

Synthesis and Fungicidal Evaluation of Novel Chalcone-Based Strobilurin Analogues

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Strobilurin derivatives have become one of the most important classes of agricultural fungicide due to a novel action mode, wide fungicidal spectrum, lower toxicity toward mammalian cells, and environmentally benign characteristics. To discover new strobilurin analogues with high activity against resistant pathogens, a series of new chalcone-based strobilurin derivatives are designed and synthesized by integrating a chalcone scaffold with a strobilurin pharmacophore. The preliminary bioassay showed that some of the chalcone analogues exhibited good *in vivo* fungicidal activities against *Pseudoperonospora cubensis* and *Sphaerotheca fuliginea* at the dosage of 200 $\mu\text{g mL}^{-1}$. Two compounds, (*E*)-methyl 2-[2-({3-[(*E*)-3-(2-chlorophenyl)acryloyl]phenoxy}methyl)phenyl]-3-methoxyacrylate (**1e**) and (*E*)-methyl 2-[2-({3-[(*E*)-3-(3-bromophenyl)acryloyl]phenoxy}methyl)phenyl]-3-methoxyacrylate (**1l**), were found to display higher fungicidal activities against *P. cubensis* ($\text{EC}_{90} = 118.52 \mu\text{g mL}^{-1}$ for **1e** and $\text{EC}_{90} = 113.64 \mu\text{g mL}^{-1}$ for **1l**) than Kresoxim-methyl ($\text{EC}_{90} = 154.92 \mu\text{g mL}^{-1}$) and were identified as the most promising candidates for further study. The present work demonstrated that strobilurin analogues containing chalcone as a side chain could be used as a lead structure for further developing novel fungicides. To our knowledge, this is the first report about the syntheses and fungicidal activities of chalcone-based strobilurin derivatives.

KEYWORDS: Strobilurins; fungicide; chalcone; structure–activity relationships

INTRODUCTION

Strobilurins, an important family of antifungal antibiotics, have been identified as one of the most promising lead compounds for the development of a new generation of industrial fungicides for crop protection (1–6). Since the first successful landing of Azoxystrobin and Kresoxim-methyl (**Figure 1**) in 1996 (2), over 10 strobilurin derivatives are commercially available. The advantages such as a novel mode of action, wide spectrum, low toxicity toward mammalian cells, and favorable profiles to humans (4–6) prompted chemists to design and synthesize novel strobilurin derivatives (7–10).

As an intermediate in the biosynthetic pathway of flavonoids, isoflavonoids, and aurone, chalcones have been shown to display a diverse array of pharmacological activities, among which are antifungal, antibacterial, antiprotozoal, anti-inflammatory, antitumor, antimalarial, and anti-HIV activities (11–15). However, to the best of our knowledge, there is, to date, no report about chalcone-based strobilurins analogues.

It has been demonstrated that the β -methoxyacrylate group is the essential pharmacophore of strobilurin fungicides. Linking

the β -methoxyacrylate group with a structurally diverse side chain is an effective way to obtain new strobilurin derivatives with high fungicidal activities (7, 10). We assume that, if the β -methoxyacrylate pharmacophore was introduced into the chalcone scaffold, the resulting (*E*)-methyl 3-methoxy-2-[2-({3-[(*E*)-3-substitutedphenylacryloyl]phenoxy}methyl)phenyl]acrylate (**1**) should be an interesting lead structure for fungicide development (**Figure 2**), which will be expected to exhibit interesting features due to the coexistence of two kinds of fungicidal pharmacophores with different action mechanisms. Then, as a continuation of our research program of the discovery of novel lead compounds (10), we described herein the synthesis and fungicidal activity of a series of new chalcone-containing strobilurin analogues (**1**). Meanwhile, as a control, we also synthesized a series of chalcone analogues (*E*)-methyl 3-methoxy-2-[2-({2-[(*E*)-3-substitutedphenylacryloyl]phenoxy}methyl)phenyl]acrylate (**2**) and (*E*)-methyl 3-methoxy-2-[2-({4-[(*E*)-3-substituted-phenylacryloyl]phenoxy}methyl)phenyl]acrylate (**3**).

MATERIALS AND METHODS

Unless otherwise noted, all materials were commercially available and were used directly without further purification. All solvents were redistilled before use. ¹H NMR spectra were recorded on a Mercury-

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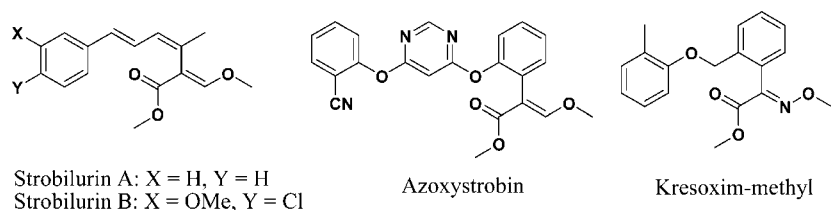


Figure 1. Structures of strobilurins, azoxystrobin, and Kresoxim-methyl.

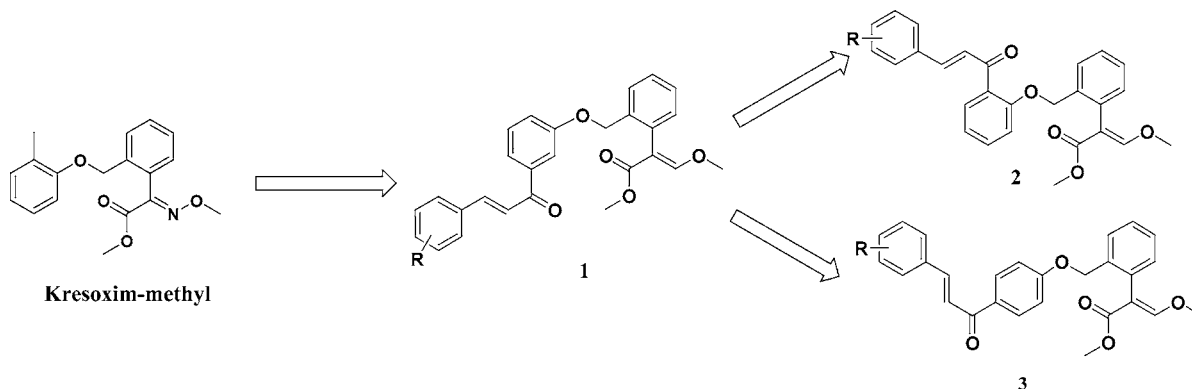


Figure 2. Design strategy of the target compounds.

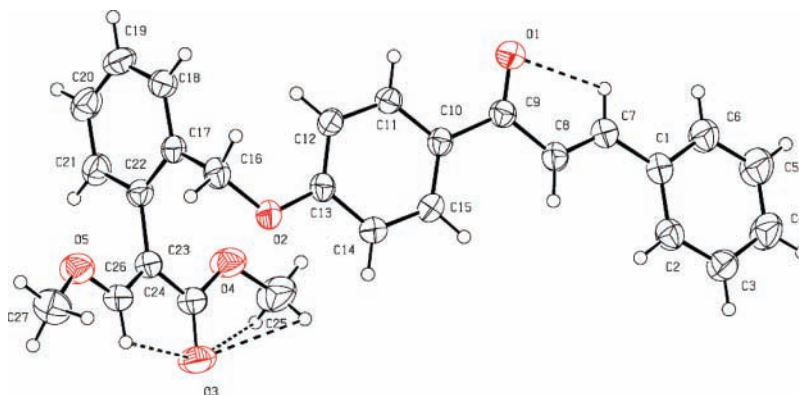


Figure 3. Molecular structure of **3s**.

Plus 400 spectrometer in CDCl_3 with tetramethylsilane as the internal reference. MS spectra were determined using a Trace MS 2000 organic mass spectrometry. Elementary analyses were performed on a Vario EL III elementary analysis instrument. Melting points were taken on a Buchi B-545 melting point apparatus and uncorrected. Intermediates **4** and **5** were prepared according to the reported methods (15, 16), and the detailed procedure can be found in the Supporting Information.

General Procedure for the Synthesis of Target Compounds 1, 2, or 3. A mixture of 1.1 mmol of chalcones (**8**) and 0.16 g (1.2 mmol) of anhydrous K_2CO_3 in dry acetone (8 mL) was stirred and refluxed for 1 h. Then, 0.28 g (1.0 mmol) of (*E*)-methyl 2-[2-(bromomethyl)phenyl]-3-methoxyacrylate (**7**) was added. The mixture was reacted for 9–24 h at the refluxing temperature. The resulting mixture was cooled to room temperature and filtered. The solvent was evaporated to give the crude product, which was purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (8:1) as an eluant to give the target compounds in yields of 51–84%. The example data of **1a** are shown as follows, while data for **1b–y**, **2a–n**, and **3a–v** can be found in the Supporting Information.

Data for 1a. Yield, 71%; mp, 101–103 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ : 2.32 (s, 3H, ArCH_3), 3.70 (s, 3H, COOCH_3), 3.81 (s, 3H, OCH_3), 5.04 (s, 2H, CH_2), 7.14–7.23 (m, 2H, ArH), 7.33–7.44 (m, 6H, ArH), 7.51–7.59 (m, 6H, ArH , $=\text{CH}-\text{CO}$, $=\text{CH}-\text{OCH}_3$), 7.78 (d, $J = 15.6$ Hz, 1H, $=\text{CH}-\text{Ar}$). MS m/z (%): 443 ($\text{M}^+ + 1$, 24), 442 (M^+ , 23), 236 (96), 222 (100), 209 (47), 203 (93), 194 (72), 177 (94), 141 (89), 114 (98), 101 (95). Anal. calcd for $\text{C}_{28}\text{H}_{26}\text{O}_5$: C, 76.00; H, 5.92. Found: C, 76.23; H, 5.75.

X-ray Diffraction. Colorless blocks of **3s** (0.30 mm \times 0.20 mm \times 0.20 mm) were counted on a quartz fiber with protection oil. Cell dimensions and intensities were measured at 299 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073$ Å), $\theta_{\text{max}} = 26.00$, 22804 measured reflections, and 4363 independent reflections ($R_{\text{int}} = 0.1146$) of which 5421 had $|F_o| > 2|F_c|$. Data were corrected for Lorentz and polarization effects and for absorption ($T_{\text{min}} = 0.9741$; $T_{\text{max}} = 0.9827$). The structure was solved by direct methods using SHELXS-97 (17); all other calculations were performed with Bruker SAINT System and Bruker SMART programs (18). Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o)^2 + (0.1010P)^2 + 0.0000P]$ gave final values of $R = 0.0618$, $\omega R = 0.1614$, and $\text{GOF}(F) = 1.030$ for 301 variables and 3201 contributing reflections. The maximum shift/error = 0.000(3), and max/min residual electron density = 0.265/−0.492 $\text{e} \text{Å}^{-3}$. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Evaluation of Fungicidal Activities. The in vivo preventive activities of compounds **1b–y**, **2a–n**, and **3a–v** against cucumber *Pseudoperonospora cubensis*, *Sphaerotheca fuliginea*, *Botrytis cinerea*, and *Rhizoctonia solani* were tested according to the procedure described previously (10, 19). The results are listed in Table 1, in which the inhibition percentage was expressed as the mean of values obtained in three independent experiments. Kresoxim-methyl, a commercial fungicide, was used as a control.

Table 1. Structures and Fungicidal Activities of Compounds **1a–y**, **2a–n**, and **3a–v**

no.	R ¹	R ²	200 mg/L			
			<i>P. cubensis</i>	<i>S. fuliginea</i>	<i>B. cinerea</i>	<i>R. solani</i>
1a	4-MeC ₆ H ₄		100	97	0	0
1b	4-OMeC ₆ H ₄		95	0	0	0
1c	4-ClC ₆ H ₄		100	96	0	0
1d	3,4-Cl ₂ C ₆ H ₃		0	0	0	0
1e	2-ClC ₆ H ₄		98	94	0	0
1f	3-ClC ₆ H ₄		33	30	0	0
1g	4-FC ₆ H ₄		97	31	0	0
1h	C ₆ H ₅		96	0	0	0
1i	4-BrC ₆ H ₄		94	45	0	0
1j	3-MeC ₆ H ₄		81	0	0	0
1k	3,4-(OMe) ₂ C ₆ H ₃		72	0	0	0
1l	3-BrC ₆ H ₄		99	99	0	0
1m	3,4-(Me) ₂ C ₆ H ₄		100	92	0	0
1n	2-F-6-ClC ₆ H ₃		97	13	0	0
1o	4-N(Me) ₂ C ₆ H ₄		0	0	0	32
1p	3,4-OCH ₂ OC ₆ H ₄		0	0	0	29
1q	4-ETOC ₆ H ₄		33	0	0	0
1r	2,4-Cl ₂ C ₆ H ₄		54	0	0	30
1s	2-C ₄ H ₃ O		0	0	16	0
1t	2-C ₄ H ₃ S		0	0	24	0
1u	3-FC ₆ H ₄		0	0	10	36
1v	2-FC ₆ H ₄		0	0	0	38
1w	2-BrC ₆ H ₄		100	59	0	31
1x	4-ETC ₆ H ₄		100	78	0	0
1y	4- <i>t</i> -BuC ₆ H ₄		28	78	0	0
2a	4-MeC ₆ H ₄	4-Cl	0	0	0	0
2b	4-MeOC ₆ H ₄	4-Cl	0	0	0	0
2c	C ₆ H ₅	4-Cl	0	0	0	0
2d	3-ClC ₆ H ₄		39	0	0	0
2e	3-BrC ₆ H ₄		78	0	0	0
2f	4-ClC ₆ H ₄	4-Me	89	0	0	0
2g	2-ClC ₆ H ₄	4-Cl	0	0	0	0
2h	4-ClC ₆ H ₄	4-Cl	0	86	21	0
2i	4-BrC ₆ H ₄		0	0	0	0
2j	4-MeOC ₆ H ₄		0	0	0	0
2k	4-ClC ₆ H ₄		0	0	0	0
2l	3-MeOC ₆ H ₄		61	0	11	0
2m	3,4-(Me) ₂ C ₆ H ₃		0	0	0	0
2n	3,4-(OMe) ₂ C ₆ H ₃		0	0	0	0
3a	4-BrC ₆ H ₄		56	0	0	0
3b	3-BrC ₆ H ₄		56	0	0	0
3c	4-MeOC ₆ H ₄		62	0	0	0
3d	3-MeC ₆ H ₄		47	0	0	0
3e	4-MeC ₆ H ₄		75	0	0	38
3f	3,4-(Me) ₂ C ₆ H ₄		67	30	0	0
3g	3,4-(OMe) ₂ C ₆ H ₄		11	0	0	0
3h	3-MeOC ₆ H ₄		86	0	0	20
3i	3,4-Cl ₂ C ₆ H ₄		33	67	0	37
3j	2-ClC ₆ H ₄		100	0	0	0
3k	3,4-OCH ₂ OC ₆ H ₃		0	0	0	0
3l	4-FC ₆ H ₄		100	0	0	23
3m	4-ETOC ₆ H ₄		59	0	0	0
3n	2,4-Cl ₂ C ₆ H ₄		67	78	0	27
3o	2-C ₄ H ₃ O		0	0	0	0
3p	2-C ₄ H ₃ S		0	0	0	0
3q	3-FC ₆ H ₄		97	0	0	0
3r	2-BrC ₆ H ₄		83	67	0	21
3s	C ₆ H ₅		0	0	0	0
3t	4-ETC ₆ H ₄		15	56	0	69
3u	4- <i>t</i> -BuC ₆ H ₄		22	67	0	0
3v	2-F-6-ClC ₆ H ₃		67	0	0	0
Kresoxim-methyl (200 mg/L)			100	100		

RESULTS AND DISCUSSION

Synthetic Chemistry. The synthetic route for the target compounds is outlined in **Scheme 1**. Methyl 2-*o*-tolylacetate (**4**), which was prepared in a good yield (94%) according to the reported method (9), reacted with methyl formate in the presence of sodium hydride to give the intermediate **5**. Fortunately, compound **5** was reacted stereoselectively with

dimethyl sulfate to afford exclusively (*E*)-methyl 3-methoxy-2-*o*-tolylacrylate (**6**). Then, compound **6** was treated with *N*-bromosuccinimide in the presence of a catalytic amount of 2,2'-azobis(isobutyronitrile) to give **7** in a yield of 83%. Subsequently, compound **7** was reacted with the chalcones **8**, which were prepared by a base-catalyzed Claisen–Schmidt condensation of *o*-, *m*-, or *p*-hydroxyacetophenone with substituted benzaldehydes (15), to afford the target compounds **1a–y**, **2a–n**, or **3a–v** in yields of 51–84%.

The structures of all of the target compounds were characterized by ¹H NMR, electron impact–mass spectrometry spectra, and elemental analyses. In addition, the crystal structure of **3s** was determined by X-ray diffraction analyses. As shown in **Figure 3**, both the chalcone moiety and the β-methoxyacrylate group adopt an *E*-configuration. C₂₅, C₂₄, C₂₅, C₂₆, O₄, and O₃ are almost coplanar due to the formation of three hydrogen bonds (C₂₅–H_A···O₃, 2.57 Å; C₂₅–H_C···O₃, 2.61 Å; and C₂₆–H···O₃, 2.62 Å). Additionally, the hydrogen bond between O₁ and C₇–H makes the *E*-configuration of the chalcone moiety more stable.

Fungicidal Activity and Structure–Activity Relationship.

The *in vivo* fungicidal results of all of the compounds against *P. cubensis*, *S. fuliginea*, *B. cinerea*, and *R. solani* were listed in **Table 1**. For the convenience of structure–activity relationship analysis, compounds **1a–y**, **2a–n**, and **3a–v** were defined as *m*-chalcone derivatives, *o*-chalcone derivatives, and *p*-chalcone derivatives, respectively. Although it seems impossible to extract an obvious structure–activity relationship from the data shown in **Table 1**, we can conclude clearly that all compounds did not exhibit good fungicidal activity against *B. cinerea* and *R. solani* at the concentration of 200 μg mL⁻¹, and overall, the sequence of fungicidal activity against *P. cubensis* and *S. fuliginea* is *m*-chalcone derivatives > *p*-chalcone derivatives > *o*-chalcone derivatives. For example, *m*-chalcone derivative **1m** (R¹ = 3,4-dimethylphenyl, 100 and 92%) displayed a much higher fungicidal activity against *P. cubensis* and *S. fuliginea* than the corresponding *p*-chalcone derivative **3f** (67 and 30%), while the *o*-chalcone derivative **2m** did not show any fungicidal activity. However, compounds **1u** and **3q** are two exceptions: Compound **1u** did not exhibit fungicidal activity against *P. cubensis* and *S. fuliginea*, while compound **3q** showed excellent fungicidal activity (97%) against *P. cubensis*. Within the series of *m*-chalcone derivatives, compounds **1a** (R¹ = 4-methylphenyl), **1c** (R¹ = 4-chlorophenyl), **1e** (R¹ = 2-chlorophenyl), **1l** (R¹ = 3-bromophenyl), and **1m** (R¹ = 3,4-dimethylphenyl) displayed excellent fungicidal activity (>90%) against both *P. cubensis* and *S. fuliginea* at the concentration of 200 μg mL⁻¹, while compounds **1b** (R¹ = 4-methoxyphenyl), **1g** (R¹ = 4-fluorophenyl), **1h** (R¹ = phenyl), **1i** (R¹ = 4-bromophenyl), **1n** (R¹ = 2-fluoro-6-chlorophenyl), **1w** (R¹ = 2-bromophenyl), and **1x** (R¹ = 4-ethylphenyl) exhibited excellent fungicidal activity (>90%) against *S. fuliginea*. However, only three compounds among 22 *p*-chalcone derivatives were found to display over 90% preventive effect against *P. cubensis* at the concentration of 200 μg mL⁻¹.

In addition, as shown in **Table 1**, compounds **1a,c,e,l,m** were found to display broad spectrum fungicidal activities. Then, these five compounds were selected for further tests, and Kresoxim-methyl was used as a control to make a judgment on the fungicidal potency of these compounds. As shown in **Table 2**, the fungicidal activities against *S. fuliginea* of compounds **1a,c,e,l,m** were much lower than that of Kresoxim-methyl. Fortunately, compounds **1e** (EC₉₀ = 118.52 μg mL⁻¹, *P. cubensis*) and **1l** (EC₉₀ = 113.64 μg mL⁻¹, *P. cubensis*) were

Table 2. Preventive Fungicidal Activities in Vivo (%) of Compounds **1a,c,e,l,m**

pathogen concentration ($\mu\text{g mL}^{-1}$)	<i>S. fuliginea</i>			<i>P. cubensis</i>			
	100	50	25	EC ₉₀ ($\mu\text{g mL}^{-1}$)		EC ₉₀ ($\mu\text{g mL}^{-1}$)	
1a	47	7		52	11		
1c	4			26			
1e	22			85	77	69	118.52
1l	22	3	3	87	37	4	113.64
1m	77	14		139.47	69	44	
Kresoxim-methyl	100	100	98	7.30	80	56	154.92

found to display higher fungicidal activity against *P. cubensis* than Kresoxim-methyl (EC₉₀ = 154.92 $\mu\text{g mL}^{-1}$, *P. cubensis*). However, compound **1l** displayed a lower activity against *P. cubensis* than Kresoxim-methyl at low concentration (50 and 25 $\mu\text{g mL}^{-1}$). On the basis of these results, it can be concluded that 3-chalcone is the best side chain among 2-, 3-, and 4-chalcone.

In conclusion, we have demonstrated the molecular designs, syntheses, and fungicidal activities of a series of chalcone analogues of strobilurin derivatives. The preliminary bioassay showed that some of the chalcone analogues exhibited good in vivo fungicidal activities against *P. cubensis* and *S. fuliginea* at the dosage of 200 mg/L. Two compounds, **1e** and **1l**, were found to display higher fungicidal activities against *P. cubensis* (EC₉₀ = 118.52 $\mu\text{g mL}^{-1}$ for **1e** and EC₉₀ = 113.64 $\mu\text{g mL}^{-1}$ for **1l**) than Kresoxim-methyl (EC₉₀ = 154.92 $\mu\text{g mL}^{-1}$) and were identified as the most promising candidate for further study. To our knowledge, this is the first report about the syntheses and fungicidal activities of chalcone-based strobilurin derivatives. Further structural optimization and fungicidal activities about the chalcone analogues are well under way.

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Supporting Information Available: ¹H NMR, MS, melting point, and element analysis data for the intermediates and the target compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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