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Synthesis and Antifungal Bioactivity of Methyl 2-Methoxyimino-2-{2-[(substituted benzylidene)aminooxymethyl]phenyl}acetate and 2-Methoxyimino-2-{2-[(substituted benzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide Derivatives

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Ten methyl 2-methoxyimino-2-{2-[(substituted benzylidene)aminooxymethyl]phenyl}acetate and 2-methoxyimino-2-{2-[(substituted benzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide derivatives were synthesized. Structures of the new compounds were characterized by IR, ^{1}H NMR and GC-MS data. These compounds at 10 μg/mL were tested *in vitro* against five pathogenic fungi, namely, *Sclerotonia*, *Botrytis cinerea* Pers, *Gibberella zeae*, *Rhizoctorua solani* and *Pyricularia oryzae*. Compounds **G$_5$**, **G$_6$**, **G$_7$** and **G$_8$** showed potent antifungal activities against *Botrytis cinerea Pers*, **G$_7$** against *Gibberella zeae* and **G$_7$**, **G$_8$** against *Rhizoctorua solani*, respectively.

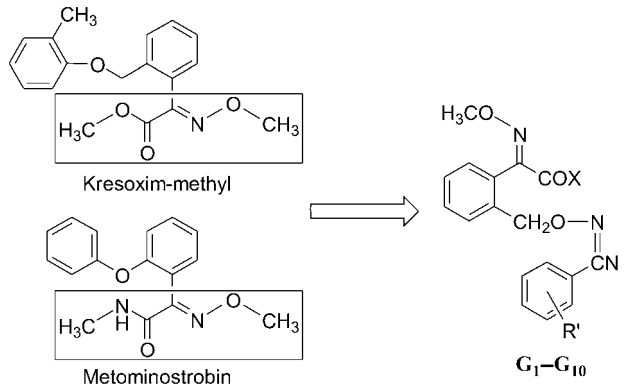
Keywords methyl 2-methoxyimino-2-{2-[(substituted benzylidene)aminooxymethyl]phenyl}acetate, methyl 2-methoxyimino-2-{2-[(substituted benzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide, synthesis, antifungal activity

Introduction

Strobilurin fungicides occupy an important position in pesticide chemistry due to their stronger biological activities and lower toxicity,[1,2] which constitute a relatively new fungicide class developed from natural fungicidal derivatives such as strobilurin A, oudemansin A or myxothiazol A.[3] Strobilurins have either an (*E*)-*β*-methyl methoxyiminoacetate moiety or isosteric (*E*)-*β*-methyl methoxyacrylate group which acts as a common pharmacophoric sub-structure. So far, some of these fungicides have been commercialized.[4-6] Analysis of action of strobilurins revealed that these compounds were a new class of substances that include quinone outside inhibitor (QoI) fungicide groups. These synthetic fungicides are active ingredients with similar action to the natural strobilurin A, which is produced by different wood-rotting fungi.[7-10] The fungicidal strobilurins display their inhibitory effect on the mitochondrial respiration by binding at the ubiquinol-oxidation centre (Qo-site) of the bc1-enzyme complex (complex III) of a fungus where electron transfer can take place.[2,11] Their wide application prospects make it very important to design and synthesize similar compounds with higher biological activity.[12]

In the process of the synthesis of new bioactive compounds, the structure of oxime ether with excellent bioactivity is commonly chosen as an active group to synthesize fungicide, herbicide and medicine.[13-16] Compounds containing an oxime ether structure affect the detoxification of monooxygenase. In the development of strobilurin fungicides, some compounds with an oxime ether group were synthesized through modification of the structure of methoxyacrylate. In the study, we chose strobilurin compounds with oxime ether moieties (kresoxim-methyl and metominostrobin) as lead compounds and synthesized 10 new compounds (Scheme 1). The synthetic route is shown in Scheme 2.

Scheme 1



G$_1$: R' = 4-CF_3, X = OCH_3; **G$_2$**: R' = 2-OH, X = OCH_3; **G$_3$**: R' = 4-NH_2, X = OCH_3; **G$_4$**: R' = 4-Cl, X = $NHCH_3$; **G$_5$**: R' = 2,4-2Cl, X = $NHCH_3$; **G$_6$**: R' = 2-Br, X = $NHCH_3$; **G$_7$**: R' = 4-Br, X = $NHCH_3$; **G$_8$**: R' = 4-CF_3, X = $NHCH_3$; **G$_9$**: R' = 2-OH, X = $NHCH_3$; **G$_{10}$**: R' = 4-NH_2, X = $NHCH_3$.

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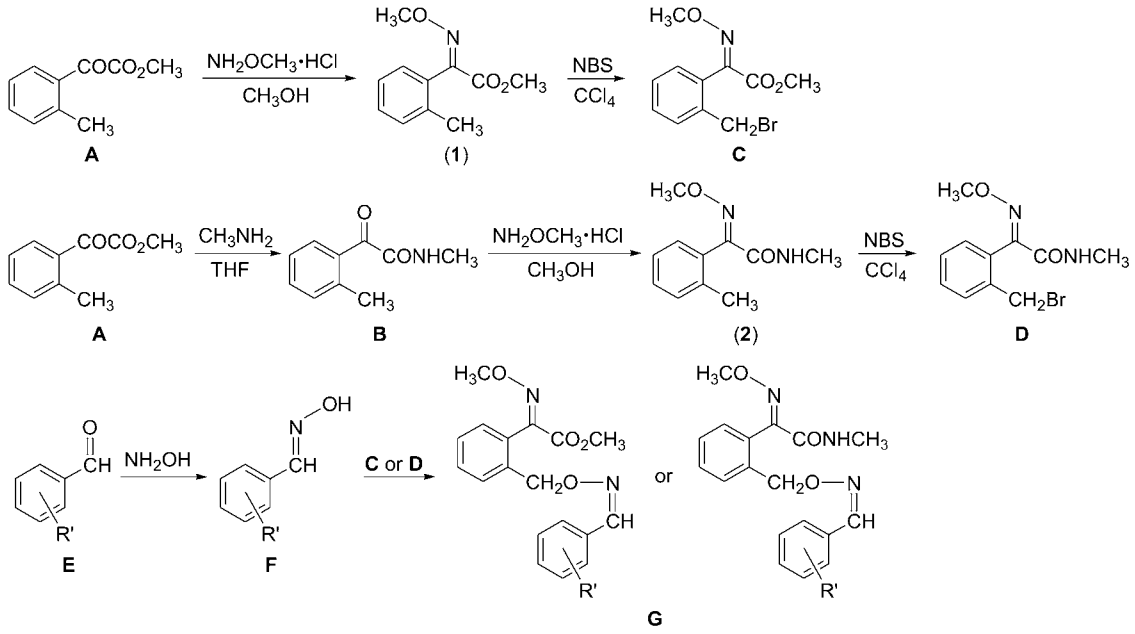
Scheme 2



The structures of the title compounds $\mathbf{G_1}$—$\mathbf{G_{10}}$ were determined by IR, ^{1}H NMR and GC-MS. Results of bioassay revealed that some of these compounds had good antifungal activities.

Results and discussion

Chemical synthesis

Intermediate **B** synthesized by chloride has a high chemical reaction rate and a high yield.[17] When chloride was replaced by ester the experiment was performed under different conditions during the synthesis of intermediate **B**. We examined the molar ratio of reaction material, reaction time and temperature, all of which were considered to affect the yield of intermediate **B**. Analytical results are summarized in Tables 1—3. When the molar ratio of compound **A** to methylamine in anhydrous ethanol (30%) was increased from 1∶1 equiv. to 1∶1.5 equiv. and 1∶2 equiv., intermediate **B** could be obtained at percentages of 56.7%, 85.2% and 85.2%, respectively, at room temperature (Table 1). With regard to the reaction time, 41.2%, 75.2%, and 85.1% yields of intermediate **B** were noted in 1, 3, and 5 h, at room temperature respectively. When the reaction time was prolonged up to 7 h, no improvement of yield was obtained (Table 2). We also tested the reaction temperature and found that lower yield was observed at lower temperature (Table 3). Also, the yield was not significantly raised when the reaction was performed above 50 ℃.

The reaction processes for intermediates **C** and **D** were free radical substitutions in nature. Solvent CCl_4 used was dried by anhydrous magnesium sulfate, because synthesis of intermediates **C** and **D** must be anhydrous. When water was used as solvent, the yield of intermediate **F** increased to 96.3%—98.0%. Title compounds **G** had a relatively high yield, provided that the structure of the benzene ring had a deactivating group, such as Cl, Br, CF_3 or NO_2. When the benzene ring had a nitro (NO_2) substituent, the nitro was reduced to amino (NH_2) by NaH. In the synthesis of title compound $\mathbf{G_{10}}$, the molar ratio of the reactant NaH to F_3 was increased from 1∶2 to 1∶4.

Table 1 Effect of molar ratio of intermediate **A** to methylamine on synthesis of intermediate **B**

Entry	Molar ratio of intermediate **A**∶methylamine	Yield/%
1	1∶1	56.7
2	1∶1.5	85.2
3	1∶2	85.2

Table 2 Effect of reaction time on synthesis of intermediate **B**

Entry	Time/h	Yield/%
1	1	41.2
2	3	75.2
3	5	85.1
4	7	85.1

Table 3 Effect of temperature on the synthesis of intermediate **B**

Entry	Temperature/℃	Yield/%
1	Room temperature	85.1
2	40	93.4
3	50	95.2
4	60	95.2

Analysis of spectra

When samples were analyzed by IR, only characteristic peaks of high intensity (such as C=O, C=N, N—H) were recognized. There were *Z* and *E* isomers in the

structures of intermediates **1**, **2**, **C**, **D** and title compounds $\mathbf{G_1}$—$\mathbf{G_{10}}$. Their *Z* and *E* isomer contents were *Z* 8.7% and *E* 83.1%.[17] There was little content of *Z* isomer in these compounds purified by silica gel chromatography and the result could be verified by the chromatogram in GC-MS. The main component of intermediate **F** is chiefly composed of *E*, because *E* is more stable than *Z*. The probability of N=CH (2s, 1H) showing two singlet peaks is due to that the *Z* and *E* isomers existed in the structures of title compounds $\mathbf{G_1}$—$\mathbf{G_{10}}$ when they were dissolved in solvent for ^{1}H NMR. Due to the instability of the title compounds $G_{1\text{-}10}$, the height of molecular ion peak was very low, but the fragments derived from the molecule gave highly useful information about the structures of the title compounds $\mathbf{G_1}$—$\mathbf{G_{10}}$. Compound G_8 was taken as an example: 384 (M^+, 7), 353 ($M-OCH_3^+$), 222 [$M-CF_3$-$C_6H_4C(CH_3)N^+$], 206 ($222-O^+$), 172 ($CF_3C_6H_4CHN^+$), 116 ($N\equiv CC_6H_4CH_2^+$), 59 ($COOCH_3^+$).

Antifungal bioactivity bioassay

We selected five fungi *Sclerotonia*, *Botrytis cinerea Pers*, *Gibberella zeae*, *Rhizoctorua solani* and *Pyricularia oryzae* for fungicidal bioassay and two commercial agricultural fungicides kresoxim-methyl and carbendazim for contrast fungicides. These fungi belong to the group of field fungi and were isolated from corresponding crops. The result of preliminary screening is demonstrated in Table 4. Compounds $\mathbf{G_5}$, $\mathbf{G_6}$, $\mathbf{G_7}$ and $\mathbf{G_8}$ showed potent antifungal activities of inhibition rate of 23.13%, 32.46%, 35.07% and 20.15%, respectively against *Botrytis cinerea* Pers growth. But antifungal activities of compounds $\mathbf{G_5}$, $\mathbf{G_6}$, $\mathbf{G_7}$ and $\mathbf{G_8}$ were lower than those of kresoxim-methyl and carbendazim. Compound $\mathbf{G_7}$ showed 44.67% of higher antifungal activities against *Gibberella zeae* than kresoxim-methyl. Compounds $\mathbf{G_7}$ and $\mathbf{G_8}$ also showed potent antifungal activities against *Rhizoctorua solani*, which had high activities as compared to kresoxim-methyl.

Experimental

General

The melting points of the products were determined by a WRS-1A melting point instrument (Shanghai Precision & Scientific Instrument Co. Ltd., China) and are not corrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer (Bruker, Germany) in KBr disks. ^{1}H NMR (solvent $CDCl_3$) was performed by a Varian Mercury plus-400 MHz NMR spectrometer (Varian, USA) at room temperature using TMS as an internal standard. Mass spectra of products were determined by the QP-2010 GC-MS (Shimadzu, Japan). Elemental analysis was performed on a PE-2400 Elemental analyser (Perkin-Elmer, USA). Analytical thin-layer chromatography (TLC) was performed on silica gel GF_{254} plates to purify products.

Synthesis of intermediates

Synthesis of methyl 2-methoxyimino-2-(2-methyphenyl)acetate (1) A dry round-bottomed flask equipped with a magnetic stirrer was charged with compound **A** (9 mmol, 1.6 g) and CH_3ONH_2•HCl (18 mmol, 1.5 g) in 20 mL of methanol. The mixture was stirred for 4 h at 40 ℃. Then 100 mL of water were added into the mixture after the reaction. The mixture was extracted with 20 mL×3 of CH_2Cl_2 and the combined organic layers were dried by anhydrous magnesium sulfate, filtered and concentrated. The light yellow residue was assigned as intermediate **1**. The yield was 98.9%. The residue was purified by silica gel chromatography [a mixture of petroleum ether/ethyl acetate (3∶1, *V*/*V*) as eluent]. Light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.59 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.19 (s, 3H, $NOCH_3$), 7.29—7.68 (m, 4H, Ar-H); IR (liquid film) ν: 1592 (C=N), 1695 (C=O) cm^{-1}. EI-MS (70 eV) *m*/*z* (%): 207 (M^+, 15), 148 (100), 117 (85), 91 (49), 65 (39), 59 (32), 39 (34). Anal. calcd for $C_{11}H_{13}NO_3$: C 63.76, H 6.32, N 6.76; found C 63.62, H 6.43, N 6.84.

Table 4 Fungicidal activity of novel compounds $\mathbf{G_1}$—$\mathbf{G_{10}}$

Compound	Inhibition rate of hypha growth/%				
	Sclerotonia	*Botrytis cinerea* Pers	*Gibberella zeae*	*Rhizoctorua solani*	*Pyricularia oryzae*
$\mathbf{G_1}$	0.00	6.92	3.47	−1.43	−0.98
$\mathbf{G_2}$	0.00	3.11	2.78	4.30	1.63
$\mathbf{G_3}$	0.00	3.81	3.47	3.94	0.00
$\mathbf{G_4}$	11.15	1.87	1.03	5.47	−2.00
$\mathbf{G_5}$	17.77	23.13	2.41	8.59	3.33
$\mathbf{G_6}$	12.20	32.46	−1.37	6.64	8.67
$\mathbf{G_7}$	16.03	35.07	44.67	55.47	9.00
$\mathbf{G_8}$	12.20	20.15	6.87	24.22	12.33
$\mathbf{G_9}$	2.09	14.93	5.50	3.91	1.33
$\mathbf{G_{10}}$	7.32	11.19	6.87	9.77	4.00
Kresoxim-methyl	36.88	36.33	33.68	3.58	54.07
Carbendazim	92.19	47.40	100.0	100.0	100.0

Synthesis of 2-methylbenzoyl-*N*-methylformamide (B) Compound **A** (3.6 g) was dissolved in 40 mL of dried THF. Methylamine in anhydrous ethanol (2.0 g, 30%) was then added slowly through a dropping funnel into the above solution within 10 min, followed by stirring at 50 ℃ for 5 h. After completion of the reaction, water (100 mL) was added into the reaction mixture, and the resulting mixture adjusted to pH below 2.0 by addition of conc. HCl and extracted with ethyl acetate (50 mL×2). The combined organic layers were dried by anhydrous magnesium sulfate, filtered and concentrated. The colorless residue was intermediate **B**, with a yield of 94.2%, which was purified by silica gel chromatography [a mixture of petroleum ether/ethyl acetate (3∶1, *V*/*V*) as eluent]. Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.58 (s, 3H, CH_3), 3.68 (d, J=4.6 Hz, 3H, N-CH_3), 6.82 (q, J=4.6 Hz, 1H, NH), 7.29—7.68 (m, 4H, Ar-H); IR (liquid film) ν: 1599, 1693 (C=O), 3198 (N—H) cm^{-1}. EI-MS (70 eV) *m*/*z* (%): 177 (M^+, 11), 119 (100), 91(58), 65 (44), 39 (32). Anal. calcd for $C_{10}H_{11}NO_2$: C 67.78, H 6.26, N 7.90; found C 67.85, H 6.17, N 8.02.

Synthesis of 2-methoxyimino-2-methylphenyl-*N*-methylacetamide (2) The same method of synthesis was used as that of intermediate **1** in a yield of 94.2%. Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.58 (s, 3H, CH_3), 3.68 (d, J=4.6 Hz, 3H, N-CH_3), 6.84 (q, J=4.6 Hz, 1H, NH), 7.29—7.68 (m, 4H, Ar-H); IR (liquid film) ν: 1599, 1693 (C=O), 3198 (N—H) cm^{-1}. EI-MS (70 eV) *m*/*z* (%): 206 (M^+, 8), 148 (100), 117 (89), 91 (52), 65 (44), 58 (24), 39 (29). Anal. calcd for $C_{11}H_{14}N_2O_2$: C 64.06, H 6.84, N 13.58; found C 63.91, H 6.78, N 13.51.

Synthesis of methyl 2-methoxyimino-2-(2-bromomethyl phenyl)acetate (C) Intermediate **1** (0.02 mol, 4.2 g) dissolved in CCl_4 (40 mL), NBS (3.9 g, 0.02 mol) and 2,2'-azobisisobutyronitrile (0.32 g, 0.002 mol) were added into a dry round-bottomed flask equipped with a magnetic stirrer. The resultant mixture was heated under reflux for 1 h and cooled to room temperature. Insoluble materials were removed by filtration. On evaporation of the solvent, the residue oil was obtained as intermediate **C** in a yield of 47.9%, which was purified by silica gel chromatography [a mixture of petroleum ether/ethyl acetate (3∶1, *V*/*V*) as eluent]. Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05 (s, 2H, CH_2Br), 3.88 (s, 3H, OCH_3), 4.03 (s, 3H, $NOCH_3$), 7.15—7.70 (m, 4H, Ar-H); IR (liquid film) ν: 1427 (C=N), 1693 (C=O) cm^{-1}. EI-MS (70 eV) *m*/*z* (%): 287 (M^++2, 4), 285 (M^+, 4), 255 (9), 227 (100), 206 (84), 65 (15), 59 (12). Anal. calcd for $C_{11}H_{12}NO_3Br$: C 46.17, H 4.23, N 4.90; found C 46.28, H 4.41, N 4.80.

Synthesis of 2-methoxyimino-2-bromomethyl-phenyl-*N*-methylacetamide (D) In the same manner as intermediate **C**, intermediate **D** was prepared from intermediate **2** in a yield of 37.8%. Light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.99 (s, 2H, CH_2Br), 3.88 (d, J=4.7 Hz, 3H, $NHCH_3$), 4.11 (s, 3H, $NOCH_3$), 6.49 (q, J=4.7 Hz, 1H, $NHCH_3$), 7.15—7.70 (m, 4H, Ar-H); IR (liquid film) ν: 1432 (C=N), 1688 (C=O), 3198 (N—H) cm^{-1}. EI-MS (70 eV) *m*/*z* (%): 286 (M+2, 7), 284 (M^+, 7), 254 (18), 227 (100), 205 (75), 65 (22), 39 (9). Anal. calcd for $C_{11}H_{13}N_2O_2Br$: C 46.33, H 4.60, N 9.82; found C 46.75, H 4.81, N 9.70.

Synthesis of substituted benzaldoxime (F) $\mathbf{F_1}$ (R'=4-CF_3), $\mathbf{F_2}$ (R'=2-OH), $\mathbf{F_4}$ (R'=4-Cl), $\mathbf{F_5}$ (R'=2,4-2Cl) and $\mathbf{F_7}$ (R'=4-Br) were obtained from commercial sources. Synthesis of intermediates $\mathbf{F_3}$ (R'=4-NO_2) and $\mathbf{F_6}$ (R'=2-Br) were performed by the method as described previously.[18] $\mathbf{F_3}$: White solid, m.p. 133.2—133.8 ℃ (Lit.[19] 133.0 ℃), yield 96.3%; $\mathbf{F_6}$: Light yellow solid, m.p. 102.1—103.9 ℃ (Lit.[20] 103.0 ℃), yield 98.0%.

Synthesis of title compounds $\mathbf{G_1}$—$\mathbf{G_{10}}$

Intermediate **F** (8.5 mmol), DMF (30 mL) and NaH (17 mmol, 0.42 g) were added into a round-bottomed flask. Intermediate **C** (or **D**) (1.03 g, 8 mmol) was then added slowly through a dropping funnel into the above mixture over a period of 10 min. The reaction mixture was kept on stirring for 2—3 h at room temperature. After the reaction was finished, the mixture was poured into 30 mL of ice-cold water and extracted with ethyl acetate (30 mL×3). The combined organic layers were dried by anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography [a mixture of petroleum ether/ethyl acetate (3∶1, *V*/*V*) as eluent] to obtain the title compounds $\mathbf{G_1}$—$\mathbf{G_{10}}$.

Methyl 2-methoxyimino-2-{2-[(4-trifluoromethyl-benzylidene)aminooxymethyl]phenyl}acetate ($\mathbf{G_1}$) Light yellow liquid, yield 50.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.38 (s, 3H, $NOCH_3$), 3.59 (s, 3H, $COOCH_3$), 5.12 (s, 2H, CH_2), 6.89—7.61 (m, 8H, Ar-H), 8.11, 8.31 (2s, 1H, N=C—H); IR (liquid film) ν: 1424, 1501 (C=N), 1729 (C=O) cm^{-1}. EI-MS (70 eV) *m*/*z* (%): 384 (M^+, 7), 353 (15), 222 (47), 206 (84), 172 (92), 116 (100), 59 (9). Anal. calcd for $C_{19}H_{17}N_2O_4F_3$: C 57.87, H 4.35, N 7.10; found C 57.69, H 4.40, N 7.12.

Methyl 2-methoxyimino-2-{2-[(2-hydroxybenzyl-idene)aminooxymethyl]phenyl}acetate ($\mathbf{G_2}$) Yellow liquid, yield 41.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.48 (s, 3H, $NOCH_3$), 3.78 (s, 3H, $COOCH_3$), 5.21 (s, 2H, CH_2), 7.10—7.91 (m, 8H, Ar-H), 8.03, 8.33 (2s, 1H, N=C—H), 8.49 (s, 1H, OH); IR (liquid film) ν: 1409, 1487 (C=N), 1724 (C=O) cm^{-1}; EI-MS (70 eV, *m*/*z*, %): 342 (M^+, 9), 311 (14), 222 (48), 206 (90), 120 (85), 116 (100), 59 (9). Anal. calcd for $C_{18}H_{18}N_2O_5$: C 63.15, H 5.30, N 8.18; found C 63.30, H 5.22, N 8.15.

Methyl 2-methoxyimino-2-{2-[(4-aminobenzyl-idene)aminooxymethyl]phenyl}acetate ($\mathbf{G_3}$) Colorless liquid, yield 52.7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.37 (s, 3H, $NOCH_3$), 3.66 (s, 3H, $COOCH_3$), 4.62 (s, Ar-NH_2), 5.12 (s, 2H, CH_2), 6.90—7.72 (m, 8H, Ar-H), 8.12, 8.29 (2s, 1H, N=C—H); IR (liquid film) ν: 1403,

1487 (C=N), 1699 (C=O) cm^{-1}; EI-MS (70 eV) *m/z* (%): 341 (M^+, 8), 310 (15), 222 (52), 206 (79), 119 (92), 116 (100), 59(9). Anal. calcd for $C_{18}H_{19}N_3O_4$: C 63.33, H 5.61, N 12.31; found C 63.38, H 5.52, N 12.39.

2-Methoxyimino-2-{2-[(4-chlorobenzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide (G_4) Yellow liquid, yield 45.3%; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.45 (s, 3H, $NOCH_3$), 3.54 (d, J = 4.6 Hz, 3H, $CONHCH_3$), 6.42 (q, J=4.6 Hz, 1H, $CONHCH_3$), 5.12 (s, 2H, CH_2), 7.04—7.74 (m, 8H, Ar-H), 8.18, 8.31 (2s, 1H, N=C—H); IR (liquid film) *v*: 1405, 1501 (C=N), 1698 (C=O), 3124 (N—H) cm^{-1}; EI-MS (70 eV) *m/z* (%): 360 (M^+, 10), 329 (19), 222 (52), 205 (90), 139 (90), 116 (100), 59 (12). Anal. calcd for $C_{18}H_{18}N_3O_3Cl$: C 60.09, H 5.04, N 11.68; found C 60.01, H 5.11, N 11.55.

2-Methoxyimino-2-{2-[(2,4-dichlorobenzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide (G_5) Orange liquid, yield 55.1%; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.49 (s, 3H, $NOCH_3$), 3.55 (d, J=4.5 Hz, 3H, $CONHCH_3$), 6.38 (q, J=4.5 Hz, 1H, $CONHCH_3$), 5.15 (s, 2H, CH_2), 7.00—7.82 (m, 7H, Ar-H), 8.07, 8.19 (2s, 1H, N=C—H); IR (liquid film) *v*: 1421, 1544 (C=N), 1727 (C=O), 3099 (N—H) cm^{-1}; EI-MS (70 eV) *m/z* (%): 395 (M^+, 5), 363 (8), 222 (45), 205 (91), 173 (94), 116 (100), 59 (7). Anal. calcd for $C_{18}H_{17}N_3O_3Cl_2$: C 54.83, H 4.35, N 10.66; found C 54.75, H 4.40, N 10.49 .

2-Methoxyimino-2-{2-[(2-bromobenzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide (G_6) Light yellow liquid, yield 48.0%; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.51 (s, 3H, $NOCH_3$), 3.57 (d, J=4.6 Hz, 3H, $CONHCH_3$), 6.46 (q, J=4.6 Hz, 1H, $CONHCH_3$), 5.07 (s, 2H, CH_2), 7.21—7.81 (m, 8H, Ar-H), 8.12, 8.32 (2s, 1H, N=C—H); IR (liquid film) *v*: 1418, 1493 (C=N), 1719 (C=O), 3079 (N—H) cm^{-1}; EI-MS (70 eV) *m/z* (%): 405 (M+2, 7), 403 (M^+, 7), 373 (9), 222 (48), 205 (87), 183 (92), 116 (100), 59 (13). Anal. calcd for $C_{18}H_{18}N_3O_3Br$: C 53.48, H 4.49, N 10.39; found C 53.60, H 4.61, N 10.18.

2-Methoxyimino-2-{2-[(4-bromobenzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide (G_7) Light yellow liquid, yield 49.2%; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.48 (s, 3H, $NOCH_3$), 3.56 (d, J=4.6 Hz, 3H, $CONHCH_3$), 6.40 (q, J=4.6 Hz, 1H, $CONHCH_3$), 5.13 (s, 2H, CH_2), 7.01—7.61 (m, 8H, Ar-H), 8.02, 8.30 (2s, 1H, N=C—H); IR (liquid film) *v*: 1422, 1504 (C=N), 1701 (C=O), 3109 (N—H) cm^{-1}; EI-MS (70 eV) *m/z* (%): 405 (M+2, 6), 403 (M^+, 6), 373 (11), 222 (51), 205 (92), 183 (89), 116 (100), 59 (8). Anal. calcd for $C_{18}H_{18}N_3O_3Br$: C 53.48, H 4.49, N 10.39; found C 53.62, H 4.65, N 10.22.

2-Methoxyimino-2-{2-[(4-trifluoromethylbenzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide (G_8) Yellow liquid, yield 53.0%; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.39 (s, 3H, $NOCH_3$), 3.58 (d, J=4.6 Hz, 3H, $CONHCH_3$), 6.43 (q, J=4.6 Hz, 1H, $CONHCH_3$), 5.11 (s, 2H, CH_2), 7.00—7.81 (m, 8H, Ar-H), 8.13, 8.280 (2s, 1H, N=C—H); IR (liquid film) *v*: 1399, 1492 (C=N), 1674 (C=O), 3089 (N—H) cm^{-1}; EI-MS (70 eV) *m/z* (%): 383 (M^+, 5), 352 (15), 222 (41), 205 (90), 172 (92), 116 (100), 59 (9). Anal. calcd for $C_{19}H_{18}N_3O_3F_3$: C 58.01, H 4.61, N 10.68; found C 58.10, H 4.71, N 10.59.

2-Methoxyimino-2-{2-[(2-hydroxybenzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide (G_9) Colorless liquid, yield 36.7%; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.45 (s, 3H, $NOCH_3$), 3.58 (d, J=4.5 Hz, 3H, $CONHCH_3$), 6.42 (q, J=4.5 Hz, 1H, $CONHCH_3$), 5.23 (s, 2H, CH_2), 6.87—7.59 (m, 8H, Ar-H), 8.09, 8.23 (2s, 1H, N=C—H), 8.52 (s, 1H, OH); IR (liquid film) *v*: 1395, 1488 (C=N), 1688 (C=O), 3077 (N—H) cm^{-1}; EI-MS (70 eV) *m/z* (%): 341 (M^+, 4), 311 (10), 222 (56), 205 (92), 120 (92), 116 (100), 59 (7). Anal. calcd for $C_{18}H_{19}N_3O_4$: C 63.33, H 5.61, N 12.31; found C 63.35, H 5.52, N 12.38.

2-Methoxyimino-2-{2-[(4-aminobenzylidene)aminooxymethyl]phenyl}-*N*-methylacetamide (G_{10}) Light red liquid, yield 49.1%; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.51 (s, 3H, $NOCH_3$), 3.64 (d, J=4.5 Hz, 3H, $CONHCH_3$), 4.60 (s, Ar-NH_2), 6.34 (q, J=4.5 Hz, 1H, $CONHCH_3$), 5.11 (s, 2H, CH_2), 7.10—7.80 (m, 8H, Ar-H), 8.08, 8.29 (2s, 1H, N=C—H); IR (liquid film) *v*: 1415, 1491 (C=N), 1701 (C=O), 3102, 3219 (N—H) cm^{-1}; EI-MS (70 eV) *m/z* (%): 340 (M^+, 5), 309 (13), 221 (47), 205 (84), 119 (91), 116 (100), 59 (11). Anal. calcd for $C_{18}H_{20}N_4O_3$: C 60.66, H 5.66, N 15.72; found C 60.77, H 5.52, N 15.65.

Antifungal biological assay

Antifungal activity of all synthesized novel compounds was tested against five pathogenic fungi, namely *Sclerotonia*, *Botrytis cinerea Pers*, *Gibberella zeae*, *Rhizoctorua solani* and *Pyricularia oryzae* by the method of poison plate technique.[21, 22] Compounds were dissolved in 1 mL of acetone before mixing with 90 mL of potato dextrose agar (PDA) or potato sucrose agar (PSA) in Petri dishes at 45 ℃. The final concentration of compounds in the medium was fixed at 10 μg/mL. Kresoxim-methyl and carbendazim (10 μg/mL, dissolved in 0.02 mol•L^{-1} HCl) served as a positive control. When the fungi on untreated PDA or PSA were incubated at (25±1) ℃ to occupy 2/3 of the Petri dishes, the diameter growth of the fungal colonies on the treated PDA or PSA was measured by a crossing method and the data were statistically analyzed. For each treatment, three replicates were conducted. The inhibiting effects of the test compounds *in vitro* on these fungi were calculated by the formula: $I\% = \frac{A-B}{A-C} \times 100$, where *A* represents the diameter of fungi growth on the untreated PDA or PSA, *B* represents the diameter of fungi on the treated PDA or PSA, and *C* represents the diameter of mycelia dish while *I*/% means the hypha growth inhibiting rate.

Conclusion

In this study, we synthesized ten 2-methoxyimino-2-

phenyl-*N*-methylacetamide and methyl 2-methoxyimino-2-phenylacetate derivatives. Their structures were identified by spectrum data. In antifungal bioassays, the title compounds **G_5**, **G_6**, **G_7** and **G_8** showed relatively high antifungal activities against *Botrytis cinerea* Pers, **G_7** against *Gibberella zeae* and **G_7**, **G_8** against *Rhzoctorua solani*.

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