Strobilurins are one of the most important classes of agricultural fungicides. To discover new strobilurin derivatives with high activity against resistant pathogens, a series of novel \(\beta\)-methoxyacrylate analogues were designed and synthesized by integrating substituted pyrimidine with a strobilurin pharmacophore. The compounds were confirmed and characterized by infrared, \(^1\)H nuclear magnetic resonance, elemental analysis and mass spectroscopy. The bioassays indicated that most of the compounds (1a-1h) exhibited potent antifungal activities against *Colletotrichum orbiculare*, *Botrytis cinerea* Pers and *Phytophthora capsici* Leonian at the concentration of 50 µg/mL. Exhilaratingly, compound 1d (R=3-trifluoromethylphenyl) showed better antifungal activity against all the tested fungi than the commercial strobilurin fungicide azoxystrobin.

**Key Words**: Synthesis, Strobilurin derivatives, Antifungal activities, Pyrimidine

**Introduction**

The strobilurins, first isolated by Schramm and co-workers in 1977 from fermentations of *Strobilurus tenacellus*,\(^1\) are one of the most important classes of agricultural fungicides, due to their positive attributes such as stronger biological activities, broader antifungal spectrum, lower toxicity towards mammalian cells and environmentally benign characteristics.\(^2\)-9 The strobilurins possess a wide range of antifungal activities as a consequence of their ability to inhibit electron transfer between mitochondrial cytochrome b and cytochrome \(c_1\) through binding at the ubiquinol-oxidation centre (Qo-site).\(^4\),\(^10\)-\(^12\) Over ten strobilurin fungicides have been commercialized since 1996.\(^6\),\(^13\),\(^14\) However, with a range of strobilurin fungicides for important plant pathogens being used in a short period of field applications, significant increases in resistance have been observed.\(^12\),\(^13\)

A large effort focusing on structural modification of strobilurins has been undertaken to overcome this issue in recent years. In this regard, strobilurin analogues that possess methoxyiminoacetate have attracted much attention from agricultural chemists owing to their powerful antifungal properties.\(^12\),\(^13\) Many studies have reported that modification of the side chain was the most effective way to obtain new strobilurin derivatives with higher biological activities.\(^15\),\(^16\),\(^18\)

Pyrimidine derivatives widely existing in nature usually have excellent biological activity.\(^19\)-\(^22\) Strobilurin derivatives containing pyrazole and pyrimidine moieties had been reported.\(^25\)-\(^26\) Utilizing the intermediate derivatisation method based on the active substructure combination and bioisosteric replacement,\(^27\) a series of novel strobilurin derivatives containing pyrimidine moieties and strobilurin pharmacophore were designed and synthesized with the aim of obtaining more active candidates than the conventional azoxystrobin, hopefully against resistant fungal strains. The bioassays showed that most of the \(\beta\)-methoxyacrylate analogues exhibited potential antifungal activities against *Colletotrichum orbiculare*, *Botrytis cinerea* Pers and *Phytophthora capsici* Leonian.

**Experimental**

**Chemicals.** All commercial reagents and solvents were used without further purification unless otherwise specified. Anhydrous solvents were distilled prior to use. THF was distilled from sodium/benzophenone and DMF was dried over P₂O₅. Column chromatography was carried out on silica gel (300-400 mesh, Qingdao Marine Chemical Ltd., Qingdao, China). Thin layer chromatography (TLC) was performed on TLC silica gel 60 F₂₅₄ plates. The infrared spectra were recorded on a Perkin-Elmer Spectrum One apparatus, for solid compounds in KBr-pressed disks, and the absorptions (\(\nu_{\text{max}}\)) were recorded in wavenumbers (cm\(^{-1}\)). \(^1\)H-NMR spectra was performed in CDCl₃ or DMSO-\(d₆\) solution on a Bruker AV-400 MHz NMR spectrophotometer with TMS as the internal standard. Mass spectra of products were determined using an Agilent 6460 Triple Quadrupole LC/MS instrument. Elemental analyses were performed on a Vario EL III elemental analysis instrument. *Colletotrichum orbiculare*, *Botrytis cinerea* Pers and *Phytophthora capsici* Leonian were provided by the institute of vegetables, Chinese Academy of Agricultural Sciences. Azoxystrobin was purchased from Sigma Chemical Co. Ltd.

**Procedures for the Preparation of the Compounds 2-3.** 3-(Methoxymethylene)-(2-(3/H)-benzofuranone (2): Trichloroethylene (10.6 g, 0.1 mol) was added to a mixture of 2-(2-hydroxyphenyl) acetic acid (7.6 g, 0.05 mol) in isobutyric anhydride (20 mL). The resulting solution was mixed and heated to 100 °C for 10 h. The process of the
reaction was monitored by thin-layer chromatography (TLC). During this time low boiling point liquids were collected using a Dean and Stark apparatus. The reaction mixture was then concentrated under reduced pressure to gain a black oil. The oily product was purified by chromatography on a silica gel column using a mixture of n-hexane and ethyl acetate (5:1) as an eluent to obtain 2 (5.2 g, 59%) as a yellow solid. 

1H NMR (400 MHz, CDCl₃) δ 6.80 (s, 1H, CH-Py), 7.14-7.17 (m, 2H, 2,6-ArH), 7.32-7.36 (t, 1H, 4-ArH), 7.45-7.50 (m, 2H, 3,5-ArH); MS (ESI): m/z 241 [M+H]⁺.

4.6-Dichloro-2-phenoxypyrimidine (4a): Yield 87%; white solid; 1H NMR (400 MHz, CDCl₃) δ 6.80 (s, 1H, CH-Py), 7.14-7.17 (m, 2H, 2,6-ArH), 7.32-7.36 (t, 1H, 4-ArH), 7.45-7.50 (m, 2H, 3,5-ArH); MS (ESI): m/z 241 [M+H]⁺.

4.6-Dichloro-2-(o-tolyloxy)pyrimidine (4b): Yield 82%; white solid; 1H NMR (400 MHz, CDCl₃) δ 2.17 (s, 3H, CH₃), 6.72 (s, 1H, CH-Py), 7.03-7.05 (d, J = 8.0 Hz, 1H, 6-ArH), 7.23-7.25 (d, J = 8.0 Hz, 1H, 4-ArH), 7.28-7.30 (m, 2H, 3,5-ArH); MS (ESI): m/z 225 [M+H]⁺.

4.6-Dichloro-2-(2,5-dimethylphenoxy)pyrimidine (4c): Yield 89%; white solid; 1H NMR (400 MHz, CDCl₃) δ 2.12 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 6.69 (s, 1H, CH-Py), 6.86 (s, 1H, 6-ArH), 7.05-7.07 (d, J = 8.0 Hz, 1H, 4-ArH), 7.18-7.20 (d, J = 8.0 Hz, 1H, 3-ArH); MS (ESI): m/z 269 [M+H]⁺, 301 [M+Na]⁺.

4.6-Dichloro-2-(3-(trifluoromethyl)phenoxy)pyrimidine (4d): Yield 65%; white solid; 1H NMR (400 MHz, CDCl₃) δ 7.17 (s, 1H, CH-Py), 7.38-7.40 (d, J = 8.0 Hz, 1H, 6-ArH), 7.47 (s, 1H, 2-ArH), 7.56-7.57 (m, 2H, 4,5-ArH); MS (ESI): m/z 309 [M+H]⁺.

Methyl 1-(2-(4,6-Dichloropyrimidin-2-yloxy)phenyl)-ethanone (4f): Yield 72%; white solid; 1H NMR (400 MHz, CDCl₃) δ 3.80 (s, 3H, -COOCH₃), 6.92 (s, 1H, CH-Py), 7.19-7.21 (d, J = 8.0 Hz, 1H, 6-ArH), 7.40-7.44 (m, 1H, 4-ArH), 7.64-7.68 (m, 1H, 5-ArH), 8.08-8.10 (d, J = 8.0 Hz, 1H, 3-ArH); MS (ESI): m/z 299 [M+H]⁺, 321 [M+Na]⁺.

Methyl 1-(2-(4,6-Dichloropyrimidin-2-yloxy)-phenyl)-ethanone (4f): Yield 72%; white solid; 1H NMR (400 MHz, CDCl₃) δ 3.80 (s, 3H, -COOCH₃), 6.92 (s, 1H, CH-Py), 7.19-7.21 (d, J = 8.0 Hz, 1H, 6-ArH), 7.40-7.44 (m, 1H, 4-ArH), 7.64-7.68 (m, 1H, 5-ArH), 8.08-8.10 (d, J = 8.0 Hz, 1H, 3-ArH); MS (ESI): m/z 283 [M+H]⁺, 305 [M+Na]⁺.

4.6-Dichlorophenyl(2-hydroxyphenyl) (4g): Yield 87%; yellow solid; 1H NMR (400 MHz, CDCl₃) δ 7.20 (s, 1H, CH-Py), 7.31-7.33 (d, J = 8.0 Hz, 1H, 6-ArH), 7.40-7.43 (t, 1H, 4-ArH), 7.67-7.72 (t, 1H, 5-ArH), 7.73-7.75 (d, J = 8.0 Hz, 1H, 3-ArH); MS (ESI): m/z 283 [M+H]⁺, 305 [M+Na]⁺.
Design and Antifungal Activities of Novel Strobilurin Derivatives  


**phenyl)-3,3-dimethoxypropanoate (5b):** Yield 89%; yellow solid; \(^1H\) NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 2.06 (s, 3H, CH\(_3\)), 3.09 (s, 3H, CH-OC\(_3\)), 3.34 (s, 3H, CH-OC\(_3\)), 3.50 (s, 3H, CO\(_2\)CH\(_3\)), 4.04-4.06 (d, \(J = 8.0\) Hz, 1H, -CH-OC\(_3\)), 5.00-5.02 (d, \(J = 8.0\) Hz, 1H, -CH-OC\(_3\)), 7.00 (s, 1H, CH-Py), 7.07-7.09 (d, \(J = 8.0\) Hz, 1H, 6-ArH), 7.17-7.24 (m, 2H, 3',4'-ArH), 7.26-7.31 (m, 2H, 3,5'-ArH), 7.33-7.40 (m, 2H, 4',5'-ArH), 7.59-7.62 (d, \(J = 8.0\) Hz, 1H, 6'-ArH); MS (ESI): \(m/z\) 459 [M+H][\(^+[\text{Na}^+]\)], 481 [M+Na\(^+\)].

**Methyl 2-(2-(6-Chloro-2-(2,5-dimethylphenyl)-pyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5e):** Yield 52%; light yellow solid; \(^1H\) NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 2.00 (s, 3H, CH\(_3\)), 2.25 (s, 3H, CH\(_3\)), 3.08 (s, 3H, CH-OC\(_3\)), 3.34 (s, 3H, CH-OC\(_3\)), 3.45 (s, 3H, CO\(_2\)CH\(_3\)), 4.03-4.05 (d, \(J = 8.0\) Hz, 1H, -CH-OC\(_3\)), 5.00-5.02 (d, \(J = 8.0\) Hz, 1H, -CH-OC\(_3\)), 6.88 (s, 1H, CH-Py), 6.97-6.99 (d, 2H, 4,5'-ArH), 7.14-7.16 (d, \(J = 8.0\) Hz, 1H, 3'-ArH), 7.25-7.27 (d, \(J = 8.0\) Hz, 1H, 3'-ArH), 7.33-7.39 (t, 2H, 4',5'-ArH), 7.59-7.61 (d, \(J = 8.0\) Hz, 1H, 6'-ArH); MS (ESI): \(m/z\) 473 [M+H][\(^+[\text{Na}^+]\)], 495 [M+Na\(^+\)].
(E)-Methyl 2-(2-(2-Acetyloxy-6-chlorophenyl)-6-chloropyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6a): Yield 82%; white solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.46 (s, 3H, CO\(\text{CH}\)), 3.67 (s, 3H, CO\(\text{CH}\)), 3.80 (s, 3H, =CH-OCH\(_3\)), 6.06 (s, 1H, CH-Py), 7.11-7.03 (d, \(J = 8.0\) Hz, 1H, 3'-ArH), 7.17-7.22 (m, 2H, 4',5'-ArH), 7.25-7.27 (m, 5H, 5,6'-ArH), 7.68-7.70 (d, \(J = 8.0\) Hz, 1H, 1,3-ArH); MS (ESI): \(m/z \) 438 [M+H]\(^+\), 460 [M+Na]\(^+\).

Procedure for the Preparation of the Target Compounds

1a-1h. A solution of 6 (1 mmol), 1,4-diazabicyclo[2.2.2]octane (0.1 mmol), anhydrous potassium carbonate (1.5 mmol) and 2-hydroxybenzonitrile (1 mmol) in dry DMF (10 mL) was stirred under the protection of nitrogen at 80 °C for 2 h (the reaction was monitored by TLC). The mixture was poured into cool H\(_2\)O (40 mL) and was extracted with dichloromethane (3 x 20 mL), followed by drying with anhydrous sodium sulfate. The solvent was removed from the filtrate in \textit{vacuo}, the residue was purified by chromatography on a silica gel column to afford the target compounds.

(E)-Methyl 2-(2-(2-(2-Acetyloxy-6-chlorophenyl)-6-chloropyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6a): Yield 77%; yellow solid; mp 109-111 °C; IR (KBr, \(v_{max}\), cm\(^{-1}\)): 2950 (C-H), 2233 (CN), 1710 (C=O), 1630 (C-C), 1594, 1567 (Ar); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.46 (s, 3H, CO\(\text{CH}\)), 3.67 (s, 3H, CO\(\text{CH}\)), 3.80 (s, 3H, =CH-OCH\(_3\)), 6.06 (s, 1H, CH-Py), 7.11-7.03 (d, \(J = 8.0\) Hz, 1H, 3'-ArH), 7.17-7.22 (m, 2H, 4',5'-ArH), 7.25-7.27 (m, 5H, 5,6'-ArH), 7.68-7.70 (d, \(J = 8.0\) Hz, 1H, 1,3-ArH); MS (ESI): \(m/z \) 438 [M+H]\(^+\), 460 [M+Na]\(^+\).

(Yield 89%; white solid; mp 107-109 °C; IR (KBr, \(v_{max}\), cm\(^{-1}\)): 2958 (C-H), 2233 (CN), 1710 (C=O), 1630 (C-C), 1594, 1567 (Ar); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.46 (s, 3H, CO\(\text{CH}\)), 3.67 (s, 3H, CO\(\text{CH}\)), 3.80 (s, 3H, =CH-OCH\(_3\)), 6.06 (s, 1H, CH-Py), 7.11-7.03 (d, \(J = 8.0\) Hz, 1H, 3'-ArH), 7.17-7.22 (m, 2H, 4',5'-ArH), 7.25-7.27 (m, 5H, 5,6'-ArH), 7.68-7.70 (d, \(J = 8.0\) Hz, 1H, 1,3-ArH); MS (ESI): \(m/z \) 438 [M+H]\(^+\), 460 [M+Na]\(^+\)].
1595, 1568 (Ar); 1H NMR (400 MHz, CDCl3) δ 2.36 (s, 3H, -CO2CH3), 3.57 (s, 3H, CO2CH3), 3.70 (s, 3H, =CH-OCH3), 5.96 (s, 1H, CH-Py), 7.00-7.02 (d, J = 8.0 Hz, 1H, 3′-ArH), 7.07-7.14 (m, 3H, 6′,4′,5′-ArH), 7.20-7.26 (m, 2H, 2,6-′ArH), 7.37-7.36 (m, 1H, 5′-ArH), 7.44 (s, 1H, =CH-OCH3), 7.45-7.47 (m, 2H, 5,4′-ArH), 7.49-7.51 (d, J = 8.0 Hz, 1H, 6′-ArH), 7.60-7.62 (d, J = 8.0 Hz, 1H, 3′-ArH), 7.64-7.66 (d, J = 8.0 Hz, 1H, 3′-ArH); MS (ESI): m/z 521 [M+H]+, 543 [M+Na]+; Anal. calcd for C27H21NO3S (537.2): C, 67.03; H, 4.11; N, 7.58; Found: C, 67.66; H, 4.46; N, 7.59.

(E)-Methyl 2-(2-(6-(2-cyanophenoxy)-2-phenylpyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1g): Yield 81%; white solid; mp 108-110 ºC; IR (KBr, νmax, cm⁻¹): 2950 (C-H), 2233 (CN), 1671 (C=O), 1635 (C=C), 1595, 1568 (Ar); 1H NMR (400 MHz, CDCl3) δ 3.65 (s, 3H, CO2CH3), 3.77 (s, 3H, =CH-OCH3), 6.12 (s, 1H, CH-Py), 7.17-7.19 (d, J = 8.0 Hz, 1H, 3′-ArH), 7.20-7.22 (t, J = 8.0 Hz, 1H, 5′-ArH), 7.23-7.25 (d, 1H, 6′-ArH), 7.28-7.36 (m, 5H, 4,6,6′,4′,5′-ArH), 7.49-7.51 (d, 2H, 5,5′-ArH), 7.53 (s, 1H, =CH-OCH3), 7.56-7.58 (d, 2H, 3,3′-ArH); MS (ESI): m/z 521 [M+H]+, 543 [M+Na]+; Anal. calcd for C30H23NO5 (521.0): C, 66.92; H, 3.87; N, 10.76; Found: C, 66.73; H, 3.96; N, 10.59.

(E)-Methyl 2-(2-(6-Chloro-2-phenylpyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (10): Compound 10 was prepared from the intermediate 9 (200 mg, 0.47 mmol) by the same procedure as that of 3. Compound 10 was obtained as a white solid (170 mg, 91%). 1H NMR (400 MHz, CDCl3) δ 3.57 (s, 3H, CO2CH3), 3.69 (s, 3H, =CH-OCH3), 6.65 (s, 1H, CH-Py), 7.24-7.26 (d, J = 8.0 Hz, 1H, 3′-ArH), 7.35-7.37 (m, 2H, 4,5′-ArH), 7.41-7.43 (t, 2H, 6,6′-ArH), 7.44-7.48 (m, 3H, 4,6,6′,4′-ArH), 7.60 (s, 1H, =CH-OCH3), 7.79-7.82 (m, 3H, 3,5,5′-ArH), 7.91-7.93 (d, J = 8.0 Hz, 1H, 3′-ArH); MS (ESI): m/z 429 [M+H]+, 451 [M+Na]+.

(E)-Methyl 2-(2-(6-Chloro-2-phenylpyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (11): The target compound 11 was obtained as a white solid (120 mg, 87%) by the same procedure as that of 1. 1H NMR (CDCl3, 400 MHz, δ 8.0 Hz, 1H, 3′-ArH), 7.24-7.26 (d, J = 8.0 Hz, 1H, 3′-ArH), 7.35-7.37 (m, 2H, 4,5′-ArH), 7.41-7.43 (t, 2H, 6,6′-ArH), 7.44-7.48 (m, 3H, 4,6,6′,4′-ArH), 7.60 (s, 1H, =CH-OCH3), 7.79-7.82 (m, 3H, 3,5,5′-ArH), 7.91-7.93 (d, J = 8.0 Hz, 1H, 3′-ArH); MS (ESI): m/z 429 [M+H]+, 451 [M+Na]+.

(E)-Methyl 2-(2-(6-Chloro-2-phenylpyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (11): The target compound 11 was obtained as a white solid (120 mg, 87%) by the same procedure as that of 1. 1H NMR (CDCl3, 400 MHz, δ 8.0 Hz, 1H, 3′-ArH), 7.24-7.26 (d, J = 8.0 Hz, 1H, 3′-ArH), 7.35-7.37 (m, 2H, 4,5′-ArH), 7.41-7.43 (t, 2H, 6,6′-ArH), 7.44-7.48 (m, 3H, 4,6,6′,4′-ArH), 7.60 (s, 1H, =CH-OCH3), 7.79-7.82 (m, 3H, 3,5,5′-ArH), 7.91-7.93 (d, J = 8.0 Hz, 1H, 3′-ArH); MS (ESI): m/z 429 [M+H]+, 451 [M+Na]+.
DMF/distilled water (1:9 v/v) was used as the blank control. The diameter of fungus spread was measured 3-4 days later. The growth inhibition rates were calculated with the following equation: \( Y = \left[ \frac{(C\text{-}K - A)}{C\text{-}K} \right] \times 100\% \). Where \( Y \) is the growth inhibition rate (%), \( C\text{-}K \) is the control settlement radius (mm), and \( A \) is the treatment group fungi settlement radius (mm).

Results and Discussion

Chemistry. The synthetic routes were shown in Scheme 1. Compound 2 was prepared starting from 2-(2-hydroxyphenyl)acetic acid and trimethyl orthoformate in one-pot reaction according to the similar method reported in the literatures.\(^2\)\(^,\)\(^28\)\(^,\)\(^29\) Compound 3 was obtained by ring opening of 2 in fresh CH\(_3\)ONa/CH\(_3\)OH at low temperature under the protection of nitrogen. The reaction of 4,6-dichloro-2-(methylsulfonyl)pyrimidine with phenols under an atmosphere of nitrogen, afforded corresponding intermediates 4, analogously to previously published procedure.\(^3\)\(^0\) Compounds 4 were treated with 3 in the presence of anhydrous potassium carbonate to give intermediates 5. The acetals were converted into corresponding intermediates 6 using methane sulfonic acid in acetic anhydride. The reaction of 6 with 2-hydroxybenzonitrile in the presence of anhydrous potassium carbonate and 1,4-diazabicyclo [2.2.2] octane (DABCO) afforded strobilurin derivatives 1a-1h.

Compound 1i was prepared according to the procedure shown in Scheme 2. Compound 7 was prepared from diethyl malonate and benzamidine hydrochloride in the presence of freshly CH\(_3\)ONa/CH\(_3\)OH according to the method published in the literature.\(^3\)\(^1\) Using POCl\(_3\) as chlorination reagent, intermediate 8 was synthesized according to the similar method reported in the literature.\(^3\)\(^2\) Compound 9, 10 and 1i were obtained by the same procedure as that of 5, 6 and 1, respectively.

Antifungal Activity. To make a judgment on the antifungal potency of the strobilurin derivatives, the commercial fungicide, azoxystrobin was used as a positive control.\(^3\)\(^3\) The antifungal results of all the compounds against \textit{Colletotrichum orbiculare}, \textit{Botrytis cinerea Pers} and \textit{Phytophthora capsici} Leonian were listed in Table 1.

As shown in Table 1, all of the compounds 1 exhibited certain growth inhibition effects against all of the tested fungi at the concentration of 50 µg/mL. The inhibition rate of most compounds against \textit{Botrytis cinerea Pers} was equal to or higher than that of the positive control, azoxystrobin. It is worth mentioning that compound 1d (R=3-trifluoromethylphenyl) displayed the most promising results, and exhibited better antifungal activity against all the tested fungi.

\begin{center}
\textbf{Scheme 1.} Synthetic route of the \(\beta\)-methoxyacrylate analogues 1a-1h.
\end{center}
than azoxystrobin.

The antifungal activities against *Colletotrichum orbiculare* and *Phytophthora capsici Leonian* are influenced by the nature of the substituted group in phenyl. When 2-substituted group in phenyl from a methyl group to an electron-withdrawing group such as acetyl (-COCH$_3$), methoxycarbonyl (-COOCH$_3$) and cyano (-CN), a slight reduction in antifungal activity was observed (1b versus 1e, 1f, 1g). It was supposed that the electron-withdrawing group in phenyl decreased the Hydrophile-Lipophile Balance (HLB) value of molecule.

When substituted group in phenyl is methyl (electron-donating group), 2-Me derivative 1b displayed a lower antifungal activity than 1a against all the tested fungi. Meanwhile, compound 1c with 2,5-dimethyl of the phenyl ring exhibited lower activity against all the tested fungi than 1b. It was supposed that antifungal activity decreased gradually with increasing density of the electron cloud on the benzene ring.

When replacing the cyano group of substituent position in phenyl, 4-CN-Ph derivative 1h (21, 8 and 24%) displayed a significant lower antifungal activity against all of the tested fungi than corresponding 2-CN-Ph derivative 1g (47, 42 and 55%). When R is an electron-withdrawing group, preliminary SAR presumed that the sequence of antifungal activity against all of the tested fungi is 2-substituted phenyl derivative > 4-substituted phenyl derivative (1g versus 1h). The result was consistent with the prior literature report.34

It was expected to improve the antifungal activity by introducing aromatic group in the side of pyrimidine by closing ring reaction. However, compounds 1i only exhibited moderate antifungal activity against all the tested fungi. Structure-based variation of activities of antifungal agents, such as conventional strobilurins, has been documented.35 Comprehensive characterization of antifungal potency of newly synthesized compounds, presented here, warrants future in vivo study.

**Conclusion**

Nine novel β-methoxyacrylate derivatives (1a-1i) had been synthesized and identified by introducing various substituted groups into the pyrimidine ring. The bioassay showed that all of the new type strobilurin derivatives exhibited moderate to remarkable antifungal activities against the three tested fungi. It is worth mentioning that compound 1d (R=3-trifluoromethylphenyl) displayed the most promising results, and exhibited better antifungal activity against all the tested fungi than the reference commercial fungicide azoxystrobin. To find some new type strobilurin fungicides with high activities and low toxicities, further structural optimization and fungicidal test by using β-methoxyacrylate derivatives are in progress.

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