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Synthesis and Antifungal Activities of New Type β-Methoxyacrylate-Based Strobilurin Analogues

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Strobilurins have become 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 **1** exhibited potent antifungal activity against *Colletotrichum orbiculare*, *Botrytis cinerea* Pers and *Phytophthora capsici* Leonian at the concentration of 50 μg/mL. Exhilaratingly, compound **1a** (R＝methyl) showed better antifungal activity against all the tested fungi than the commercial strobilurin fungicide azoxystrobin.

Keywords synthesis, strobilurin derivatives, antifungal activities, substituted pyrimidine, SAR

Introduction

The strobilurins, first isolated by Schramm and co-workers in 1977 from fermentations of S*troblurus tenacellus*, 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 toward mammalian cells, and higher security than previous fungicides.[1-8] 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 c1 through binding at the ubiquinol-oxidation centre (Qo-site).[3,9-11] Over ten strobilurin fungicides have been commercialized since 1996.[2,3,12,13] 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.[11,12]

The general structure of strobilurin fungicides consists of three parts (Figure 1):[2,14,15] (1) the pharmacophore, which is indispensable for antifungal activity; (2) the aromatic bridge, which helps to stabilize the molecule and photo-stability; and (3) the side chain, which is essential for an optimal lipophilicity.

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

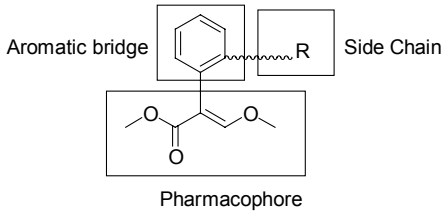

Figure 1 General structure for β-methoxyacrylates.

powerful antifungal activities against resistant pathogens.[16-18] Because the pharmacophore is indispensable for antifungal activity of strobilurin fungicides and the aromatic bridge helps to stabilize the molecule and photo-stability, many studies have reported that modification of the side chain was the most effective way to obtain new strobilurin derivatives with higher biological activities.[16,17,19,20]

Pyrimidine derivatives widely existing in nature usually have excellent biological activity.[21-24] Utilizing the intermediate derivatisation method based on the active substructure combination and bioisosteric replacement,[25] 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

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Pers and *Phytophthora capsici* Leonian.

Results and Discussion

Synthesis

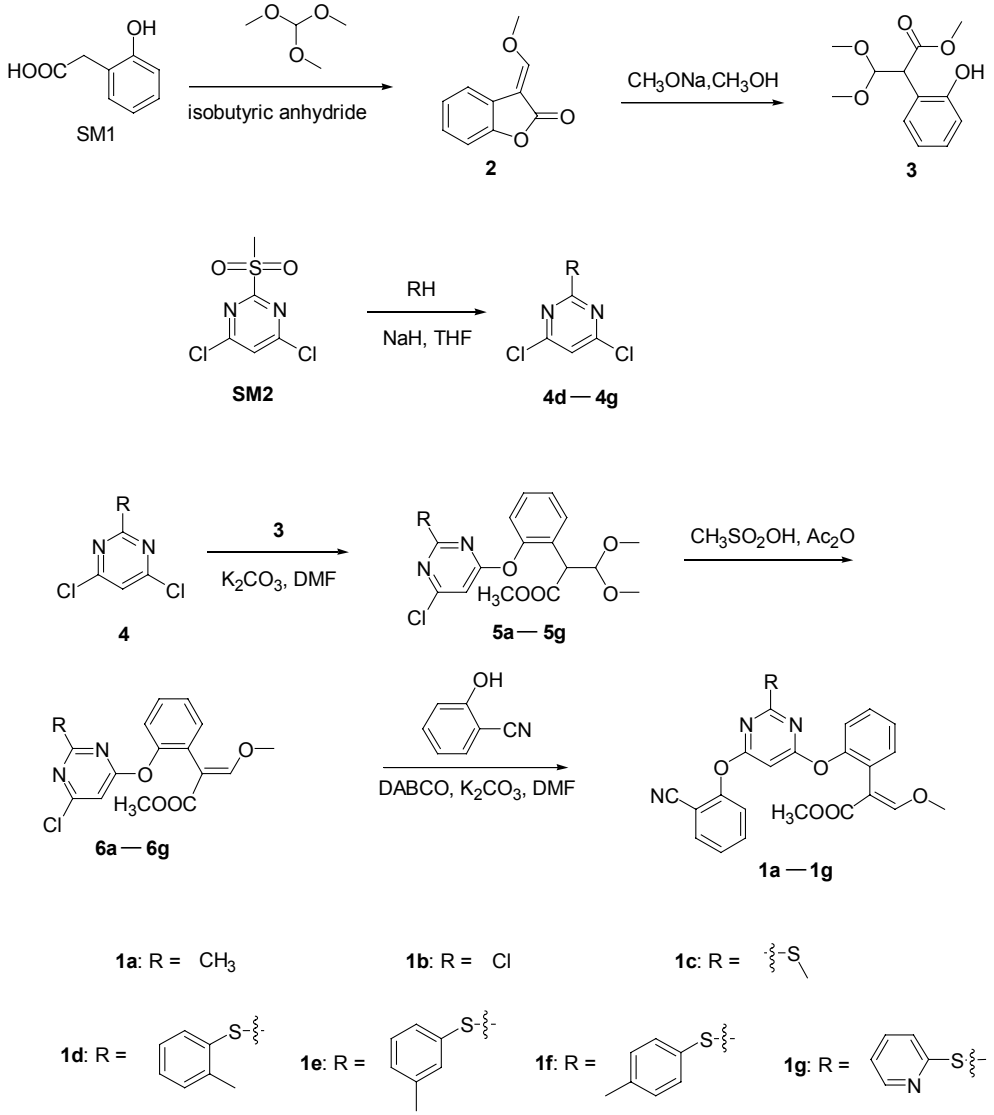
The synthetic route was shown in Scheme 1. Compound **2** was prepared starting from simple 2-(2-hydroxyphenyl)acetic acid (SM1) and trimethyl orthoformate in one-pot reaction according to the similar method reported in the literatures.[1,26,27] Compound **3** was obtained by ring opening of **2** in fresh CH_3ONa/CH_3OH at low temperature under the protection of nitrogen. Analogous to previously published procedure,[28] reacting 4,6-dichloro-2-(methylsulfonyl) pyrimidine with thiophenols afforded corresponding intermediates **4** in the presence of sodium hydride in anhydrous tetrahyrofuran under an atmosphere of nitrogen. 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.[29,30] Reacting **6** with 2-hydroxybenzonitrile afforded strobilurin derivatives **1a**—**1h** in the presence of anhydrous potassium carbonate and 1,4-diazabicyclo[2.2.2]octane (DABCO).

Compound **1h** was prepared according to the procedure shown in Scheme 2. Compound **7** was prepared from diethyl malonate and 4-chlorobenzamidine hydrochloride in the presence of freshly prepared CH_3ONa/CH_3OH according to the method published in the literature.[31-33] Using $POCl_3$ as chlorination reagent, intermediate **8** was synthesized according to the similar method reported in the literature.[34] Compounds **9**, **10** and **1h** were obtained by the same procedure as those of **5**, **6** and **1**, respectively.

Biological activities

The fungistatic activities of the synthesized compounds were carried out at the concentration of 50 μg/mL. To make a judgment on the antifungal potency

Scheme 1 Synthetic route of the *β*-methoxyacrylate analogues **1a**—**1g**



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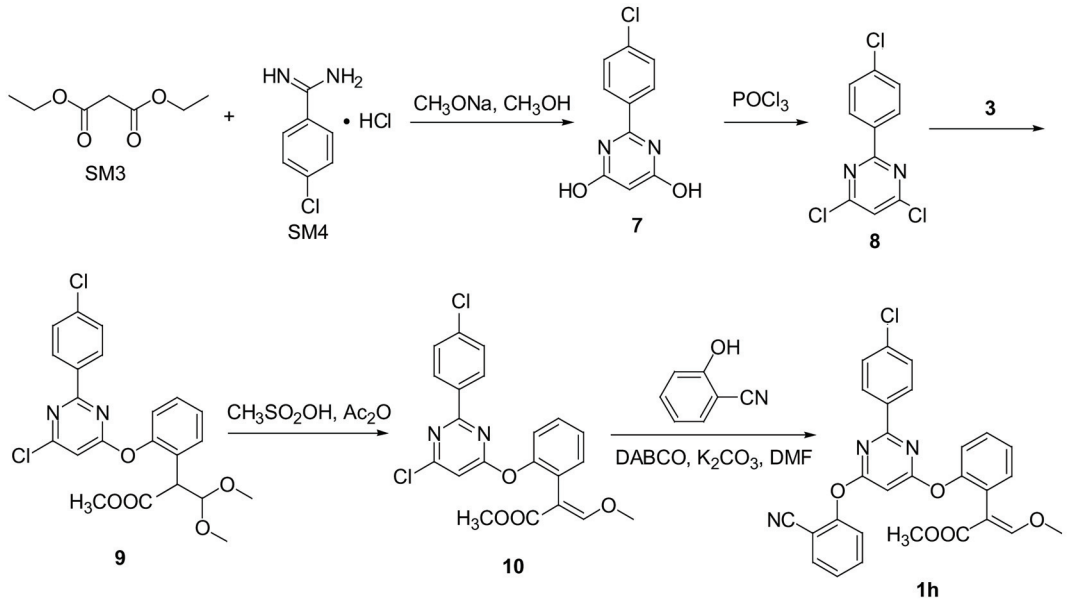
Scheme 2 Synthetic route of compound **1h**



of the strobilurin derivatives, the commercial fungicide, azoxystrobin was used as a positive control. The antifungal results of all the compounds against *Colletotrichum orbiculare*, *Botrytis cinerea* Pers and *Phytophthora capsici* Leonian were listed in Table 1.

Table 1 Antifungal activities of β-methoxyacrylate derivatives **1** (50 μg/mL, relative inhibitory rate/%)

Entry	Compd.	Antifungal activity (inhibitory rate/%)		
		Colletotrichum orbiculare	*Botrytis cinerea* Pers	*Phytophthora capsici* Leonian
1	**1a**	75	79	77
2	**1b**	48	27	42
3	**1c**	69	66	65
4	**1d**	59	53	46
5	**1e**	64	56	55
6	**1f**	67	62	64
7	**1g**	42	47	24
8	**1h**	71	73	22
9	Azoxystrobin	68	63	69

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, and the results provided useful information to study the structure-activity relationship (SAR) for these new structures. 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 **1a** (R＝methyl) displayed the most promising results, and exhibited better antifungal activity against all the tested fungi than azoxystrobin.

The antifungal activities against all the tested fungi are influenced by the nature of the substituted group in pyrimidine. When substituted group in pyrimidine was changed from an electron-donating group (R＝methyl or methylthio) to an electron-withdrawing group (R＝Cl), a significant reduction in antifungal activity was observed (**1b** versus **1a**, **1c**). It was supposed that the electron-withdrawing group in pyrimidine decreased the Hydrophile-Lipophile Balance (HLB) value of molecule.

When replacing the methyl of substituent position in phenyl, 4-Me-Ph derivative **1f** displayed a little better antifungal activity against all of the tested fungi (67%, 62% and 64%) than corresponding 2-Me-Ph derivative **1d** (59%, 53% and 46%) and 3-Me-Ph derivative **1e** (64%, 56% and 55%). Preliminary SAR presumed that the sequence of antifungal activity against all of the tested fungi is 4-substituted phenyl derivative＞3-substituted phenyl derivative＞2-substituted phenyl derivative (**1d** versus **1e** and **1f**). Compound **1g** by replacing the phenyl substituent attached to the pyrimidine ring with pyridine-2-thiol, a noticeable reduction in antifungal activity was observed against all the tested fungi (**1g** versus **1d**, **1e**, **1f**). It was supposed that antifungal activity decreased gradually with decreasing density of the electron cloud on the pyrimidine ring.

It was expected to improve the antifungal activity by introducing aromatic group in the side of pyrimidine by ring closing reaction. Interestingly, compound **1h** displayed strong antifungal activity (71% and 73% respectively) against *Colletotrichum orbiculare* and *Botrytis cinerea*, but exhibited low antifungal activity (22%) against *Phytophthora capsici* Leonian.

In addition, as shown in Table 1, compound 1a was found to display broad spectrum of fungicidal activity, and then was selected for further tests, and azoxystrobin was used as a control to make a judgment on the fungicidal potency of the compound. As shown in Table 2, compound **1a** has IC50 values of 14.3, 18.2 and 9.9 μg/mL in preventive treatment against *Colletotrichum orbiculare*, *Botrytis cinerea* Pers and *Phytophthora capsici* Leonian, respectively. The IC50 values of compound **1a** against all the tested fungi are better than those of the commercial strobilurin fungicide azoxystrobin.

Experimental

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 *v* values were recorded in wavenumbers (cm^{-1}). ^1H NMR spectra were performed in $CDCl_3$ or DMSO-d_6 solution by 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. 4,6-Dichloro-2-methylpyrimidine, 2,4,6-trichloropyrimidine, 4,6-dichloro-2-(methylthio)pyrimidine, azoxystrobin were purchased from Sigma Chemical Co., Ltd.

Synthesis of 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 ℃ 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, DMSO-d_6) δ: 4.20 (s, 3H, OCH3), 7.15—7.19 (m, 2H, 4,6-ArH), 7.26—7.28 (m, 1H, 5-ArH), 7.53 (d, J=8.0 Hz, 1H, 3-ArH), 7.95 (s, 1H, =CHOCH$_3$); ESI *m*/*z*: 177 $(M+H)^+$.

Synthesis of 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 ℃, 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 1 h (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 (30 mL×3), 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. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.31 (s, 3H, $CHOCH_3$), 3.48 (s, 3H, $CHOCH_3$), 3.75 (s, 3H, CO_2CH_3), 4.04 (d, J=8.0 Hz, 1H, $CHCOOCH_3$), 4.14 (s, 1H, OH), 5.01 (d, J=8.0 Hz, 1H, $CHOCH_3$), 7.07 (d, J=8.0 Hz, 1H, 3-ArH), 7.12—7.14 (m, 1H, 5-ArH), 7.19—7.24 (m, 1H, 4-ArH), 7.57 (d, J=8.0 Hz, 1H, 6-ArH). ESI *m*/*z*: 263 $(M+Na)^+$.

General procedure for the preparation of the compounds 4d—4g

Sodium hydride (60%, dispersion in oil, 4.5 mmol) was added slowly in portions to a stirred solution of the corresponding thiophenols (3 mmol) in dry tetrahyrofuran (10 mL) at 0 ℃ under an atmosphere of nitrogen, and the resulting mixture was 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 1 h. The reaction mixture was poured into cool H_2O (20 mL) and was extracted with ethyl acetate (10 mL×3), the combined ethyl acetate extracts were washed with brine, 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-(*o*-tolylthio)pyrimidine (4d) Yield 67%, white solid; ^1H NMR (400 MHz, $CDCl_3$) δ:

Table 2 Preventive fungicide activities (%) of compound **1a**

	Colletotrichum orbiculare					*Botrytis cinerea Pers*					*Phytophthora capsici Leonian*				
	Pathogen concn./(μg•mL^{-1})				IC50/	Pathogen concn./(μg•mL^{-1})				IC50/	Pathogen concn./(μg•mL^{-1})				IC50/
	100	50	25	12.5	(μg•mL^{-1})	100	50	25	12.5	(μg•mL^{-1})	100	50	25	12.5	(μg•mL^{-1})
1a	81	75	62	47	14.3	84	79	54	39	18.2	89	77	69	54	9.9
Azoxystrobin	79	68	55	46	17.1	71	63	36	11	50.4	87	69	61	47	15.9

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2.42 (s, 3H, CH_3), 7.01 (s, 1H, CH-Py), 7.25—7.28 (m, 1H, 3-ArH), 7.36—7.39 (m, 2H, 4,5-ArH), 7.56 (d, J= 8.0 Hz, 1H, 6-ArH); *m*/*z* (ESI): 271 $(M+H)^+$.

4,6-Dichloro-2-(*m*-tolylthio)pyrimidine (4e) Yield 62%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H, CH_3), 7.02 (s, 1H, CH-Py), 7.27 (s, 1H, 2-ArH), 7.31 (t, J=12.0 Hz, 1H, 4-ArH), 7.38 (d, J= 12.0 Hz, 2H, 5,6-ArH); *m*/*z* (ESI): 271 $(M+H)^+$, 282 $(M+Na)^+$.

4,6-Dichloro-2-(*p*-tolylthio)pyrimidine (4f) Yield 79%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H, CH_3), 7.01 (s, 1H, CH-Py), 7.23 (d, J=12.0 Hz, 2H, 2,6-ArH), 7.45 (d, J=12.0 Hz, 2H, 3,5-ArH); *m*/*z* (ESI): 271 $(M+H)^+$, 282 $(M+Na)^+$.

4,6-Dichloro-2-(pyridin-2-ylthio)pyrimidine (4g) Yield 61%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.01 (s, 1H, CH-Py), 7.26—7.27 (m, 1H, 4-PyH), 7.70 (d, J=4.0 Hz, 2H, 5,6-PyH), 8.58 (d, J=4.0 Hz, 1H, 3-PyH); *m*/*z* (ESI): 258 $(M+H)^+$.

General procedure for the preparation of the compounds 5a—5g

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 ℃ for 8 h. The reaction mixture was poured into cool H_2O (30 mL) and was extracted with ethyl acetate (20 mL×3), 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-methylpyrimidin-4-yloxy)-phenyl)-3,3-dimethoxypropanoate (5a) Yield 73%, yellow solid; 1H NMR (400 MHz, $CDCl_3$) δ: 2.58 (s, 3H, CH_3), 3.18 (s, 3H, $CHOCH_3$), 3.42 (s, 3H, $CHO-CH_3$), 3.59 (s, 3H, CO_2CH_3), 4.19 (d, J=8.0 Hz, 1H, $CHCOOCH_3$), 4.98 (d, J=8.0 Hz, 1H, $CHOCH_3$), 6.59 (s, 1H, CH-Py), 7.09 (d, J=8.0 Hz, 1H, 3'-ArH), 7.31—7.40 (m, 2H, 4',5'-ArH), 7.65 (d, J=8.0 Hz, 1H, 6'-ArH); *m*/*z* (ESI): 367 $(M+H)^+$, 389 $(M+Na)^+$.

Methyl 2-(2-(2,6-dichloropyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5b) Yield 58%, yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.10 (s, 3H, $CHOCH_3$), 3.32 (s, 3H, $CHOCH_3$), 3.49 (s, 3H, CO_2CH_3), 4.01 (d, J=8.0 Hz, 1H, $CHCOOCH_3$), 5.00 (d, J=8.0 Hz, 1H, $CHOCH_3$), 7.29 (d, J=8.0 Hz, 1H, 3'-ArH), 7.35—7.39 (m, 1H, 5'-ArH), 7.42—7.46 (m, 1H, 4'-ArH), 7.51 (s, 1H, CH-Py), 7.62 (d, J=8.0 Hz, 1H, 6'-ArH); ESI *m*/*z*: 387 $(M+H)^+$, 409 $(M+Na)^+$.

Methyl 2-(2-(6-chloro-2-(methylthio)pyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5c) Yield 66%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.22 (s, 3H, SCH_3), 3.16 (s, 3H, $CHOCH_3$), 3.42 (s, 3H, $CHOCH_3$), 3.58 (s, 3H, CO_2CH_3), 4.15 (d, J=8.0 Hz, 1H, $CHCOOCH_3$), 4.15 (d, J=8.0 Hz, 1H, $CHOCH_3$), 6.52 (s, 1H, CH-Py), 7.08 (d, J=8.0 Hz, 1H, 3'-ArH), 7.29—7.38 (m, 2H, 4',5'-ArH), 7.62 (d, J=4.0 Hz, 1H, 6'-ArH); ESI *m*/*z*: 399 $(M+H)^+$, 421 $(M+Na)^+$.

Methyl 2-(2-(6-chloro-2-(*o*-tolylthio)pyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5d) yield 52%, White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.17 (s, 3H, CH_3), 3.01 (s, 3H, $CHOCH_3$), 3.33 (s, 3H, $CHO-CH_3$), 3.50 (s, 3H, CO_2CH_3), 4.02 (d, J=8.0 Hz, 1H, $CHCOOCH_3$), 4.83 (d, J=8.0 Hz, 1H, $CHOCH_3$), 6.48 (s, 1H, CH-Py), 6.75 (d, J=8.0 Hz, 1H, 3'-ArH), 6.98—7.00 (m, 1H, 5'-ArH), 7.02—7.06 (m, 2H, 3,5-ArH), 7.10 (t, J=8.0 Hz, 1H, 4'-ArH), 7.15 (t, J=8.0 Hz, 1H, 4-ArH), 7.32 (d, J=8.0 Hz, 1H, 6'-ArH), 7.42 (d, J= 8.0 Hz, 1H, 6-ArH); ESI *m*/*z*: 443 $(M+H)^+$.

Methyl 2-(2-(6-chloro-2-(*m*-tolylthio)pyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5e) Yield 61%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3), 3.08 (s, 3H, $CHOCH_3$), 3.40 (s, 3H, $CHOCH_3$), 3.58 (s, 3H, CO_2CH_3), 4.08 (d, J=8.0 Hz, 1H, $CHCOOCH_3$), 4.92 (d, J=8.0 Hz, 1H, $CHOCH_3$), 6.57 (s, 1H, CH-Py), 6.85 (d, J=8.0 Hz, 1H, 3'-ArH), 7.07—7.14 (m, 2H, 4,5'-ArH), 7.16—7.23 (m, 4H, 2,5,4',6'-ArH), 7.51 (d, J=8.0 Hz, 1H, 6-ArH); *m*/*z* (ESI): 443 $(M+H)^+$; ESI *m*/*z*: 475 $(M+H)^+$, 497 $(M+Na)^+$.

Methyl 2-(2-(6-chloro-2-(*p*-tolylthio)pyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5f) Yield 57%, light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (s, 3H, CH_3), 3.09 (s, 3H, $CHOCH_3$), 3.40 (s, 3H, $CHOCH_3$), 3.57 (s, 3H, CO_2CH_3), 4.07 (d, J=8.0 Hz, 1H, $CHCOOCH_3$), 4.91 (d, J=8.0 Hz, 1H, $CHOCH_3$), 6.57 (s, 1H, CH-Py), 6.85 (d, J=8.0 Hz, 1H, 3'-ArH), 6.96 (d, J=12.0 Hz, 1H, 6'-ArH), 7.14 (d, J=8.0 Hz, 2H, 3,5-ArH), 7.20—7.24 (m, 2H, 4',5'-ArH), 7.51 (d, J=12.0 Hz, 2H, 2,6-ArH); *m*/*z* (ESI): 443 $(M+H)^+$; ESI *m*/*z*: 475 $(M+H)^+$, 497 $(M+Na)^+$.

Methyl 2-(2-(6-chloro-2-(pyridin-2-ylthio)pyrimidin-4-yloxy)phenyl)-3,3-dimethoxypropanoate (5g) Yield 62%, light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.03 (s, 3H, CH_3), 3.33 (s, 3H, CO_2CH_3), 3.47 (s, 3H, =$CHOCH_3$), 3.98 (d, J=8.0 Hz, 1H, $CHCOOCH_3$), 4.85 (d, J=8.0 Hz, 1H, $CHOCH_3$), 6.60 (s, 1H, CH-Py), 6.87 (d, J=8.0 Hz, 1H, ArH), 7.11—7.14 (m, 3H, 4',5',6'-ArH), 7.25 (t, J=8.0 Hz, 1H, 4-PyH), 7.33 (t, J=12.0 Hz, 1H, 5-PyH), 7.48 (d, J= 8.0 Hz, 1H, 6-PyH), 8.36 (d, J=8.0 Hz, 1H, 3-PyH); ESI *m*/*z*: 462 $(M+H)^+$, 484 $(M+Na)^+$.

General procedure for the preparation of the compounds 6a—6g

Methane sulphonic 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 ℃

for 2 h. The reaction mixture was poured into cool H_2O (30 mL) and was extracted with ethyl acetate (20 mL×3), the organic layer was washed with brine and followed by drying with anhydrous sodium sulfate. The solvent was removed from the filtrate in vacuo to give the residue **6**, which was used for the next step without further purification.

(*E*)-Methyl 2-(2-(6-chloro-2-methylpyrimidin-4-yloxy) phenyl)-3-methoxyacrylate (6a) Yield 90%, yellow solid; ESI *m/z*: 335 $(M+H)^+$, 357 $(M+Na)^+$.

(*E*)-Methyl 2-(2-(2,6-dichloropyrimidin-4-yloxy) phenyl)-3-methoxyacrylate (6b) Yield 86%, yellow solid; ESI *m/z*: 355 $(M+H)^+$, 377 $(M+Na)^+$.

(*E*)-Methyl 2-(2-(6-chloro-2-(methylthio)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6c) Yield 88%, white solid; ESI *m/z*: 367 $(M+H)^+$, 389 $(M+Na)^+$.

(*E*)-Methyl 2-(2-(6-chloro-2-(*o*-tolylthio)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6d) Yield 86%, white solid; ESI *m/z*: 443 $(M+H)^+$, 465 $(M+Na)^+$.

(*E*)-Methyl 2-(2-(6-chloro-2-(*m*-tolylthio)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6e) Yield 90%, white solid; ESI *m/z*: 443 $(M+H)^+$, 465 $(M+Na)^+$.

(*E*)-Methyl 2-(2-(6-chloro-2-(*p*-tolylthio)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6f) Yield 89%, light yellow solid; *m/z* (ESI): 443 $(M+H)^+$, 465 $(M+Na)^+$.

(*E*)-Methyl 2-(2-(6-chloro-2-(pyridin-2-ylthio) pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (6g) Yield 82%, light yellow solid; ESI *m/z*: 430 $(M+H)^+$, 451 $(M+Na)^+$.

General procedure for the preparation of the target compounds 1a—1g

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 ℃ for 2 h (the reaction was monitored by TLC). The mixture was poured into cool H_2O (40 mL) and was extracted with dichloromethane (20 mL×3), 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-methylpyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1a) Yield 71%, yellow solid, m.p. 99—104 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43 (s, 3H, CH_3), 3.64 (s, 3H, CO_2CH_3), 3.77 (s, 3H, $=CHOCH_3$), 6.08 (s, 1H, CH-Py), 7.19 (d, J=8.0 Hz, 1H, 3'-ArH), 7.28—7.34 (m, 4H, 4',5',4",6"-ArH), 7.38—7.42 (m, 1H, 6'-ArH), 7.49 (s, 1H, $=CHOCH_3$), 7.60 (t, J=12.0 Hz, 1H, 5"-ArH), 7.67 (d, J=8.0 Hz, 1H, 3"-ArH); IR (KBr) ν: 2950 (C—H), 2233 (C≡N), 1710 (C=O), 1634 (C=C), 1590, 1567 (Ar) cm^{-1}; ESI *m/z*: 418 $(M+H)^+$, 440 $(M+Na)^+$. Anal. calcd for $C_{23}H_{19}N_3O_5$ (417.1): C 66.18, H 4.59, N 10.07; found C 66.07, H 4.79, N 9.92.

(*E*)-Methyl-2-(2-(2-chloro-6-(2-cyanophenoxy)-pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1b) Yield 76%, light yellow solid; m.p. 102—106 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.50 (s, 3H, CO_2CH_3), 3.72 (s, 3H, $=CHOCH_3$), 6.90 (s, 1H, CH-Py), 7.00 (d, J=8.0 Hz, 1H, 3'-ArH), 7.26—7.28 (m, 2H, 4',5'-ArH), 7.35—7.39 (m, 1H, 6"-ArH), 7.48—7.53 (m, 2H, 6',4"-ArH), 7.58 (s, 1H, $=CHOCH_3$), 7.77 (t, J=8.0 Hz, 1H, 5"-ArH), 7.93 (d, J=8.0 Hz, 1H, 3"-ArH); IR (KBr) ν: 2950 (C—H), 2231 (C≡N), 1710 (C=O), 1630 (C=C), 1594, 1567 (Ar) cm^{-1}; ESI *m/z*: 438 $(M+H)^+$, 460 $(M+Na)^+$. Anal. calcd for $C_{22}H_{16}ClN_3O_5$: (437.1): C 60.35, H 3.68, N 9.60; found C 60.27, H 3.79, N 9.49.

(*E*)-Methyl-2-(2-(6-(2-cyanophenoxy)-2-(methylthio)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1c) Yield 82%, white solid; m.p. 123—127 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.22 (s, 3H, SCH_3), 3.65 (s, 3H, CO_2CH_3), 3.78 (s, 3H, $=CHOCH_3$), 6.00 (s, 1H, CH-Py), 7.19 (d, J=8.0 Hz, 1H, 3'-ArH), 7.28—7.40 (m, 5H, 4',5',6',4",6"-ArH), 7.52 (s, 1H, $=CHOCH_3$), 7.60 (t, J=12.0 Hz, 1H, 5"-ArH), 7.67 (d, J=8.0 Hz, 1H, 3"-ArH); IR (KBr) ν: 2950 (C—H), 2231 (C≡N), 1710 (C=O), 1630 (C=C), 1594, 1567 (Ar); ESI *m/z*: 450 $(M+H)^+$, 472 $(M+Na)^+$. Anal. calcd for $C_{23}H_{19}N_3O_5S$ (449.1): C 61.46, H 4.26, N 9.35; found C 61.27, H 4.42, N 9.29.

(*E*)-Methyl-2-(2-(6-(2-cyanophenoxy)-2-(*o*-tolylthio)-pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1d) Yield 78%, white solid; m.p. 119—121 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.25 (s, 3H, CH_3), 3.69 (s, 3H, CO_2CH_3), 3.81 (s, 3H, $=CHOCH_3$), 6.02 (s, 1H, CH-Py), 7.03—7.06 (m, 3H, 3,3',5'-ArH), 7.16 (t, J=8.0 Hz, 1H, 5-ArH), 7.18—7.23 (m, 2H, 4,6"-ArH), 7.28—7.30 (m, 1H, 4'-ArH), 7.33 (t, J=12.0 Hz, 2H, 6,4"-ArH), 7.40 (t, J=12.0 Hz, 2H, 6',5"-ArH), 7.50 (d, J=4.0 Hz, 1H, 3"-ArH), 7.54 (s, 1H, $=CHOCH_3$); IR (KBr) ν: 2950 (C—H), 2233 (C≡N), 1711 (C=O), 1635 (C=C), 1591, 1567 (Ar); ESI *m/z*: 526 $(M+H)^+$, 548 $(M+Na)^+$. Anal. calcd for $C_{29}H_{23}N_3O_5S$ (525.1): C 66.27, H 4.41, N 8.00; found C 66.05, H 4.59, N 7.76.

(*E*)-Methyl-2-(2-(6-(2-cyanophenoxy)-2-(*m*-tolylthio)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1e) Yield 86%, white solid; m.p. 115—117 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.15 (s, 3H, CH_3), 3.58 (s, 3H, CO_2CH_3), 3.71 (s, 3H, $=CHOCH_3$), 5.92 (s, 1H, CH-Py), 6.97 (t, J=12.0 Hz, 3H, 4,3',5'-ArH), 7.05 (d, J=8.0 Hz, 1H, 6-ArH), 7.10—7.14 (m, 3H, 2,5,4'-ArH), 7.18—7.20 (m, 1H, 6"-ArH), 7.23 (t, J=12.0 Hz, 2H, 6',4"-ArH), 7.32 (t, J=8.0 Hz, 1H, 5"-ArH), 7.39 (t, J=12.0 Hz, 1H, 3"-ArH), 7.43 (s, 1H, $=CHOCH_3$); IR (KBr) ν: 2950 (C—H), 2233 (C≡N), 1714 (C=O), 1635 (C=C), 1591, 1568 (Ar); ESI *m/z*: 526 $(M+H)^+$, 548 $(M+Na)^+$. Anal. calcd for $C_{29}H_{23}N_3O_5S$ (525.1): C 66.27, H 4.41, N 8.00; found C 66.07, H 4.59, N 7.81.

(*E*)-Methyl 2-(2-(6-(2-cyanophenoxy)-2-(*p*-tolylthio)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1f) Yield 85%, light yellow solid; m.p. 100—104 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.25 (s, 3H, CH_3), 3.58 (s, 3H, CO_2CH_3), 3.71 (s, 3H, =CHOCH$_3$), 5.91 (s, 1H, CH-Py), 6.86 (d, J=8.0 Hz, 2H, 3,5-ArH), 6.97 (d, J=8.0 Hz, 1H, 3'-ArH), 7.05 (d, J=4.0 Hz, 1H, 6''-ArH), 7.13—7.17 (m, 3H, 4',5',4''-ArH), 7.20—7.21 (m, 1H, 6'-ArH), 7.23—7.25 (m, 2H, 2,6-ArH), 7.32 (t, J=12.0 Hz, 1H, 5''-ArH), 7.43 (s, 1H, =CHOCH$_3$), 7.43 (d, J=4.0 Hz, 1H, 3''-ArH); IR (KBr) v: 2958 (C—H), 2233 (C≡N), 1715 (C=O), 1635 (C=C), 1595, 1568 (Ar); ESI m/z: 526 (M+H)$^+$, 548 (M+Na)$^+$. Anal. calcd for $C_{29}H_{23}N_3O_5S$ (525.1): C 66.27, H 4.41, N 8.00; found C 66.13, H 4.54, N 7.89.

(*E*)-Methyl 2-(2-(6-(2-cyanophenoxy)-2-(pyridin-2-ylthio)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1g) Yield 77%, light grey solid; m.p. 102—106 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.57 (s, 3H, CO_2CH_3), 3.69 (s, 3H, =CHOCH$_3$), 6.02 (s, 1H, CH-Py), 6.98 (t, J=8.0 Hz, 1H, 3'-ArH), 7.05—7.09 (m, 2H, 4',5'-ArH), 7.19—7.22 (m, 1H, 6''-ArH), 7.24—7.28 (m, 3H, 4,6',4''-ArH), 7.42 (s, 1H, =CHOCH$_3$), 7.43—7.47 (m, 2H, 5,5''-PyH), 7.50 (d, J=8.0 Hz, 1H, 6-PyH), 7.64 (d, J=8.0 Hz, 1H, 3''-ArH), 8.33 (d, J=4.0 Hz, 1H, 3-PyH); IR (KBr) v: 2950 (C—H), 2233 (C≡N), 1715 (C=O), 1635 (C=C), 1595, 1568 (Ar); ESI m/z: 513 (M+H)$^+$, 535 (M+Na)$^+$. Anal. calcd for $C_{27}H_{20}N_4O_5S$ (512.1): C 63.27, H 3.93, N 10.93; found C 63.15, H 4.16, N 10.76.

Procedure for the preparation of target compound 1h

Synthesis of 2-(4-chlorophenyl)pyrimidine-4,6-diol (7) Sodium (115 mg, 5 mmol) was added slowly in portions to 10 mL of CH_3OH with stirring at −10 ℃, and the reaction was stirred for 30 min. The resulting mixture was added to the solution of diethyl malonate (640 mg, 4 mmol) and 4-chlorobenzamidine hydrochloride (760 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 h. Then the mixture was cooled to room temperature and concentrated under reduced pressure. The crude was dissolved in water, and acidified with 2 equiv. hydrochloric acid. White solid obtained was filtered off, washed with water and dried to afford the compound **7** (430 mg, 49%) as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.37 (s, 1H, CH-Py), 7.58 (d, J=8.0 Hz, 2H, 3,5-ArH), 8.10 (d, J=8.0 Hz, 2H, 2,6-ArH), 11.82—11.95 (bs, 2H, Py-OH); ESI m/z: 223 (M+H)$^+$.

Synthesis of 4,6-dichloro-2-(4-chlorophenyl)pyrimidine (8) A mixture of **7** (300 mg, 1.4 mmol) in phosphorus oxychloride (4 mL, 40.8 mmol) was heated to 110 ℃ for 3 h. The resulting mixture was added to crushed ice (50 mL) and extracted with ethyl acetate (20 mL × 3), the combined ethyl acetate extracts were washed with brine, 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** (320 mg, 90%) as a light gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (s, 1H, CH-Py), 7.45—7.47 (m, 2H, 3,5-ArH), 8.38 (d, J=8.0 Hz, 2H, 2,6-ArH); ESI m/z: 259 (M+H)$^+$.

Synthesis of 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, $CHOCH_3$), 3.40 (s, 3H, $CHOCH_3$), 3.42 (s, 3H, CO_2CH_3), 4.18 (d, J=12.0 Hz, 1H, $CHCOOCH_3$), 4.97 (d, J=12.0 Hz, 1H, $CHOCH_3$), 6.77 (s, 1H, CH-Py), 7.13 (d, J=12.0 Hz, 1H, 3'-ArH), 7.34—7.40 (m, 4H, 3,5,4',5'-ArH), 7.67—7.70 (m, 1H, 6'-ArH), 8.13 (d, J=12.0 Hz, 2H, 2,6-ArH); ESI m/z: 463 (M+H)$^+$, 485 (M+Na)$^+$.

Synthesis of (*E*)-methyl 2-(2-(6-chloro-2-(4-chlorophenyl)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (10) Compound **10** was prepared from the intermediate **9** (200 mg, 0.43 mmol) by the same procedure as that of **6**. Compound **10** was obtained as a white solid (172 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.48 (s, 3H, CO_2CH_3), 3.69 (s, 3H, =CHOCH$_3$), 6.57 (s, 1H, CH-Py), 7.14 (d, J=8.0 Hz, 1H, 3'-ArH), 7.26—7.28 (m, 2H, 4',5'-ArH), 7.29—7.32 (m, 2H, 3,5-ArH), 7.34—7.36 (m, 2H, 6'-ArH and =CHOCH$_3$), 8.16 (d, J=8.0 Hz, 2H, 2,6-ArH); ESI m/z: 431 (M+H)$^+$; 452 (M+Na)$^+$.

Synthesis of (*E*)-methyl 2-(2-(2-(4-chlorophenyl)-6-(2-cyanophenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate (1h) The target compound **1h** was obtained as a light yellow solid (120 mg, 87%) by the same procedure as that of **1**. m.p. 117—120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.52 (s, 3H, CO_2CH_3), 3.64 (s, 3H, =CHOCH$_3$), 6.21 (s, 1H, CH-Py), 7.24 (t, J=12.0 Hz, 1H, 3'-ArH), 7.29 (t, J=12.0 Hz, 2H, 4',5'-ArH), 7.33—7.36 (m, 1H, 6''-ArH), 7.38—7.40 (m, 2H, 4'',5''-ArH), 7.41 (s, 1H, =CHOCH$_3$), 7.43 (d, J=4.0 Hz, 2H, 3,5-ArH), 7.60—7.63 (m, 1H, 6'-ArH), 7.67 (d, J=4.0 Hz, 1H, 3''-ArH), 7.91 (d, J=4.0 Hz, 2H, 2,6-ArH); IR (KBr) v: 2948 (C—H), 2230 (C≡N), 1714 (C=O), 1635 (C=C), 1595, 1568 (Ar); ESI m/z: 514 (M+H)$^+$, 536 (M+Na)$^+$. Anal. calcd for $C_{28}H_{20}ClN_3O_5$ (513.1): C 65.44, H 3.92, N 8.18; found C 65.17, H 4.07, N 8.02.

Biological activities

The fungistatic activities of the synthesized com-

pounds were measured 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. The solutions (1 mL) were thoroughly mixed by shaking with thawed potato glucose (for C*olletotrichum 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 ℃. 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 d later. The growth inhibition rates were calculated with the following equation: $Y=[(CK-A)/CK]\times 100\%$. Here, Y is the growth inhibition rate, CK is the control settlement radius, and A is the treatment group fungi settlement radius.

Conclusions

Eight novel *β*-methoxyacrylate derivatives (**1a**—**1h**) 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 **1a** (R＝methyl) displayed the most promising results, and exhibited better antifungal activity against all the tested fungi than the reference commercial fungicide azoxystrobin. Expecting to find some new type strobilurin fungicides with high activities and low toxicities, further structural optimization and antifungal test by using *β*-methoxyacrylate derivatives are in progress.

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