.17.

{2-[4-Amino-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylsulfanylmethyl)-4H-[1,2,4]triazol-3-ylsulfanylmethyl]phenyl}-3-methoxyacrylic Acid Methyl Ester 3l. Yield 81% (68%) mp, 144−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (s, 3H, 5-HetCH$_3$), 2.73 (s, 3H, 7-HetCH$_3$), 3.71 (s, 3H, =CH−OCH$_3$), 3.86(s, 3H, COOCH$_3$), 4.07 (s, 2H, -CH$_2$-), 4.57 (s, 2H, HetN-NH$_2$), 4.63 (s, 2H, -Het-CH$_2$-), 6.75 (s, 1H, HetCH), 6.94 (d, $J = 7.2$ Hz, 1H, 3-ArH), 7.13 (t, $J = 7.2$ Hz, 1H, 5-ArH), 7.33 (t, $J = 7.2$ Hz, 1H, 4-ArH), 7.50 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.58 (s, 1H, Het-CH), 7.62 (s, 1H, CH−OCH$_3$). EI MS: *m*/*z* (%) 512 (M$^+$, 7), 484 (17), 438 (5), 347 (13), 281 (14), 207 (100), 180 (35), 116 (96). Anal. Calcd for $C_{22}H_{24}N_8O_3S_2$: C, 51.55; H, 4.72; N, 21.86; Found: C, 51.38; H, 4.92; N, 21.72.

2-{2-[5-(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylsulfanylmethyl)-4-phenyl-4H-[1,2,4]triazol-3-ylsulfanylmethyl]phenyl}-3-methoxyacrylic Acid Methyl Ester 3m. Yield 90% (78%) mp, 184−185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (s, 3H, 5-HetCH$_3$), 2.68 (s, 3H, 7-HetCH$_3$), 3.76 (s, 3H, =CH−OCH$_3$), 3.96(s, 3H, COOCH$_3$), 4.31 (s, 2H, -CH$_2$-), 4.60 (s, 2H, -Het-CH$_2$-), 6.71 (s, 1H, 6-HetCH), 7.10 (d, $J = 6.4$ Hz, 1H, 3-ArH), 7.20 (d, $J = 8.0$ Hz, 2H, 2′,6′-ArH), 7.31−7.35 (m, 5H, 4,5-ArH, 3′,4′,5′-ArH), 7.49 (d, $J = 6.4$ Hz, 1H, 6-ArH), 7.58 (s, 1H, HetCH), 7.62 (s, 1H, CH−OCH$_3$). EI MS: *m*/*z* (%) 573 (M$^+$, 11), 484 (7), 383 (8), 295 (38), 237 (6), 180 (64), 148 (100), 115 (42), 107 (25). Anal. Calcd for $C_{28}H_{27}N_7O_3S_2$: C, 58.62; H, 4.74; N, 17.09; Found: C, 58.41; H, 4.99; N, 16.94.

Methoxyimino-[2-(4-oxo-4H-thiochromen-2-ylsulfanyl-methyl)-phenyl]acetic Acid Methyl Ester 4a. Yield 80% (64%) mp, 128−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3H, N-OCH$_3$), 4.08 (s, 3H, COOCH$_3$), 4.17 (s, 2H, -CH$_2$-), 6.95 (s, 1H, 3′-HetCH), 7.17 (d, $J = 4.4$ Hz, 1H, 3-ArH), 7.39 (t, $J = 4.4$ Hz, 2H, 4,5-ArH), 7.47−7.54 (m, 3H, 6-ArH, 6′,7′-ArH), 7.57 (d, $J = 8.0$ Hz, 1H, 8′-ArH), 8.45 (d, $J = 8.0$ Hz, 1H, 5′-ArH). EI MS: *m*/*z* (%) 400 (M$^+$, 4), 368 (15), 353 (10), 194 (4), 164 (50), 136 (26), 115 (100), 88 (53). Anal. Calcd for $C_{20}H_{17}NO_4S_2$: C, 60.13; H, 4.29; N, 3.51; Found: C, 59.94; H, 4.40; N, 3.37.

Table 2. In Vitro Fungicidal Activities of Compounds **3a**–**m** and **4a**–**g**

	inhibition rate (%, 50 μg mL^{-1})					
compound	*F. oxysporium*	*R. solani*	*B. cinereapers*	*G. zeae*	*D. gregaria*	*C. gossypii*
3a	48 ± 2	64 ± 2	18 ± 5	53 ± 3	14 ± 4	52 ± 3
3b	79 ± 1	83 ± 2	52 ± 3	74 ± 2	91 ± 2	52 ± 3
3c	65 ± 2	61 ± 3	11 ± 5	40 ± 3	55 ± 3	39 ± 4
3d	76 ± 1	84 ± 1	41 ± 3	69 ± 2	76 ± 2	64 ± 2
3e	45 ± 3	78 ± 2	47 ± 3	53 ± 3	87 ± 2	52 ± 3
3f	69 ± 2	78 ± 2	47 ± 3	81 ± 2	46 ± 4	83 ± 2
3g	69 ± 2	87 ± 1	47 ± 4	74 ± 1	94 ± 1	86 ± 2
3h	59 ± 2	83 ± 1	41 ± 3	53 ± 3	82 ± 2	50 ± 3
3i	61 ± 2	66 ± 3	7 ± 5	47 ± 3	78 ± 2	39 ± 4
3j	36 ± 4	73 ± 2	36 ± 4	36 ± 4	73 ± 3	39 ± 4
3k	61 ± 2	58 ± 4	14 ± 3	44 ± 3	69 ± 3	39 ± 3
3l	44 ± 3	73 ± 2	14 ± 4	43 ± 3	78 ± 2	35 ± 3
3m	40 ± 3	37 ± 5	7 ± 5	36 ± 3	11 ± 5	17 ± 4
4a	44 ± 3	73 ± 2	23 ± 3	61 ± 2	19 ± 4	48 ± 3
4b	76 ± 1	73 ± 3	27 ± 3	61 ± 2	82 ± 2	59 ± 2
4c	72 ± 2	90 ± 1	77 ± 2	69 ± 2	87 ± 2	82 ± 2
4d	74 ± 2	82 ± 2	52 ± 3	81 ± 1	84 ± 2	75 ± 2
4e	50 ± 3	69 ± 3	14 ± 4	50 ± 2	78 ± 3	35 ± 4
4f	63 ± 3	88 ± 1	77 ± 2	41 ± 3	70 ± 3	36 ± 4
4g	54 ± 2	78 ± 3	64 ± 2	45 ± 2	58 ± 3	32 ± 5
Kresoxim-methyl	61 ± 2	70 ± 3	50 ± 3	53 ± 3	82 ± 2	50 ± 4
Triadimefon	86 ± 1	90 ± 1	84 ± 2	72 ± 2	61 ± 3	95 ± 2

[2-(4,6-Dimethyl-pyrimidin-2-ylsulfanylmethyl)phenyl]methoxyiminoacetic Acid Methyl Ester 4b. Yield 78% (70%) mp, 127−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 6H, 2×HetCH$_3$), 3.88 (s, 3H, N-OCH$_3$), 4.08 (s, 3H, COOCH$_3$), 4.32 (s, 2H, -CH$_2$-), 6.69 (s, 1H, HetCH), 7.12 (d, $J = 7.6$ Hz, 1H, 3-ArH), 7.28−7.35 (m, 4H, 4,5-ArH), 7.60 (d, $J = 7.6$ Hz, 1H, 6-ArH). EI MS: *m*/*z* (%) 345 (M$^+$, 11), 313 (100), 280 (67), 253 (55), 204 (28), 145 (18). Anal. Calcd for $C_{17}H_{19}N_3O_3S$: C, 59.11; H, 5.54; N, 12.17; Found: C, 58.971; H, 5.68; N, 12.01.

[2-(1H-Benzoimidazol-2-ylsulfanylmethyl)phenyl]methoxyiminoacetic Acid Methyl Ester 4c. Yield 87% (76%) mp, 101−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H, N-OCH$_3$), 4.08 (s, 3H, COOCH$_3$), 4.28 (s, 2H, -CH$_2$-), 5.37 (s, 1H, Het-NH), 7.13−7.15 (m, 2H, 3,5-ArH), 7.22−7.30 (m, 4H, 4,6-ArH, 5′,6′-ArH), 7.46−7.48 (m, 2H, 4′,7′-ArH). EI MS: *m*/*z* (%)355 (M$^+$, 21), 320 (17), 276 (53), 217 (22), 145 (100), 115 (42). Anal. Calcd for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.82; Found: C, 60.74; H, 4.98; N, 11.70.

[2-(Benzothiazol-2-ylsulfanylmethyl)phenyl]methoxyiminoacetic Acid Methyl Ester 4d. Yield 80% (64%) mp, 67−69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3H, N-OCH$_3$), 4.09 (s, 3H, COOCH$_3$), 4.53 (s, 2H, -CH$_2$-), 7.16 (d, $J = 6.4$. Hz, 1H, 3-ArH), 7.32−7.39 (m, 3H, 4,5-ArH, 6′-ArH), 7.44 (t, $J = 8.0$ Hz, 1H, 5′-ArH), 7.61 (d, $J = 6.4$ Hz, 1H, 6-ArH), 7.75 (d, $J = 8.0$ Hz, 1H, 4′-ArH), 7.93 (d, $J = 8.0$ Hz, 1H, 7′-ArH). EI MS: *m*/*z* (%) 372 (M$^+$, 4), 341 (31), 327 (100), 281 (20), 248 (7), 205 (14), 166 (11), 114 (11). Anal. Calcd for $C_{18}H_{16}N_2O_3S_2$: C, 58.04; H, 4.33; N, 7.52; Found: C, 57.90; H, 4.56; N, 7.36.

[2-(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylsulfanylmethyl)phenyl]methoxyiminoacetic Acid Methyl Ester 4e. Yield 87% (75%) mp, 150−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H, 5-HetCH$_3$), 2.73 (s, 3H, 7-HetCH$_3$), 3.90 (s, 3H, N-OCH$_3$), 4.09 (s, 3H, COOCH$_3$), 4.43 (s, 2H, -CH$_2$-), 6.75 (s, 1H, HetCH), 7.15 (d, $J = 6.8$. Hz, 1H, 3-ArH), 7.35 (t, $J = 8.0$ Hz, 2H, 4,5-ArH), 7.68 (d, $J = 6.8$. Hz, 1H, 6-ArH). EI MS: *m*/*z* (%) 385 (M$^+$, 4), 354 (100), 323 (31), 293 (9), 178 (30), 145 (32), 115 (59), 88 (23). Anal. Calcd for $C_{18}H_{19}N_5O_3S$: C, 56.09; H, 4.97; N, 18.17; Found: C, 55.92; H, 5.10; N, 18.02.

{2-[5-(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylsulfanylmethyl)-[1,3,4]-oxadiazol-2-ylsulfanylmethyl]phenyl}-methoxyiminoacetic Acid Methyl Ester 4f. Yield 85% (72%) mp, 146−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H, 5-HetCH$_3$), 2.73 (s, 3H, 7-HetCH$_3$), 3.88 (s, 3H, N-OCH$_3$), 4.06 (s, 3H, COOCH$_3$), 4.30 (s, 2H, -CH$_2$-), 4.71 (s, 2H, Het-CH$_2$-), 6.78 (s, 1H, HetCH), 7.13 (d, $J =$

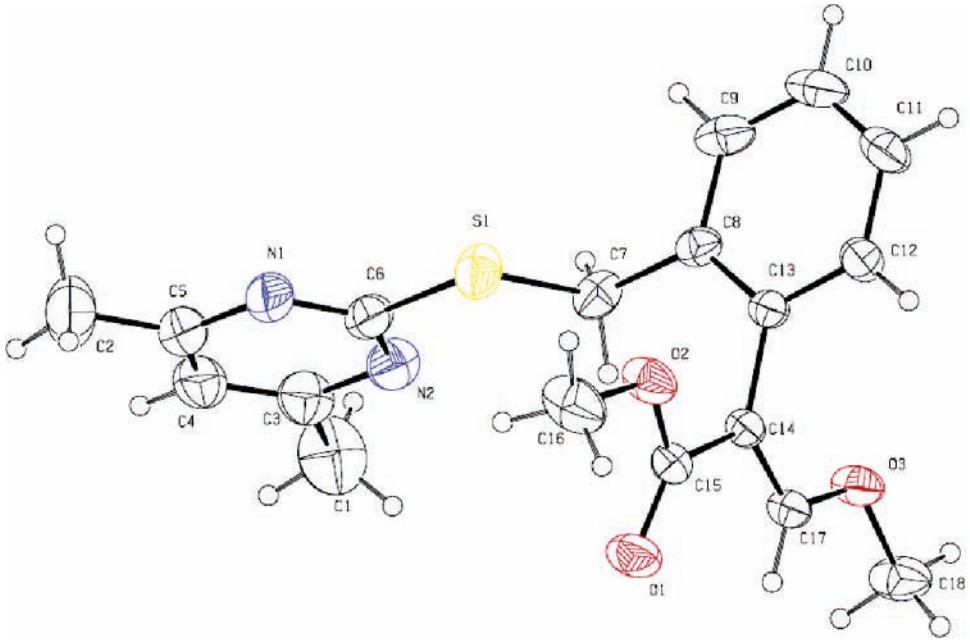


Figure 4. Molecular structure of **3b**.

7.2 Hz, 1H, 3-ArH), 7.36 (t, J = 7.2 Hz, 2H, 4,5-ArH), 7.55 (d, J = 7.2. Hz, 1H, 6-ArH). EI MS: m/z (%) 499 (M^+, 10), 294 (14), 261 (100), 242 (20), 205 (22), 180 (57), 148 (21), 116 (53), 107 (54). Anal. Calcd for $C_{21}H_{21}N_7O_4S_2$: C, 50.49; H, 4.24; N, 19.63; Found: C, 50.28; H, 4.40; N, 19.49.

{2-[5-(5,7-Dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylsulfanylmethyl)-[1,3,4]-thiadiazol-2-ylsulfanylmethyl]phenyl}-methoxyiminoacetic Acid Methyl Ester 4g. Yield 81% (70%) mp, 152−153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (s, 3H, 5-HetCH_3), 2.75 (s, 3H, 7-HetCH_3), 3.87 (s, 3H, N-OCH_3), 4.05 (s, 3H, $COOCH_3$), 4.39 (s, 2H, -CH_2-), 4.86 (s, 2H, -Het-CH_2-), 6.81 (s, 1H, HetCH), 7.13 (d, J = 7.2 Hz, 1H, 3-ArH), 7.34 (t, J = 7.2 Hz, 2H, 4,5-ArH), 7.53 (d, J = 7.2. Hz, 1H, 6-ArH). EI MS: m/z (%) 515 (M^+, 5), 484 (8), 425 (5), 324 (12), 310 (8), 237 (16), 205 (32), 115 (100), 107 (57). Anal. Calcd for $C_{21}H_{21}N_7O_3S_3$: C, 48.92; H, 4.11; N, 19.01; Found: C, 48.77; H, 4.21; N, 18.85.

X-ray Diffraction. Colorless blocks of **3b** (0.30 mm × 0.20 mm × 0.12 mm) were mounted on a quartz fiber. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å); θ_{max} = 28.00; 17450 measured reflections; 4388 independent reflections (R_{int} = 0.0576). Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.9526 and T_{max} = 0.9807). The structure was solved by direct methods using SHELXS-2001 (*20*); all other calculations were performed with Bruker SAINT system and Bruker SMART programs (*21*). Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0930P)^2 + 0.0000P]$ gave final values of R = 0.0684, ωR = 0.1528, and GOF (F) = 1.011 for 221 variables and 3123 contributing reflections. Maximum shift/error = 0.0000(3) and max/min residual electron density = 0.295/−0.196 e Å^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Biological Assay. The fungicidal activities against *F. oxysporium*, *R. solani*, *B. cinereapers*, *G. zeae*, *D. gregaria*, *B. mayclis*, and *C. gossypii* in vitro were tested according to our previously reported method (*8*). The preventive activities of compounds **3b**, **3g**, **4c**, and **4d** against cucumber *S. fuliginea* and *P. cubensis* in vivo were tested according to the following procedure (*22*): cucumber plants were grown under greenhouse conditions (T = 20 ± 5 °C, RH = 90 ± 10%) in plastic planting pots (6 cm diameter × 10 cm). The tested compounds dissolved in acetone/distilled water (1:4 v/v) containing Tween 80 (0.4 μg mL^{-1}) at the given concentration were sprayed over the plant. One day later, the cucumber plants were inoculated by a spore suspension of *S. fuliginea* (1.0 × 10^5 spores mL^{-1}) or *P. cubensi* (3 × 10^5 spores mL^{-1}). One week later, the symptoms were examined. Three replicates were done for each concentration. The inhibition percentage was expressed as the mean of values obtained in three independent experiments. From a concentration−preventive ranking ralationship as exemplified in **Figures 1**−**3** for compounds **3g**, **4d**, and Kresoxim-methyl, the concentration to give 90% preventive effect was defined as EC_{90}. The results are summarized in **Table 2**.

RESULTS AND DISCUSSION

Chemistry. Microwave-assisted organic synthesis (MAOS) has been developed as a powerful tool for medicinal and pesticide chemistry due to its higher synthetic efficiency (*23*, *24*). Our recent success in application of microwave irradiation (*25*−*28*) prompted us to synthesize the title compounds under microwave irradiation. The synthetic route of the target compounds **3a**−**m** and **4a**−**g** and the reaction results under microwave irradiation and conventional heating are listed in Table **1**, and the optimized conditions for microwave irradiation were an adjustable microwave power range from 90 to 150 W with a reaction temperature of 90 °C. We can conclude from **Table 1** that microwave-assisted irradiation resulted in an improvement in yields from 8 to 17% and that the reaction times were reduced greatly from 2 to 4 h to 6−10 min. It thus turned out that this microwave-assisted synthetic method was an efficient protocol for synthesizing novel strobilurin thioether derivatives.

The structures of all the target compounds were characterized by elemental analyses and ^{1}H NMR and EI-MS spectra. In addition, the crystal structure of **3b** was determined by X-ray diffraction analyses. As shown in **Figure 4**, the plane of pyrimidine and the benzene are nearly orthogonal with a dihedral angel of 83.09°.

Fungicidal Activity and Structure−Activity Relationship. In Vitro Test. To make a judgment on the fungicidal potency of the synthesized compounds, two commercial fungicides, Kresoxim-methyl and Triadimefon, were used as controls. The fungicidal results of all the compounds against *F. oxysporium*, *R. solani*, *B. cinereapers*, *G. zeae*, *D. gregaria*, *B. mayclis*, and *C. gossypii* are listed in **Table 2**. As shown in **Table 2**, Kresoxim-methyl did not exhibit significant fungitoxicity against *F. oxysporium*, *R. solani*, *B. cinereapers*, *G. zeae*, *B. mayclis*, and *C. gossypii* at a concentration of 50 μg mL^{-1}, although it

Table 3. Preventive Fungicidal Activities in Vivo ±%) of Compounds **3b**, **3g**, **4c**, and **4d**

pathogen	*S. fuliginea*				*P. cubensis*			
concentration (μg mL^{-1})	**100**	**50**	**25**	**EC_{90}**	**100**	**50**	**25**	**EC_{90}**
3b	70	40			0			
3g	100	100	100	6.17	100	94	62	46.32
4c	0				0			
4d	100	100	97	9.60	84	66	39	150.32
Kresoxim-methyl	100	100	98	7.30	80	56	27	154.92

exhibited an 82% inhibition effect against the mycelial elongation of *D. gregaria*. However, Triadimefon showed an 86, 90, 84, and 95% inhibition effect against the mycelial elongation of *F. oxysporium*, *R. solani*, *B. cinereapers*, and *C. gossypii*, respectively. As compared with Triadimefon, all the compounds exhibited lower activities against *F. oxysporium*, *R. solani*, *B. cinereapers*, and *C. gossypii*. However, compounds **3b** (pyrimidine as side chain), **3f** (benzoxoazole as side chain), **3g** (benzothiazole as side chain), and **4d** (benzothiazole as side chain) exhibited higher fungicidal activity against *G. zeae* than Triadimefon, and most of the compounds, except **3a**, **3c**, **3f**, **3m**, **4a**, and **4g**, exhibited higher activities against *D. gregaria* than Triadimefon. Additionaly, **Table 2** also shows that compounds **3b**, **3g**, **4c** (benzimidazole as side chain), and **4d** exhibited higher activities against all the tested fungi than Kresoxim-methyl. On the basis of the previous results, those derivatives bearing pyrimidine (**3b** and **4b**), benzimidazole (**4c**), and benzothiazole (**3g** and **4d**) as side chains showed promising fungicidal activities, and triazole (**3d**), benzoxoazole (**3f**), and triazole-thidiazole (**3h**) as side chains also exhibited good fungicidal activities in some cases. However, triazole-pyrimidine (**3i**−**3m** and **4e**−**4g**) and other related heterocyclic side chains always resulted in lower or no fungicidal activities.

In Vivo Test. From the results of the in vitro test, we can identify compounds **3b**, **3g**, **4c**, and **4d** as the most promising candidates for further study, and their in vivo fungicidal activities against *S. fuliginea* and *P. cubensis* are summarized in **Table 3**, which also showed the results of Kresoxim-methyl. As shown in **Table 3**, compounds **3g** and **4d** exhibited 100% and 62, 97, and 39% preventive effects against *S. fuliginea* and *P. cubensis* at a concentration of 25 μg mL^{-1}, respectively. However, at the same concentration, the controlled Kresoxim-methyl exhibited a 98 and 27% preventive effect against *S. fuliginea* and *P. cubensis*, respectively. The further determination of EC_{90} values indicated that the EC_{90} values of compounds **3g**, **4d**, and Kresoxim-methyl for *S. fuliginea* are 6.17, 9.60, and 7.30 μg mL^{-1}, respectively, and that the EC_{90} values of **3g**, **4d**, and Kresoxim-methyl for *P. cubensis* are 46.32, 150.32, and 154.92 μg mL^{-1}, respectively. These results indicated that compound **3g** is more active than Kresoxim-methyl against *S. fuliginea* and *P. cubensis* and that compound **4d** exhibited little higher activity against *P. cubensis* and little lower activity against *S. fuliginea* than Kresoxim-methyl. On the basis of these results, it can be concluded that benzothiazole should be identified as the best side chain among all of the screened heterocycles.

Conclusion. In summary, a series of new strobilurin derivatives bearing structurally diverse heterocycle side chains **3a**−**m** and **4a**−**g** were designed and synthesized via a microwave-assisted procedure. The in vitro and in vivo tests indicated that compounds **3g** and **4d** exhibited excellent preventive effects against cucumber *S. fuliginea* and *P. cubensis* and that the activities of compound **3g** against cucumber *S. fuliginea* and *P. cubensis* are much higher than that of Kresoxim-methyl, while a very similar fungicidal activity level of compound **4d** and Kresoxim-methyl against cucumber *S. fuliginea* and *P. cubensis* was observed. Therefore, the present work demonstrates that benzothiazole could be identified as the best side chain among all of the screened heterocycles. Further field trial and structural modifications of compounds **3g** and **4d** are underway.

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