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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 *Pseudoperoniospora cubensis* and *Sphaerotheca fuliginea* at the dosage of 200 μg 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* (EC_{90} = 118.52 μg mL^{-1} for **1e** and EC_{90} = 113.64 μg mL^{-1} for **1l**) than Kresoxim-methyl (EC_{90} = 154.92 μg 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. ^{1}H NMR spectra were recorded on a Mercury-

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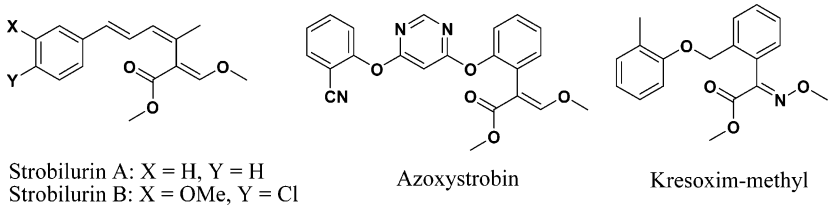

Figure 1. Structures of strobilurins, azoxystrobin, and Kresoxim-methyl.

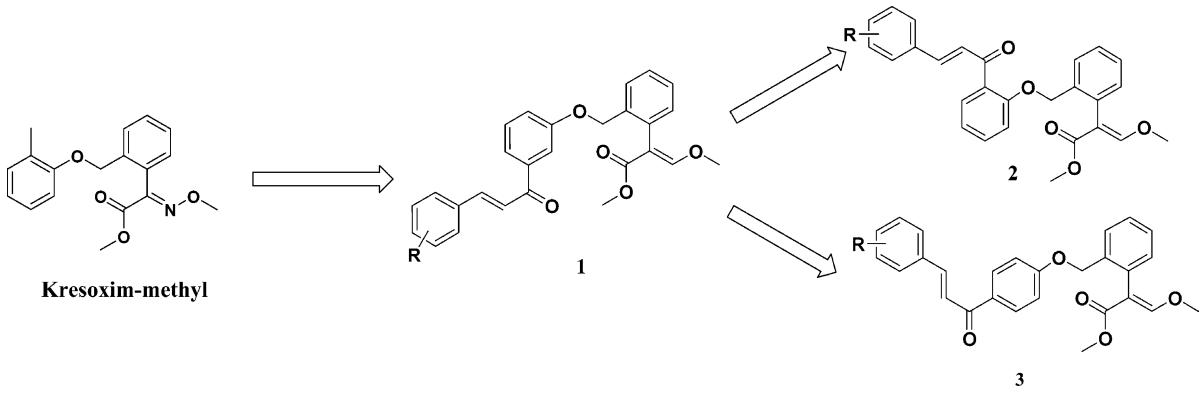

Figure 2. Design strategy of the target compounds.

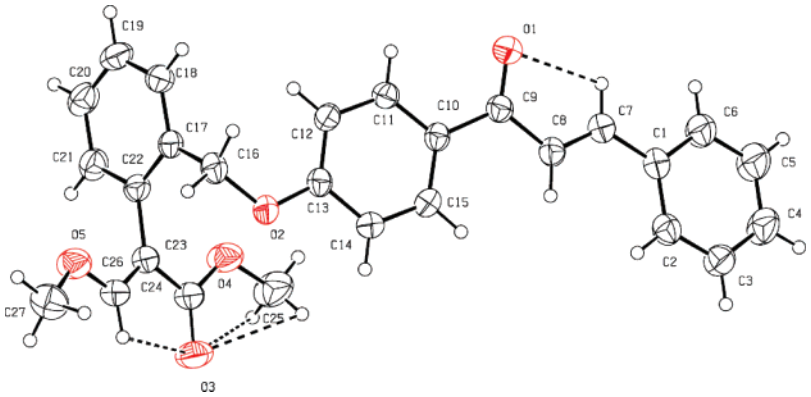

Figure 3. Molecular structure of **3s**.

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}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, =CH−CO, =C*H*−OCH_3), 7.78 (d, J = 15.6 Hz, 1H, =CH−Ar). MS *m*/*z* (%): 443 (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 $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 76.23; H, 5.75.

X-ray Diffraction. Colorless blocks of **3s** (0.30 mm × 0.20 mm × 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 Kα radiation (λ = 0.71073 Å), θ_{max} = 26.00, 22804 measured reflections, and 4363 independent reflections (R_{int} = 0.1146) of which 5421 had $|F_o| > 2|F_o|$. Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.9741; T_{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, ωR = 0.1614, and 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 e 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 *Pseudoperoniospora 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**

			200 mg/L			
no.	R^1	R^2	*P. cubensis*	*S. fuliginea*	*B. cinerea*	*R. solani*
1a	4-MeC_6H_4		100	97	0	0
1b	4-$OMeC_6H_4$		95	0	0	0
1c	4-ClC_6H_4		100	96	0	0
1d	3,4-$Cl_2C_6H_3$		0	0	0	0
1e	2-ClC_6H_4		98	94	0	0
1f	3-ClC_6H_4		33	30	0	0
1g	4-FC_6H_4		97	31	0	0
1h	C_6H_5		96	0	0	0
1i	4-BrC_6H_4		94	45	0	0
1j	3-MeC_6H_4		81	0	0	0
1k	3,4-$(OMe)_2C_6H_3$		72	0	0	0
1l	3-BrC_6H_4		99	99	0	0
1m	3,4-$(Me)_2C_6H_4$		100	92	0	0
1n	2-F-6-ClC_6H_3		97	13	0	0
1o	4-$N(Me)_2C_6H_4$		0	0	0	32
1p	3,4-$OCH_2OC_6H_4$		0	0	0	29
1q	4-$EtOC_6H_4$		33	0	0	0
1r	2,4-$Cl_2C_6H_4$		54	0	0	30
1s	2-C_4H_3O		0	0	16	0
1t	2-C_4H_3S		0	0	24	0
1u	3-FC_6H_4		0	0	10	36
1v	2-FC_6H_4		0	0	0	38
1w	2-BrC_6H_4		100	59	0	31
1x	4-EtC_6H_4		100	78	0	0
1y	4-*t*-BuC_6H_4		28	78	0	0
2a	4-MeC_6H_4	4-Cl	0	0	0	0
2b	4-$MeOC_6H_4$	4-Cl	0	0	0	0
2c	C_6H_5	4-Cl	0	0	0	0
2d	3-ClC_6H_4		39	0	0	0
2e	3-BrC_6H_4		78	0	0	0
2f	4-ClC_6H_4	4-Me	89	0	0	0
2g	2-ClC_6H_4	4-Cl	0	0	0	0
2h	4-ClC_6H_4	4-Cl	0	86	21	0
2i	4-BrC_6H_4		0	0	0	0
2j	4-$MeOC_6H_4$		0	0	0	0
2k	4-ClC_6H_4		0	0	0	0
2l	3-$MeOC_6H_4$		61	0	11	0
2m	3,4-$(Me)_2C_6H_3$		0	0	0	0
2n	3,4-$(OMe)_2C_6H_3$		0	0	0	0
3a	4-BrC_6H_4		56	0	0	0
3b	3-BrC_6H_4		56	0	0	0
3c	4-$MeOC_6H_4$		62	0	0	0
3d	3-MeC_6H_4		47	0	0	0
3e	4-MeC_6H_4		75	0	0	38
3f	3,4-$(Me)_2C_6H_4$		67	30	0	0
3g	3,4-$(OMe)_2C_6H_4$		11	0	0	0
3h	3-$MeOC_6H_4$		86	0	0	20
3i	3,4-$Cl_2C_6H_4$		33	67	0	37
3j	2-ClC_6H_4		100	0	0	0
3k	3,4-$OCH_2OC_6H_3$		0	0	0	0
3l	4-FC_6H_4		100	0	0	23
3m	4-$EtOC_6H_4$		59	0	0	0
3n	2,4-$Cl_2C_6H_4$		67	78	0	27
3o	2-C_4H_3O		0	0	0	0
3p	2-C_4H_3S		0	0	0	0
3q	3-FC_6H_4		97	0	0	0
3r	2-BrC_6H_4		83	67	0	21
3s	C_6H_5		0	0	0	0
3t	4-EtC_6H_4		15	56	0	69
3u	4-*t*-BuC_6H_4		22	67	0	0
3v	2-F-6-ClC_6H_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 ^{1}H 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. C_{25}, C_{24}, C_{25}, C_{26}, O_4, and O_3 are almost coplanar due to the formation of three hydrogen bonds ($C_{25}-H_A\cdots O_3$, 2.57 Å; $C_{25}-H_C\cdots O_3$, 2.61 Å; and $C_{26}-H\cdots O_3$, 2.62 Å). Additionally, the hydrogen bond between O_1 and C_7-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** (R^1 = 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** (R^1 = 4-methylphenyl), **1c** (R^1 = 4-chlorophenyl), **1e** (R^1 = 2-chlorophenyl), **1l** (R^1 = 3-bromophenyl), and **1m** (R^1 = 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** (R^1 = 4-methoxylphenyl), **1g** (R^1 = 4-fluorophenyl), **1h** (R^1 = phenyl), **1i** (R^1 = 4-bromophenyl), **1n** (R^1 = 2-fluoro-6-chlorophenyl), **1w** (R^1 = 2-bromophenyl), and **1x** (R^1 = 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** (EC_{90} = 118.52 μg mL^{-1}, *P. cubensis*) and **1l** (EC_{90} = 113.64 μg mL^{-1}, *P. cubensis*) were

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

pathogen	*S. fuliginea*				*P. cubensis*			
concentration (μg mL^{-1})	100	50	25	EC_{90} (μg mL^{-1})	100	50	25	EC_{90} (μg 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	27	154.92

found to display higher fungicidal activity against *P. cubensis* than Kresoxim-methyl (EC_{90} = 154.92 μg mL^{-1}, *P. cubensis*). However, compound **1l** displayed a lower activity against *P. cubensis* than Kresoxim-methyl at low concentration (50 and 25 μg 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* (EC_{90} = 118.52 μg mL^{-1} for **1e** and EC_{90} = 113.64 μg mL^{-1} for **1l**) than Kresoxim-methyl (EC_{90} = 154.92 μg 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: ^{1}H 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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