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Synthesis and Fungicidal Activities of Novel Bis(trifluoromethyl)phenyl-Based Strobilurins

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Strobilurins have become one of the most important classes of agricultural fungicides. To search for novel strobilurin compounds with unique biological activities, novel bis(trifluoromethyl)phenyl-based strobilurin analogues were synthesized by the reaction of 1-bis(trifluoromethyl)phenyl based methanone oxime with corresponding strobilurin pharmacophores in the presence of bases such as potassium hydroxide, potassium carbonate, or sodium hydride. (*E*)-Methyl 2-(2-((((*Z*)(1-(3,5-bis(trifluoromethyl) phenyl)-1-methoxymethylidene)amino)oxy)methyl)phenyl)-3-methoxyacrylate and (*Z*)-methyl-*N*-(*E*)-2-((*E*)-(5,6-dihydro-1,4,2-dioxazin-3-yl)(methoxyimino)methyl)benzyloxy-3,5-bis(trifluoromethyl)benzimidate were more effective against *Erysiphe graminis* and *sphaerotheca fuligine* than commercial strobilurin fungicides metominostrobin, azoxystrobin, and trifloxystrobin.

KEYWORDS: Strobilurins; fungicide; bis(trifluoromethyl)phenyl; structure−activity relationships

INTRODUCTION

Strobilurins and oudemansins are naturally occurring β-methoxyacrylate fungicides. Their primary mechanism of action is the inhibition of mitochondrial respiration. Since 1996, thousands of analogues of diverse structures have been synthesized (*1–8*) leading to over 10 commercialized products including metominostrobin, azoxystrobin, and trifloxystrobin (**Figure 1**).

Strobilurins have become one of the most important classes of agricultural fungicides due to their positive attributes such as a novel action mode, broad fungicidal spectrum, lower toxicity toward mammalian cells, and environmentally benign characteristics. However, a short period of repeated field application of strobilurin fungicides has led to the development of resistance in a range of important plant pathogens (*9, 10*). As a consequence, new types of fungicides must be continually developed to overcome this problem.

In our previous work, a series of novel sulfur-containing oxime-ethers (**Figure 1**) had shown remarkable insecticidal activity, but their fungicidal activity was weak (*11–14*). To search for novel strobilurin compounds with unique biological activities, an optimization program was carried out by introducing the essential pharmacophore T (**Figure 2**) of the commercialized strobilurin fungicides to oxime-ethers (**Figure 3**). Compounds containing the bis(trifluoromethyl)phenyl moiety showed remarkable fungicidal, insecticidal, and/or acaricidal activities. Compounds **5f** [(*E*)-methyl 2-(2-((((*Z*)(1-(3,5-bis(trifluoromethyl)phenyl)-1-methoxymethylidene)amino)oxy) methyl)phenyl)-3-methoxyacrylate] and **5h** [(*Z*)-methyl-*N*-(*E*)-2-((*E*)-(5,6-dihydro-1,4,2-dioxazin-3-yl)(methoxyimino)methyl)benzyloxy-3,5-bis(trifluoromethyl)benzimidate] (**Figure 4**) possess commercial levels of fungicidal activity comparable to those of commercial strobilurin fungicides such as metominostrobin, azoxystrobin, and trifloxystrobin; **5f** also exhibits potent insecticidal activities, and **5a** [(*E*)-methyl-2-(2-((((*Z*)(1-(3,5-bis(trifluoromethyl)phenyl)-1-methylthiomethylidene)amino)oxy)methyl)phenyl)-3-methoxyacrylate] gave good control against adults, larva, and eggs of various acarids and possesses a level of acaricidal activity comparable to those of commercial acaricides such as fluacyprim, tebufenpyrad, and chlorfenapyr.

This paper reports the synthesis, fungicidal activity, and the structure−activity relationships of the target bis(trifluoromethyl)phenyl-based strobilurins (**Figure 3**).

MATERIALS AND METHODS

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. ^{1}H NMR spectra were obtained with a Varian INOVA-300 spectrometer using tetramethylsilane (TMS) as the internal standard and deuterochloroform ($CDCl_3$) as the solvent. Mass spectra (MS) were obtained with both Hewlett-Packard 6890-5973 GC/MS and Agilent 1100 Series LC/MSD. Uncorrected melting points were taken on a WRS-1A digital melting points apparatus.

Synthesis. The general synthetic methods for compounds **5a**−**5v** are shown in **Figure 5**. Representative procedures are given below. Yields were not optimized. All reactions were carried out under a protective atmosphere of dry nitrogen or utilizing a calcium chloride tube.

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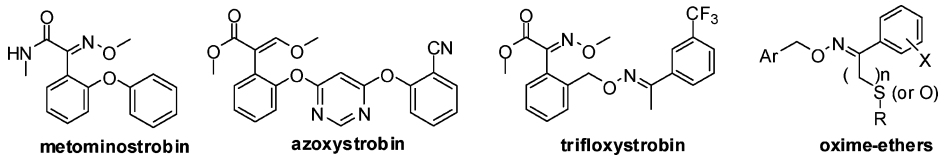


Figure 1. Structures of metominostrobin, azoxystrobin, trifloxystrobin, and oxime-ethers in our previous work.

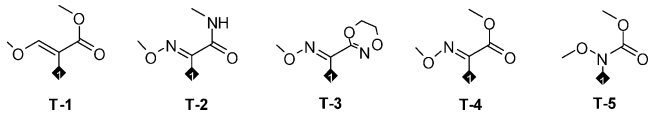


Figure 2. Structures of **T-1** to **T-5**: the essential pharmacophores of commercialized strobilurin fungicides.

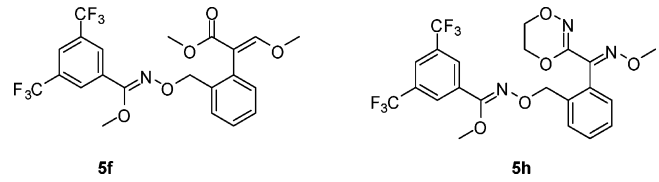


Figure 4. Structures of **5f** and **5h**.

*(Z)-3,5-Bis(trifluoromethyl)benzaldehyde Oxime (**2**).* 3,5-Bis(trifluoromethyl)benzaldehyde (**1**) (24.2 g, 0.10 mol) was added dropwise to a solution of hydroxyamine hydrochloride (7.30 g, 0.105 mol) in methanol (100 mL), and the reaction mixture was refluxed for 4−5 h. The reaction was cooled to room temperature and poured into ice−water. Precipitates formed, which were filtered and washed with cool methanol, then dried under vacuum to yield compound **2** as a white solid: 23.4 g (91.0%), mp 91.2−91.3 °C (lit. (*15*) 92−93 °C); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.88 (s, 1H, 4-Ph−H), 8.03 (s, 2H, 3,5-Ph−H), 8.22 (s, 1H, CH═); GC-MS (EI, 70Ev) (*m*/*z* 258 (M^+).

*N-Hydroxy-3,5-bis(trifluoromethyl)benzimidoyl Chloride (**3**).* *tert*-Butylhypochlorite (5.5 g, 0.05 mol) was added dropwise to a solution of compound **2** (12.85 g, 0.05 mol) in methanol (200 mL) at −5 to 0 °C over 0.5 h, and the reaction mixture was then stirred at the same temperature for an additional 1.0 h. Reaction solvent was evaporated under reduced pressure to give compound **3** as an oil: 13.08 g, 90.0% (GC), GC-MS (EI, 70Ev) (*m*/*z* 291 (M^+). Without further purification, compound **3** was used in the next reaction.

*Methyl-N-hydroxy-3,5-bis(trifluoromethyl)benzimidate (**4**).* Compound **3** (90.0%, 4.70 g, 14.5 mmol) was added dropwise to a solution of sodium methoxide in methanol (8.0 wt.%, 30.5 g, 45.0 mmol) at 15−20 °C. The reaction mixture was then stirred at the same temperature for an additional 1.0 h after which the reaction was poured into ice−water and extracted with ethyl ether (3 × 100 mL). The combined ether extracts were washed with water, dried (anhydrous magnesium sulfate), and filtered, and the solvent was removed under reduced pressure to yield compound **4** as a white viscous solid: 4.08 g, GC-MS (EI, 70Ev) (*m*/*z* 287 (M^+). Without further purification, compound **4** was used in the next reaction.

*(E)-Methyl-2-(2-((((Z)(1-(3,5-bis(trifluoromethyl)phenyl)-1-methoxymethylidene)amino)oxy) methyl)phenyl)-3-methoxyacrylate (**5f**).* A solution of compound **4** (70.5%, 2.85 g, 7.0 mmol) in *N,N*-dimethylformamide (DMF) (5 mL) was added dropwise over 0.5 h to a solution of potassium hydroxide (0.56 g, 10 mmol) in DMF (15 mL) at −5 to 0 °C. The mixture was stirred at the same temperature for 0.5 h then a solution of (*E*)-methyl-2-(2-(bromomethyl)phenyl)-3-methoxyacrylate (2.58 g, 9.0 mmol) in DMF (10 mL) was added dropwise. The mixture was stirred at 20−25 °C for 10−12 h. The reaction was poured into ice−water and extracted with ethyl ether. The combined ether extracts were washed with water, dried (anhydrous magnesium sulfate), and filtered, and the solvent was removed, The residue material was separated by silica-gel column chromatography with petroleum ether−ethyl acetate (15:1/10:1 by volume) as eluant to yield **5f** as a white solid: 1.01 g (27.9%), mp 86.3−86.6 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 3.69 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 5.06 (s, 2H, OCH_2), 7.17−8.18 (m, 8H, PhH + CH═); GC-MS (EI, 70Ev) (*m*/*z* 491 (M^+); LC-MS (APCI, Pos) (*m*/*z* 492 ($M^+ + 1$); calcd for $C_{22}H_{19}F_6NO_5$: C, 53.77; H, 3.90; N, 2.85; found: C, 53.91; H, 3.83; N, 2.88.

5a, **5c**−**5e**, and **5h**−**5t** could be synthesized by the method similar to that described in the synthesis of **5f**.

*(Z)-Methyl-N-2-((E)-1-(methoxyimino)-2-(methylamino)-2-oxoethyl)-benzyloxy-3,5-bis(trifluoro methyl)benzimidothioate (**5b**).* Compound **5a** (1.52 g, 3 mmol) was added to a solution of methylamine in methanol (30 wt.%, 5 mL). The reaction mixture was stirred at 20 °C for 15 h after which the reaction was continued as described in the synthesis of **5f** to yield compound **5g** as a white solid: 0.96 g (63.3%), mp 132.1−133.9 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 2.15 (s, 3H, SCH_3), 2.87 (d, J = 5.1 Hz, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 5.18 (s, 2H, OCH_2), 6.76 (s, 1H, NH), 7.19−7.95 (m, 7H, Ph−H); LC-MS(APCI, Pos) (*m*/*z* 508 ($M^+ + 1$); calcd for $C_{21}H_{19}F_6N_3O_3S$: C, 49.70; H, 3.77; N, 8.28; found: C, 49.86; H, 3.81; N, 8.16.

5g could be synthesized by the method similar to that described in the synthesis of **5b**.

*(E)-Methyl-2-(2-(((Z)(1-(3,5-bis(trifluoromethyl)phenyl)-1-methylsulfinyl)methylideneaminooxy) methyl)phenyl)-3-methoxyacrylate (**5u**).* Hydrogen peroxide (30 wt.%, 5 g) was added dropwise to a solution of **5a** (0.51 g, 1 mmol) in methanol (10 mL) and acetic acid (2 mL). The reaction mixture was stirred at 20 °C for 20 h after which the reaction was continued as described in the synthesis of **5f** to yield **5u** as an oil: 0.31 g (58%); ^{1}H NMR ($CDCl_3$) δ (ppm) 2.92 (s, 3H, $SOCH_3$), 3.69 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.24 (s, 2H, OCH_2), 7.18−8.18 (m, 8H, Ph−H + CH═); LC-MS(APCI, Pos) (*m*/*z* 524).

5v could be synthesized by the method similar to that described in the synthesis of **5u**.

Structures of **5a**−**5v** were supported by spectroscopic data shown in **Tables 1** and **2**.

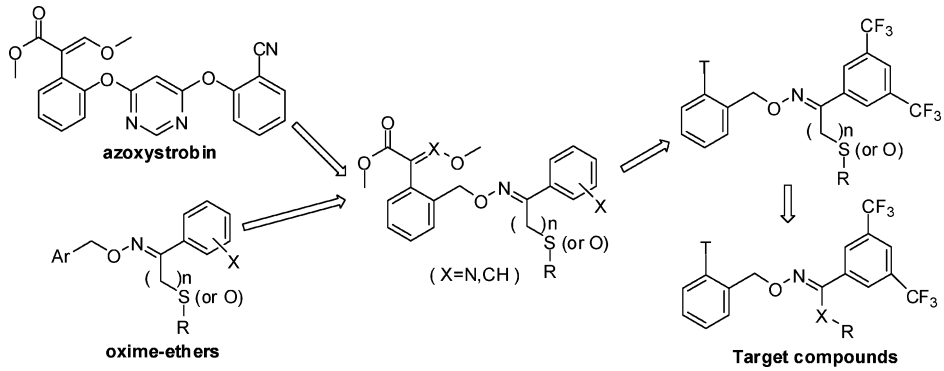


Figure 3. Design strategy of the target compounds containing bis(trifluoromethyl)phenyl.

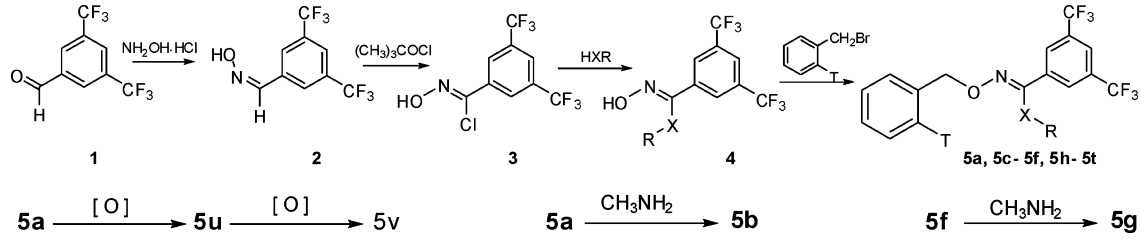
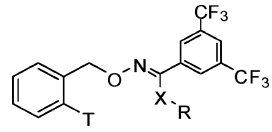


Figure 5. Synthetic pathways for the novel bis(trifluoromethyl)phenyl-based strobilurins.

Table 1. Chemical Structures, Physical Characteristics, Yield, and Preventive Activities against *Erysiphe graminis* (**7d**) of Compounds **5a**−**5v**



5a - 5v

	chemical structure										
compd	T[a]	X	R	formula	mp (°C)	yield[b] (%)	500 ppm	100 ppm	6.2 ppm	3.1 ppm	1.5 ppm
5a	T-1	S	CH_3	$C_{22}H_{19}F_6NO_4S$	79.6−80.1	28.9	100	100	98	93	75
5b	T-2	S	CH_3	$C_{21}H_{19}F_6N_3O_3S$	132.1−133.9	63.3	100	100	40	25	[a]
5c	T-3	S	CH_3	$C_{22}H_{19}F_6N_3O_4S$	oil	26.6	100	100	20	10	
5d	T-4	S	CH_3	$C_{21}H_{18}F_6N_2O_4S$	oil	27.4	100	80			
5e	T-5	S	CH_3	$C_{20}H_{18}F_6N_2O_4S$	oil	26.2	90	90	65	30	
5f	T-1	O	CH_3	$C_{22}H_{19}F_6NO_5$	86.3−86.6	27.9	100	100	100	100	98
5g	T-2	O	CH_3	$C_{21}H_{19}F_6N_3O_4$	156.5−157.4	55.1	90				
5h	T-3	O	CH_3	$C_{22}H_{19}F_6N_3O_5$	oil	28.2	100	100	100	96	95
5i	T-4	O	CH_3	$C_{21}H_{18}F_6N_2O_5$	71.6−73.7	29.6	100	100	100	98	80
5j	T-5	O	CH_3	$C_{20}H_{18}F_6N_2O_5$	oil	25.8	100	100	80	60	10
5k	T-1	NH	CH_3	$C_{22}H_{20}F_6N_2O_4$	oil	29.9	100	100	90	65	25
5l	T-4	NH	CH_3	$C_{21}H_{19}F_6N_3O_4$	89.6−89.9	32.1	100	100	93	90	70
5m	T-1	NH	H	$C_{21}H_{18}F_6N_2O_4$	113.5−114.7	23.6	100	95	90	75	40
5n	T-4	NH	H	$C_{20}H_{17}F_6N_3O_4$	viscous solid	25.2	30				
5o	T-1	O	CH_3CH_2	$C_{23}H_{21}F_6NO_5$	oil	31.6	100	100	90	60	35
5p	T-4	O	CH_3CH_2	$C_{22}H_{20}F_6N_2O_5$	oil	36.5	100	100	80	50	15
5q	T-1	S	CH_3CH_2	$C_{23}H_{21}F_6NO_4S$	oil	28.9	85				
5r	T-4	S	CH_3CH_2	$C_{22}H_{20}F_6N_2O_4S$	oil	38.8	85				
5s	T-1	S	$(CH_3)_2CH$	$C_{24}H_{23}F_6NO_4S$	oil	22.8	85				
5t	T-4	S	$CH(CH_3)_2$	$C_{23}H_{22}F_6N_2O_4S$	oil	32.7	85				
5u	T-1	SO	CH_3	$C_{22}H_{19}F_6NO_5S$	oil	48.8	70				
5v	T-1	SO_2	CH_3	$C_{22}H_{19}F_6NO_6S$	oil	54.6	70				
				metominostrobin			100	100	95	85	65
				azoxystrobin			100	100	85	80	62
				trifloxystrobin			100	100	100	98	75

[a] See **Figure 2**. [b] Yield after purification by column chromatography on silica gel.

Biological Assay. *Test Compounds.* Stock solution of every test compound was prepared in DMF at a concentration of 1.0 g L^{-1} and then diluted to the required test concentrations (0.10−200 mg L^{-1}) with water containing Tween 80 (0.4 mg L^{-1}).

Preventive Activity against Sphaerotheca fuligine or Erysiphe graminis. Cucumber plants or wheat plants were grown under greenhouse conditions (T = 22 °C, 60 (±5)% relative humidity and a 12 h light cycle). Plants were maintained in plastic pots (6 cm diameter × 10 cm). Test compound solutions were sprayed over the plants. One day later, plants were inoculated by a spore suspension of *Sphaerotheca fuligine* or *Erysiphe graminis* (1.0×10^5 spores mL^{-1}). One or two weeks later, the symptoms were examined. Each bioassay was conducted in triplicate, and the biological effect was reported as the average of the triplicates. The dose−response data were analyzed by probit analysis as described by Finney (*16*), and the activities were evaluated as EC_{50} and EC_{90} values (95% FL).

Curative Activity against Sphaerotheca fuligine or Erysiphe graminis. Cucumber plants or wheat plants were grown under greenhouse conditions (T = 22 °C, 60 (±5)% relative humidity and a 12 h light cycle). Plants were maintained in plastic pots (6 cm diameter × 10 cm) and were inoculated by a spore suspension of *Sphaerotheca fuligine* or *Erysiphe graminis* (1.0×10^5 spores mL^{-1}). After one day, test compounds were sprayed over the plants. After one or two weeks, symptoms were examined. Each bioassay was conducted in triplicate, and the biological effect was reported as the average of the triplicates. Biological data were analyzed as in the test of preventive activity against *Sphaerotheca fuligine* or *Erysiphe graminis*.

RESULTS AND DISCUSSION

Synthesis. The synthesis scheme shown in **Figure 5** provided an efficient high yield synthesis of the test compounds. Their structures were confirmed by spectroscopic and elemental analysis. **Table 1** summarizes the chemical structures, physical characteristics, and yields of the new compounds **5a**−**5v**. MS and ^1H NMR data are listed in **Table 2**. The observed molecular weight for each compound of **5a**−**5v** was as expected in the MS analysis.

Fungicidal Activity. Table 1 shows the preventive activities of the synthesized strobilurins against *E. graminis*. The activity of commercial strobilurin fungicides such as metominostrobin, azoxystrobin, and trifloxystrobin are also presented in **Table 1**.

As shown in **Table 1**, all the compounds **5** exhibit remarkable fungicidal activity against *E. graminis*, and some compounds **5**

Table 2. ^{1}H NMR Data of the Novel Bis(trifluoromethyl)phenyl-Based Strobilurins

compd	MS (*m*/*e*)	^{1}H NMR ($CDCl_3$), δ
5a	507	2.17 (s, 3H, SCH_3), 3.68 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.21 (s,2H, OCH_2), 7.16∼7.98 (m, 8H, Ph−H + CH═)
5b	507	2.15 (s, 3H, SCH_3), 2.87 (d, J = 5.1 Hz, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 5.18 (s, 2H, OCH_2), 6.76 (s, 1H, NH), 7.19−7.95 (m, 7H, Ph−H)
5c	535	2.17 (s, 3H, SCH_3), 3.98 (s, 3H, OCH_3), 4.16 (t, J = 4.2 Hz, 2H, CH_2), 4.48 (t, J = 4.2 Hz, 2H, CH_2), 5.22 (s, 2H, OCH_2), 7.18−7.98 (m, 7H, Ph−H)
5d	508	2.15 (s, 3H, SCH_3), 3.82 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 5.17 (s, 2H, OCH_2), 7.18∼7.95 (m, 7H, Ph-H)
5e	496	2.19 (s, 3H, SCH_3), 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.34 (s, 2H, OCH_2), 7.37−7.96 (m, 7H, Ph−H).
5f	491	3.69 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 5.06 (s, 2H, OCH_2), 7.17−8.18 (m, 8H, Ph−H + CH═)
5g	491	2.86 (d, J = 5.1 Hz, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 5.17 (s, 2H, OCH_2), 6.80 (s, 1H, NH), 7.21−7.95 (m, 7H, Ph−H)
5h	519	3.81 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.16 (t, J = 4.2 Hz, 2H, CH_2), 4.48 (t, J = 4.2 Hz, 2H, CH_2), 5.08 (s, 2H, CH_2), 7.15−7.53 (m, 7H, Ph-H)
5i	492	3.84 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 5.02 (s, 2H, OCH_2), 7.19−8.14 (m, 7H, Ph−H)
5j	480	3.70 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.12 (s, 2H, CH_2), 7.34−8.34 (m, 7H, Ph−H)
5k	490	2.68 (d, J = 5.4 Hz, 3H, NCH_3), 3.70 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.99 (s, 2H, CH_2), 5.30 (br, 1H, NH), 7.16−7.94 (m, 8H, Ph−H + ═CH)
5l	491	2.68 (d, J = 5.4 Hz, 3H, NCH_3), 3.87 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.99 (s, 2H, CH_2), 5.47 (br, 1H, NH) 7.18−7.92 (m, 7H, Ph−H)
5m	476	3.72 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.98 (br, 2H, NH_2), 5.07 (s, 2H, CH_2), 7.16−8.08 (m, 8H, Ph−H + ═CH).
5n	477	3.85 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.95 (br, 2H, NH_2), 5.05 (s, 2H, CH_2), 7.19−8.09 (m, 7H, Ph−H)
5o	505	1.34 (t, J = 7.05 Hz, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.47 (q, J = 7.10 Hz, 2H, CH_2), 5.06 (s, 2H,CH_2), 7.16−8.32 (m, 8H, ═CH + Ph−H)
5p	506	1.34 (t, J = 7.05 Hz, 3H, CH_3), 3.87 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 4.43 (q, J = 7.0 Hz, 2H, CH_2), 5.01 (s, 2H, CH_2), 7.15−7.531 (m, 7H, Ph−H)
5q	521	1.14 (t, J = 7.35 Hz, 3H, CH_3), 2.68 (q, J = 7.35 Hz, 2H, SCH_2), 3.70 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.22 (s, 2H, OCH_2), 7.16−8.04 (m, 8H, Ph-H)
5r	522	1.15 (t,J = 7.35 Hz, 3H, CH_3), 2.69 (q, J = 7.35 Hz, 2H, SCH_2), 3.83 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 5.17 (s, 2H, OCH_2), 7.19−8.00 (m, 7H, Ph−H)
5s	535	1.20 (d, J = 6.9 Hz, 6H, $2CH_3$), 3.48−3.57 (m, 1H, CH), 3.66 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.23 (s, 2H, OCH_2), 7.16−8.13 (m, 8H, Ph−H + CH═)
5t	536	1.18 (d, J = 6.9 Hz, 6H, $2CH_3$), 3.42−3.50 (m, 1H, CH), 3.83 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 5.18 (s, 2H, OCH_2), 7.18−8.10 (m,7H, Ph−H)
5u	523	2.92 (s, 3H, $SOCH_3$), 3.70 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.24 (s, 2H, OCH_2), 7.18−8.18 (m, 8H, Ph−H + CH═)
5v	539	3.18 (s, 3H, SO_2CH_3), 3.57 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 5.25 (s, 2H, OCH_2), 7.09−8.05 (m, 8H, Ph−H + CH═)

Table 3. Preventive Activities of **5f**, **5h**, and Azoxystrobin (14 d after Treatment)

Pathogen	*Erysiphe graminis*						*Sphaerotheca fuligine*					
dose (mg L^{-1})	6.25	3.12	1.56	0.78	EC_{50}	EC_{90}	6.25	3.12	1.56	0.78	EC_{50}	EC_{90}
5f	100	81	60	20	1.2	2.8	100	100	80	59	0.8	1.5
5h	100	98	75	30	0.9	2.0	100	100	75	55	0.8	1.6
azoxystrobin	90	65	50	20	1.7	7.0	95	80	60	35	1.2	4.5

Table 4. Curative Activities of **5f**, **5h**, and Azoxystrobin (14 d after Treatment)

pathogen	*Erysiphe graminis*						*Sphaerotheca fuligine*					
dose (mg L^{-1})	6.25	3.12	1.56	0.78	EC_{50}	EC_{90}	6.25	3.12	1.56	0.78	EC_{50}	EC_{90}
5f	94	82	50	20	1.5	4.8	100	100	92	56	0.8	1.4
5h	100	90	70	35	1.0	2.4	100	100	80	60	0.8	1.5
azoxystrobin	89	78	52	15	1.7	5.9	100	90	80	55	0.8	2.1

show high fungicidal activity. For example, compounds **5a**, **5f**, **5h**, **5i**, and **5l** have ≥90% fungicidal activity at 3.1 mg L^{-1}, compounds **5f** and **5h** still have ≥95% fungicidal activity at 1.5 mg L^{-1}, while the commercial strobilurin fungicides such as metominostrobin, azoxystrobin, and trifloxystrobin only exhibit ≤75% fungicidal activity at the same treatment dose.

In order to compare fungicidal activities of compounds **5** with that of the commercial strobilurin fungicide azoxystrobin, the

preventive and curative activities of the more active compounds **5f**, **5h**, and azoxystrobin against *E. graminis* and *S. fuligine* are presented in **Tables 3** and **4**, respectively.

The results in **Tables 3** and **4** show that **5f** and **5h** have high preventive and curative activities against *Erysiphe graminis* and *Sphaerotheca fuligine,* respectively. For example, compound **5f** has EC_{90} (mg L^{-1}) values of 2.8 and 1.5 in preventive treatment and 4.8 and 1.4 in curative treatment against *Erysiphe graminis* and *Sphaerotheca fuligine,* respectively; compound **5h** has EC_{90} (mg L^{-1}) values of 2.0 and 1.6 in preventive treatment and 2.4 and 1.5 in curative treatment against *Erysiphe graminis* and *Sphaerotheca fuligine*, respectively. Both EC_{50} and EC_{90} values of compounds **5f** and **5h** are better than that of the commercial strobilurin fungicide azoxystrobin.

Apparent Structure−Activity Relationship. In the general formula for compounds **5** (**Figure 5**), structural optimization was carried out with three primary substructures: the R, X, and T moieties. Variances among R, X, and T can greatly effect fungicidal activity against *Erysiphe graminis* (**Table 1**).

When X and T are kept constant, the fungicidal activities of the synthesized compounds are influenced by the nature of the R group. Modification of the R group from a hydrogen atom to a methyl group maintains or increases the fungicidal activity (e.g., the fungicidal activity of **5l** is better than that of **5n**, while **5k** has a similar level of fungicidal activity to **5m**). When the methyl group is changed to ethyl or isopropyl, the fungicidal activity of the corresponding compound decreases; for example, the fungicidal activities are correlated as follows: **5o** < **5f**, **5p** < **5i**, **5q** = **5s** < **5a**, and **5r** = **5t** < **5d**. This suggests that the dealkylation of the alkyl moiety could be an activation process for this group of compounds.

When R and T are kept constant, the fungicidal activity of the synthesized compounds is influenced by the nature of the X group. When X is changed from O to S, NH, SO, and SO_2, the fungicidal activity of the corresponding compound decreases; for example, fungicidal activities are correlated as follows: **5f** > **5a** > **5k** > **5u** = **5v** and **5i** > **5l** > **5d**. When X equals O, all of the compounds (**5f**, **5h−5j**, **5o−5p**), except for **5g**, show high fungicidal activity.

When R and X are kept constant, the fungicidal activity of the synthesized compounds is influenced by the nature of the T group (**Figure 2**). When R is kept as methyl, X is S, the fungicidal activity of the T-1 derivative **5a** is the highest. When T is changed from T-1 to T-2, T-3, T-4, and T-5, the fungicidal activity of the corresponding compound decreases; for example, fungicidal activities are correlated as follows: **5a** > **5b** > **5c** > **5d** > **5e**. When R is methyl, X is O, the fungicidal activity of the T-1 and T-3 derivatives are almost equal and higher than other T-2, T-4, and T-5 derivatives; for example, fungicidal activities are correlated as follows: **5f** ≈ **5h** > **5i** > **5j** > **5g**.

In general, for the synthesized compounds **5**: (1) The activity order of R is CH_3 > H > CH_2CH_3 > $CH(CH_3)_2$. This suggests that the metabolic dealkylation of alkyl to H is an important process. Compounds in which R equals methyl could be profungicides. (2) Activity order of pharmacophore T is T-1 > T-2 > T-3 > T-4 > T-5 (X = S, R = CH_3) and T-1 ≈ T-3 > T-4 > T-5> T-2 (X = O, R = CH_3). Further studies on the biological activity and structure−activity relationships of this series compounds are in progress.

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