Synthesis and Fungicidal Activities of Novel Indene-Substituted Oxime Ether Strobilurins

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Nineteen novel indene-substituted oxime ether strobilurins, which used an indene group to stabilize the (*E*)-styryl group in SYP-Z071 (an unsaturated oxime strobilurin fungicide under development by the Shenyang Research Institute of Chemical Industry), were designed and synthesized. The biological assay results showed that all compounds possessed good or excellent fungicidal activities. It was found that most of the compounds showed higher fungicidal activities against *Pyricularia oryzae*, *Phytophthora infestans*, *Erysiphe graminis*, and *Colletotrichum lagenarium* than SYP-Z071 at the tested concentration. The biological assay results also indicated that most of the compounds exhibited higher in vivo fungicidal activities against cucumber *Pseudoperonospora cubensis* and *C. lagenarium* than the commercial fungicides trifloxystrobin and kresoxim-methyl at a concentration of 6.25 mg/L. Furthermore, it was found that α-(methoxyimino)-*N*-methylphenylacetamide oxime ethers **6m**−**s** exhibited a broad spectrum and remarkably higher activities against all tested fungi. Especially, the 6-methylindene-substituted compound **6p** was identified as the most promising candidate for further study.

KEYWORDS: Indene; oxime ether; strobilurins; fungicide; fungicidal activities

INTRODUCTION

Strobilurins, which are naturally occurring derivatives of *β*-methoxyacrylic acid, are an important class of agricultural fungicides (*1–4*). However, it was clear that many natural products themselves could not be used directly because of insufficient levels of photochemical stability and volatility (*2, 5*). The first two commercial strobilurin fungicides azoxystrobin (ICI A 5504) and kresoxim-methyl (BAS 490 F) were discovered by ICI and BASF from stilbene compound **a**, respectively, by using a benzene ring as an aromatic bridge to stabilize the triene system in strobilurin A (**Figure 1**) (*2*). Many synthetic chemists also did much remarkable work on the synthetic analogues of strobilurin A as fungicides, such as using a *trans*-1,2-disubstituted cyclopropane group (*6*) and a *cis*-1,2-disubstituted cyclopentene group (*5, 7*) to stabilize the triene system in strobilurin A to obtain analogues of strobilurin A (compounds **b** and **c** (**Figure 1**)).

In recent years, oxime ether strobilurins have aroused the interest of many synthetic and agricultural chemists since trifloxystrobin (discovered by Novartis and sold to Bayer later) was launched in 1999 (*8–16*). Subsequently, a series of active

oxime ether strobilurins were prepared, such as compounds **d** and **e** (**Figure 2**). Compounds **d**, which were discovered by Rohm and Hass Co. (the 4-Cl-substituted derivative of compounds **d** is under development by Shenyang Research Institute of Chemical Industry now and is named SYP-Z071 (*17*)), contained an unsaturated oxime ether group and exhibited very good fungicidal activities (*18*). It was also reported that arylcyclopropyl oxime ether compounds **e**, which used a *trans*-arylcyclopropyl group to displace the (*E*)-styryl group in compounds **d**, also had excellent fungicidal activities (*19*).

In view of these facts, we have reported a series of novel oxime ethers which used a benzopentatomic ring to stabilize the (*E*)-styryl group in SYP-Z071 (*16*). Especially, it was found that indene-substituted compounds possessed remarkable fungicidal activities in this type of oxime ether strobilurins (*16*). To study the structure−activity relationships of this type of compound, a series of novel indene-substituted oxime ethers **6** were designed and synthesized in this study. The biological assay results showed that all compounds exhibited good or excellent fungicidal activities.

MATERIALS AND METHODS

DMF was distilled and dried over 4 Å sieves. Other solvents and reagents were obtained from commercial sources and used without further purification. Silica gel (100−140 mesh) was used for column chromatography. The intermediate (*E*)-methyl 2-(2-(bromomethyl)phe-

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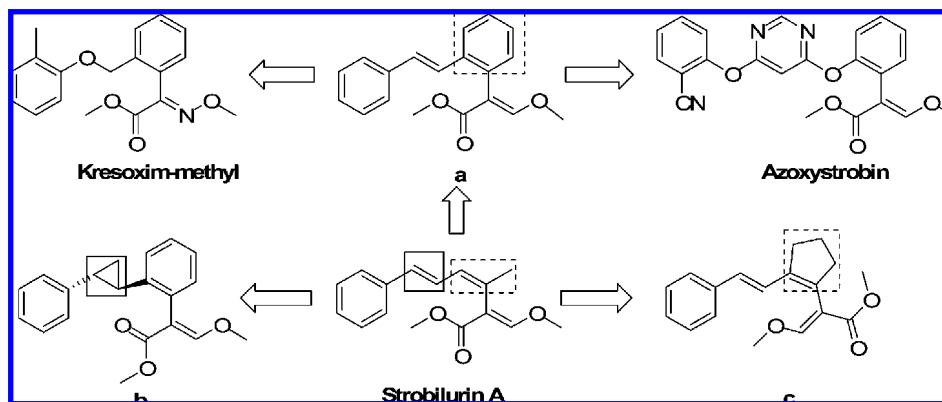‡ Shenyang Research Institute of Chemical Industry.

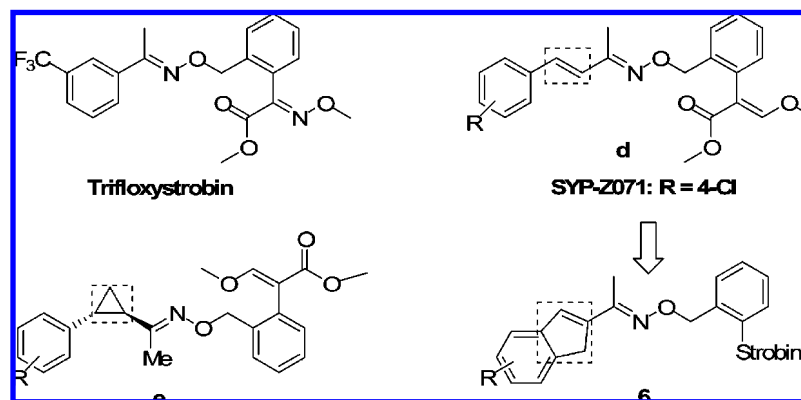**Figure 1.** Structures of strobilurin A and its analogues.

Figure 2. Structures of trifloxystrobin and other oxime ether strobilurins.

nyl)-3-methoxyacrylate and (*E*)-methyl 2-(2-(bromomethyl)phenyl)-2-(methoxyimino)acetate were provided by Shenyang Research Institute of Chemical Industry. Melting points were determined with a Tech X-6 micromelting point apparatus made in Beijing and are uncorrected. The ¹H NMR spectra were recorded in CDCl₃ solution on a Varian Mercury V × 300 NMR spectrophotometer with TMS as the internal standard. A Perkin-Elmer 983 was used to determine the IR spectra. Elemental analyses were performed on a Vario EL III elemental analysis instrument, and the results were within 0.3% of the calculated value.

General Procedure for the Synthesis of Ortho-Halogenated Benzaldehydes 3b, 3c, 3e, and 3g. A mixture of the corresponding ortho-halogenated toluene **1** (4.8 mmol), acetic anhydride (6.9 g), acetic acid (5.2 g), and concentrated sulfuric acid (2.8 g) was cooled to 0 °C in an ice bath. Then an acetic acid (5.2 g) solution of CrO₃ (1.8 g, 18 mmol) was dropped into the mixture over 1.5 h. Stirring of the mixture was continued for 2 h at 0 °C. Then the reaction mixture was poured into 120 mL of cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under vacuum. The residue (crude product **2**) and concentrated hydrochloric acid were heated for 2.5 h in dioxane under reflux. Then the reaction mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 10/1) to afford ortho-halogenated benzaldehydes **3b**, **3c**, **3e**, and **3g**. The yields of the products were 74.3−86.3%.

General Procedure for the Synthesis of 1-(1*H*-Inden-2-yl)ethanone Oximes 5a−g. The ortho-halogenated benzaldehyde **3** (3.0 mmol), 3-buten-2-ol (3.6 mmol), tetrabutylammonium chloride (TBAC) (6.0 mmol), NaOAc (7.5 mmol), LiCl (6.0 mmol), and Pd(OAc)₂ (36 mg, 5 mol %) were added to a sealed flask. After the flask was evacuated and purged with nitrogen, 30 mL of DMF was added to the flask via syringe. Then the flask was placed in a 110 °C oil bath, and stirring was continued for 1.5−4 h. The reaction mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under vacuum. The residue was purified by flash

chromatography (hexane/EtOAc = 5/1) to afford the products 1-(1*H*-inden-2-yl)ethanones **4**. The yields of the products were 51.9−64.2%.

A mixture of the corresponding 1-(1*H*-inden-2-yl)ethanones **4** (3 mmol), hydroxylamine hydrochloride (4.5 mmol), NaOAc (4.5 mmol), ethanol (10 mL), and H₂O (10 mL) was heated for 2.5−5 h under reflux. Then the reaction mixture was cooled to room temperature, poured into 50 mL of hydrochloric acid (0.5 mol/L), and extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 4/1) to afford products **5a−g**.

Data for 1-(1H-Inden-2-yl)ethanone Oxime (5a). Straw yellow solid. Yield: 89.7%. Mp: 175.8−177.5 °C. ¹H NMR (CDCl₃, 300 MHz): δ 2.25 (s, 3H, N=CC*H₃*), 3.70 (s, 2H, C*H₂*), 7.13 (s, 1H, C*H*=C), 7.23−7.28 (m, 2H, ArH), 7.39−7.46 (m, 2H, ArH). IR (KBr): ν 3200−3400 (br), 2390, 1635, 1010, 930, 850, 755, 715 cm⁻¹.

Data for 1-(6-Chloro-1H-inden-2-yl)ethanone Oxime (5b). White solid. Yield: 83.6%. Mp: 179.2−180.6 °C. ¹H NMR (CDCl₃, 300 MHz): δ 2.19 (s, 3H, N=CC*H₃*), 3.65 (s, 2H, C*H₂*), 7.02 (d, *J* = 7.2 Hz, 1H, ArH), 7.15−7.25 (m, 1H, ArH), 7.28−7.35 (m, 1H, ArH), 7.39 (s, 1H, C*H*=C). IR (KBr): ν 3425, 1630, 1420, 1370, 1020, 930, 875, 760 cm⁻¹.

Data for 1-(6-Fluoro-1H-inden-2-yl)ethanone Oxime (5c). White solid. Yield: 77.8%. Mp: 171.6−173.6 °C. ¹H NMR (CDCl₃, 300 MHz): δ 2.20 (s, 3H, N=CC*H₃*), 3.64 (s, 2H, C*H₂*), 6.99−7.04 (m, 1H, ArH), 7.21−7.27 (m, 1H, ArH), 7.31−7.37 (m, 1H, ArH), 7.45−7.49 (m, 1H, ArH). IR (KBr): ν 3200−3400 (br), 2380, 1630, 1020, 940, 840, 760 cm⁻¹.

Data for 1-(6-Methyl-1H-inden-2-yl)ethanone Oxime (5d). White solid. Yield: 86.3%. Mp: 181.8−183.5 °C. ¹H NMR (CDCl₃, 300 MHz): δ 2.23 (s, 3H, N=CC*H₃*), 2.39 (s, 3H, ArC*H₃*), 3.65 (s, 2H, C*H₂*), 7.07−7.09 (m, 2H, ArH), 7.21−7.31 (m, 2H, ArH). IR (KBr): ν 3200−3400 (br), 1625, 1400, 1015, 925, 875, 820, 760 cm⁻¹.

Data for 1-(5-Chloro-1H-inden-2-yl)ethanone Oxime (5e). White solid. Yield: 83.5%. Mp: 173.3−174.8 °C. ¹H NMR (CDCl₃, 300 MHz): δ 2.19 (s, 3H, N=CC*H₃*), 3.65 (s, 2H, C*H₂*), 7.02 (d, *J* = 8.1 Hz, 1H, ArH), 7.18−7.25 (m, 1H, ArH), 7.32−7.35 (m, 1H, ArH), 7.40−7.43

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(m, 1H, ArH). IR (KBr): ν 3430, 1630, 1420, 1365, 1015, 930, 870, 815, 765 cm⁻¹.

Data for 1-(5-Fluoro-1H-inden-2-yl)ethanone Oxime (5f). White solid. Yield: 97.8%. Mp: 168.7−169.8 °C. ¹H NMR (CDCl₃, 300 MHz): δ 2.16 (s, 3H, N=CC*H₃*), 3.60 (s, 2H, C*H₂*), 6.86−7.00 (m, 1H, C*H*=C), 7.04−7.22 (m, 2H, ArH), 7.24−7.38 (m, 1H, ArH). IR (KBr): ν 3420, 2960, 1635, 1475, 1380, 1220, 1005, 870 cm⁻¹.

Data for 1-(4-Chloro-1H-inden-2-yl)ethanone Oxime (5g). White solid. Yield: 77.3%. Mp: 173.8−175.2 °C. ¹H NMR (CDCl₃, 300 MHz): δ 2.18 (s, 3H, N=CC*H₃*), 3.61 (s, 2H, C*H₂*), 7.11−7.18 (m, 2H, ArH), 7.31−7.34 (m, 1H, ArH), 7.47 (s, 1H, C*H*=C). IR (KBr): ν 3200−3400 (br), 2390, 1635, 1030, 960, 850, 760, 710 cm⁻¹.

General Procedure for the Synthesis of Methyl 3-Methoxypropenoate Oxime Ethers 6a−e and Methyl α-(Methoxyimino)benzeneacetate Oxime Ethers 6f−l. A mixture of the corresponding 1-(1*H*-inden-2-yl)ethanone oximes **5** (1.75 mmol), (*E*)-methyl 2-(2-(bromomethyl)phenyl)-3-methoxyacrylate or (*E*)-methyl 2-(2-(bromomethyl)-phenyl)-2-(methoxyimino)acetate (1.75 mmol), and potassium carbonate (3.5 mmol) were heated for 4−5 h in 10 mL of ethanol under reflux. Then the reaction mixture was cooled to room temperature and extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 10/1) to afford the products methyl 3-methoxypropenoate oxime ethers **6a−e** and methyl α-(methoxyimino)benzeneacetate oxime ethers **6f−l**.

Data for Methyl (E,E)-3-Methoxy-2-[2-((((1-(6-chloro-1H-inden-2-yl)ethylidene)amino)oxy)methyl)phenyl]propenoate (6a). Yellow viscous liquid. Yield: 68.4%. ¹H NMR (CDCl₃, 300 MHz): δ 2.08 (s, 3H, C*H₃*C=N), 3.63 (s, 2H, C*H₂*), 3.68 (s, 3H, C=CHOC*H₃*), 3.80 (s, 3H, COOC*H₃*), 5.08 (s, 2H, C*H₂*O), 7.11−7.15 (m, 1H, ArH), 7.17−7.21 (m, 1H, ArH), 7.28−7.41 (m, 5H, ArH), 7.48−7.51 (m, 1H, ArH), 7.58 (s, 1H, C=C*H*OCH₃). IR (KBr): ν 2950, 1710, 1640, 1430, 1255, 1125, 1020, 760 cm⁻¹. Anal. Calcd for C₂₃H₂₂ClNO₄: C, 67.07; H, 5.38; N, 3.40. Found: C, 67.21; H, 5.59; N, 3.27.

Data for Methyl (E,E)-3-Methoxy-2-[2-((((1-(6-fluoro-1H-inden-2-yl)ethylidene)amino)oxy)methyl)phenyl]propenoate (6b). Straw yellow viscous liquid. Yield: 61.7%. ¹H NMR (CDCl₃, 300 MHz): δ 2.10 (s, 3H, C*H₃*C=N), 3.64 (s, 2H, C*H₂*), 3.69 (s, 3H, C=CHOC*H₃*), 3.79 (s, 3H, COOC*H₃*), 5.10 (s, 2H, C*H₂*O), 7.12−7.16 (m, 1H, ArH), 7.18−7.21 (m, 1H, ArH), 7.32−7.46 (m, 5H, ArH), 7.49−7.53 (m, 1H, ArH), 7.59−7.62 (m, 1H, ArH). IR (KBr): ν 2960, 1715, 1630, 1430, 1260, 1020, 760 cm⁻¹. Anal. Calcd for C₂₃H₂₂FNO₄: C, 69.86; H, 5.61; N, 3.54. Found: C, 69.67; H, 5.72; N, 3.29.

Data for Methyl (E,E)-3-Methoxy-2-[2-((((1-(6-methyl-1H-inden-2-yl)ethylidene)amino)oxy)methyl)phenyl]propenoate (6c). Yellow viscous liquid. Yield: 71.0%. ¹H NMR (CDCl₃, 300 MHz): δ 2.11 (s, 3H, C*H₃*C=N), 2.39 (s, 3H, ArC*H₃*), 3.64 (s, 2H, C*H₂*), 3.68 (s, 3H, C=CHOC*H₃*), 3.81 (s, 3H, COOC*H₃*), 5.10 (s, 2H, C*H₂*O), 7.04−7.09 (m, 1H, ArH), 7.12−7.15 (m, 1H, ArH), 7.21−7.35 (m, 5H, ArH), 7.47−7.50 (m, 1H, ArH), 7.56 (s, 1H, C=C*H*OCH₃). IR (KBr): ν 2950, 1715, 1630, 1420, 1120, 1020, 760 cm⁻¹. Anal. Calcd for C₂₄H₂₅NO₄: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.58; H, 6.46; N, 3.52.

Data for Methyl (E,E)-3-Methoxy-2-[2-((((1-(5-chloro-1H-inden-2-yl)ethylidene)amino)oxy)methyl)phenyl]propenoate (6d). Yellow viscous liquid. Yield: 66.3%. ¹H NMR (CDCl₃, 300 MHz): δ 2.13 (s, 3H, C*H₃*C=N), 3.61 (s, 2H, C*H₂*), 3.68 (s, 3H, C=CHOC*H₃*), 3.81 (s, 3H, COOC*H₃*), 5.10 (s, 2H, C*H₂*O), 7.10−7.14 (m, 1H, ArH), 7.19−7.31 (m, 5H, ArH), 7.38−7.41 (m, 1H, ArH), 7.48−7.51 (m, 1H, ArH), 7.59 (s, 1H, C=C*H*OCH₃). IR (KBr): ν 2950, 1710, 1635, 1460, 1250, 1120, 1020, 760 cm⁻¹. Anal. Calcd for C₂₃H₂₂ClNO₄: C, 67.07; H, 5.38; N, 3.40. Found: C, 67.23; H, 5.54; N, 3.29.

Data for Methyl (E,E)-3-Methoxy-2-[2-((((1-(4-chloro-1H-inden-2-yl)ethylidene)amino)oxy)methyl)phenyl]propenoate (6e). Yellow viscous liquid. Yield: 63.5%. ¹H NMR (CDCl₃, 300 MHz): δ 2.11 (s, 3H, C*H₃*C=N), 3.60 (s, 2H, C*H₂*), 3.66 (s, 3H, C=CHOC*H₃*), 3.80 (s, 3H, COOC*H₃*), 5.11 (s, 2H, C*H₂*O), 7.10−7.19 (m, 2H, ArH), 7.22−7.29 (m, 4H, ArH), 7.38−7.41 (m, 1H, ArH), 7.48−7.51 (m, 1H, ArH), 7.59 (s, 1H, C=C*H*OCH₃). IR (KBr): ν 2950, 1710, 1635, 1460, 1250, 1120, 1020, 760 cm⁻¹. Anal. Calcd for C₂₃H₂₂ClNO₄: C, 67.07; H, 5.38; N, 3.40. Found: C, 67.18; H, 5.46; N, 3.31.

Data for Methyl (E,E)-α-(Methoxyimino)-2-[(((1-(1H-inden-2-yl)-ethylidene)amino)oxy)methyl]benzeneacetate (6f). Colorless viscous liquid. Yield: 61.3%. ¹H NMR (CDCl₃, 300 MHz): δ 2.11 (s, 3H, C*H₃*C=N), 3.64 (s, 2H, C*H₂*), 3.85 (s, 3H, COOC*H₃*), 4.04 (s, 3H, C=NOC*H₃*), 5.09 (s, 2H, C*H₂*O), 7.03 (s, 1H, C*H*=C), 7.19−7.25 (m, 3H, ArH), 7.35−7.43 (m, 4H, ArH), 7.48−7.51 (m, 1H, ArH). IR (KBr): ν 2940, 1730, 1220, 1070, 1020, 760 cm⁻¹. Anal. Calcd for C₂₂H₂₂N₂O₄: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.78; H, 5.95; N, 7.47.

Data for Methyl (E,E)-α-(Methoxyimino)-2-[(((1-(6-chloro-1H-2-yl)ethylidene)amino)oxy)methyl]benzeneacetate (6g). Colorless viscous liquid. Yield: 64.5%. ¹H NMR (CDCl₃, 300 MHz): δ 2.10 (s, 3H, C*H₃*C=N), 3.63 (s, 2H, C*H₂*), 3.84 (s, 3H, COOC*H₃*), 4.05 (s, 3H, C=NOC*H₃*), 5.08 (s, 2H, C*H₂*O), 7.10−7.15 (m, 1H, ArH), 7.17−7.24 (m, 2H, ArH), 7.30−7.42 (m, 4H, ArH), 7.48−7.51 (m, 1H, ArH). IR (KBr): ν 2960, 1725, 1220, 1080, 1020, 760 cm⁻¹. Anal. Calcd for C₂₂H₂₁ClN₂O₄: C, 64.00; H, 5.13; N, 6.79. Found: C, 64.12; H, 5.22; N, 6.71.

Data for Methyl (E,E)-α-(Methoxyimino)-2-[(((1-(6-fluoro-1H-inden-2-yl)ethylidene)amino)oxy)methyl]benzeneacetate (6h). Straw yellow viscous liquid. Yield: 58.7%. ¹H NMR (CDCl₃, 300 MHz): δ 2.11 (s, 3H, C*H₃*C=N), 3.64 (s, 2H, C*H₂*), 3.80 (s, 3H, COOC*H₃*), 4.04 (s, 3H, C=NOC*H₃*), 5.09 (s, 2H, C*H₂*O), 7.12−7.16 (m, 1H, ArH), 7.18−7.24 (m, 2H, ArH), 7.31−7.43 (m, 4H, ArH), 7.48−7.51 (m, 1H, ArH). IR (KBr) ν 2960, 1730, 1220, 1080, 1260, 1020, 760 cm⁻¹. Anal. Calcd for C₂₂H₂₁FN₂O₄: C, 66.66; H, 5.34; N, 7.07. Found: C, 66.62; H, 5.42; N, 7.17.

Data for Methyl (E,E)-α-(Methoxyimino)-2-[(((1-(6-methyl-1H-inden-2-yl)ethylidene)amino)oxy)methyl]benzeneacetate (6i). Yellow viscous liquid. Yield: 71.5%. ¹H NMR (CDCl₃, 300 MHz): δ 2.10 (s, 3H, C*H₃*C=N), 2.39 (s, 3H, ArC*H₃*), 3.64 (s, 2H, C*H₂*), 3.82 (s, 3H, COOC*H₃*), 4.04 (s, 3H, C=NOC*H₃*), 5.10 (s, 2H, C*H₂*O), 7.05−7.09 (m, 1H, ArH), 7.12−7.15 (m, 1H, ArH), 7.20−7.34 (m, 5H, ArH), 7.47−7.50 (m, 1H, ArH). IR (KBr): ν 2950, 1715, 1220, 1120, 1020, 760 cm⁻¹. Anal. Calcd for C₂₃H₂₄N₂O₄: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.28; H, 6.11; N, 7.28.

Data for Methyl (E,E)-α-(Methoxyimino)-2-[(((1-(5-chloro-1H-inden-2-yl)ethylidene)amino)oxy)methyl]benzeneacetate (6j). Straw yellow viscous liquid. Yield: 64.5%. ¹H NMR (CDCl₃, 300 MHz): δ 2.11 (s, 3H, C*H₃*C=N), 3.60 (s, 2H, C*H₂*), 3.82 (s, 3H, COOC*H₃*), 4.03 (s, 3H, C=NOC*H₃*), 5.11 (s, 2H, C*H₂*O), 7.10−7.14 (m, 1H, ArH), 7.18−7.34 (m, 5H, ArH), 7.39−7.42 (m, 1H, ArH), 7.47−7.50 (m, 1H, ArH). IR (KBr): ν 2950, 1725, 1230, 1120, 1020, 760 cm⁻¹. Anal. Calcd for C₂₂H₂₁ClN₂O₄: C, 64.00; H, 5.13; N, 6.79. Found: C, 64.09; H, 5.12; N, 6.70.

Data for Methyl (E,E)-α-(Methoxyimino)-2-[(((1-(5-fluoro-1H-inden-2-yl)ethylidene)amino)oxy)methyl]benzeneacetate (6k). Yellow viscous liquid. Yield: 57.8%. ¹H NMR (CDCl₃, 300 MHz): δ 2.42 (s, 3H, C*H₃*C=N), 3.62 (s, 2H, C*H₂*), 3.81 (s, 3H, COOC*H₃*), 4.04 (s, 3H, C=NOC*H₃*), 5.11 (s, 2H, C*H₂*O), 7.03−7.15 (m, 1H, ArH), 7.28−7.34 (m, 4H, ArH), 7.45−7.47 (m, 1H, ArH), 7.49−7.51 (m, 1H, ArH), 7.93−7.95 (m 1H, ArH). IR (KBr): ν 2950, 1730, 1250, 1020, 870, 760 cm⁻¹. Anal. Calcd for C₂₂H₂₁FN₂O₄: C, 66.66; H, 5.34; N, 7.07. Found: C, 66.75; H, 5.44; N, 7.01.

Data for Methyl (E,E)-α-(Methoxyimino)-2-[(((1-(4-chloro-1H-inden-2-yl)ethylidene)amino)oxy)methyl]benzeneacetate (6l). Straw yellow viscous liquid. Yield: 61.7%. ¹H NMR (CDCl₃, 300 MHz): δ 2.11 (s, 3H, C*H₃*C=N), 3.62 (s, 2H, C*H₂*), 3.81 (s, 3H, COOC*H₃*), 4.05 (s, 3H, C=NOC*H₃*), 5.11 (s, 2H, C*H₂*O), 7.11−7.19 (m, 2H, ArH), 7.23−7.30 (m, 4H, ArH), 7.38−7.41 (m, 1H, ArH), 7.48−7.52 (m, 1H, ArH). IR (KBr): ν 2960, 1710, 1250, 1120, 1020, 760 cm⁻¹. Anal. Calcd for C₂₂H₂₁ClN₂O₄: C, 64.00; H, 5.13; N, 6.79. Found: C, 64.11; H, 5.10; N, 6.68.

General Procedure for the Synthesis of α-(Methoxyimino)-*N*-methylphenylacetamide Oxime Ethers 6m−s. A mixture of the corresponding methyl α-(methoxyimino)benzeneacetate oxime ethers **6f−l** (0.5 mmol) and methylamine (0.37 g, 3 mmol, 25% in water) was heated for 4−5 h in 5 mL of methanol under reflux. Then the reaction mixture was cooled to room temperature and extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO₄

Table 1. Fungicidal Activities of Compounds **6a**−**s** (Inhibitory Ratio, %)
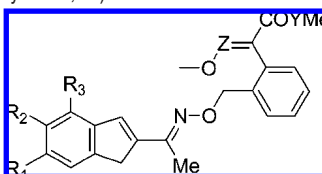
no.	R$_1$	R$_2$	R$_3$	Z	Y	25 mg/mL testing concn			6.25 mg/mL testing concn		
						P. oryzae	B. cinerea	P. infestans	P. cubensis	E. graminis	C. lagenarium
6a	Cl	H	H	CH	O	50	80	100	40	100	60
6b	F	H	H	CH	O	100	50	100	a	100	60
6c	CH$_3$	H	H	CH	O	100	80	100	80	100	70
6d	H	Cl	H	CH	O	100	80	100	30	100	30
6e	H	H	Cl	CH	O	100	80	100	0	85	30
6f	H	H	H	N	O	100	80	100	30	10	30
6g	Cl	H	H	N	O	100	80	100	50	90	65
6 h	F	H	H	N	O	100	50	100	85	85	40
6i	CH$_3$	H	H	N	O	100	80	100	100	100	90
6j	H	Cl	H	N	O	100	80	100	95	95	90
6k	H	F	H	N	O	50	80	100	70	100	40
6l	H	H	Cl	N	O	100	100	100	90	100	100
6m	H	H	H	N	NH	100	100	100	95	100	95
6n	Cl	H	H	N	NH	100	100	100	85	100	100
6o	F	H	H	N	NH	100	80	100	100	100	100
6p	CH$_3$	H	H	N	NH	100	100	100	100	100	100
6q	H	Cl	H	N	NH	80	100	80	90	100	98
6r	H	F	H	N	NH	100	80	80	30	100	30
6s	H	H	Cl	N	NH	100	80	100	100	100	80
SYP-Z071						50	100	80	100	62.5	50
trifloxystrobin						100	100	100	50	100	60
kresoxim-methyl						100	100	100	0	100	30

a The compound appeared to be phytotoxic.

and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 1/1) to afford the products α-(methoxyimino)-*N*-methylphenylacetamide oxime ethers **6m**−**s**.

Data for (E,E)-α-(Methoxyimino)-N-methyl-2-[(((1-(1H-inden-2-yl)ethylidene)amino)oxy)methyl]phenylacetamide (6m). Straw yellow viscous liquid. Yield: 84.8%. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.10 (s, 3H, CH_3C=N), 2.88 (d, J = 4.8 Hz, 3H, CH_3NH), 3.63 (s, 2H, CH_2), 3.94 (s, 3H, C=NOCH_3), 5.08 (s, 2H, CH_2O), 6.75 (br s, 1H, CH$_3$NH), 7.00 (s, 1H, CH=C), 7.18−7.25 (m, 3H, ArH), 7.33−7.42 (m, 4H, ArH), 7.47−7.50 (m, 1H, ArH). IR (KBr): ν 3360, 2940, 1670, 1520, 1030, 980, 760 cm^{-1}. Anal. Calcd for C$_{22}$H$_{23}$N$_3$O$_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.12; H, 6.26; N, 11.04.

Data for (E,E)-α-(Methoxyimino)-N-methyl-2-[(((1-(6-chloro-1H-inden-2-yl)ethylidene)amino)oxy)methyl]phenylacetamide (6n). Yellow viscous liquid. Yield: 84.5%. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.09 (s, 3H, CH_3C=N), 2.87 (d, J = 5.1 Hz, 3H, CH_3NH), 3.63 (s, 2H, CH_2), 3.95 (s, 3H, C=NOCH_3), 5.09 (s, 2H, CH_2O), 7.10−7.15 (m, 1H, ArH), 7.17−7.24 (m, 2H, ArH), 7.30−7.41 (m, 4H, ArH), 7.48−7.51 (m, 1H, ArH). IR (KBr): ν 3360, 2960, 1670, 1520, 1020, 980, 760 cm^{-1}. Anal. Calcd for C$_{22}$H$_{22}$ClN$_3$O$_3$: C, 64.15; H, 5.38; N, 10.20. Found: C, 64.28; H, 5.45; N, 10.11.

Data for (E,E)-α-(Methoxyimino)-N-methyl-2-[(((1-(6-fluoro-1H-inden-2-yl)ethylidene)amino)oxy)methyl]phenylacetamide (6o). Yellow viscous liquid. Yield: 81.3%. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.10 (s, 3H, CH_3C=N), 2.85 (d, J = 5.1 Hz, 3H, CH_3NH), 3.64 (s, 2H, CH_2), 3.96 (s, 3H, C=NOCH_3), 5.10 (s, 2H, CH_2O), 7.11−7.17 (m, 1H, ArH), 7.18−7.26 (m, 2H, ArH), 7.31−7.44 (m, 4H, ArH), 7.47−7.51 (m, 1H, ArH). IR (KBr): ν 3360, 2960, 1660, 1520, 1040, 760 cm^{-1}. Anal. Calcd for C$_{22}$H$_{22}$FN$_3$O$_3$: C, 66.82; H, 5.61; N, 10.63. Found: C, 66.78; H, 5.65; N, 10.52.

Data for (E,E)-α-(Methoxyimino)-N-methyl-2-[(((1-(6-methyl-1H-inden-2-yl)ethylidene)amino)oxy)methyl]phenylacetamide (6p). Yellow viscous liquid. Yield: 84.5%. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.09 (s, 3H, CH_3C=N), 2.87 (d, J = 5.1 Hz, 3H, CH_3NH), 3.63 (s, 2H, CH_2), 3.95 (s, 3H, C=NOCH_3), 5.09 (s, 2H, CH_2O), 7.10−7.15 (m, 1H, ArH), 7.17−7.24 (m, 2H, ArH), 7.30−7.41 (m, 4H, ArH), 7.48−7.51 (m, 1H, ArH). IR (KBr): ν 3360, 2960, 1670, 1520, 1020, 980, 760 cm^{-1}.

Anal. Calcd for C$_{23}$H$_{25}$N$_3$O$_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.63; H, 6.48; N, 10.68.

Data for (E,E)-α-(Methoxyimino)-N-methyl-2-[(((1-(5-chloro-1H-inden-2-yl)ethylidene)amino)oxy)methyl]phenylacetamide (6q). Yellow viscous liquid. Yield: 86.6%. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.11 (s, 3H, CH_3C=N), 2.88 (d, J = 4.8 Hz, 3H, CH_3NH), 3.63 (s, 2H, CH_2), 3.96 (s, 3H, C=NOCH_3), 5.11 (s, 2H, CH_2O), 7.10−7.14 (m, 1H, ArH), 7.17−7.34 (m, 5H, ArH), 7.38−7.41 (m, 1H, ArH), 7.47−7.50 (m, 1H, ArH). IR (KBr): ν 3360, 2950, 1670, 1510, 1040, 980, 760 cm^{-1}. Anal. Calcd for C$_{22}$H$_{22}$ClN$_3$O$_3$: C, 64.15; H, 5.38; N, 10.20. Found: C, 64.24; H, 5.49; N, 10.13.
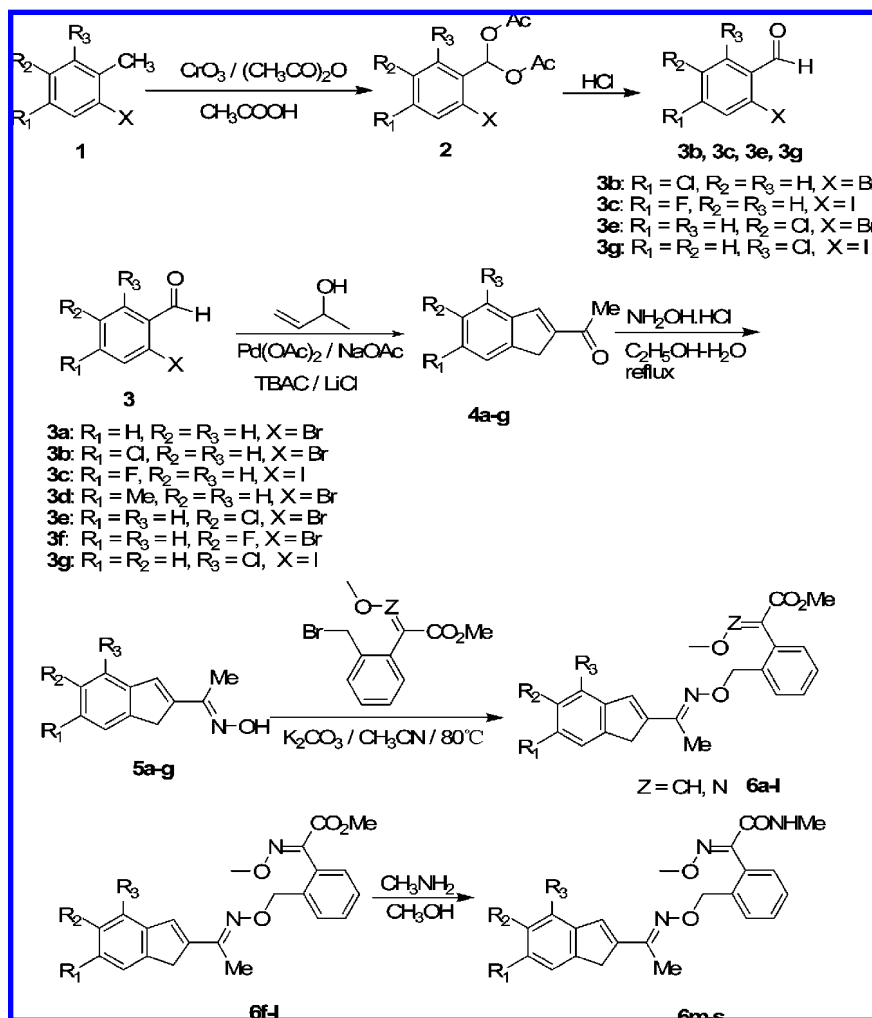
Data for (E,E)-α-(Methoxyimino)-N-methyl-2-[(((1-(5-fluoro-1H-inden-2-yl)ethylidene)amino)oxy)methyl]phenylacetamide (6r). Yellow viscous liquid. Yield: 88.2%. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.41 (s, 3H, CH_3C=N), 2.88 (d, J = 5.1 Hz, 3H, CH_3NH), 3.62 (s, 2H, CH_2), 3.96 (s, 3H, C=NOCH_3), 5.11 (s, 2H, CH_2O), 7.03−7.14 (m, 1H, ArH), 7.28−7.34 (m, 4H, ArH), 7.44−7.47 (m, 1H, ArH), 7.48−7.51 (m, 1H, ArH), 7.92−7.95 (m 1H, ArH). IR (KBr): ν 3360, 2960, 1675, 1520, 1040, 980, 760 cm^{-1}. Anal. Calcd for C$_{22}$H$_{22}$FN$_3$O$_3$: C, 66.82; H, 5.61; N, 10.63. Found: C, 66.91; H, 5.67; N, 10.47.

Data for (E,E)-α-(Methoxyimino)-N-methyl-2-[(((1-(4-chloro-1H-inden-2-yl)ethylidene)amino)oxy)methyl]phenylacetamide (6s). Straw yellow viscous liquid. Yield: 81.4%. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.10 (s, 3H, CH_3C=N), 2.87 (d, J = 4.8 Hz, 3H, CH_3NH), 3.62 (s, 2H, CH_2), 3.97 (s, 3H, C=NOCH_3), 5.10 (s, 2H, CH_2O), 7.11−7.18 (m, 2H, ArH), 7.23−7.31 (m, 4H, ArH), 7.38−7.41 (m, 1H, ArH), 7.48−7.52 (m, 1H, ArH). IR (KBr): ν 3360, 2950, 1670, 1520, 1040, 980, 760 cm^{-1}. Anal. Calcd for C$_{22}$H$_{22}$ClN$_3$O$_3$: C, 64.15; H, 5.38; N, 10.20. Found: C, 64.27; H, 5.45; N, 10.11.

Biological Assay. The fungicidal activities of compounds **6a**−**s** against *Pyricularia oryzae*, *Botrytis cinerea*, and *Phytophthora infestans* in vitro were tested according to the following procedure (*20*): The synthesized target compounds were dissolved in DMF to a concentration of 250 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) at 50 °C. The mixtures were poured into Petri dishes. After the dishes were cooled to room temperature, the solidified plates were incubated with a 4 mm mycelium

Indene-Substituted Oxime Ether Strobilurins

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Scheme 1. General Synthetic Route for the Target Compounds **6a**−**s**

3b: R_1 = Cl, R_2 = R_3 = H, X = Br
3c: R_1 = F, R_2 = R_3 = H, X = I
3e: R_1 = R_3 = H, R_2 = Cl, X = Br
3g: R_1 = R_2 = H, R_3 = Cl, X = I

3a: R_1 = H, R_2 = R_3 = H, X = Br
3b: R_1 = Cl, R_2 = R_3 = H, X = Br
3c: R_1 = F, R_2 = R_3 = H, X = I
3d: R_1 = Me, R_2 = R_3 = H, X = Br
3e: R_1 = R_3 = H, R_2 = Cl, X = Br
3f: R_1 = R_3 = H, R_2 = F, X = Br
3g: R_1 = R_2 = H, R_3 = Cl, X = I

Z = CH, N   **6a-l**

disk at 28 °C for 48 h. Water was used as the blank control. The mycelial elongation radius (mm) of the fungus settlements was measured after 48 h of culture. The growth inhibition rates were calculated with the following equation: $I = [(C - T)/C] \times 100$. Here, I is the growth inhibition rate (%), C is the control settlement radius (mm), and T is the treatment group fungus settlement radius (mm).

The fungicidal activities of compounds **6a**−**s** against cucumber *Pseudoperonospora cubensis*, wheat *Erysiphe graminis*, and cucumber *Colletotrichum lagenarium* in vivo were tested according to the following procedure (*21*): The synthesized target compounds (0.0111 g) were dissolved in 0.5 mL of DMF, and then distilled water (containing 0.1% Tween 80) was added to the solution to a concentration of 1000 mg/L. The solution was diluted to the tested concentration, sprayed onto the plants, and allowed to dry for 2 h. Twenty-four hours later, the plants were inoculated with fungal spores. Each test utilized control plants which were sprayed with a 1/1/2 (by volume) mixture of acetone, methanol, and water (containing 0.1% Tween 80) and inoculated with fungal spores. The results are percent disease control as compared to that of the untreated check, wherein 100 is rated as complete disease control and 0 as no disease control. The remainder of the technique of each of the tests is as follows: (1) For cucumber *P. cubensis*, large and fully expanded leaves were collected from the cucumber plants which were maintained in the greenhouse. The cucumber leaves were sprayed with the solution of the synthesized compound and inoculated by a spore suspension of *P. cubensis* (1×10^5 spores/mL of water) which was cultured on cucumber plants. The cucumber leaves were returned to a controlled environmental chamber ($T = 20$ °C, RH = 90%) for 5 days. Then the leaves were examined for disease development. (2) For wheat *E. graminis*, the fungal pathogen *E. graminis* was cultured on wheat seedlings in a greenhouse conditions (18 °C). 7-Day old wheat seedlings which had been previously sprayed

with the solution of the synthesized compound were inoculated by *E. graminis* spores. The inoculated seedlings were kept in greenhouse conditions (18 °C) and subirrigated. The percent disease control was rated 7 days after the inoculation. (3) For cucumber *C. lagenarium*, the fungal pathogen *C. lagenarium* was cultured on potato dextrose agar (PAD) in the dark at 22 °C for a period of 8−14 days. Spores of *C. lagenarium* were removed from the PAD plates. The spore suspension of *C. lagenarium* (3×10^6 spores/mL of water) was sprayed onto the upper leaf surface of 15 day old cucumber plants which had been previously treated with the solution of the synthesized compound. The plants were placed in a fluorescent-lighted mist chamber (12 h light, 12 h dark) for 48 h. After that infection period, the plants were placed in a growth chamber ($T = 25$ °C, RH = 80%) for 3 days. The treated plants were then evaluated for disease control.

The results are listed in **Table 1**, in which the inhibition percentage was expressed as the mean of values obtained in three independent experiments. To make a judgment on the fungicidal potency of the synthesized compounds, the developing unsaturated oxime ether fungicide SYP-Z071 and two commercial fungicides, trifloxystrobin and kresoxim-methyl, were used as standards.

RESULTS AND DISCUSSION

Synthetic Chemistry. The synthetic route for the target compounds is outlined in **Scheme 1**. The key intermediates 2-acetylindenes **4** were prepared on the basis of previous literature (*16, 22*). First, ortho-halogenated benzaldehydes **3** were reacted with 3-buten-2-ol in the presence of 5% Pd(OAc)$_2$, 2.5 equiv of NaOAc, 2 equiv of *n*-Bu$_4$NCl (TBAC), and 2 equiv of LiCl at 110 °C to give 2-acetylindenes **4** in good yields. Then

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2-acetylindenes **4** were reacted with hydroxylamine hydrochloride to produce 1-(1*H*-inden-2-yl)ethanone oximes **5** in high yield according to the method described previously (*23, 24*). Subsequently, the target compounds methyl 3-methoxypropenoate oxime ethers **6a**−**e** and methyl α-(methoxyimino)benzeneacetate oxime ethers **6f**−**l** were obtained by the reaction of ethanone oximes **5** with (*E*)-methyl 2-(2-(bromomethyl)phenyl)-3-methoxyacrylate or (*E*)-methyl 2-(2-(bromomethyl)phenyl)-2-(methoxyimino)acetate in the presence of base according to the literature (*16, 25*). The target compounds **6m**−**s** were produced by ammonolysis of the corresponding methyl α-(methoxyimino)benzeneacetate oxime ethers **6f**−**l** (*11*). The structures of the desired compounds were confirmed by ¹H NMR, IR, and elemental analyses.

Fungicidal Activities. The in vitro fungicidal activity results of all compounds against *P. oryzae, B. cinerea,* and *P. infestans* at a concentration of 25 mg/L are listed in **Table 1**. The results of preliminary bioassays were compared with those of SYP-Z071 and two commercial fungicides. As shown in **Table 1**, all of the compounds **6a**−**s** showed potent fungicidal activities against the three tested fungi. Most of the compounds had more potent fungicidal activities against *P. oryzae* and *P. infestans* but a little lower activities against *B. cinerea* compared with SYP-Z071. As compared with trifloxystrobin and kresoximmethyl, it was found that most of the compounds had similar fungicidal activities against *P. oryzae* and *P. infestans* but showed a little lower activities against *B. cinerea.*

The in vivo fungicidal activity results of all compounds against cucumber *P. cubensis,* wheat *E. graminis,* and cucumber *C. lagenarium* at a concentration of 6.25 mg/L are listed in **Table 1**. As indicated in **Table 1**, most of the compounds showed good fungicidal activities against the three tested fungi. It was found that most of the compounds exhibited higher fungicidal activities against wheat *E. graminis* and cucumber *C. lagenarium* but lower activities against cucumber *P. cubensis* than SYP-Z071. Additionally, it was found that 12 synthesized compounds exhibited a 70% or more inhibition effect against cucumber *P. cubensis* while trifloxystrobin and kresoxim-methyl showed only a lower inhibition effect at the same test conditions. On the other hand, most of the compounds showed similar fungicidal activities against wheat *E. graminis* compared with trifloxystrobin and kresoxim-methyl. It was also found that 13 compounds exhibited a 60% or more inhibition effect against cucumber *C. lagenarium* while trifloxstrobin and kresoximmethyl showed 60% and 30% inhibition effects, respectively, at the same test conditions. Analyzing all test results, it was clear that α-(methoxyimino)-*N*-methylphenylacetamide oxime ethers **6m**−**s** exhibited broad spectra and remarkably higher activities against all tested fungi. Furthermore, it can be concluded that 6-methylindene-substituted compound **6p** was the most promising candidate for further study because it showed a 100% inhibition effect against all tested fungi at the test concentration.

Conclusion. A series of new indene-substituted oxime ether strobilurins **6** were designed and synthesized by modifying the side chain of unsaturated oxime ether strobilurin fungicide SYP-Z071. The biological assay results indicated that all compounds exhibited good or excellent fungicidal activities. It was found that α-(methoxyimino)-*N*-methylphenylacetamide oxime ethers **6m**−**s** exhibited broad spectra and remarkably higher activities against all tested fungi. Especially, 6-methylindene-substituted compound **6p** was identified as the most promising candidate for further study. Further investigation of this type of compound is also in progress now.

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