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Design, Synthesis and Antifungal Activities of Novel Strobilurin Derivatives Containing Pyrimidine Moieties

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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 β-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 *Stroblurus 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 (Q_o-site).[4,10-12] Over ten strobilurin fungicides have been commercialized since 1996.[3,4,13,14] 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 activities against resistant pathogens.[15-17] 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.[23-26] 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 β-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 P_2O_5. 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 (ν_{max}) were recorded in wavenumbers (cm^{-1}). ^{1}H-NMR spectra was performed in $CDCl_3$ or DMSO-d_6 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): Trimethyl orthoformate (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 ºC 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. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.20 (s, 3H, -OCH_3), 7.15-7.19 (m, 2H, 4,6-ArH), 7.26-7.28 (m, *J* = 8.0 Hz, 1H, 5-ArH), 7.53-7.55 (d, *J* = 8.0 Hz, 1H, 3-ArH), 7.95 (s, 1H, =CH-OCH_3); MS (ESI): *m/z* 177 $[M+H]^+$.

Methyl 2-(2-Hydroxyphenyl)-3,3-dimethoxypropanoate (3): Sodium (1.5 g, 0.065 mol) was added slowly in portions to 20 mL of CH_3OH with stirring at −10 ºC, and the reaction was stirred for 30 min. The resulting mixture was added to the solution of **3** (9.0 g, 0.051 mol) in 20 mL of CH_3OH slowly with stirring under the nitrogen atmosphere. After the final addition, the reaction mixture was stirred under the temperature for another 1 hour (the reaction was monitored by TLC). Then the reaction mixture was neutralized with acetic acid, quenched with water, and the product was extracted with dichloromethane (3 × 30 mL), the organic layer was washed with brine twice, and then dried over anhydrous sodium sulfate. The solvent was removed from the filtrate *in vacuo*, and the residue was purified by chromatography on a silica gel column using a mixture of *n*-hexane and ethyl acetate (5:1) to afford **3** (10.5 g, 86%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 3H, CH-OCH_3), 3.48 (s, 3H, CH-OCH_3), 3.75 (s, 3H, CO_2CH_3), 4.04-4.06 (d, *J* = 8.0 Hz, 1H, CH-$COOCH_3$), 4.14 (s, 1H, OH), 5.01-5.03 (d, *J* = 8.0 Hz, 1H, CH-OCH_3), 7.07-7.09 (d, *J* = 8.0 Hz, 1H, 3-ArH), 7.12-7.14 (m, *J* = 8.0 Hz, 1H, 5-ArH), 7.19-7.24 (m, 1H, 4-ArH), 7.57-7.59 (d, 1H, *J* = 8.0 Hz, 6-ArH); MS (ESI): *m/z* 263 $[M+Na]^+$.

Procedure for the Preparation of the Compounds 4a-4h. Sodium hydride (60 percent dispersion in oil, 4.5 mmol) was added slowly in portions to a stirred solution of the corresponding phenols (3 mmol) in dry tetrahyrofuran (10 mL) at 0 ºC under an atmosphere of nitrogen, and the resulting mixture stirred for 30 min. To the stirred reaction mixture was added 4,6-dichloro-2-(methylsulfonyl)pyrimidine (3 mmol) in a single portion, and stirring was continued for another 1 h. The reaction mixture was poured into cool H_2O (20 mL) and was extracted with ethyl acetate (3 × 10 mL), the combined ethyl acetate extracts were washed with brine and followed by drying with anhydrous sodium sulfate. The solvent was removed from the filtrate *in vacuo*, the residue was purified by chromatography on a silica gel column using a mixture of *n*-hexane and ethyl acetate to afford **4**.

4,6-Dichloro-2-phenoxypyrimidine (4a): Yield 87%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H, CH_3), 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* 255 $[M+H]^+$.

4,6-Dichloro-2-(2,5-dimethylphenoxy)pyrimidine (4c): Yield 89%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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 2-(4,6-Dichloropyrimidin-2-yloxy)benzoate (4e): Yield 69%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H, -$COOCH_3$), 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H, -$COCH_3$), 7.12 (s, 1H, CH-Py), 7.20-7.22 (d, *J* = 8.0 Hz, 1H, 6-ArH), 7.37-7.41 (t, 1H, 4-ArH), 7.58-7.62 (m, 1H, 5-ArH), 7.68-7.88 (d, *J* = 8.0 Hz, 1H, 3-ArH); MS (ESI): *m/z* 283 $[M+H]^+$, 305 $[M+Na]^+$.

2-(4,6-Dichloropyrimidin-2-yloxy)benzonitrile (4g): Yield 87%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 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* 266 $[M+H]^+$, 288 $[M+Na]^+$.

4-(4,6-Dichloropyrimidin-2-yloxy)benzonitrile (4h): Yield 62%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H, CH-Py), 7.32-7.34 (d, *J* = 8.0 Hz, 2H, 2,6-ArH), 7.74-7.76 (d, *J* = 8.0 Hz, 2H, 3,5-ArH); MS (ESI): *m/z* 266 $[M+H]^+$, 288 $[M+Na]^+$.

Procedure for the Preparation of the Compounds 5a-5h. Compound **4** (2 mmol) was added to a solution of **3** (2 mmol) and anhydrous potassium carbonate (3 mmol) in dry *N,N*-dimethylformamide (DMF) (10 mL). The resulting solution was mixed and heated to 60 ºC for 8 h. The reaction mixture was poured into cool H_2O (30 mL) and was extracted with ethyl acetate (3 × 20 mL), the combined ethyl acetate extracts were washed with brine and followed by drying with anhydrous sodium sulfate. The solvent was removed from the filtrate *in vacuo*, the residue was purified by chromatography on a silica gel column using a mixture of n-hexane and ethyl acetate to afford **5**.

Methyl 2-(2-(6-Chloro-2-phenoxypyrimidin-4-yloxy)-phenyl)-3,3-dimethoxypropanoate (5a): Yield 63%; white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (s, 3H, CH-OCH_3), 3.33 (s, 3H, CH-OCH_3), 3.49 (s, 3H, CO_2CH_3), 4.03-4.05 (d, *J* = 8.0 Hz, 1H, -CH-$COOCH_3$), 5.00-5.02 (d, *J* = 8.0 Hz, 1H, -CH-OCH_3), 7.04 (s, 1H, CH-Py), 7.15-7.17 (d, *J* = 8.0 Hz, 2H, 2,6-ArH), 7.25-7.29 (m, 2H, 4,3'-ArH), 7.33-7.43 (m, 4H, 3,5,4',5'-ArH), 7.59-7.61 (d, *J* = 8.0 Hz, 1H, 6'-ArH); MS (ESI): *m/z* 445 $[M+H]^+$, 467 $[M+Na]^+$.

Methyl 2-(2-(6-Chloro-2-(*o*-tolyloxy)pyrimidin-4-yloxy)-

phenyl)-3,3-dimethoxypropanoate (5b): Yield 89%; yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 3H, CH_3), 3.09 (s, 3H, CH-OCH_3), 3.34 (s, 3H, CH-OCH_3), 3.50 (s, 3H, CO_2CH_3), 4.04-4.06 (d, J = 8.0 Hz, 1H, -CH-$COOCH_3$), 5.00-5.02 (d, J = 8.0 Hz, 1H, -CH-OCH_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 $[M+H]^+$, 481 $[M+Na]^+$.

Methyl 2-(2-(6-Chloro-2-(2,5-dimethylphenoxy)pyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5c): Yield 52%; light yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.00 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.08 (s, 3H, CH-OCH_3), 3.34 (s, 3H, CH-OCH_3), 3.45 (s, 3H, CO_2CH_3), 4.03-4.05 (d, J = 8.0 Hz, 1H, -CH-$COOCH_3$), 5.00-5.02 (d, J = 8.0 Hz, 1H, -CH-OCH_3), 6.88 (s, 1H, CH-Py), 6.97-6.99 (d, 2H, 4,6-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 $[M+H]^+$, 495 $[M+Na]^+$.

Methyl 2-(2-(6-Chloro-2-(3-(trifluoromethyl)phenoxy)-pyrimidin-4-yloxy)phenyl)-3,3-dimethoxy-propanoate (5d): Yield 55%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (s, 3H, CH-OCH_3), 3.31 (s, 3H, CH-OCH_3), 3.48 (s, 3H, CO_2CH_3), 4.01-4.03 (d, J = 8.0 Hz, 1H, -CH-$COOCH_3$), 4.95-4.97 (d, J = 8.0 Hz, 1H, -CH-OCH_3), 7.12 (s, 1H, CH-Py), 7.21-7.23 (d, J = 8.0 Hz, 1H, 3'-ArH), 7.27-7.33 (m, 2H, 4',5'-ArH), 7.49-7.50 (d, 1H, 6-ArH), 7.55-7.56 (d, 1H, 4-ArH), 7.60-7.63 (m, 3H, 2,5,6'-ArH); MS (ESI): *m/z* 513 $[M+H]^+$, 535 $[M+Na]^+$.

Methyl 2-(4-Chloro-6-(2-(1,3,3-trimethoxy-1-oxopropan-2-yl)phenoxy)pyrimidin-2-yloxy)benzoate (5e): Yield 64%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (s, 3H, CH-OCH_3), 3.42 (s, 3H, CH-OCH_3), 3.62 (s, 3H, CO_2CH_3), 3.77 (s, 3H, -$COOCH_3$), 4.18-4.20 (d, J = 8.0 Hz, 1H, -CH-$COOCH_3$), 4.95-4.97 (d, J = 8.0 Hz, 1H, -CH-OCH_3), 6.50 (s, 1H, CH-Py), 7.03-7.05 (d, J = 8.0 Hz, 1H, 3'-ArH), 7.14-7.16 (d, J = 8.0 Hz, 1H, 6-ArH), 7.22-7.26 (m, 2H, 4',5'-ArH), 7.28-7.32 (m, 1H, 4-ArH), 7.52-7.59 (m, 2H, 5,6'-ArH), 7.98-8.00 (d, J = 8.0 Hz, 1H, 3-ArH); MS (ESI): *m/z* 525 $[M+Na]^+$.

Methyl 2-(2-(2-(2-Acetylphenoxy)-6-chloropyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5f): Yield 58%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H, -$COCH_3$), 3.05 (s, 3H, CH-OCH_3), 3.34 (s, 3H, CH-OCH_3), 3.53 (s, 3H, CO_2CH_3), 4.09-4.10 (d, J = 4.0 Hz, 1H, -CH-$COOCH_3$), 4.87-4.88 (d, J = 4.0 Hz, 1H, -CH-OCH_3), 6.47 (s, 1H, CH-Py), 6.95-6.94 (d, J = 4.0 Hz, 1H, 3'-ArH), 7.04-7.05 (d, J = 4.0 Hz, 1H, 6-ArH), 7.16-7.18 (m, 1H, 4-ArH), 7.21-7.23 (m, 2H, 4',5'-ArH), 7.39-7.42 (t, 1H, 5-ArH), 7.49-7.50 (d, 1H, 6'-ArH), 7.70-7.72 (d, 1H, 3-ArH); MS (ESI): *m/z* 487 $[M+Na]^+$, 509 $[M+Na]^+$.

Methyl 2-(2-(6-Chloro-2-(2-cyanophenoxy)pyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5g): Yield 64%; light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (s, 3H, CH-OCH_3), 3.41 (s, 3H, CH-OCH_3), 3.60 (s, 3H, CO_2CH_3), 4.15-4.17 (d, J = 8.0 Hz, 1H, -CH-$COOCH_3$), 4.93-4.95 (d, J = 8.0 Hz, 1H, -CH-OCH_3), 6.64 (s, 1H, CH-Py), 7.08-7.10 (d, J = 8.0 Hz, 1H, 3'-ArH), 7.20-7.22 (d, J = 8.0 Hz, 1H, 6-ArH), 7.27-7.29 (t, 1H, 5'-ArH), 7.30-7.32 (m, 2H, 4,4'-ArH), 7.56-7.59 (m, 2H, 5,6'-ArH), 7.62-7.65 (d, 1H, 3-ArH); MS (ESI): *m/z* 470 $[M+H]^+$, 492 $[M+Na]^+$.

Methyl 2-(2-(6-Chloro-2-(4-cyanophenoxy)pyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5h): Yield 54%; light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (s, 3H, CH-OCH_3), 3.43 (s, 3H, CH-OCH_3), 3.59 (s, 3H, CO_2CH_3), 4.12-4.14 (d, J = 8.0 Hz, 1H, -CH-$COOCH_3$), 4.95-4.97 (d, J = 8.0 Hz, 1H, -CH-OCH_3), 6.65 (s, 1H, CH-Py), 7.05-7.07 (m, J = 8.0 Hz, 1H, 3'-ArH), 7.22-7.25 (m, 2H, 4',5'-ArH), 7.32-7.49 (m, 2H, 2,6-ArH), 7.60-7.64 (m, 3H, 3,5,6'-ArH); MS (ESI): *m/z* 470 $[M+H]^+$, 492 $[M+Na]^+$.

Procedure for the Preparation of the Compounds 6a-6h. Methanesulphonic acid (0.05 mmol) was added to a solution of **5** (1.5 mmol) in 10 mL of acetic anhydride. The resulting solution was mixed and heated to 90 ºC for 2 h. The reaction mixture was poured into cool H_2O (30 mL) and was extracted with ethyl acetate (3 × 20 mL), the organic layer was washed with brine and followed by drying with anhydrous sodium sulfate. The solvent was removed from the filtrate *in vacuo*, the residue was purified by chromatography on a silica gel column using a mixture of *n*-hexane and ethyl acetate to afford **6**.

(*E*)-Methyl 2-(2-(6-Chloro-2-phenoxypyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6a): Yield 92%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 3H, CO_2CH_3), 3.68 (s, 3H, =CH-OCH_3), 6.33 (s, 1H, CH-Py), 7.06-7.08 (t, 3H, 2,6,3'-ArH), 7.12-7.15 (t, 1H, 4-ArH), 7.21-7.24 (m, 2H, 3,5-ArH), 7.25-7.29 (m, 3H, 4',5',6'-ArH), 7.38 (s, 1H, =CH-OCH_3); MS (ESI): *m/z* 413 $[M+H]^+$.

(*E*)-Methyl 2-(2-(6-chloro-2-phenoxypyrimidin-4-yloxy)-phenyl)-3-methoxyacrylate (6b): Yield 85%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H, CH_3), 3.61 (s, 3H, CO_2CH_3), 3.75 (s, 3H, =CH-OCH_3), 6.36 (s, 1H, CH-Py), 7.04-7.06 (d, 1H, 6-ArH), 7.10-7.23 (m, 4H, 3,4,5,3'-ArH), 7.28-7.32 (m, 3H, 4',5',6'-ArH), 7.45 (s, 1H, =CH-OCH_3); MS (ESI): *m/z* 427 $[M+H]^+$, 449 $[M+Na]^+$.

(*E*)-Methyl 2-(2-(6-Chloro-2-(2,5-dimethylphenoxy)-pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6c): Yield 90%; light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.61 (s, 3H, CO_2CH_3), 3.75 (s, 3H, =CH-OCH_3), 6.35 (s, 1H, CH-Py), 6.81 (s, 1H, 6-ArH), 6.92-6.95 (d, 1H, 4-ArH), 7.04-7.13 (m, 3H, 3,3',5'-ArH), 7.30-7.32 (m, 2H, 4',6'-ArH), 7.45 (s, 1H, =CH-OCH_3); MS (ESI): *m/z* 441 $[M+H]^+$, 463 $[M+Na]^+$.

(*E*)-Methyl 2-(2-(6-Chloro-2-(3-(trifluoromethyl)phenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6d): Yield 88%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H, CO_2CH_3), 3.81 (s, 3H, =CH-OCH_3), 6.11 (s, 1H, CH-Py), 7.20-7.21 (d, 2H, 6,3'-ArH), 7.27-7.27 (m, 1H, 5'-ArH), 7.30-7.32 (m, 1H, 4'-ArH), 7.33-7.36 (m, 2H, 2,4-ArH), 7.54 (s, 1H, =CH-OCH_3), 7.55-7.57 (d, 1H, 5-ArH), 7.60-7.61 (d, 1H, 6'-ArH); MS (ESI): *m/z* 438 $[M+H]^+$, 460 $[M+Na]^+$.

(*E*)-Methyl 2-(4-Chloro-6-(2-(1,3-dimethoxy-1-oxoprop-2-en-2-yl)phenoxy)pyrimidin-2-yloxy)benzoate (6e): Yield

79%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 3.81 (s, 3H, =CH-OCH_3), 6.00 (s, 1H, CH-Py), 7.12-7.14 (d, *J* = 8.0 Hz, 1H, 3'-ArH), 7.18-7.20 (m, 2H, 6,5'-ArH), 7.22-7.25 (m, 1H, 4'-ArH), 7.47-7.51 (m, 2H, 4,5-ArH), 7.53 (s, 1H, =CH-OCH_3), 7.59-7.60 (d, 1H, 6'-ArH), 7.91-7.93 (d, 1H, 3-ArH); MS (ESI): *m/z* 413 $[M+H]^+$, 435 $[M+Na]^+$.

(*E*)-Methyl 2-(2-(2-(2-Acetylphenoxy)-6-chloropyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6f): Yield 82%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H, -$COCH_3$), 3.67 (s, 3H, CO_2CH_3), 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, 4,6-ArH), 7.33-7.36 (m, 2H, 4',5'-ArH), 7.43-7.46 (m, 1H, 5-ArH), 7.54 (s, 1H, =CH-OCH_3), 7.59-7.61 (d, *J* = 8.0 Hz, 1H, 6'-ArH), 7.70-7.72 (d, *J* = 8.0 Hz, 1H, 3-ArH); MS (ESI): *m/z* 455 $[M+H]^+$, 477 $[M+Na]^+$.

(*E*)-Methyl 2-(2-(6-Chloro-2-(2-cyanophenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6g): Yield 87%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H, CO_2CH_3), 3.77 (s, 3H, =CH-OCH_3), 6.51 (s, 1H, CH-Py), 7.14-7.16 (d, *J* = 8.0 Hz, 1H, 3'-ArH), 7.27-7.37 (m, 4H, 4,6,4',5'-ArH), 7.50 (s, 1H, =CH-OCH_3), 7.59-7.64 (m, 2H, 5,6'-ArH), 7.68-7.70 (d, *J* = 8.0 Hz, 1H, 3-ArH); MS (ESI): *m/z* 438 $[M+H]^+$, 460 $[M+Na]^+$.

(*E*)-Methyl 2-(2-(6-Chloro-2-(4-cyanophenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6h): Yield 85%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H, CO_2CH_3), 3.76 (s, 3H, =CH-OCH_3), 6.50 (s, 1H, CH-Py), 7.08-7.11 (d, 1H, 3'-ArH), 7.28-7.31 (m, 2H, 4',5'-ArH), 7.32-7.34 (m, 3H, 2,6,6'-ArH), 7.46 (s, 1H, =CH-OCH_3), 7.60-7.62 (t, 1H, 5-ArH), 7.63-7.65 (d, 1H, 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 ºC for 2 h (the reaction was monitored by TLC). The mixture was poured into cool H_2O (40 mL) and was extracted with dichloromethane (3 × 20 mL), followed by drying with anhydrous sodium sulfate. The solvent was removed from the filtrate *in vacuo*, the residue was purified by chromatography on a silica gel column to afford the target compounds.

(*E*)-Methyl 2-(2-(6-(2-Cyanophenoxy)-2-phenoxypyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1a): Yield 77%; white solid; mp 100-102 ºC; IR (KBr, ν_{max}, cm^{-1}): 2950 (C-H), 2233 (CN), 1710 (C≡O), 1634 (C=C), 1590, 1567 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.58 (s, 3H, CO_2CH_3), 3.70 (s, 3H, =CH-OCH_3), 5.96 (s, 1H, CH-Py), 6.96-6.98 (d, *J* = 8.0 Hz, 2H, 2,6-ArH), 7.02-7.04 (t, 1H, 5'-ArH), 7.11-7.18 (m, 5H, 4,3',4',4",6"-ArH), 7.24-7.28 (m, 2H, 3,5-ArH), 7.43 (s, 1H, =CH-OCH_3), 7.44-7.46 (d, 1H, 6'-ArH), 7.51-7.53 (d, 2H, 3",5"-ArH); MS (ESI): *m/z* 496 $[M+H]^+$, 518 $[M+Na]^+$; Anal.calcd for $C_{28}H_{21}N_3O_6$ (495.1): C, 67.87; H, 4.27; N, 8.48; Found: C, 67.72; H, 4.41; N, 8.33.

(*E*)-Methyl 2-(2-(6-(2-Cyanophenoxy)-2-phenoxypyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1b): Yield 72%; yellow solid; mp 109-111 ºC; IR (KBr, ν_{max}, cm^{-1}): 2950 (C-H), 2231 (CN), 1710 (C≡O), 1630 (C=C), 1594, 1567 (Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H, CH_3), 3.58 (s, 3H, CO_2CH_3), 3.70 (s, 3H, =CH-OCH_3), 5.92 (s, 1H, CH-Py), 6.94-6.96 (t, 1H, 6-ArH), 6.98-7.02 (m, 2H, 4,3'-ArH), 7.09-7.11 (m, 2H, 3,5-ArH), 7.14-7.17 (t, 1H, 5'-ArH), 7.24-7.27 (m, 2H, 4',6"-ArH), 7.34-7.37 (t, 1H, 4"-ArH), 7.40-7.42 (t, 2H, 6',5"-ArH), 7.44 (s, 1H, =CH-OCH_3), 7.46-7.48 (d, 1H, 3"-ArH); MS (ESI): *m/z* 510 $[M+H]^+$, 533 $[M+Na]^+$; Anal.calcd for $C_{29}H_{23}N_3O_6$ (509.1): C, 68.36; H, 4.55; N, 8.25; Found: C, 68.23; H, 4.69; N, 8.09.

(*E*)-Methyl 2-(2-(6-(2-Cyanophenoxy)-2-(2,5-dimethylphenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1c): Yield 82%; light yellow solid; mp 117-120 ºC; IR (KBr, ν_{max}, cm^{-1}): 2950 (C-H), 2233 (CN), 1711 (C≡O), 1635 (C=C), 1591, 1567 (Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.58 (s, 3H, CO_2CH_3), 3.70 (s, 3H, =CH-OCH_3), 5.91 (s, 1H, CH-Py), 6.98 (s, 1H, 6-ArH), 6.75-6.77 (d, *J* = 8.0 Hz, 1H, 4-ArH), 6.89-6.91 (d, *J* = 8.0 Hz, 1H, 3'-ArH), 7.10-7.12 (m, 2H, 3,5'-ArH), 7.10-7.21 (m, 2H, 4',5"-ArH), 7.21-7.26 (m, 2H, 4",6"-ArH), 7.41-7.42 (d, *J* = 8.0 Hz, 1H, 6'-ArH), 7.43 (s, 1H, =CH-OCH_3), 7.48-7.50 (d, *J* = 8.0 Hz, 1H, 3"-ArH); MS (ESI): *m/z* 524 $[M+H]^+$, 546 $[M+Na]^+$; Anal.calcd for $C_{30}H_{25}N_3O_6$ (523.1): C, 68.82; H, 4.81; N, 8.03; Found: C, 68.66; H, 4.97; N, 7.91.

(*E*)-Methyl 2-(2-(6-(2-Cyanophenoxy)-2-(2-(trifluoromethyl)phenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1d): Yield 87%; white solid; mp 115-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 2950 (C-H), 2233 (CN), 1715 (C≡O), 1635 (C=C), 1591, 1568 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.59 (s, 3H, CO_2CH_3), 3.71 (s, 3H, =CH-OCH_3), 6.01 (s, 1H, CH-Py), 7.10-7.11 (d, 2H, 6,3'-ArH), 7.15-7.17 (m, 1H, 5'-ArH), 7.19-7.22 (m, 2H, 4,4'-ArH), 7.24-7.29 (m, 5H, 2,5,4",5",6"-ArH), 7.44 (s, 1H, =CH-OCH_3), 7.45-7.46 (d, 1H, 6'-ArH), 7.50-7.51 (d, 1H, 3"-ArH); MS (ESI): *m/z* 496 $[M+H]^+$, 518 $[M+Na]^+$; Anal.calcd for $C_{29}H_{20}F_3N_3O_6$ (563.1): C, 61.81; H, 3.58; N, 7.46; Found: C, 61.68; H, 3.71; N, 7.32.

(*E*)-Methyl 2-(4-(2-Cyanophenoxy)-6-(2-(1,3-dimethoxy-1-oxoprop-2-en-2-yl)phenoxy)pyrimidin-2-yloxy)benzoate (1e): Yield 83%; white solid; mp 112-114 ºC; IR (KBr, ν_{max}, cm^{-1}): 2950 (C-H), 2233 (CN), 1714 (C≡O), 1635 (C=C), 1591, 1568 (Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 3.71 (s, 3H, =CH-OCH_3), 5.90 (s, 1H, CH-Py), 7.02-7.04 (d, *J* = 8.0 Hz, 1H, 3'-ArH), 7.08-7.10 (m, 2H, 6,5'-ArH), 7.12-7.15 (t, 1H, 4'-ArH), 7.16-7.18 (m, 1H, 4"-ArH), 7.23-7.50 (m, 3H, 4,6',6"-ArH), 7.37-7.42 (m, 2H, 5,5"-ArH), 7.43 (s, 1H, =CH-OCH_3), 7.49-7.50 (d, 1H, 3"-ArH), 7.81-7.83 (d, 1H, 3-ArH); MS (ESI): *m/z* 521 $[M+H]^+$, 543 $[M+Na]^+$; Anal.calcd for $C_{30}H_{23}N_3O_8$ (553.2): C, 65.10; H, 4.19; N, 7.59; Found: C, 64.93; H, 4.36; N, 7.46.

(*E*)-Methyl 2-(2-(2-(2-Acetylphenoxy)-6-(2-cyanophenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1f): Yield 89%; white solid; mp 107-109 ºC; IR (KBr, ν_{max}, cm^{-1}): 2958 (C-H), 2233 (CN), 1715 (C≡O), 1635 (C=C),

1595, 1568 (Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H, -$COCH_3$), 3.57 (s, 3H, CO_2CH_3), 3.70 (s, 3H, =CH-OCH_3), 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, 4,6"-ArH), 7.33-7.36 (m, 1H, 5"-ArH), 7.44 (s, 1H, =CH-OCH_3), 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 $C_{30}H_{23}N_3O_7$ (537.2): C, 67.03; H, 4.31; N, 7.82; Found: C, 66.86; H, 4.46; N, 7.59.

(*E*)-Methyl 2-(2-(2,6-bis(2-cyanophenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1g): Yield 78%; light yellow solid; mp 108-110 ºC; IR (KBr, ν_{max}, cm^{-1}): 2950 (C-H), 2233 (CN), 1715 (C≡O), 1635 (C=C), 1595, 1568 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.65 (s, 3H, CO_2CH_3), 3.77 (s, 3H, =CH-OCH_3), 6.12 (s, 1H, CH-Py), 7.17-7.19 (d, *J* = 8.0 Hz, 1H, 3'-ArH), 7.20-7.22 (t, 1H, 5'-ArH), 7.23-7.25 (d, 1H, 6"-ArH), 7.28-7.36 (m, 5H, 4,6,4',6',4"-ArH), 7.49-7.51 (d, 2H, 5,5"-ArH), 7.53 (s, 1H, =CH-OCH_3), 7.56-7.58 (d, 2H, 3,3"-ArH); MS (ESI): *m/z* 521 $[M+H]^+$, 543 $[M+Na]^+$; Anal.calcd for $C_{29}H_{20}N_4O_6$ (520.1): C, 66.92; H, 3.87; N, 10.76; Found: C, 66.73; H, 3.96; N, 10.59.

(*E*)-Methyl 2-(2-(6-(2-Cyanophenoxy)-2-(4-cyanophenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1h): Yield 81%; white solid; mp 104-106 ºC; IR (KBr, ν_{max}, cm^{-1}): 2948 (C-H), 2230 (CN), 1714 (C≡O), 1635 (C=C), 1595, 1568 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.53 (s, 3H, CO_2CH_3), 3.76 (s, 3H, =CH-OCH_3), 6.32 (s, 1H, CH-Py), 7.14-7.16 (d, *J* = 8.0 Hz, 1H, 3'-ArH), 7.27-7.30 (t, 2H, 5',6"-ArH), 7.32-7.38 (m, 2H, 2,6-ArH), 7.44-7.51 (m, 3H, 4',6',4"-ArH), 7.60 (s, 1H, =CH-OCH_3), 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* 521 $[M+H]^+$, 543 $[M+Na]^+$; Anal.calcd for $C_{29}H_{20}N_4O_6$ (520.1): C, 66.92; H, 3.87; N, 10.76; Found: C, 66.73; H, 3.96; N, 10.59.

Procedures for the Preparation of Target Compounds 1i.

2-Phenylpyrimidine-4,6-diol (7): Sodium (115 mg, 5 mmol) was added slowly in portions to 10 mL of CH_3OH with stirring at −10 ºC, and the reaction was stirred for 30 min. The resulting mixture was added to the solution of diethyl malonate (640 mg, 4 mmol) and benzamidine hydrochloride (624 mg, 4 mmol) in 20 mL of CH_3OH slowly with stirring under the nitrogen atmosphere. After the final addition, the reaction mixture was allowed to stir at refluxing temperature for 6 hours. Then the mixture was cooled to room temperature and concentrated under reduced pressure. The crude was dissolved in water, and acidified with 2 N hydrochloric acid. White solid obtained was filtered off, washed with water and dried to afford the compound **7** (350 mg, 47%) as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.34 (s, 1H, CH-Py), 7.49-7.57 (m, 3H, 3,4,5-ArH), 8.07-8.09 (d, *J* = 8.0 Hz, 2H, 2,6-ArH); MS (ESI): *m/z* 189 $[M+H]^+$, 212 $[M+Na]^+$.

4,6-Dichloro-2-phenylpyrimidine (8): A mixture of **7** (300 mg, 1.8 mmol) in phosphorus oxychloride (4 mL, 40.8 mmol) was heated to 110 ºC for 3 h. The resulting mixture was added to crushed ice (50 mL) and extracted with ethyl acetate (3 × 20 mL), the combined ethyl acetate extracts were washed with brine and followed by drying with anhydrous sodium sulfate. The solvent was removed from the filtrate *in vacuo*, the residue was purified by chromatography on a silica gel column using a mixture of *n*-hexane and ethyl acetate (10:1) to afford **8** (370 mg, 92%) as a light gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H, CH-Py), 7.48-7.55 (m, 3H, 3,4,5-ArH), 8.44-8.46 (d, *J* = 8.0 Hz, 2H, 2,6-ArH); MS (ESI): *m/z* 225 $[M+H]^+$.

Methyl 2-(2-(6-Chloro-2-phenylpyrimidin-4-yloxy)-phenyl)-3,3-dimethoxypropanoate (9): Compound **9** was prepared from the intermediate **3** (240 mg, 1 mmol) and **8** (224 mg, 1 mmol) by the same procedure as that of **5**. Compound **9** was obtained as a white solid (270 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (s, 3H, CH-OCH_3), 3.40 (s, 3H, CH-OCH_3), 3.41 (s, 3H, CO_2CH_3), 4.20-4.22 (d, *J* = 8.0 Hz, 1H, -CH-$COOCH_3$), 4.98-5.00 (d, *J* = 8.0 Hz, 1H, -CH-OCH_3), 6.77 (s, 1H, CH-Py), 7.16-7.18 (d, *J* = 8.0 Hz, 1H, 3'-ArH), 7.33-7.40 (m, 4H, 3,4,5,5'-ArH), 7.43-7.47 (m, 1H, 4'-ArH), 7.68-7.70 (d, *J* = 8.0 Hz, 1H, 6'-ArH), 8.20-8.22 (d, *J* = 8.0 Hz, 2H, 2,6-ArH); MS (ESI): *m/z* 429 $[M+H]^+$, 451 $[M+Na]^+$.

(*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 **6**. Compound **10** was obtained as a white solid (170 m g, 91%).^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 3H, CO_2CH_3), 3.69 (s, 3H, =CH-OCH_3), 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, 4,6'-ArH), 7.44-7.48 (m, 3H, 3,5-ArH + =CH-OCH_3), 8.31-8.33 (d, *J* = 8.0 Hz, 2H, 2,6-ArH); MS (ESI): *m/z* 397 $[M+H]^+$, 419 $[M+Na]^+$.

(*E*)-Methyl 2-(2-(6-(2-Cyanophenoxy)-2-phenylpyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1i): The target compound **1i** was obtained as a white solid (120 mg, 87%) by the same procedure as that of **1**. mp 108-111 ºC; IR (KBr, ν_{max}, cm^{-1}): 2948 (C-H), 2231 (CN), 1708 (C≡O), 1635 (C=C), 1590, 1558 (Ar); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.46 (s, 3H, CO_2CH_3), 3.69 (s, 3H, =CH-OCH_3), 6.48 (s, 1H, CH-Py), 7.33-7.35 (t, 2H, 3',5'-ArH), 7.38-7.42 (t, 3H, 4',6',6"-ArH), 7.52-7.61 (m, 6H, 3,4,5,4",5"-ArH), 7.85-7.90 (t, 2H, 2,6-ArH), 8.02-8.04 (d, *J* = 8.0 Hz, 1H, 3"-ArH); MS (ESI): *m/z* 481 $[M+H]^+$; 502 $[M+Na]^+$; Anal.calcd for $C_{28}H_{21}N_3O_5$(479.1): C, 70.14; H, 4.41; N, 8.76; Found: C, 69.97; H, 4.58; N, 8.59.

Antifungal Bioassay. The antifungal activities of the synthesized compounds were carried out according to the following procedures. Each of the test compounds was first dissolved in DMF/distilled water (1:9 v/v) containing 0.1% Tween 80 at a concentration of 1.0 g/L. And then the solutions (1 mL) were thoroughly mixed by shaking with thawed potato glucose (for *Colletotrichum orbiculare* and *Botrytis cinerea Pers*) or oat agar culture medium (for *Phytophthora capsici Leonian*) (19 mL). The mixtures were poured into Petri dishes. After the dishes were cooled, the solidified plates were incubated with 5 mm mycelium disk and incubated in the culture tank at 24-26 ºC. The solution of

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: $Y = [(CK\text{-}A)/CK]\ 100\%$. Where Y is the growth inhibition rate (%), CK is the control settlement radius (mm), and A is the treatment group fungi settlement radius (mm).

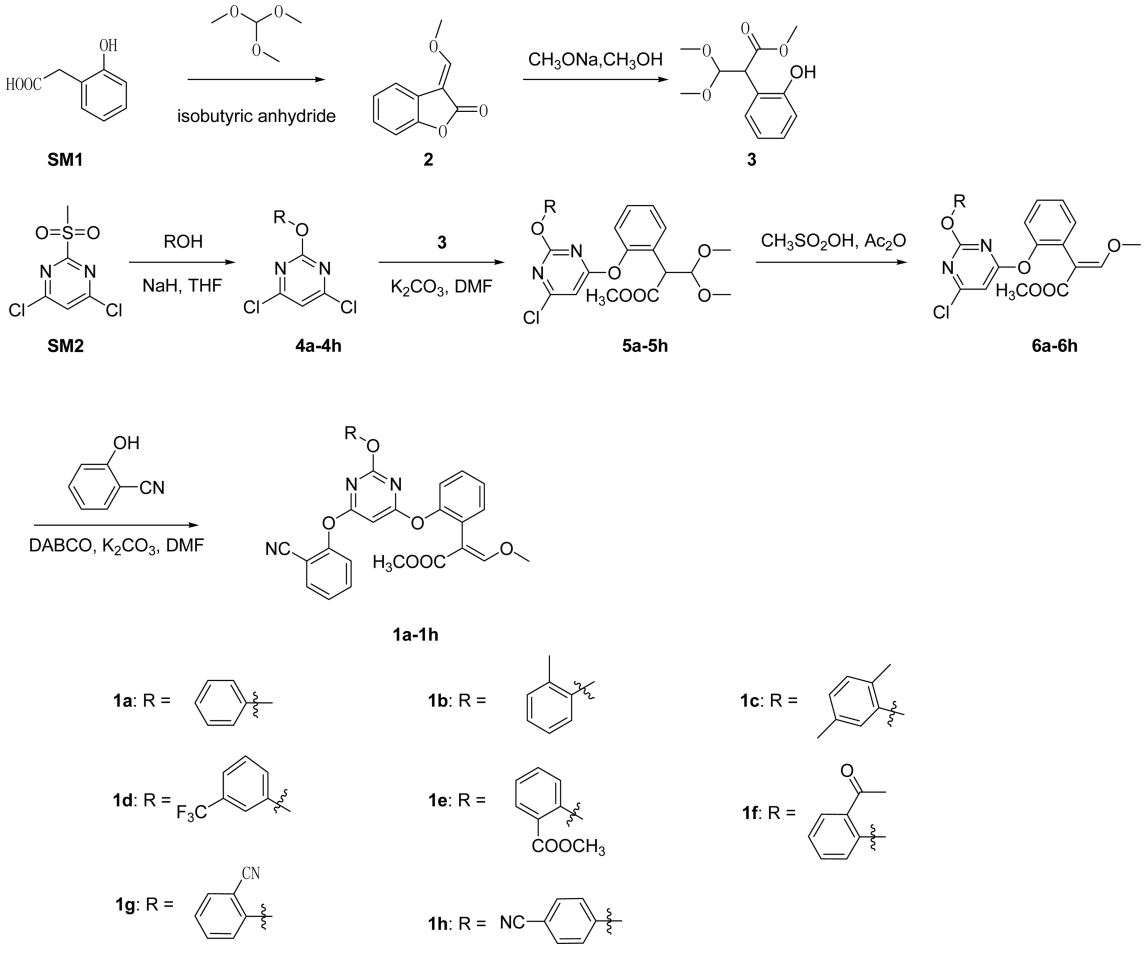
Results and Discussion

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_3ONa/CH_3OH 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.[30] 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 sulphonic 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**.

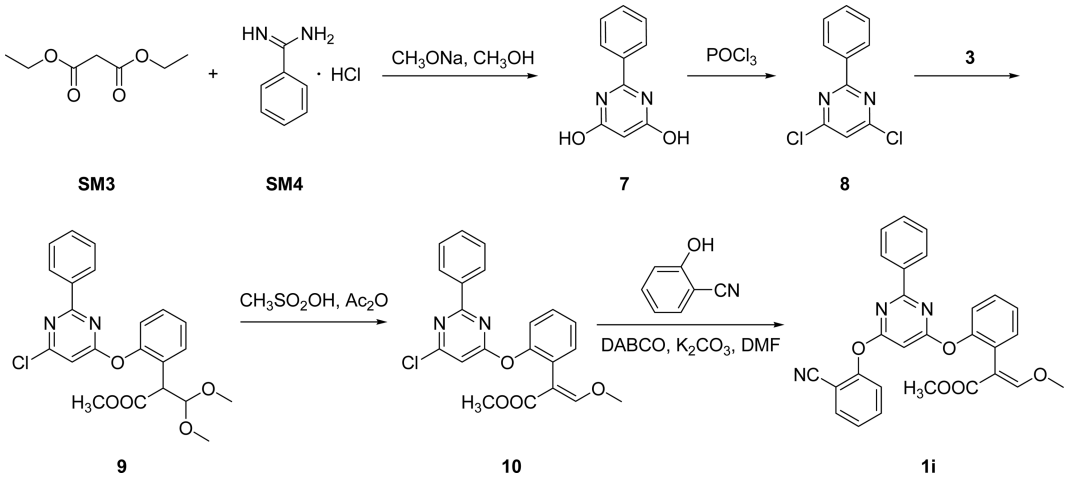
Compound **1i** was prepared according to the procedure shown in Scheme 2. Compound **7** was prepared from diethyl malonate and benzamidine hydrochloride in the presence of freshly CH_3ONa/CH_3OH according to the method published in the literature.[31] Using $POCl_3$ as chlorination reagent, intermediate **8** was synthesized according to the similar method reported in the literature.[32] 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.[33] The antifungal results of all the compounds against *Colletotrichum orbiculare*, *Botrytis cinerea Pers* and *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 *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



Scheme 1. Synthetic route of the β-methoxyacrylate analogues **1a-1h**.



Scheme 2. Synthetic route of compound **1i**.

Table 1. Antifungal activities of β-methoxyacrylate derivatives **1** (50 μg/mL, Relative Inhibitory Rate %)

Entry	Compd	Antifungal activities inhibitory rate %		
		Colletotrichum orbiculare	*Botrytis cinerea Pers*	*Phytophthora capsici Leonian*
1	**1a**	73 ± 4	66 ± 4	62 ± 2
2	**1b**	70 ± 4	64 ± 3	56 ± 3
3	**1c**	55 ± 5	60 ± 3	51 ± 3
4	**1d**	76 ± 3	71 ± 3	82 ± 4
5	**1e**	61 ± 4	57 ± 5	56 ± 10
6	**1f**	67 ± 5	63 ± 3	60 ± 5
7	**1g**	47 ± 1	42 ± 2	52 ± 4
8	**1h**	21 ± 3	8 ± 3	24 ± 4
9	**1i**	62 ± 2	56 ± 3	67 ± 6
10	Azoxystrobin	68 ± 6	63 ± 2	69 ± 3
11	control	/	/	/

Control: DMF/distilled water (1:9 v/v) containing 0.1% Tween 80. "/" means no inhibition circle.

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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