2-(置換ピリジルオキシメチル)フェニル-2-メトキシイミノ-N-メチルアセトアミド誘導体の構造と殺菌活性

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Original Article

Structure and Fungicidal Activities of 2-Methoxyimino-*N*-methyl-2-[2-(substituted pyridyloxymethyl)phenyl]acetamide Derivatives[1]

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A number of 2-methoxyimino-*N*-methyl-2-[2-(substituted 2-pyridyloxymethyl)phenyl]acetamides were synthesized and their fungicidal activities were examined. The activities and fungicidal spectra of the derivatives varied markedly depending upon the substituents on the pyridine ring. Incorporation of either one or two substituent(s) at the 3-, 5- and/or 6-positions of the pyridine ring resulted in increases in fungicidal activity compared with the unsubstituted compound. Among the 2-pyridyl derivatives synthesized in this study, 3-CF_3-5-Cl, 5-CF_3-3-Cl and 3-CF_3-6-Cl derivatives exhibited the strongest preventive and curative activities against wide range of diseases. 3,5,6-Tri-substituted derivatives demonstrated strong preventive and curative activities against cucumber and wheat powdery mildew, however, they exhibited excellent preventive but weak curative activities against cucumber downy mildew. Between the two geometrical isomers, the *E*-form exhibited stronger activity than the *Z*-form.

INTRODUCTION

Strobilurin analogues were first isolated from Basidiomycotina fungi.[1-7] In 1981 Becker *et al.*[8] reported the fungicidal activities and the mode of action of strobilurins to be respiratory inhibition of mitochondria. Since then, many studies have been performed with structural modification of strobilurin analogues.[9-14] The strobilurin analogues consist of three parts; a pharmacophore, a bridging ring and a side chain attached to the *ortho* position of the bridging ring. In 1992, the Zeneca[15] and the BASF[16] groups independently reported the strobilurin analogues ICIA5504 and BAS-490F as a promising new class of agricultural fungicide with broad spectra and a new mode of action. ICIA5504 synthesized by the Zeneca group has a methoxyacrylic acid methyl ester as a pharmacophore and a substituted pyrimidine ring as a side chain, while BAS-490F synthesized by the BASF group has a methoxyiminoacetic acid methyl ester as a pharmacophore and a substituted phenoxymethyl side chain.

In our previous studies,[17,18] 2-methoxyimino-*N*-methyl-2-(2-phenoxyphenyl)acetamide, consists of methoxyiminoacetamide as a pharmacophore and a phenoxy side chain, and 2-methoxyimino-*N*-methyl-2-[2-(substituted phenoxymethyl)phenyl]acetamide derivatives with the same pharmacophore and a substituted phenoxymethyl side chain, exhibited excellent fungicidal activities against a wide range of crop diseases. Among the former, the unsubstituted phenoxy derivative SSF-126 was selected as a candidate fungicide for control of rice diseases by paddy water application, and among the later, 2,4- or 2,5-di-substituted phenoxymethyl derivatives showed excellent control against a wide range of diseases of upland crops by foliar application.

The benzene ring of some biologically active compounds can be replaced with heterocyclic structures such as a pyridine or pyrimidine ring without influencing the configuration or the bulkiness of the molecule, and as a consequence of the changes of the physico-chemical characteristics or electronic influences on the molecule, improvement of the biological performance can be obtained.[19-21] Therefore, the phenoxymethyl side chain of the 2-methoxyimino-*N*-methyl-2-[2-(substituted phenoxymethyl)phenyl]acetamide derivatives was replaced with a pyridyloxymethyl group in an attempt to further improve the activity and fungicidal spectrum.

[1] Structure and Fungicidal Activities of New Alkoxyiminoacetamide Derivatives (Part 3). For Part 1 and Part 2, see Refs. 17 and 18.

This paper deals with the structures and fungicidal activities of the 2-methoxyimino-*N*-methyl-2-[2-(substituted pyridyloxymethyl)phenyl]acetamide derivatives, with special reference to the effects of the substituents on the pyridine ring.

MATERIALS AND METHODS

1. Chemicals

The synthetic pathways of 2-(*E*)-methoxyimino-*N*-methyl-2-[2-(substituted pyridyloxymethyl)phenyl] acetamide derivatives are shown in Fig. 1. These compounds were prepared by reaction of 2-(2-hydroxymethylphenyl)-2-(*E*)-methoxyimino-*N*-methylacetamide and 2-chloropyridine in the presence of sodium hydride (method A), or condensation of methyl 2-(2-bromomethylphenyl)-2-(*E*)-methoxyiminoacetate and 2-hydroxypyridine with silver carbonate or potassium carbonate followed by aminolysis of the methyl ester (method B). The corresponding oxime *Z*-isomers (**1*Z***, **9*Z***) were synthesized by the same procedures. Methyl 2-(2-bromomethylphenyl)-2-(*Z*)-methoxyiminoacetate and 2-hydroxypyridine provides **1*Z***. **9*Z*** was prepared from 2-(2-hydroxymethylphenyl)-2-(*Z*)-methoxyimino-*N*-methylacetamide and 2-chloro-6-trifluoromethylpyridine according to the method A. 3-Pyridyl derivative (**27**) was prepared according to the method A. 4-Pyridyl derivative (**28**) was prepared according to the method B. The methods for synthesis of these derivatives are described in the patents.[22-25] Typical procedures for method A and method B are as follows. Structures of the compounds reported here were confirmed by proton NMR, and elemental analysis (C, H, N). All melting points were uncorrected. The physical properties of these compounds are listed in Tables 1 through 5.

1.1 Typical procedure of method A: 2-[2-(5-Chloro-3-trifluoromethylpyridin-2-yloxymethyl)phenyl]-2-(E)-methoxyimino-N-methylacetamide (15)

To a suspension of sodium hydride (60%, 2.94 g, 73.6 mmol) in THF (20 ml) was added dropwise a solution of (*E*)-2-methoxyimino-*N*-methyl-2-(2-hydroxyphenyl) acetamide (13.6 g, 61.3 mmol) in THF (150 ml) over 30 min at 0°C. The reaction mixture was stirred for a further 20 min, and a solution of 2,5-dichloro-3-trifluoromethylpyridine (15.9 g, 73.6 mmol) in THF (30 ml) was added at 0°C, then the whole mixture was stirred for 3 hr. The mixture was diluted with 1 N hydrochloric acid and extracted with ethyl acetate. The extracts were washed with brine, dried and evaporated to leave a residue, which was purified by column chromatography on silica gel (20% ethyl acetate/hexane) to afford 2-[2-(5-chloro-3-trifluoromethylpyridin-2-yloxymethyl)phenyl]-2-(*E*)-methoxyimino-*N*-methylacetamide (**15**) (17.9 g, yield: 72.6%). mp 105–106°C, ^{1}H-NMR(δ ppm in $CDCl_3$), 2.95 (3H, d, J=4.8 Hz), 3.96 (3H, s), 5.32 (2H, s), 6.80 (1H, brs), 7.21 (1H, dd, J=7.6, 1.5 Hz), 7.36 (1H, td, J=7.6, 1.5 Hz), 7.42 (1H, td, J=7.6, 1.5 Hz), 7.58 (1H, brd, J=7.6 Hz), 7.81 (1H, dd, J=2.6, 0.7 Hz), 8.16 (1H, dd, J=2.6, 0.7 Hz).

1.2 Typical procedure of method B: 2-[2-(6-Chloropyridin-2-yloxymethyl)phenyl]-2-(E)-methoxyimino-N-methylacetamide (4)

To a solution of methyl 2-(2-bromomethylphenyl)-2-(*E*)-methoxyiminoacetate (500 mg, 1.74 mmol) in hexane (10 ml), silver carbonate (486 mg, 1.74 mmol) and 6-chloro-2-hydroxypyridine (454 mg, 3.50 mmol) were added, and the mixture was heated under reflux and vigorously stirred for 7 hr. The reaction mixture was cooled to room temperature, and insoluble materials were removed by filtration. The filtrate was evaporated and the resulting crude product was dissolved in 30%

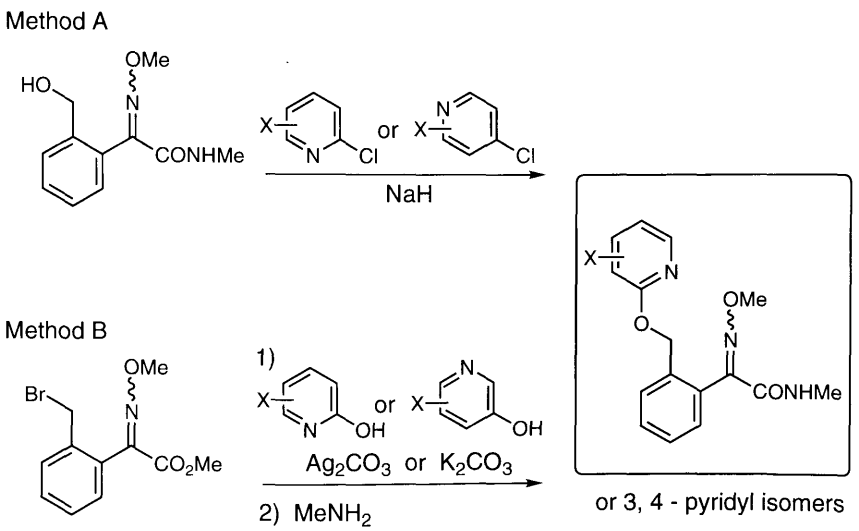


Fig. 1 The synthetic pathways of 2-methoxyimino-*N*-methyl-2-[2-(substituted pyridyloxymethyl)phenyl] acetamides.

methanolic methylamine (2 ml). The mixture was stirred for 2 hr and methylamine was removed *in vacuo*. The residue was purified by column chromatography on silica gel (30% ethyl acetate/hexane) to afford 2-[2-(6-chloropyridin-2-yloxymethyl)phenyl]-2-(*E*)-methoxyimino-*N*-methylacetamide (**4**) (404 mg, yield: 69.5%). mp 74-75°C, ^{1}H-NMR (δ ppm in $CDCl_3$), 2.90 (3H, d, J= 5.1 Hz), 3.93 (3H, s), 5.24 (2H, s), 6.61 (1H, dd, J=8.5, 0.5 Hz), 6.70 (1H, brs), 6.89 (1H, dd, J=7.7, 0.5 Hz), 7.22 (1H, dd, J=7.3, 2.0 Hz), 7.35-7.45 (2H, m), 7.47-7.55 (2H, m).

2. *Plant Materials*

Cucumber (*Cucumis sativus* L. cv. Tsukuba-shiroibo), wheat (*Triticum aestivum* L. cv. Nohrin-61) and rice (*Oryza sativa* L. cv. Aichi-asahi) seedlings were used for the assay of disease controlling activity by foliar application. The seedlings were prepared as described previously.[17,18]

3. *Assay Methods for Disease Controlling Activity*

Preventive and curative activities of the test compounds on rice blast, wheat powdery mildew, cucumber powdery mildew, cucumber gray mold and cucumber downy mildew were assessed by foliar application. The preventive activity tests were carried out by inoculating the pathogen 24 hr after treatment of the test compounds. For the curative tests of rice blast, wheat powdery mildew and cucumber gray mold, the pathogen were inoculated 24 hr before treatment, and for cucumber powdery mildew and cucumber downy mildew, the pathogen were inoculated 48 hr before treatment. The details of the fungicidal assay were described previously.[17,18]

The fungicidal activities were 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 and less than 90% control at 125 ppm, respectively.

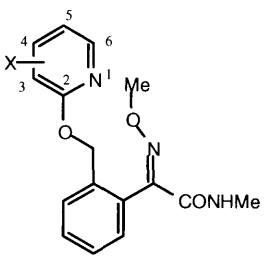
Unless otherwise stated, the *E*-form of each compound was used for assessment of the fungicidal activity.

RESULTS AND DISCUSSION

1. *Fungicidal Activities of the Mono-substituted Pyridyl Derivatives*

The disease controlling activities of the mono-substituted derivatives on the pyridine ring of the 2-pyridyloxymethylphenyl analogues as well as unsubstituted compound by foliar application were shown in Table 1. The activity of the unsubstituted compound (**1**) was moderate against wheat and cucumber diseases and weak against rice blast. Among the mono-substituted derivatives, 3-CF_3 derivative (**6**) exhibited good preventive and curative control against all diseases tested except cucumber downy mildew, followed by 3-Cl (**2**), 5-Cl (**3**), 6-Cl (**4**), 6-Br (**5**), 5-CF_3 (**8**) and 6-CF_3 (**9**)

Table 1 Fungicidal activities[a] of mono-substituted pyridyl derivatives by foliar application.



Compound			Rice		Wheat		Cucumber					
			Blast		P. mildew		P. mildew		Gray mold		D. mildew	
No.	X	mp (°C)	Pre.[b]	Cur.[c]	Pre.[b]	Cur.[c]	Pre.[b]	Cur.[c]	Pre.[b]	Cur.[c]	Pre.[b]	Cur.[c]
1	H	73-74	0	0	3	2	3	2	2	2	2	1
2	3-Cl	oil	2	3	3	3	3	3	2	4	3	2
3	5-Cl	117.5-118.5	1	2	3	4	2	2	4	4	3	2
4	6-Cl	74-77	2	2	4	3	3	3	3	3	4	2
5	6-Br	oil	2	3	4	2	2	3	2	3	3	1
6	3-CF_3	96-97	4	4	4	4	3	4	3	4	2	2
7	4-CF_3	108-109	2	2	1	2	1	1	0	0	3	0
8	5-CF_3	108-109	2	2	3	3	2	3	3	4	3	2
9	6-CF_3	68-69	2	3	4	3	3	3	2	1	4	2
10	6-OCH_3	88-89	2	2	2	3	3	3	1	1	2	1
11	6-SCH_3	130-132	0	NT	1	0	2	2	1	0	3	1
12	6-O-i-Pr	115-120	2	2	1	1	2	2	1	0	2	0

[a] The fungicidal activities were exPressed as an index of 4, 3, 2, 1 and 0, each corresponding to approximately 90% control at 2.0, 7.8, 31.3, 125 ppm and less than 90% control at 125 ppm, respectively. [b] Preventive application. [c] Curative application. NT: not tested.

derivatives. Especially, 6-Cl (**4**) and 6-CF_3 (**9**) derivatives showed excellent preventive activity against cucumber downy mildew, and 5-Cl (**3**) derivative also exhibited excellent preventive and curative control against cucumber gray mold. On the other hand, incorporation of trifluoromethyl group at the 4-position of the pyridine ring (**7**) seemed to decrease the activity against cucumber gray mold, cucumber powdery mildew and wheat powdery mildew compared to the 3-, 5- and 6-CF_3 derivatives. Incorporation of an alkylthio substituent at the 6-position of the pyridine ring (**11**) also resulted in marked decrease in the activity against all diseases tested except in the preventive activity on cucumber downy mildew.

2. *Fungicidal Activities of the Di-substituted Pyridyl Derivatives*

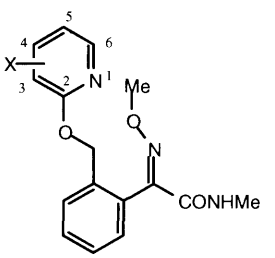
The fungicidal activities of the di-substituted derivatives are shown in Table 2. Incorporation of Cl and CF_3 at two of 3-, 5- and 6-positions of the pyridine ring (**13**–**16**, **18**) exhibited superior activity compared to the unsubstituted derivative (**1**). Especially, 3-Cl-5-CF_3 (**13**), 3-CF_3-5-Cl (**15**) and 3-CF_3-6-Cl (**16**) derivatives demonstrated good to excellent control by both preventive and curative applications against all diseases examined. 3,5-Dichloro derivative (**14**) also demonstrated excellent control against powdery mildew and downy mildew of cucumber. Incorporation of an alkoxy substituent at the 6-position of the pyridine ring accompanied with the 3-CF_3 (**19**, **20**) or 5-CF_3 (**21**, **22**) group reduced the activity against all diseases examined except cucumber powdery mildew compared with each corresponding 6-Cl derivatives (**16** and **18**). Furthermore, it was observed that the activities of 6-OMe derivatives (**19**, **21**) were superior to 6-O-*i*-Pr derivatives (**20**, **22**) against all diseases tested with the exception for **19** against rice blast and wheat powdery mildew. The activity of 4-CF_3-6-Cl derivative (**17**) was weak against all diseases tested except for the preventive activity on cucumber downy mildew. All of the di-substituted derivatives, with a single exception of **17**, demonstrated good to excellent control against cucumber powdery mildew.

From the above mentioned results, it will be concluded that incorporation of a chlorine atom and a trifluoromethyl group at either two of 3-, 5- and 6-position of the pyridine ring is favorable for fungicidal activity.

3. *Fungicidal Activities of the Tri- and Tetra-substituted Pyridyl Derivatives*

The fungicidal activities of the tri- and tetra-substituted derivatives are shown in Table 3. The tri-substituted derivatives (**24**, **25**) exhibited good to excellent control against powdery mildew of wheat and cucumber by both preventive and curative application, and cucumber downy mildew by preventive application. However, the activities of these compounds against cucumber gray mold were inferior to those of cucumber and wheat powdery mildew. And poor activities of these compounds against cucumber downy mildew were observed

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



No.	Compound X	mp (°C)	Rice Blast Pre.[b]	Rice Blast Cur.[c]	Wheat P. mildew Pre.[b]	Wheat P. mildew Cur.[c]	Cucumber P. mildew Pre.[b]	Cucumber P. mildew Cur.[c]	Cucumber Gray mold Pre.[b]	Cucumber Gray mold Cur.[c]	Cucumber D. mildew Pre.[b]	Cucumber D. mildew Cur.[c]
13	3-Cl-5-CF_3	114	3	3	4	4	4	4	4	4	4	3
14	3,5-Cl_2	141–142	3	2	3	3	4	4	2	2	4	4
15	3-Cl_3-5-Cl	112–114	3	3	4	4	4	4	3	4	4	3
16	3-CF_3-6-Cl	111–112	3	3	4	4	4	4	3	3	4	4
17	4-CF_3-6-Cl	114.5–117.5	1	0	1	1	1	1	0	0	3	0
18	5-CF_3-6-Cl	139–140	3	3	3	3	3	4	3	3	4	2
19	3-CF_3-6-OCH_3	126–130	1	1	2	1	4	4	2	0	3	1
20	3-CF_3-6-O-i-Pr	126–129	2	2	3	2	3	3	1	0	3	0
21	5-CF_3-6-OCH_3	123–125	1	1	2	3	4	4	3	1	4	2
22	5-CF_3-6-O-i-Pr	124–127	1	1	1	1	3	3	0	0	2	0
23	5-CF_3-6-$NHCH_3$	66–67	0	0	2	1	3	3	1	1	3	1

[a] Fungicidal activities are expressed as in Table 1. [b] Preventive application. [c] Curative application.

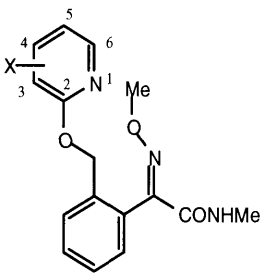
by curative application despite excellent control by preventive application. The activity of the tetra-substituted derivative (**26**) was extremely weak against all diseases tested.

Powdery mildew fungus develops its hyphae on the surface of the epidermis of the host plant and invade its haustoria into the host cell. In contrast, the symptoms of gray mold and downy mildew are due to penetration of the host tissues by the hyphae. The differences in the process of disease development between powdery mildew and gray mold or downy mildew are responsible for the different responses to the fungicides. Some compounds with strong fungicidal activities but less systemic activities presumably due to high log *P* value, will exhibit good preventive and curative control against powdery mildew, which the hyphae develop on the surface of the host plant. Such compounds, in contrast, will exhibit good preventive but less curative control against gray mold or downy mildew, which the hyphae invade into the host plant. It will be assumed that the poor activities of the tri-substituted pyridine analogues against cucumber gray mold and downy mildew by curative application are due to the less systemic feature of the compounds, as was observed in the case of phenoxymethyl type analogues.[18]

4. *Fungicidal Activities of 3-Pyridyl and 4-Pyridyl Derivatives*

All of the compounds used in the above experiments were 2-pyridyl derivatives. The fungicidal activities of 3-pyridyl and the 4-pyridyl derivatives were then also assessed (Table 4). The 3-pyridyl derivative with 2-chloro substituent (**27**) exhibited moderate to weak activity against cucumber powdery mildew and gray mold,

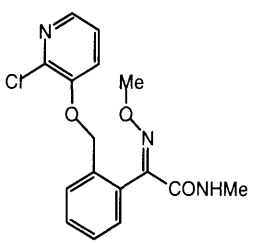
Table 3 Fungicidal activities[a] of tri- and tetra-substituted pyridyl derivatives by foliar application.



No.	Compound X	mp (°C)	Rice Blast Pre.[b]	Rice Blast Cur.[c]	Wheat P. mildew Pre.[b]	Wheat P. mildew Cur.[c]	Cucumber P. mildew Pre.[b]	Cucumber P. mildew Cur.[c]	Cucumber Gray mold Pre.[b]	Cucumber Gray mold Cur.[c]	Cucumber D. mildew Pre.[b]	Cucumber D. mildew Cur.[c]
24	3,5-$(CF_3)_2$-6-Cl	155.5–156	1	0	4	3	4	3	2	1	4	0
25	3,6-Cl_2-5-CF_3	141–142	2	2	3	4	4	4	3	2	4	1
26	3,5,6-Cl_3-4-CF_3	119–120	0	NT	0	0	1	1	0	NT	1	0

[a] Fungicidal activities are expressed as in Table 1. [b] Preventive application. [c] Curative application. NT: not tested.

Table 4 Fungicidal activities[a] of substituted 3-pyridyl and 4-pyridyl derivatives by foliar application.



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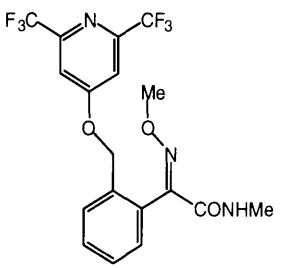
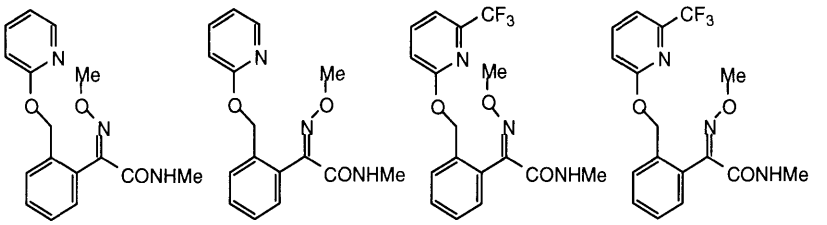


28

Compound No.	mp (°C)	Rice Blast Pre.[b]	Rice Blast Cur.[c]	Wheat P. mildew Pre.[b]	Wheat P. mildew Cur.[c]	Cucumber P. mildew Pre.[b]	Cucumber P. mildew Cur.[c]	Cucumber Gray mold Pre.[b]	Cucumber Gray mold Cur.[c]	Cucumber D. mildew Pre.[b]	Cucumber D. mildew Cur.[c]
27	128–129	0	NT	0	0	2	2	3	3	0	NT
28	145–148.5	0	NT	0	0	0	0	0	NT	0	0

[a] Fungicidal activities are expressed as in Table 1. [b] Preventive application. [c] Curative application. NT: not tested.

Table 5 Comparison of geometrical isomers on fungicidal activities[a] by foliar application.



1 **1Z** **9** **9Z**

Compound No.	mp (°C)	Rice Blast Pre.[b]	Rice Blast Cur.[c]	Wheat P. mildew Pre.[b]	Wheat P. mildew Cur.[c]	Cucumber P. mildew Pre.[b]	Cucumber P. mildew Cur.[c]	Cucumber Gray mold Pre.[b]	Cucumber Gray mold Cur.[c]	Cucumber D. mildew Pre.[b]	Cucumber D. mildew Cur.[c]
1	73–74	0	0	3	2	3	2	2	2	2	1
1Z	107–108	0	NT	1	0	0	0	0	NT	0	NT
9	68–69	3	4	4	3	3	3	3	1	4	2
9Z	oil	2	2	2	2	1	2	1	0	3	1

[a] Fungicidal activities are expressed as in Table 1. [b] Preventive application. [c] Curative application. NT: not tested.

but extremely weak activities against rice blast, wheat powdery mildew and cucumber downy mildew. The 4-pyridyl derivative (**28**) also exhibited extremely weak activity against all diseases Tested.

5. *Comparison of the Geometrical Isomers*

The fungicidal activities of two geometrical isomers at the oxime moiety were compared by foliar application (Table 5). The activities of the *E*-isomers were much stronger against all diseases examined than those of each corresponding *Z*-isomer, suggesting that the *E*-configuration is favorable for fungicidal activity. The differences in the fungicidal activities between the two geometrical isomers showed the same tendency as the diphenylether type and the phenoxymethyl type compounds.[17,18]

From the above results, we concluded that the fungicidal activities are excellent when either two of 3, 5 and 6-positions on the pyridine ring of the 2-(*E*)-methoxyimino-*N*-methyl-2-(2-pyridyloxymethylphenyl)acetamides are substituted with a trifluoromethyl group and a chlorine atom. The tri-substituted analogues exhibited excellent activities against cucumber and wheat powdery mildew by both preventive and curative application, as well as cucumber downy mildew by preventive application. The tetra-substituted derivative showed extremely weak activity.

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要　　約

2-(置換ピリジルオキシメチル)フェニル-2-メトキシイミノ-*N*-メチルアセトアミド誘導体の構造と殺菌活性

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種々の2-(置換-2-ピリジルオキシメチル)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，ピリジン環の置換基が殺菌活性に及ぼす影響について，茎葉散布試験を実施して調べた．その結果，無置換の化合物に比較して，ピリジン環の3位，5位または6位にトリフルオロメチル基またはハロゲンが導入された化合物群は明らかに活性が高かった．さらにトリフルオロメチル基やハロゲンが同時に導入された化合物の中では，3,5-，3,6-または5,6-ジ-置換体が予防効果，治療効果ともに高く抗菌スペクトラムも広がる傾向が見られた．3,5,6-トリ-置換体はキュウリおよびコムギのうどんこ病に対しては予防効果，治療効果ともに高かったが，キュウリべと病に対しては予防効果は高いものの，治療効果が劣る傾向が見られた．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．