Original Article

Fungicidal Activities of α -Methoxyphenylacetic Acid DerivativesTsuneo ICHIBA,*[‡] Takami MURASHI, Toshikazu OHTSUKA and Michio MASUKO

Aburahi Laboratories, Shionogi and Co., Ltd., 1405 Gotanda, Koka-cho, Koka-gun, Shiga 520-3423, Japan

(Received August 24, 2001 ; Accepted December 7, 2001)

A number of α -alkoxyphenylacetic acid derivatives were synthesized and their fungicidal activities were examined. Studies of structure-activity relationships revealed strong fungicidal activity when the substituent at the α -position was a methoxy group and a substituted phenoxymethyl group was introduced to the 2-position of the benzene ring of the phenylacetic acid moiety. When a substituted phenoxy group was introduced to this position, the fungicidal activity was very weak. It was also shown that *N*-methyl-phenylacetamide derivatives had stronger activities than phenylacetic acid methyl ester derivatives. Among the compounds synthesized in this study, 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methyl-*N*-methylacetamide (**35**) showed the most potent fungicidal activity against a wide range of crop diseases.

Key words: α -methoxyphenylacetic acid derivatives, fungicide, strobilurin analogue.

INTRODUCTION

After strobilurin analogues were first isolated from Basidiomycotina fungi,^{1–7)} many studies were performed to examine the effects of structural modifications.^{8–13)} In 1992, the ZENECA group¹⁴⁾ and the BASF group¹⁵⁾ independently reported the strobilurin analogues azoxystrobin (ICIA5504) and kresoxim-methyl (BAS-490F) as a promising new class of agricultural fungicides with a broad spectrum and a new mode of action. Azoxystrobin synthesized by the ZENECA group has a β -methoxyacrylic acid methyl ester as a pharmacophore and a substituted pyrimidine ring as a side chain, while kresoxim-methyl synthesized by the BASF group has a β -methoxyiminoacetic acid methyl ester as a pharmacophore and a substituted phenoxymethyl side chain. Previously,^{16–18)} we synthesized different types of strobilurin analogues with β -methoxyiminoacetamide as a pharmacophore and phenoxy, phenoxymethyl or pyridyloxymethyl side chains, and reported excellent fungicidal activity. Among the β -methoxyiminoacetamide derivatives, the unsubstituted phenoxy derivative, metominostrobin (SSF-126), has been developed as a fungicide for the control of rice diseases.¹⁹⁾

Sauter *et al.* summarized the structure and fungicidal activities of strobilurin derivatives.²⁰⁾ They described in their review that the atom at the α -position of the phar-

macophore is preferentially an sp^2 -hybridized carbon or sp^2 -like nitrogen with trigonal geometry for fungicidal activity. In fact, all of the strobilurin analogues mentioned above contain an olefinic carbon-carbon or carbon-nitrogen double bond, and the double bond seems to be essential for the fungicidal activity. In the course of studying the structure-activity relationships of strobilurin analogues, we synthesized a number of α -methoxy phenylacetic acid derivatives, which diminished the α - β double bond, and assessed their fungicidal activities. This paper deals with the fungicidal activities of α -methoxy phenylacetic acid derivatives.

MATERIALS AND METHODS

1. Chemicals

The pathways for the synthesis of α -methoxyphenylacetic acids are shown in Fig. 1. The methods used to synthesize these derivatives are described in the patents.^{21–24)} The procedure for 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxy-*N*-methylacetamide (**35**) is shown below, as a typical example.

2,5-xylene (**I**, Y = 2,5-Me₂; 110 g, 0.90 mol), dimethylsulfoxide (400 ml) and potassium hydroxide (59.8 g, 1.07 mol) were added successively to a 2 l flask, and stirred for 1 hr at 130°C. A solution of 2-bromobenzyl bromide (**II**, Q = -CH₂-, X = Br, 200 g, 0.80 mol) in dimethylsulfoxide (70 ml) was added dropwise to the reaction mixture in an ice bath. The reaction mixture was stirred for 2 hr at room temperature. Ice and water were added, and the mixture was extracted with ether. The organic layer was washed with a 0.1 *N* sodium hydroxide aqueous solution

* To whom correspondence should be addressed.

[‡]Present address: Aventis CropScience Shionogi Co. Ltd., 2894-1 Naruto, Naruto-machi, Sanbu-gun, Chiba 289-1326, Japan

Fig. 1 The synthetic pathway of 2-alkoxy-2-(substituted phenyl)acetic acid derivatives.

and then brine, and dried over anhydrous sodium sulfate. After filtering off anhydrous sodium sulfate, the solvent was evaporated to yield the crude 2-(2,5-dimethylphenoxy)methyl)bromobenzene (**III**, $M = -CH_2O-$, $X = Br$, $Y = 2,5-Me_2$; 232 g) as crystals. 1H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 2.25 (3H, s), 2.32 (3H, s), 5.10 (2H, s), 6.70 (2H, m), 7.01 (1H, d, $J = 7.9$), 7.10 (1H, t, $J = 7.9$), 7.35 (1H, t, $J = 7.9$), 7.65–7.75 (2H, m).

Magnesium (14.6 g, 0.60 mol) and tetrahydrofuran (200 ml) were added successively to a 1 l flask and stirred under a nitrogen atmosphere. Bromoethane (0.88 g) was then added. After 10 min, a tetrahydrofuran (80 ml) solution of the crude 2-(2,5-dimethylphenoxy)methyl)bromobenzene (**III**, $M = -CH_2O-$, $X = Br$, $Y = 2,5-Me_2$; 116.5 g, 0.40 mol) was added dropwise to the reaction mixture for 40 min at 60–65°C. Grignard reagent was prepared by stirring the mixture for an additional 1 hr. The Grignard reagent was added dropwise for 40 min at –70––60°C to the stirring tetrahydrofuran (400 ml) solution of dimethyl oxalate (94.5 g, 0.80 mol) in the 2 l flask under the nitrogen atmosphere. After 80 min at –20––10°C, a saturated ammonium chloride aqueous solution (500 ml) was added and the reaction mixture was stirred for 30 min at room temperature. The mixture was extracted with ether. The combined organic layer was washed with water followed by brine and dried over anhydrous magnesium sulfate. The solvent filtered off of the anhydrous magnesium sulfate was evaporated, and the residual solid was recrystallized in hexane/ethyl acetate (2/1) to give the desired compound, methyl 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-oxoacetate (**IV**, $M = -CH_2O-$, $R = Me$, $Y = 2,5-Me_2$; 42 g, 35%) as white crystals. mp: 104–106°C.

A solution of methyl 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-oxoacetate (**IV**, $M = -CH_2O-$, $R = Me$,

$Y = 2,5-Me_2$; 3.00 g, 10.1 mmol) and tetrahydrofuran (20 ml) was stirred at 0°C, and sodium borohydride (0.19 g, 5.0 mol) was added. After 30 min, acetic acid was added and the reaction mixture was stirred for 5 min. Water was added next and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent filtered off of the anhydrous sodium sulfate was evaporated, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=4/1) to give the desired compound, methyl 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-hydroxyacetate (**V**, $M = -CH_2O-$, $R = Me$, $Y = 2,5-Me_2$; 2.90 g, 96%) as white crystals. mp: 61–63°C, 1H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 2.22 (3H, s), 2.33 (3H, s), 3.45 (1H, d, $J = 4.9$), 3.75 (3H, s), 5.19 (2H, s), 5.50 (1H, d, $J = 4.9$), 6.71 (1H, d, $J = 7.3$), 6.75 (1H, s), 7.04 (1H, d, $J = 7.3$), 7.34–7.41 (3H, m), 7.51–7.56 (1H, m).

A 60% oily sodium hydride (0.13 g, 3.3 mmol) was added to a solution of methyl 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-hydroxyacetate (**V**, $M = -CH_2O-$, $R = Me$, $Y = 2,5-Me_2$; 0.72 g, 2.4 mmol) and methyl iodide (0.68 g, 4.8 mmol) in *N,N*-dimethylformamide (6 ml) at 0°C with stirring. After 30 min, ice and water were added in that order, and the mixture was extracted with ethyl acetate, washed successively with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent filtered off of the anhydrous sodium sulfate was evaporated, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=9/1) to give the desired compound, methyl 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxyacetate (0.69 g, 92%) as an oil. 1H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 2.21 (3H, s), 2.33 (3H, s), 3.40 (3H, s), 3.70 (3H, s), 5.10 (1H, d, $J = 12.2$), 5.14 (1H, s), 5.28 (1H, d, $J = 12.2$), 6.71 (1H, d, $J = 7.3$), 6.76 (1H, s), 7.04 (1H, d, $J = 7.3$), 7.33–7.40 (2H, m),

7.50–7.56 (2H, m).

A solution of methyl 2-[2-(2,5-dimethylphenoxy-methyl)phenyl]-2-methoxyacetate (**V**, $M = -CH_2O-$, $R = Me$, $Y = 2,5-Me_2$; 0.44 g, 1.4 mmol) in methanol (5 ml) was stirred at room temperature. A 40% methylamine/methanol solution (0.33 g, 4.2 mmol) was added. After 22 hr, the mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=2/1) to give the desired compound 2-[2-(2,5-dimethylphenoxy-methyl)phenyl]-2-methoxy-*N*-methylacetamide (**35**, 0.36 g, 82%) as white crystals. mp: 86–88°C, 1H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 2.19 (3H, s), 2.32 (3H, s), 2.83 (3H, t, $J=4.9$), 3.36 (3H, s), 5.04 (1H, s), 5.07 (1H, d, $J=11.6$), 5.47 (1H, d, $J=11.6$), 6.70 (1H, d, $J=7.3$), 6.79 (1H, brs), 6.79 (1H, s), 7.03 (1H, d, $J=7.9$), 7.33–7.43 (3H, m), 7.49–7.54 (1H, m). Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47%. Found: C, 72.72; H, 7.34; N, 4.47%.

2. Plant Materials

Rice (*Oryza sativa* L. cv. Aichi-asahi), wheat (*Triticum aestivum* L. cv. Nohrin-61), and cucumber (*Cucumis sativus* L. cv. Sagami-hanjiro) seedlings were used for the assay of fungicidal activity by foliar application. Seeds were sown in plastic cups containing sterilized soil and grown in a greenhouse. Two weeks later, the seedlings were used to tests for activity against rice blast, wheat powdery mildew, cucumber powdery mildew, cucumber gray mold and cucumber downy mildew.

3. Fungicidal Activity Assay

Rice blast, cucumber powdery mildew and cucumber gray mold were used in the primary screening to detect fungicidal activity by preventive foliar application. After the selection of promising compounds through the primary screening, fungicidal characteristics were assessed by preventive and curative applications against rice sheath blight, wheat powdery mildew and cucumber downy mildew in addition to the above three diseases.

3.1 Rice blast

The test compounds were dissolved in a small amount of *N,N*-dimethylformamide (DMF) and diluted from 500 to 0.125 ppm with distilled water containing sticker. The test solutions or suspensions were sprayed onto the host plant 24 hr before (preventive) or after (curative) inoculation. Inoculation was carried out by spraying a conidial suspension of *Pyricularia oryzae* Cav. race 003 (teleomorph: *Magnaporthe grisea* Hebert) precultured on oatmeal agar medium onto the rice seedlings. After five days incubation in a humid chamber (100% R.H., at $27 \pm 2^\circ C$), the infected leaf area was assessed and controlling percent was calculated.

3.2 Rice sheath blight

The compounds were applied as described above for rice blast. The mycelia of *Thanatephorus cucumeris*

(A. B. Frank) Donk (anamorph: *Rhizoctonia solani* Kühn, AG-1) grown on rice bran medium were placed with rice bran at the foot of the rice seedlings, and the inoculated plants were kept in a humid chamber (98% R. H., at $26 \pm 2^\circ C$) for five days. The degree of activity was assessed by measuring the height of mycelia along the sheaths of the rice seedlings, and controlling percent was calculated.

3.3 Wheat powdery mildew

The compounds were applied as described above for rice blast except that the curative application was carried out 48 hr after the inoculation. The inoculation was performed by sprinkling the conidia of *Blumeria graminis* (de Candolle) Speer f. sp. *tritici* over the wheat seedlings. The inoculated seedlings were kept in a greenhouse at $22 \pm 2^\circ C$ for ten days. The infected leaf area was assessed and a controlling percent was calculated.

3.4 Cucumber powdery mildew

The compounds were applied as described above for wheat powdery mildew. Inoculation was carried out by spraying the conidial suspension of *Sphaerotheca fuliginea* (Schlechtend.: Fr.) Pollacci onto the adaxial surface of the cucumber leaf where the compound was applied. After ten days incubation in a greenhouse at $23 \pm 2^\circ C$, the percent infected leaf area was assessed and a controlling percent was calculated.

3.5 Cucumber gray mold

The compounds were applied as described above for rice blast. Inoculation was carried out by placing mycelial disks (4 mm in diameter) of *Botrytis cinerea* Pers. precultured on PSA medium onto the adaxial (treated) surface of the cucumber leaf. The inoculated seedlings were kept in a humid chamber (98% R.H., $22 \pm 2^\circ C$) for three days. The diameter of the lesion around the inoculum was measured and a controlling percent was calculated.

3.6 Cucumber downy mildew

Test compounds were applied as described above for cucumber powdery mildew. A zoospore suspension of *Pseudoperonospora cubensis* (Berk. & M. A. Curtis) Rostovzev was used as the inoculum. To examine preventive activity, five droplets of the inoculum (each 10 μ l), were placed onto the adaxial (treated) surface of half of a leaf across the midrib. To examine translaminar activity, another five droplets of the inoculum were applied to the abaxial (untreated) surface of the opposite half of the leaf at 24 hr after treatment with the test compounds. To examine the curative activity, 10 droplets of the inoculum (each 10 μ l) were placed onto the adaxial surface, the plant kept in a humid chamber (98% R.H., $22 \pm 2^\circ C$) for 48 hr, and the compound sprayed onto the inoculated surface. An assessment was carried out by scoring the degree of infection around the inoculum at ten days after inoculation, and a

controlling percent was calculated.

Disease control of rice blast, rice sheath blight, wheat powdery mildew, cucumber powdery mildew and cucumber downy mildew on foliar application was expressed as an index of 4, 3, 2, 1 and 0, corresponding to approximately 90% control at 7.8, 31.3, 125 and 500 ppm and less than 90% control at 500 ppm, respectively. The fungicidal activity against cucumber gray mold was expressed similarly, but each criterion corresponded to approximately 50% control at 7.8, 31.3, 125 and 500 ppm and less than 50% control at 500 ppm, respectively.

RESULTS AND DISCUSSION

1. Physical and Chemical Properties of α -Methoxyphenylacetic Acid Derivatives

The chemical structures and physical properties of the compounds synthesized in this study are listed in Tables 1 through 6. The structures of the compounds reported here were confirmed by ^1H NMR, IR and elemental analyses (C, H, N). All melting points are given uncorrected.

2. Fungicidal Activities of 2-Methoxy-2-[2-(substituted phenoxy)phenyl]acetic Acid Derivatives

Fungicidal activities of 2-methoxy-2-[2-(substituted phenoxy)phenyl]acetic acid methyl ester and *N*-methylacetamide derivatives are shown in Table 1. Among the derivatives, 2-[2-(3,4- or 3,5-dimethylphenyl)phenyl]-2-methoxy derivatives of *N*-methylacetamides (4, 5) exhibited moderate to good activity against cucum-

ber powdery mildew. However, the methyl ester derivatives with the same substituents (6, 7) showed extremely weak activity. The activities of 2-methoxy-*N*-methyl-2-[2-(substituted phenoxy)phenyl]acetamide derivatives were obviously inferior to those of 2-methoxyimino-*N*-methyl-2-[2-(substituted phenoxy)phenyl]acetamide compounds.¹⁶⁾

3. Fungicidal Activities of 2-Methoxy-2-[2-(substituted phenoxymethyl)phenyl]acetic Acid Derivatives

The level of activity of 2-methoxy-2-[2-(substituted phenoxymethyl)phenyl]acetic acid methyl ester derivatives is shown in Table 2. The unsubstituted compound (8) showed a moderate activity against cucumber powdery mildew. All of the derivatives showed some level of activity against rice blast, cucumber powdery mildew or cucumber gray mold, the 2,4-dichloro derivative (15) being the most effective against cucumber powdery mildew. The incorporation of a chlorine atom or methyl group at the 2-position (9, 11) increased the activity against rice blast and cucumber gray mold. However, the incorporation of bulky substituents such as an ethyl group at the 2-position (14) reduced the activity, and the incorporation of any substituent at the 3- or 4-position (10, 12, 13) did not increase the activity. None of the 2-methoxy-2-[2-(substituted phenoxymethyl)phenyl]acetic acid methyl ester derivatives showed strong fungicidal activity against cucumber gray mold.

The level of activity of 2-methoxy-*N*-methyl-2-[2-

Table 1 Disease controlling activities^{a)} of 2-methoxy-2-[2-(substituted phenoxy)phenyl]acetic acid methyl ester and phenoxy- α -methoxy-*N*-methylphenylacetamide in a preventive manner.

No.	Compound		mp(°C)	Rice	Cucumber	
	Z	Y		Blast	P. mildew ^{b)}	Gray mold
1	CONHCH ₃	H	oil	0	0	0
2	CONHCH ₃	3-CH ₃	oil	0	0	0
3	CONHCH ₃	4-CH ₃	oil	0	0	0
4	CONHCH ₃	3,4-(CH ₃) ₂	oil	0	2	0
5	CONHCH ₃	3,5-(CH ₃) ₂	oil	0	3	0
6	COOCH ₃	3,4-(CH ₃) ₂	oil	0	1	0
7	COOCH ₃	3,5-(CH ₃) ₂	oil	0	1	0

a) Disease controlling activities are expressed as indexes of 4, 3, 2, 1 or 0, corresponding to approximately 90% control at 7.8, 31.3, 125, 500ppm and less than 90% control at 500ppm respectively. In the case of cucumber gray mold, the respective index corresponded to 50% control at the indicated concentrations.

b) P. mildew: Powdery mildew.

Table 2 Disease controlling activities^{a)} of 2-methoxy-2-[2-(substituted phenoxyethyl)phenyl]acetic acid methyl esters in a preventive manner.

Compound No.	Y	mp(°C)	Rice	Cucumber	
			Blast	P. mildew ^{b)}	Gray mold
8	H	oil	0	2	0
9	2-Cl	oil	2	2	1
10	4-Cl	oil	0	2	0
11	2-CH ₃	oil	2	2	1
12	3-CH ₃	oil	0	2	0
13	4-CH ₃	oil	0	2	0
14	2-C ₂ H ₅	oil	0	0	0
15	2,4-Cl ₂	oil	0	4	0
16	3,5-Cl ₂	69-72	0	2	0
17	2,3-(CH ₃) ₂	oil	1	0	0
18	2,4-(CH ₃) ₂	oil	1	0	1
19	2,5-(CH ₃) ₂	oil	2	0	1

a) The indexes for disease controlling activities are described in Table 1.

b) P. mildew: Powdery mildew.

(substituted phenoxyethyl)phenyl]acetamides is shown in Table 3. The unsubstituted compound (**20**) showed a moderate activity against cucumber powdery mildew. Derivatives with any substituent except a methoxy group at the 2-position (**21**, **22**, **25**, **26**, **29**, **31**, **33-35**, **39-41**, **43**) had an excellent effect on cucumber powdery mildew. However, the incorporation of a methoxy group at the 2-position (**30**, **42**) and a simultaneous substitution at the 2- and 6-positions (**36**) reduced the fungicidal activity markedly. These findings were the same as those for the methyl ester derivative mentioned above and the 2-methoxyimino-*N*-methyl-2-[2-(substituted phenoxyethyl)phenyl]acetamide type compounds described previously.¹⁷⁾ The compounds in which the benzene ring of the phenoxyethyl moiety was substituted with a methyl group at the 2-position (**26**, **33-35**, **41**, **43**), as well as 2-Cl-5-CH₃ (**40**) derivatives exhibited excellent activity against cucumber gray mold. Furthermore, 2,4- and 2,5-dimethyl derivatives (**34**, **35**) and 2,3,5-trimethyl derivative (**43**) demonstrated good activity against rice blast.

These results suggested that the substituents on the benzene ring of the phenoxyethyl moiety influence the fungicidal activity. The incorporation of a lower alkyl or halogen substituent at the 2-, 3-, 4- or 5-position would increase the fungicidal activity due to an increase in the affinity for the target site of the pathogen. The substituents at the 2-position might play a more important

role in the fungicidal activity than those at other positions. The bulkiness of the substituent at the 2-position affected the fungicidal activity; a methyl group seemed to be the most favorable for the activity. The reduction in activity caused by the simultaneous incorporation of a methyl group at the 2- and 6-positions was presumably due to steric hindrance.

Among the derivatives of 2-methoxy-*N*-methyl-2-[2-(substituted phenoxyethyl)phenyl]acetamide synthesized in this study, the 2,4-dimethyl (**34**), 2,5-dimethyl (**35**) and 2,3,5-trimethyl (**43**) derivatives exhibited good to excellent activity against all diseases tested.

4. Effects of α -Alkoxy Substituents (R^1) on Fungicidal Activity

The experiments described above indicated that when the 2- and 5-positions of the benzene ring of the phenoxyethyl moiety were substituted with methyl groups, the activity was excellent. Next, the effects of alkoxy substituents at the α -position were examined when the substituents of the 2-phenoxyethyl moiety of *N*-methylphenylacetamide were fixed with a 2,5-dimethyl group. The results are shown in Table 4. When the α -position was a methoxy derivative (**35**), the fungicidal activity was good (rice blast) to excellent (cucumber powdery mildew and gray mold), and an ethoxy derivative (**44**) also exhibited excellent activity against cucumber powdery mildew but no activity against rice blast or cucumber gray mold. Bulky substituents at the α -position seemed to depress the fungicidal activity.

5. Effects of Substituents (Z) of the α -Methoxyphenylacetic Acid Moiety on Fungicidal Activity

The fungicidal activity of the α -methoxyphenylacetic acid and acetamide derivatives were examined (Table 5). Among the derivatives tested in this study, the *N*-methylacetamide derivative (**35**) was superior to the *N*-ethylacetamide (**50**), *N*-butylacetamide (**51**), *N,N*-dimethylacetamide (**53**) and unsubstituted acetamide (**52**) derivatives in its activity against all diseases tested. The α -methoxyphenylacetic acid methyl ester derivative (**19**) demonstrated a moderate level of activity against rice blast. The acetic acid derivative (**48**) showed excellent activity against cucumber powdery mildew, but weak activity against rice blast and cucumber gray mold. The methyl thioester derivative (**49**) showed no activity against any of the diseases tested. The results suggested that *N*-methylacetamide derivatives are the most favorable structures for fungicidal activity, as was shown for the β -methoxyiminoacetamide derivatives.^{16,17)}

6. Effects of the Bridge (M) between the Two Benzene Rings

The effects of the bridge (M) between the two benzene

Table 3 Disease controlling activities^{a)} of 2-methoxy-*N*-methyl-2-[2-(substituted phenoxy)methyl]phenyl]acetamide derivatives in a preventive manner.

No.	Compound Y	mp(°C)	Rice	Cucumber	
			Blast	P. mildew ^{b)}	Gray mold
20	H	oil	0	2	1
21	2-F	oil	1	3	1
22	2-Cl	86-87	1	4	0
23	3-Cl	oil	0	3	1
24	4-Cl	87-88	0	3	0
25	2-Br	87-88	2	4	2
26	2-CH ₃	91-92	1	4	4
27	3-CH ₃	oil	1	2	0
28	4-CH ₃	98-100	1	3	0
29	2-C ₂ H ₅	95-97	2	4	1
30	2-OCH ₃	oil	0	0	0
31	2,4-Cl ₂	121-123	0	4	0
32	3,5-Cl ₂	oil	0	3	0
33	2,3-(CH ₃) ₂	70-72	2	4	4
34	2,4-(CH ₃) ₂	106-107	3	4	4
35	2,5-(CH ₃) ₂	103-104	3	4	4
36	2,6-(CH ₃) ₂	oil	0	0	0
37	3,4-(CH ₃) ₂	oil	2	3	1
38	3,5-(CH ₃) ₂	oil	2	0	3
39	2-Cl, 4-CH ₃	97-99	2	4	1
40	2-Cl, 5-CH ₃	110-112	2	4	4
41	2-CH ₃ , 4-Cl	114-116	2	4	4
42	2-OCH ₃ , 4-CH ₃	oil	0	0	1
43	2,3,5-(CH ₃) ₃	oil	3	4	4

a) The indexes for disease controlling activities are described in Table 1.

b) P. mildew: Powdery mildew.

rings were examined. The results are shown in Table 6. The derivatives in which the substituent on the benzene ring (Y) was 2,5-dimethyl or 4-chloro exhibited good to excellent fungicidal activity when the bridge was an oxymethylene group (**35**, **24**). On the other hand, when the bridge (M) was a thiomethylene, the 2,5-dimethyl derivative (**54**) showed only weak activity against cucumber powdery mildew and gray mold. These results suggested that the bridge between the two benzene rings should be oxymethylene.

7. Disease Controlling Activity of 2-[2-(2,5-Dimethylphenoxy)methyl]phenyl]-2-methoxy-*N*-methylacetamide (**35**)

Compound **35** showed good fungicidal activity in the primary screening tests as mentioned above. Its fungicidal characteristics such as preventive and curative activity, fungicidal spectrum and translaminar activity were assessed by foliar application (Table 7). Compound **35** exhibited good preventive and curative activity against rice blast, rice sheath blight, wheat powdery mildew, cucumber powdery mildew and cucumber gray mold, and good preventive activity against cucumber downy mildew. In contrast, kresoxim-methyl showed

Table 4 Disease controlling activities of 2-alkoxy-[2-(2,5-dimethylphenoxy)methyl]phenyl]-*N*-methyl acetamide in a preventive manner.

Compound No.	R ₁	mp(°C)	Rice	Cucumber	
			Blast	P. mildew ^{b)}	Gray mold
35	CH ₃	103-104	3	4	4
44	C ₂ H ₅	98-100	0	4	0
45	C ₄ H ₉	58-60	0	3	0
46	COCH ₃	97-99	0	0	0
47	CH ₂ OCH ₃	81-82	0	0	0

a) The indexes for disease controlling activities are described in Table 1.

b) P. mildew: Powdery mildew.

Table 5 Disease controlling activities^{a)} of 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxy-acetic acid derivatives in a preventive manner.

Compound No.	Z	mp(°C)	Rice	Cucumber	
			Blast	P.mildew ^{b)}	Gray mold
48	COOH	oil	1	4	0
19	COOCH ₃	oil	2	0	1
49	COSCH ₃	oil	0	0	0
35	CONHCH ₃	103-104	3	4	4
50	CONHC ₂ H ₅	oil	0	3	2
51	CONHC ₄ H ₉	oil	0	0	0
52	CONH ₂	oil	1	3	0
53	CON(CH ₃) ₂	oil	1	2	0

a) The indexes for disease controlling activities are described in Table 1.

b) P.mildew: Powdery mildew.

preventive activity against rice blast and good preventive but less curative activity against rice sheath blight, cucumber gray mold and cucumber downy mildew, and good preventive and curative activity against wheat and cucumber powdery mildew. Compound **35** was superior to kresoxim-methyl in terms of its preventive and curative activities against wheat powdery mildew and cucumber gray mold, and preventive activity against cucumber powdery mildew. It showed good preventive

activity against cucumber downy mildew when inoculated onto the untreated (abaxial) as well as treated (adaxial) surface. The symptoms of wheat or cucumber powdery mildew are due to the growth of mycelia on the surface of the leaves, while those of rice blast, cucumber gray mold and cucumber downy mildew are due to the invasion of the mycelia into the host tissue. These results demonstrated that compound **35** has good translaminar activity, while kresoxim-methyl does not.

Table 6 Effects of the bridge part between the two benzene rings of 2-methoxy-*N*-methyl-2-phenylacetamide derivatives on disease controlling activities^{a)} in a preventive manner.

No.	Compound		mp(°C)	Rice	Cucumber	
	Y	M		Blast	P. mildew ^{b)}	Gray mold
35	2,5-(CH ₃) ₂	-OCH ₂ -	103-104	3	4	4
54	2,5-(CH ₃) ₂	-SCH ₂ -	oil	0	1	0
55	4-Cl	-O-	oil	0	0	0
24	4-Cl	-OCH ₂ -	87-88	0	3	0
56	4-Cl	-CH ₂ O-	84-86	0	0	0
57	4-Cl	-COOCH ₂ -	oil	0	0	0

a) The indexes for disease controlling activities are described in Table 1.

b) P.mildew: Powdery mildew.

Table 7 Disease controlling activity of 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxy-*N*-methyl acetamides by foliar application (Pot test).

Compound	Conc. (ppm)	Rice			Wheat		Cucumber						
		Blast	Sheath blight		P. mildew ^{a)}		P. mildew ^{a)}		Gray mold		Downy mildew		
		Pre. ^{b)}	Pre. ^{b)}	Cur. ^{c)}	Pre. ^{b)}	Cur. ^{c)}	Pre. ^{b)}	Cur. ^{c)}	Pre. ^{b)}	Cur. ^{c)}	Pre. ^{d)}	Pre. ^{e)}	Cur. ^{c)}
35	125	95	80	70	97	97	-	-	80	80	97	70	30
	31.3	90	40	40	97	97	-	-	80	60	97	70	30
	7.8	70	20	30	90	90	99	100	50	50	97	70	0
	2.0	30	10	20	90	90	90	100	50	20	97	50	0
	0.5	-	-	-	-	-	70	70	-	-	-	-	-
	0.125	-	-	-	-	-	30	30	-	-	-	-	-
Kresoxim -methyl	125	97	50	50	90	90	-	-	50	30	97	30	30
	31.3	70	30	30	70	90	-	-	50	10	97	0	0
	7.8	50	30	0	50	70	97	100	50	0	97	0	0
	2.0	30	30	0	30	50	80	90	20	0	97	0	0
	0.5	-	-	-	-	-	20	80	-	-	-	-	-
	0.125	-	-	-	-	-	0	50	-	-	-	-	-
Reference		Ferimzone	Flutolanil		Triadimefon		Fenarimol		Iprodione		Benalaxyl		
	125	97	90	80	-	-	-	-	100	80	97	97	80
	31.3	90	80	80	97	-	-	-	100	70	70	70	80
	7.8	50	70	70	97	90	100	100	50	60	20	40	40
	2.0	30	20	40	50	90	95	99	20	20	20	20	10
	0.5	-	-	-	30	50	80	99	-	-	0	0	0
	0.125	-	-	-	-	-	0	80	-	-	-	-	-

a) P. mildew: Powdery mildew.

b) Preventive activity.

c) Curative activity.

d) Inoculated onto the adaxial(treated) surface of the cucumber leaf.

e) Inoculated onto the abaxial(untreated) surface of the cucumber leaf.

Compound **35** exhibited a similar level of activity to currently used fungicides, ferimzone, triadimefon, fenarimol and iprodione against rice blast, wheat powdery

mildew, cucumber powdery mildew and cucumber gray mold, respectively, suggesting that the compound is a promising new type of strobilurin fungicide.

As the 2-methoxy-2-[2-(substituted phenoxyethyl)-phenyl]acetamide derivatives that do not contain an olefinic double bond in the pharmacophore exhibited strong fungicidal activity, we assumed that an sp^2 -hybridized carbon or sp^2 -like nitrogen with a trigonal geometry in the α -position of the pharmacophore is not always necessary for fungicidal activity in strobilurin analogues.

As 2-methoxy-2-[2-(substituted phenoxy or substituted phenoxyethyl)phenyl]acetamide derivatives have an asymmetric carbon at the α -position of the acetamide moiety, further study of the activities of the stereoisomers is necessary.

ACKNOWLEDGMENTS

We thank Dr. Akira Murabayashi, Dr. Akira Mizutani, Dr. Nobuo Miki and Dr. Reiji Takeda of Shionogi and Co., Ltd., for helpful advice, and all staff of the organic synthesis and agrochemical groups of Aburahi Laboratories for their invaluable support in this study.

REFERENCES

- 1) V. Musilek: British Pat. GB1163910 (1965)
- 2) V. Musilek, J. Cerna, V. Sasek, M. Semerdzieva & M. Vondracek: *Folia Microbiol.* (Prague), **14**, 377 (1969)
- 3) M. Vondracek, J. Capkova, J. Slechta, A. Benda, V. Musilek & J. Cdlin: British Pat. GB 1181892 (1973)
- 4) M. Vondracek, J. Capkova & K. Culik: Czech Pat. CS1180775 (1974)
- 5) T. Anke, F. Oberwinkler, W. Steglich & G. Schramm: *J. Antibiot.* **30**, 806 (1977)
- 6) T. Anke, H. J. Hecht, G. Schramm & W. Steglich: *J. Antibiot.* **32**, 1112 (1979)
- 7) W. Steglich, G. Schramm, T. Anke & F. Oberwinkler: Eur. Pat. EP444448 (1982)
- 8) U. Schirmer, S. Karbach, E. H. Pommer, E. Ammermann, W. Steglich, B. A. M. Schwlge & T. Anke (BASF): Eur. Pat. EP203608 (1985)
- 9) U. Schirmer, S. Karbach, E. H. Pommer, E. Ammermann, W. Steglich, B. A. M. Schwlge & T. Anke (BASF): Eur. Pat. EP226917 (1985)
- 10) U. Schirmer, S. Karbach, E. H. Pommer, E. Ammermann, W. Steglich, B. A. M. Schwlge & T. Anke (BASF): Eur. Pat. EP229974 (1985)
- 11) T. Anke, G. Schramm, W. Steglich & G. von Jagow: "The Roots of Modern Biochemistry," ed. by H. Kleinkauf, H. von Dhrem and L. Jaenicke, de Gruyter, Berlin and New York, p. 657, 1988
- 12) T. Anke & W. Steglich: "Biologically Active Molecules, Identification, Characterization and Synthesis," ed. by U. P. Schlunegger, Springer-Verlag, Berlin and Heidelberg, p. 9, 1989
- 13) K. Beaument, J. M. Clough, P. J. de Fraine & C. R. A. Godfrey: *Pestic. Sci.* **31**, 499 (1991)
- 14) J. R. Goodwin, V. M. Anthony, J. M. Clough & C. R. A. Godfrey: "Brighton Crop Protection Conference—Pests and Diseases—1992, Vol. 1," British Crop Protection Council, Farnham, U. K., pp. 435–442, 1992
- 15) E. Ammermann, G. Lorenz, K. Schelberger, B. Wenderoth, H. Sauter & C. Rentzea: "Brighton Crop Protection Conference—Pests and Diseases—1992, Vol. 1," British Crop Protection Council, Farnham, U. K., pp. 403–410, 1992
- 16) T. Kataoka, Y. Hayase, M. Masuko, M. Niikawa, M. Ichinari, H. Takenaka, N. Tanimoto, Y. Hayashi & R. Takeda: *J. Pesticide Sci.* **23**, 95–106 (1998)
- 17) H. Takenaka, M. Ichinari, N. Tanimoto, Y. Hayase, M. Niikawa, T. Ichiba, M. Masuko, Y. Hayashi & R. Takeda: *J. Pesticide Sci.* **23**, 107–112 (1998)
- 18) H. Takenaka, Y. Hayase, R. Hasegawa, T. Ichiba, M. Masuko, A. Murabayashi & R. Takeda: *J. Pesticide Sci.* **23**, 379–385 (1998)
- 19) T. Furuta: *Agrochemicals Japan* **74**, 20–21, (1999)
- 20) H. Sauter, E. Ammermann & F. Roehl: "Crop Protection Agents from Nature," ed. by L. G. Copping, The Royal Soc. of Chem. pp. 50–81, 1996
- 21) T. Ohtsuka, T. Murashi, S. Suzuki, M. Masuko & H. Takenaka: WO95/27693 (1995)
- 22) T. Ohtsuka, T. Murashi & A. Murabayashi: JP9-95462 (1997)
- 23) T. Ohtsuka & T. Murashi: WO97/30965 (1997)
- 24) T. Ohtsuka: WO98/29381 (1998)

要 約

α -Methoxyphenylacetic acid 誘導体の殺菌活性

市場常男, 村司孝己, 大塚俊一, 益子道生
種々の α -置換フェニル酢酸誘導体を合成し, 殺菌活性における構造と活性相関について調べた。2-フェノキシ- α -置換フェニル酢酸誘導体には高活性の化合物を見出せなかったが, 2-フェノキシメチル- α -置換フェニル酢酸エステル誘導体ではフェノキシメチル基のベンゼン環の2位がメチル基または塩素原子で置換された化合物に幅広い活性スペクトラムが認められた。また同酢酸アミド誘導体では, ベンゼン環の2-メチルまたは2-塩素置換に高い活性が認められた。モノ-置換体と比較し2,3-, 2,4-, 2,5-ジメチル置換体および2,3,5-トリメチル置換体の活性はさらに高く, スペクトラムも広がった。2,5-ジメチル置換体の α -置換基はメトキシ基, 酢酸アミド部分はモノメチルアミド, 2つのベンゼン環の架橋部はメチレンオキシ基が最も活性が高かった。本化合物はイネいもち病, コムギうどんこ病, キュウリうどんこ病および灰色かび病に高い予防および治療効果を示した。以上の結果より, ストロビルリン系殺菌剤の構造には必ずしも, sp^2 -結合炭素または sp^2 様窒素による立体構造が必要ではないことがわかった。