2-(置換フェノキシメチル)フェニル-2-メトキシイミノアセトアミド誘導体の殺菌活性

誌名	日本農薬学会誌
ISSN	03851559
著者名	竹中,秀行 市成,光広 谷本,憲彦
発行元	日本農薬学会
巻/号	23巻2号
掲載ページ	p. 107-112
発行年月	1998年5月

J. Pesticide Sci. 23, 107–112 (1998)

Original Article

Fungicidal Activities of 2-(Substituted Phenoxymethyl)phenyl-2-methoxyiminoacetamide Derivatives*

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(Received June 20, 1997; Accepted November 20, 1997)

A number of 2-(substituted phenoxymethyl)phenyl-2-methoxy iminoacetamides were synthesized and their fungicidal activities were examined. The strength of activities and fungicidal spectra varied markedly depending upon the substituents on the benzene ring of the 2-phenoxymethyl group of phenylacetamide moiety. Incorporation of either one or two substituent(s) at 2-, 3-, 4- and/or 5-positions on the benzene ring resulted in an increase of fungicidal activity compared to the unsubstituted compound. However, introduction of a bulky substituent at the 2-position or simultaneous substitution at 2- and 6-positions resulted in decrease of activity. When 2- and 4-, or 2- and 5-positions of the benzene ring were substituted with chlorine and/or methyl groups, in addition to the 2,5-difluoro derivative (**30**), the activities were excellent against wheat powdery mildew, cucumber powdery mildew, cucumber gray mold and cucumber downy mildew. Between the two geometrical isomers, the *E*-form was much stronger than the *Z*-form.

INTRODUCTION

In our previous studies,[1] a number of 2-(phenoxyphenyl)-2-alkoxyiminoacetamides (hereafter abbreviated as diphenylether type) were synthesized and their fungicidal activities were examined. From the studies of the structure-activity relationships, (*E*)-2-methoxyimino-*N*-methyl-2-(2-phenoxyphenyl)acetamide (SSF-126) was selected as the best agent from a group of diphenylether type derivatives. This previous study also demonstrated that 2-methoxyimino-*N*-methyl-2-[2-(phenoxymethyl)phenyl]acetamide (hereafter abbreviated as phenoxymethyl type) exhibited some extent of activity against a wide range of plant diseases. The biological performance of phenoxymethyl type compounds was not always the same as those of the diphenylether type compounds, especially with regard to the fungicidal spectrum.

Since Becker *et al.*[2] reported the fungicidal activity of strobilurins, structural modification of these lead compounds has progressed. The β-methoxyacrylate fungicides derived from the strobilurins did not always exhibit good performance under the field condition due to less persistency. In order to photo-stabilize the strobilurin analogues, the styryl side chain of the stilbene analogue which was derived from strobilurin A was replaced with a phenoxy group.[3–5] The diphenylether type compounds were synthesized through this course of idea,[6–14] and ICIA5504 was introduced into the agrochemical field as a promising fungicide by the ZENECA group.[15] Independently, the BASF group also synthesized strobilurin analogues.[16–18] BAS-490F has a phenoxymethyl side chain.[19]

In this study, we synthesized a number of 2-[2-(substituted phenoxymethyl)phenyl]-2-methoxyiminoacetamide derivatives and examined their fungicidal activities with reference to the effects of the substituents on the phenoxymethyl moiety.

MATERIALS AND METHODS

1. Chemicals

The synthetic pathways of 2-[2-(substituted phenoxymethyl)phenyl]-2-methoxyimino-*N*-methylacetamides are shown in Fig. 1. The methods for synthesis of these

* Structure and Fungicidal Activities of New Alkoxyiminoacetamide Derivatives (Part 2). For Part 1, see Ref. 1.

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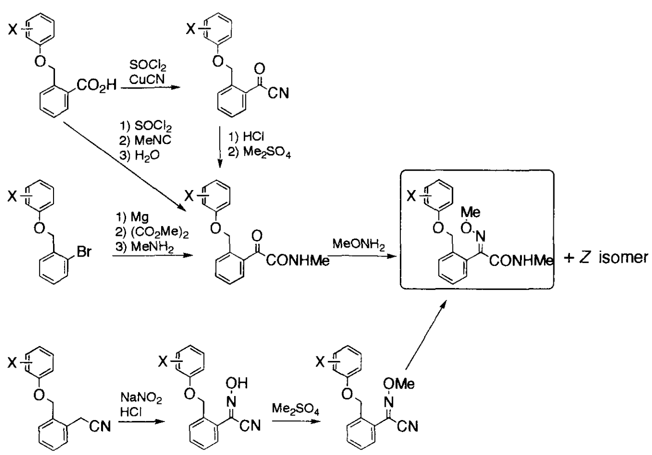


Fig. 1 The synthetic pathway of 2-[2-(substituted phenoxymethyl)phenyl]-2-methoxyimino-*N*-methylacetamides.

derivatives are described in the patents.[20-25]

2. *Plant Materials*

Cucumber (*Cucumis sativus* cv. Tsukuba-shiroibo) and rice (*Oryza sativa* cv. Aichi-asahi) seedlings were used for the assay of disease controlling activity. *in vivo*. The seedlings were prepared as described previously.[1] Wheat seedlings were used for controlling activity tests against powdery mildew. The seeds of wheat (*Triticum aestivum* cv. Nohrin-61) were sown in plastic cups containing sterilized soil and grown in the greenhouse for 2 weeks.

3. *Method for Fungicidal Activity Assay*

Disease controlling activity by foliar application on rice blast, rice sheath blight, cucumber powdery mildew, cucumber gray mold and cucumber downy mildew were

Table 1 Controlling activities[a)] of mono-substituted derivatives against crop diseases by preventive application.

No.	Compound X	mp (°C)	Rice		Wheat	Cucumber			
			Blast	Sheath blight	Powdery mildew	Powdery mildew	Gray mold	Downy mildew[b)] Ad[1)]	Ab[2)]
1	H	120	2	1	3	2	2	3	2
2	2-F	103	2	1	3	3	3	3	3
3	3-F	104-105	2	1	3	2	2	3	3
4	4-F	100	1	1	4	3	3	3	2
5	2-Cl	123-124	2	1	4	3	3	3	1
6	3-Cl	76-78	2	2	3	3	3	4	3
7	4-Cl	132-133	2	0	4	4	3	4	3
8	3-Br	56-58	1	0	NT	3	3	4	3
9	4-Br	144	2	0	4	3	3	3	2
10	2-CF_3	112-113	4	3	4	3	2	3	1
11	3-CF_3	92	3	1	4	3	3	3	3
12	4-CF_3	89-90	2	0	3	3	3	3	3
13	2-CH_3	116-117	4	2	4	4	3	4	1
14	4-CH_3	128-129	2	0	4	4	3	4	0
15	2-O-i-Pr	oil	1	0	0	1	0	2	0
16	3-O-i-Pr	oil	3	1	4	3	3	3	2
17	4-O-i-Pr	oil	2	2	3	3	3	2	2
18	2-$OCH_2C\equiv CH$	oil	1	0	0	1	0	1	0
19	3-$OCH_2C\equiv CH$	oil	1	0	1	1	2	4	1
20	4-$OCH_2C\equiv CH$	oil	2	0	1	3	3	3	2
21	2-Ph	oil	1	0	0	1	0	1	0
22	3-Ph	oil	4	2	3	4	4	4	3
23	4-Ph	138	4	2	4	4	3	4	1
24	4-CH=CH-Ph	215-216	0	0	1	0	0	NT	0
25	4-CO-Ph	oil	1	0	1	0	3	3	0
26	4-CN	162	0	0	1	0	2	2	1
27	3-NO_2	127-129	1	0	1	0	2	3	0
28	3-$N(CH_3)_2$	oil	1	0	0	0	2	2	0

[a)] Fungicidal activities are expressed as an index of 4, 3, 2, 1 or 0, each corresponding to approximately 90% control at 2.0, 7.8, 31.3, 125 ppm or less than 90% control at 125 ppm, respectively.

[b)] Cucumber downy mildew was inoculated by two different methods as follows: [1)] inoculated onto the adaxial (treated) surface of the cucumber leaf, [2)] inoculated onto the abaxial (untreated) surface of the cucumber leaf.

assessed as described previously.[1] In addition, the controlling activity against wheat powdery mildew was assessed by the same method as for the other diseases except the inoculation which was carried out by sprinkling the conidia of *Erysiphe graminis* f. sp. *tritici* over the wheat seedlings 24 hr after (preventive) or before (curative) treatment with the test compound. The inoculated seedlings were kept in a greenhouse at 22±2°C for ten days, and the infected area of the leaf was assessed and control percent was calculated.

The fungicidal activity by foliar application is expressed as an index of 4, 3, 2, 1 or 0, each corresponding to approximately 90% control at 2.0, 7.8, 31.3 and 125 ppm and less than 90% control at 125 ppm, respectively.

Unless otherwise stated, the *E*-form of each compound was used for assessment of fungicidal activity.

RESULTS AND DISCUSSION

1. Physical and Chemical Properties of the Phenoxymethyl Type Derivatives

The chemical structures and physical properties of the compounds synthesized in this study are listed in Tables 1 to 5. The structures of the compounds (Fig. 2) reported here were confirmed by proton NMR, IR and elemental analysis (C, H, N). All melting points were uncorrected.

2. Fungicidal Activities of Mono-substituted Derivatives

The disease controlling activities of the mono-substituted compounds as well as unsubstituted compound are shown in Table 1. The activity of the unsubstituted compound (**1**) was moderate against cucumber powdery mildew, cucumber gray mold, cucumber downy mildew and wheat powdery mildew. However, the activity against rice blast and rice sheath blight was poor. Among the mono-substituted derivatives, 4-chloro (**7**) and 4-methyl (**14**) as well as 2-methyl (**13**) derivatives showed excellent activity against wheat and cucumber powdery mildew. Incorporation of chlorine or bromine atom at the 3- or 4-position (**6**–**9**) increased the activity against cucumber downy mildew. The derivatives with

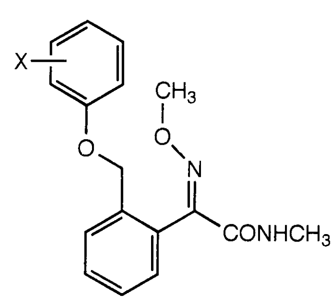


Fig. 2 The chemical structure of (*E*)-2-[2-(substituted phenoxymethyl)phenyl]-2-methoxyimino-*N*-methylacetamides.

larger substituents such as isopropoxy, propargyloxy or phenyl showed various activities depending upon the position of the substituent. 3-Isopropoxy (**16**), 4-isopropoxy (**17**), 3-phenyl (**22**) and 4-phenyl (**23**) derivatives exhibited good control against wheat and cucumber powdery mildew and cucumber gray mold. On the other hand, incorporation of these substituents into **2** (*ortho*)-position (**15**, **18**, **21**) reduced the activities. The decrease in activity by introduction of such larger substituents at the *ortho* position could be a consequence of steric hindrance. The activities of the propargyloxy derivatives (**18**–**20**) were weak against rice and wheat diseases regardless of the substitution position. The activities of 4-styryl (**24**) or 4-benzoyl (**25**) derivatives were also weak against all of the diseases examined. Introduction of substituents which increase the hydrophilicity of the molecule such as cyano (**26**), nitro (**27**) or dimethylamino (**28**) group caused marked decrease in activity.

3. Fungicidal Activity of Di-substituted Derivatives

The fungicidal activities of the di-substituted derivatives are shown in Table 2. When the 2- and 4-, or 2- and 5-positions of the benzene ring of the phenoxymethyl moiety were substituted with chlorine and/or methyl groups (**35**, **36**, **41**, **42**, **46**), the activities were excellent against wheat powdery mildew, cucumber powdery mildew, cucumber gray mold and cucumber downy mildew, followed by 3,4- and 3,5-di-substituted derivatives (**38**, **39**, **44**, **45**, **47**). However the activity of 2,6-di-substituted derivatives with chlorine or methyl group (**37**, **43**) were markedly reduced against all diseases tested.

These results suggested that 2,4- or 2,5-di-substituted derivatives are the most favorable structures for fungicidal activity, and 2,6-di-substitution is not.

4. Fungicidal Activities of Tri-substituted Derivatives

The fungicidal activities of tri-substituted derivatives are shown in Table 3. Among the tri-substituted derivatives, the 2,3,5-trimethyl derivative (**52**) demonstrated excellent control against all diseases except cucumber downy mildew, of which pathogen was inoculated onto the untreated (abaxial) surface of the cucumber leaf, indicating that the compound lacks the translaminar activity through the epidermic tissue. Furthermore, 2,3,5-trichloro (**48**) and 2,4,5-trichloro (**49**) derivatives also exhibited good control against cucumber powdery mildew, gray mold and downy mildew. Similarly to di-substituted derivatives, the tri-substituted compounds of which 2- and 6-position were substituted simultaneously with chlorine or methyl groups (**50**, **51**, **53**, **54**) exhibited weak activities against all diseases examined. Especially the activities of 2,3,6-trichloro (**50**) and 2,3,6-trimethyl (**53**) derivatives were extremely weak against

Table 2 Fungicidal activities[a] of di-substituted derivatives by preventive application.

No.	Compound X	mp (°C)	Rice Blast	Rice Sheath blight	Wheat Powdery mildew	Cucumber Powdery mildew	Cucumber Gray mold	Cucumber Downy mildew[b] Ad[1]	Cucumber Downy mildew[b] Ab[2]
29	2,3-F_2	147–148	0	0	4	3	3	3	0
30	2,5-F_2	83	2	2	4	3	3	4	3
31	2,6-F_2	89–92	2	1	3	3	2	3	2
32	3,4-F_2	107–109	2	0	2	2	3	0	0
33	3,5-F_2	102–103	2	1	4	3	3	3	2
34	2,3-Cl_2	134–135	2	0	2	4	2	4	0
35	2,4-Cl_2	123	2	0	4	4	4	3	2
36	2,5-Cl_2	153–154	2	2	4	4	3	4	4
37	2,6-Cl_2	135–136	1	0	2	0	1	0	0
38	3,4-Cl_2	124–126	2	0	3	4	3	3	2
39	3,5-Cl_2	102–104	1	0	3	3	3	4	2
40	2,3-$(CH_3)_2$	145	4	1	2	2	2	4	1
41	2,4-$(CH_3)_2$	85–86	1	3	4	3	4	4	1
42	2,5-$(CH_3)_2$	136–137	4	3	4	4	3	4	3
43	2,6-$(CH_3)_2$	99	1	0	1	1	1	0	0
44	3,4-$(CH_3)_2$	115–116	3	1	4	3	3	4	1
45	3,5-$(CH_3)_2$	107–109	2	2	4	3	3	4	0
46	2-CH_3-4-Cl	69–70	3	2	4	4	4	4	3
47	3-CH_3-4-Cl	72–73	3	0	4	3	3	4	3

[a] Fungicidal activities are expressed as in Table 1.
[b] Cucumber downy mildew was inoculated by two different methods as follows: [1] inoculated onto the adaxial (treated) surface of the cucumber leaf, [2] inoculated onto the abaxial (untreated) surface of the cucumber leaf.

Table 3 Fungicidal activities[a] of tri-substituted derivatives by preventive application.

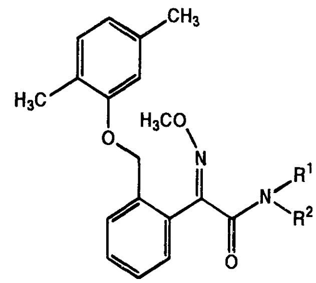
No.	Compound X	mp (°C)	Rice Blast	Rice Sheath blight	Wheat Powdery mildew	Cucumber Powdery mildew	Cucumber Gray mold	Cucumber Downy mildew[b] Ad[1]	Cucumber Downy mildew[b] Ab[2]
48	2,3,5-Cl_3	126	0	0	2	4	3	4	0
49	2,4,5-Cl_3	143	2	2	2	4	3	4	2
50	2,3,6-Cl_3	122–124	1	0	1	1	1	2	0
51	2,4,6-Cl_3	125–126	1	0	2	1	2	2	0
52	2,3,5-$(CH_3)_3$	109	3	3	4	4	4	4	1
53	2,3,6-$(CH_3)_3$	117–118	1	0	0	0	0	0	1
54	2,4,6-$(CH_3)_3$	106–107	1	0	1	1	2	3	0
55	2-Cl-4,5-$(CH_3)_2$	135	1	0	1	3	3	4	0
56	4-Cl-3,5-$(CH_3)_2$	136–137	2	0	3	3	3	4	1

[a] Fungicidal activities are expressed as in Table 1.
[b] Cucumber downy mildew was inoculated by two different methods as follows: [1] inoculated onto the adaxial (treated) surface of the cucumber leaf, [2] inoculated onto the abaxial (untreated) surface of the cucumber leaf.

all diseases tested.

These results suggested that the substituents on the benzene ring of the phenoxymethyl moiety play an important role in fungicidal activity. Incorporation of lower alkyl or halogen substituents at 2-, 3-, 4- or 5-positions of the benzene ring would increase the fungicidal activity due to increased affinity to the target site of the pathogen. On the other hand, introduction of bulky substituents at the 2-position or relatively less bulky substituents simultaneously at 2- and 6-positions depressed the activities presumably due to steric hindrance. Halogen substituents on the benzene ring of the phenoxymethyl moiety tended to increase the activity against cucumber downy mildew.

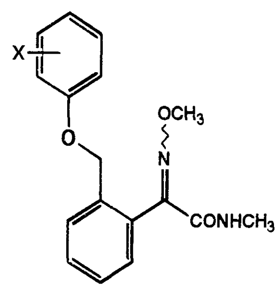
Table 4 Effects of *N*-substituents R^1 and R^2 of the amide moiety.[a)]



Compound				Rice		Cucumber			
				Blast		Powdery mildew		Gray mold	
No.	R^1	R^2	mp (°C)	Pre.[b)]	Cur.[c)]	Pre.[b)]	Cur.[c)]	Pre.[b)]	Cur.[c)]
57	H	H	77–77.5	2	3	4	3	2	3
42	H	CH_3	136–137	4	4	4	4	3	4
58	CH_3	CH_3	115–117	2	1	2	3	1	0
59	H	NH_2	109–110	1	0	1	0	0	NT
60	H	OCH_3	122–124	1	0	2	3	1	0

a) Fungicidal activities are expressed as in Table 1.
b) Preventive activity.
c) Curative activity.

Table 5 Fungicidal activities[a)] of two geometric isomers by foliar application.



Compound			Rice		Wheat		Cucumber			
			Blast		P. mildew		P. mildew		Gray mold	
No.	X	*E*/*Z*	Pre.[b)]	Cur.[c)]	Pre.	Cur.	Pre.	Cur.	Pre.	Cur.
1	H	*E*	2	2	3	2	2	2	2	3
61	H	*Z*	0	0	1	0	1	0	0	0
7	4-Cl	*E*	2	3	4	4	4	4	3	4
62	4-Cl	*Z*	0	0	0	0	1	0	0	0
16	3-O-i-Pr	*E*	3	3	4	3	3	3	3	3
63	3-O-i-Pr	*Z*	1	0	1	1	2	1	1	0
23	4-Ph	*E*	4	4	4	3	4	4	3	3
64	4-Ph	*Z*	0	0	0	1	2	0	0	0
42	2,5-$(CH_3)_2$	*E*	4	4	4	4	4	4	3	4
65	2,5-$(CH_3)_2$	*Z*	2	1	4	3	3	3	3	3

a) Fungicidal activities are expressed as in Table 1.
b) Preventive activity.
c) Curative activity.

5. *Effects of N-Substituents of the Amide Moiety*

The effects of *N*-substituents (R^1, R^2) of the acetamide moiety on the disease controlling activities were examined (Table 4). The experiments described above indicated that when the 2- and 5-positions of the benzene ring of the phenoxymethyl moiety were substituted with methyl groups, the activity was excellent. The effects of *N*-substituents were then examined when the substituents on the benzene ring were fixed at these positions. The unsubstituted amide derivative (**57**) exhibited weaker activity than the monomethyl amide derivative (**42**), and the activity of the dimethyl amide derivative (**58**) was much weaker than those of the above two compounds. Other substituents of the amide moiety such as amino (**59**) or methoxy (**60**) group caused decreases in activity. The results regarding *N*-substituents of the amide group were the same as those of diphenylether type compounds.[1]

6. *Comparison of Two Geometrical Isomers*

The fungicidal activities of two geometrical isomers at the oxime moiety were compared by foliar application (Table 5). The activities of *E*-isomers were much stronger against all diseases tested than *Z*-isomers regardless of the substituents and their positions on the benzene ring, suggesting that the *E*-configuration is favorable for fungicidal activity as it was in diphenylether type compounds.[1]

ACKNOWLEDGMENTS

We wish to thank Dr. Akira Murabayashi, Dr. Masami Doteuchi and Dr. Takeo Ishiguro, of Shionogi & Co., Ltd., for their helpful advice, and all the staff of the organic thynsesis and the agrochemical groups of Aburahi Laboratories for their invaluable support for this study.

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要　約

2-(置換フェノキシメチル)フェニル-2-メトキシイミノアセトアミド誘導体の殺菌活性

竹中秀行，市成光広，谷本憲彦，早瀬善男，新川　求
市場常男，益子道生，林　幸之，武田禮二

種々の2-(置換フェノキシメチル)フェニル-2-メトキシイミノアセトアミド誘導体を合成し，フェノキシメチル部の置換基と殺菌活性における構造と活性相関について調べた．その結果，フェノキシメチル部のベンゼン環が無置換の化合物に比較して，ベンゼン環の2位，3位または4位がメチル基またはハロゲンで置換された化合物の方が活性が高かったが，ベンゼン環の2位に比較的嵩高い置換基が導入された化合物は活性が低下する傾向が見られた．また，モノ-置換体より2,3-，2,4-または2,5-ジ-置換体の方が活性が高く，とくに2,4-ジメチル，2,4-ジクロル，2,5-ジメチルおよび2,5-ジクロル体の活性が最も高く，スペクトラムも広かった．一方，2位と6位に同時に置換基が導入された化合物は著しく活性が低下した．メトキシイミノ部の幾何異性体間では*E*-体の方が*Z*-体より活性が高かった．