カルボキシン関連カルボキサミド系殺菌剤の構造活性相関

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Original Article

Structure-activity relationship of carboxin-related carboxamides as fungicide

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Various carboxamides were synthesized and their structure-activity relationships were examined as fungicides. The fungicidal activity and spectrum depended on the aromatic ring and *N*-substituent at the amide moiety. Among them, *N*-(biphenyl-2-yl)-2-chloropyridine-3-carboxamide exhibited high activity against gray mold, and the corresponding 3-CF_3-pyrazole-4-carboxamide exhibited higher activity. Moreover, it was found that compounds with hydrophobic branched alkyl groups at the *ortho* position of the *N*-phenyl group exhibited high and broad-spectrum fungicidal activity. The benzene ring of the *N*-phenyl group can be replaced with a thiophene ring, and optimization of the alkyl groups on the thiophene ring led to penthiopyrad (**1**); *N*-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide, which proved to be very effective against various diseases.

Keywords: penthiopyrad, MTF-753, 3-(trifluoromethyl)pyrazole-4-carboxamide, aminothiophene, carboxamide, fungicide.

Introduction

The discovery of the systemic fungicide carboxin greatly encouraged further optimization of the chemical structure. Thus, a number of carboxin-related carboxamides have been shown to be effective in the control of plant diseases as shown in Fig. 1.[1,2] Carboxin is a narrow-spectrum fungicide with specific potency against Basidiomycetes. In the 1980s, mepronil and flutolanil, which contain a (3-isopropyloxy)phenyl group, were developed. In the 1990s, two azole carboxamides, furametpyr[3] and thifluzamide,[4] were launched onto the Japanese market to control *Rhizoctonia solani* (rice sheath blight).

On the other hand, *N*-(biphenyl-2-yl)-2-methyl-1,4-thioxolane-3-carboxamide (F-427; **2**) is unique in that it exhibits a broader spectrum of activity and could control Deuteromycete and Phycomycete species as well as Basidiomycetes[5] compared with carboxin. In 1989, the Mitsubishi Kasei Corporation discovered that a 2-chloropyridine-3-carboxamide derivative (BC-723; **3**) exhibited fungicidal activity against Deuteromycetes (gray mold and apple scab) as well as Basidiomycetes.[6]

At that time, the authors were engaged in a project aimed to discover a broad-spectrum fungicide whose structure was different from that of existing fungicides. We considered BC-723 to be a suitable lead compound because it showed the potential for broad-spectrum activity. In the course of our research, we realized the importance of the aromatic rings and *N*-substituent in the carboxamide compounds and attempted to increase fungicidal activity by structural modification.[7–13] This led to the identification of (penthiopyrad; **1**) (*RS*)-*N*-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)-pyrazole-4-carboxamide as a potent fungicide for various plant diseases involving Basidiomycetes. Furthermore, it was observed that **1** exhibited high activity against fungicide-resistant strains of various diseases, such as gray mold, cucumber powdery mildew, and apple scab.[13–15]

Penthiopyrad has been tested in official trials with the code

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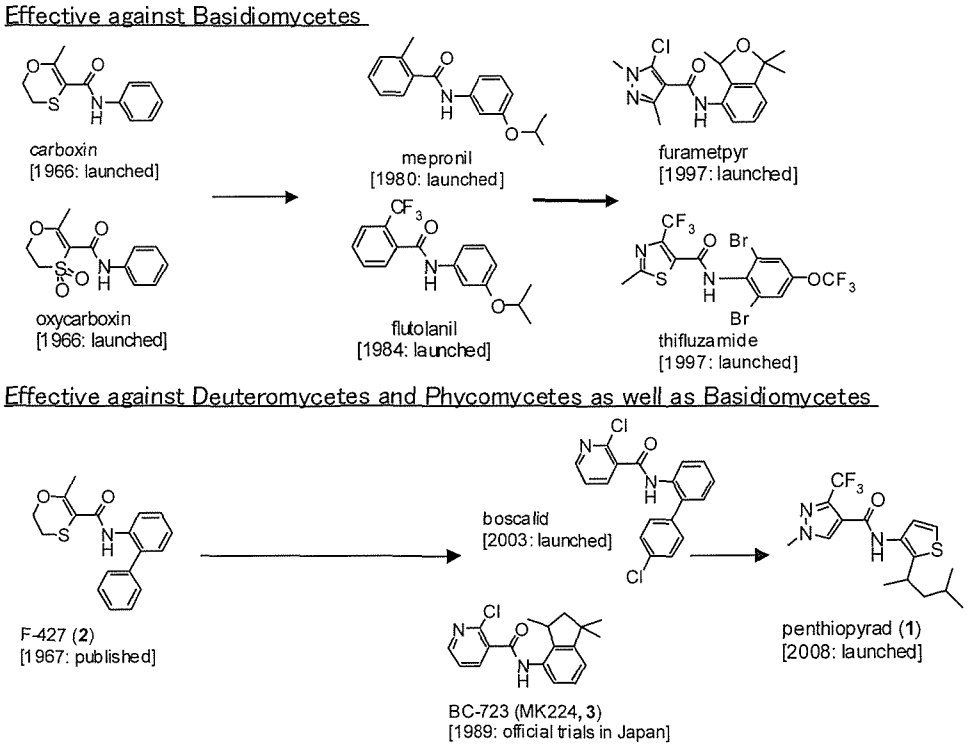


Fig. 1. Development of carboxin-related carboxamides as fungicides.

number MTF-753 in Japan since 1997. The fungicide was registered in 2008 in Japan, and the registration covers its use on turf, vegetables, and fruits. Registration in the US, Canada, and EU is planned for after 2011.

In this paper, we describe the details of the discovery, synthesis, and fungicidal properties of penthiopyrad.

Materials and Methods

1. Preparation of compounds

Melting points (mp) were uncorrected. IR spectra were measured with a JASCO FT-IR-7300 spectrometer. ^{1}H-NMR spectra were measured with a JEOL JNM-A400 FT-NMR system at 400 MHz using tetramethylsilane as the internal standard.

1.1. Pyrazole carboxylic acid

Ethyl 2-ethoxymethylene-4,4,4-trifluoroacetoacetate[16] (9.7 g, 0.041 mol) was added dropwise to a solution of methyl hydrazine (1.9 g, 0.041 mol) in ethyl acetate (50 mL) at 5–10°C. The reaction mixture was refluxed with stirring for 3 h. The solvent was distilled off under reduced pressure, and the residue was purified with silica gel to give ethyl 1-methyl-3-(trifluoromethyl)pyrazole-4-carboxylate (7.7 g, 85%) as a white solid.[16] This ester compound was hydrolyzed to 1-methyl-3-(trifluoromethyl)pyrazole-4-carboxylic acid.

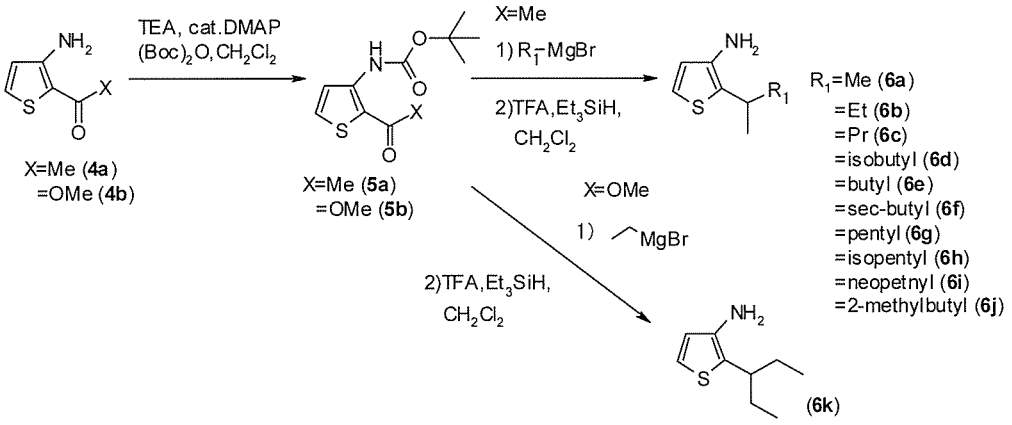
1.2. 3-Amino-2-substituted thiophene derivatives

The 3-amino-2-substituted thiophene derivatives described in this paper were synthesized according to Schemes 1–3. ^{1}H-NMR spectrum data of the 3-amino-2-substituted thiophene derivatives are given in Supplemental Table S1.

*1.2.1. (RS)-3-Amino-2-(1,3-dimethylbutyl)thiophene (**6d**) (Scheme 1)*

A mixture of di-*tert*-butyl dicarbonate (38.7 g, 0.180 mol) and methylene chloride (30 mL) was added dropwise to a solution of 2-acetyl-3-aminothiophene[17] (4.25 g, 0.18 mol) in methylene chloride (500 mL), and the reaction mixture was stirred for 1 hr at room temperature. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel (hexane : ethyl acetate = 10 : 1) to give *N*-(2-acetylthiophene-3-yl) *tert*-butylcarbamate (**5a**) (23.5 g, 54%) as a colorless oil.

The mixture of the above carbamate (**5a**; 1.0 g, 3.9 mmol) and THF (10 mL) was added dropwise under nitrogen to 1.07 M isobutyl magnesium bromide THF solution (20 mL) below 15°C. The mixture was stirred for 1 hr at room temperature and poured into a saturated ammonium chloride solution (100 mL). The mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with brine (70 mL) and dried over Na_2SO_4. The solvent was distilled off under reduced pressure to give crude *N*-[2-(1,3-dimethyl-1-hydroxybutyl) thiophene-3-yl] *tert*-butylcarbamate (1.2 g). Trifluoroacetic acid (4.3 g, 38 mmol) was added to a methylene chloride (10 mL) solution of the above carbamate (1.2 g) and triethylsilane (0.44 g, 3.8 mmol) at room temperature. The mixture was stirred overnight and poured into saturated sodium hydrogen carbonate solution (100 mL). The mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with brine (70 mL) and then dried over Na_2SO_4. The solvent was distilled off under reduced pressure, and the



Scheme 1.

residue was purified with silica gel (hexane : ethyl acetate =85 : 15) to give (*RS*)-3-amino-2-(1,3-dimethylbutyl)thiophene (**6d**) (0.50 g, 70%) as a yellow oil.

1.2.2. 3-Amino-2-isopentylthiophene (9b) (Scheme 2)

Catalytic amounts of 1,2-dibromoethane and ether (5 mL), magnesium (0.186 g), and isopentyl bromide (1.17 g, 7.74 mmol) were used to prepare a solution of isopentylmagnesium bromide, which was added dropwise under nitrogen to a solution of 3-nitrothiophene [19] (**7**; 0.5 g, 3.87 mmol) in THF (12 mL) at –50°C. The mixture was stirred at –50°C for 20 min. A solution of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (1.05 g, 4.64 mmol) in THF was added, and the mixture was stirred at –50°C for 1 hr and poured into a saturated ammonium chloride solution (50 mL). Ethyl acetate (50 mL) was added to the mixture, and a gummy solid was removed by Celite filtration. The organic phase was separated from the filtrate, washed with brine (50 mL), and dried over Na_2SO_4. The solvent was distilled off under reduced pressure, and the residue was purified with silica gel (hexane : toluene=20 : 1) to afford 2-isopentyl-3-nitrothiophene [18] (**8b**) (0.37 g, 48%) as a yellow oil.

Iron (0.49 g) was added to a solution of the compound **8b** (0.31 g, 1.55 mmol) and concentrated hydrochloric acid (3.0 mL) in methanol (10 mL). The mixture was stirred at 60°C for 1 h, cooled, and poured into water (50 mL). The resulting mixture was neutralized with potassium carbonate and extracted with ethyl acetate (30 mL). The organic layer was extracted with 5% hydrochloric acid solution (20 mL×4). The acid layer was neutralized with potassium carbonate and extracted with ethyl acetate (80 mL). The organic layer was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was distilled off under reduced pressure to give 3-amino-2-isopentylthiophene (**9b**) (0.11 g, 42%) as a yellow oil.

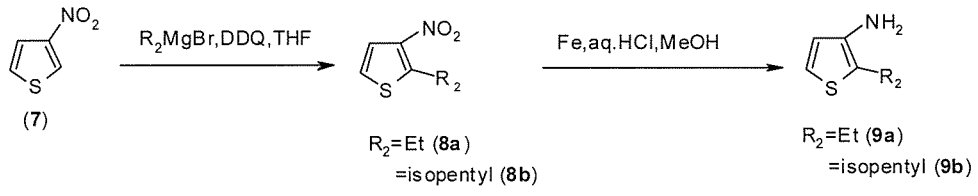
1.2.3. 3-Amino-2-phenylthiophene (13) (Scheme 3)

Tetrakis(triphenylphosphine)palladium (0.33 g, 0.29 mmol) was added under nitrogen to a solution of 2-bromo-3-nitrothiophene[20,21] (**10**) (0.6 g, 2.88 mmol), phenyl boronic acid (**11**; 0.35 g, 2.88 mmol), ethanol (2 mL), and 2 M potassium carbonate solution (5 mL) in toluene (30 mL). The mixture was refluxed with stirring for 9 hr. The cooled mixture was washed with water (20 mL), and the organic layer was dried over Na_2SO_4. The solvent was distilled off under reduced pressure, and the residue was purified with silica gel (hexane: ethyl acetate=20:1) to give 3-nitro-2-phenylthiophene (**12**) (0.50 g, 85%) as a yellow oil.

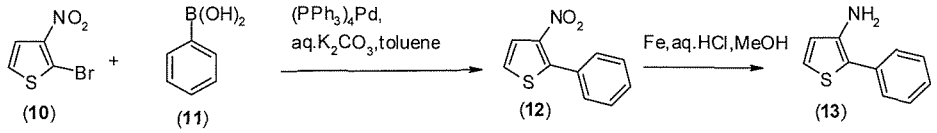
Compound **12** was converted to the corresponding aminothiophene (**13**) by a method similar to that shown above.

1.3. (RS)-N-[2-(1,3-Dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide (penthiopyrad; 1)

1-Methyl-3-(trifluoromethyl)pyrazole-4-carbonyl chloride, which was prepared by the reaction of 1-methyl-3-(trifluoromethyl)pyrazole-4-carboxlic acid (0.53 g, 2.7 mmol) with thionyl chloride (1 mL), was added to a solution of *(RS)*-3-amino-2-(1,3-dimethylbutyl)thiophene (**6d**; 0.5 g, 2.7 mmol) in pyridine (5 mL) at room temperature. The reaction mixture was stirred for 1 hr at room temperature, poured into the 5% hydrochloric acid solution (30 mL), and then extracted with ethyl acetate (30 mL). The organic layer was washed successively with saturated sodium hydrogen carbonate solution and



Scheme 2.



Scheme 3.

brine and then dried over Na_2SO_4. The solvent was distilled off under reduced pressure and the residue was purified by silica gel (hexane : ethyl acetate=6 : 4) to give the compound (**1**) (0.40 g, 41%) as a white solid.

Other carboxamide derivatives were prepared by the reaction of the corresponding carboxylic acids[22–30] and amines.[31] The melting points, IR spectrum data, and ^{1}H-NMR spectrum data of carboxamide derivatives are given in Supplemental Table S2.

2. *Biological evaluation*

2.1. *Kidney bean gray mold*

Because BC-723 (**3**) did not show activity against gray mold by the usual screening using a mycelium agar disk of *Botrytis cinerea* as the inoculum, we used a spore solution of *B. cinerea* as the inoculum described below:

Each compound was dissolved in acetone and then diluted with water to prepare the test solution. Each test solution was sprayed on kidney beans at the seed-leaf stage until run off. After the leaves dried, they were cut and placed in plastic cups covered with wet paper disks to maintain humidity. Spores of gray mold were collected with potato sucrose broth medium and inoculated with paper disk soaked spore solution. Four days after inoculation, the size of the lesion was measured, and the control percentage was calculated. Activity levels of compounds were shown by the following index for the control percentage in the tables.

Control percentage=[(diameter of lesion on untreated leaf
−diameter of lesion on treated leaf)
/(diameter of lesion on untreated leaf)]
×100

0: 500 ppm <95% (500 ppm)
1: 500 ppm ≧95% (500 ppm) and <50% (62.5 ppm)
2: 62.5 ppm ≧50–95% (62.5 ppm)
3: 62.5 ppm ≧95% (62.5 ppm)

2.2. *Cucumber powdery mildew*

Each test solution was sprayed on 1.5-leaf-stage cucumber plants until run off. After the leaves had dried, spores of cucumber powdery mildew were shaken off onto the sprayed leaves. Seven days after inoculation, the infected lesion area was assessed, the control percentage was calculated using the following formula, and activity levels of the compounds are shown by the following index for the control percentage listed in the tables.

Control percentage=[(percentage lesion of untreated leaf
−percentage lesion of treated leaf)
/percentage lesion of untreated leaf)]
×100

0: 250 ppm <95% (250 ppm)
1: 250 ppm ≧95% (250 ppm) and <50% (25 ppm)
2: 25 ppm ≧50–95% (25 ppm)
3: 25 ppm ≧95% (25 ppm)

2.3. *Wheat brown rust*

Each test solution was sprayed on 1.5-leaf-stage wheat plants until run off. After the leaves had dried, spores of brown rust were sprayed on them and the leaves were kept in a cold condition at high humidity for two days. The plants were maintained for further eight days in a growth chamber at 18°C, and the number of colonies derived was counted. The control percentage was calculated by the following formula, and the activity levels of compounds are shown by the following index for the control percentage in the tables.

Control percentage=[(colony number of untreated pot
−colony number of treated pot)
/(colony number of untreated pot)]×100

0: 250 ppm <95% (250 ppm)
1: 250 ppm ≥95% (250 ppm) and <50% (25 ppm)
2: 25 ppm ≥50–95% (25 ppm)
3: 25 ppm ≧95% (25 ppm)

2.4. *Rice blast*

Each test solution was sprayed on 2- or 3-leaf stage rice plants until run off. After the leaves had dried, a spore suspension of rice blast was sprayed on the plants, which were maintained in a growth chamber at 25°C and high humidity. Seven days after inoculation, the number of lesions was counted. The control percentage was calculated using the following formula, and the activity levels of compounds are shown by the following index for the control percentage in the tables.

Control percentage=100×(lesion number of untreated pot
−lesion number of treated pot)
/lesion number of untreated pot)

0: 250 ppm <95% (250 ppm)
1: 250 ppm ≧95% (250 ppm) and <50% (50 ppm)
2: 50 ppm ≧50–95% (50 ppm)
3: 50 ppm ≧95% (50 ppm)

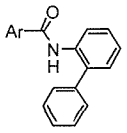
** het/aryl group=heterocyclic or aryl group

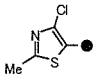
Results and Discussion

1. *N-(Biphenyl-2-yl) het/aryl carboxamides*

In the case of *N*-(biphenyl) het/aryl** carboxamides, activity against gray mold varied markedly with the substitution mode of the *N*-(biphenyl) group on the carbamoyl group. *N*-(biphenyl-2-yl) 2-chloropyridine-3-carboxamide (**14**) exhibited relatively high activity against gray mold, whereas its corresponding *N*-(biphenyl-3-yl) and *N*-(biphenyl-4-yl) derivatives showed a lower level of activity. In order to study the importance of het/aryl groups on the carbon atom of the carbamoyl group, we evaluated the activity of various *N*-(biphenyl-2-yl) het/aryl carboxamides against various diseases and the results are summarized in Table 1. Among the

Table 1. *N*-(Biphenyl-2-yl) het/aryl carboxamides and fungicidal activity



Compound No.	Ar	Fungicidal activity			
		Gray mold	Powdery mildew	Brown rust	Blast
15		3	2	1	0
16		2	0	N.T.	0
17		0	0	0	0
18		3	2	N.T.	1
19		3	2	0	1
20		2	1	N.T.	0
21		0	0	0	0
22		3	1	0	0
23		3	0	1	1
14		2	0	N.T.	0
24		3	1	0	0
25		3	0	N.T.	0
26		2	3	2	0
2		3	2	0	0
3 (BC-723)		2	0	0	0

Disease (crop): Gray mold (Kidney Beans); Powdery mildew (Cucumber); Brown rust (Wheat); Blast (Rice). N.T.: not tested.

N-(biphenyl-2-yl) het/aryl carboxamides, pyrazole derivative (**15**) or thiazole derivative (**18**, **19**) with *o*-CF_3 or *o*-CHF_2 group to the amide moiety not only exhibited high activity against gray mold but also moderate activity against powdery mildew. In addition, their methyl-substituted derivatives (**16**, **20**) exhibited moderate activity against gray mold, whereas their chloro-substituted derivatives (**17**, **21**) were inactive. In the case of the five-membered heterocyclic compounds, methyl-substituted thiophene (**22**) and furan derivatives (**23**) exhibited high activity against gray mold, but low or no activity against wheat brown rust and rice blast. In the case of the six-membered heterocyclic compounds (**2**, **14**, **24**–**26**), they exhibited high activity against gray mold. In particular, the pyran derivative (**26**) was effective against powdery mildew and wheat brown rust. Therefore, when the substituent at the *N*-phenyl ring of the amide moiety is a 2-phenyl group, it is considered to be essential for a compound exhibiting activity against gray mold to have a het/aryl carboxamide moiety with an *o*-hydrophobic substituent on the het/aryl group.

Taking into account the activity against gray mold and powdery mildew and the residual activity as a whole, we considered 1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide as the most suitable structure, and hence we evaluated its fungicidal activity in the following research.

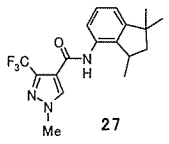
2. *N-(2-Alkylphenyl or 2-alkyl-3-thienyl)-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamides*

The fungicidal activity of various 1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamides against various diseases is listed in Table 2. Compound **27**, which has an 1,1,3-trimethylindane-4-yl group similar to that of the *N*-substituent at the amide group in BC-723, exhibited higher activity against gray mold and wheat brown rust than BC-723. Compounds having an isopropyl or a *sec*-butyl group on the *N*-phenyl ring at the amide group (**28**, **29**) also exhibited high activity against gray mold and wheat brown rust and higher activity against powdery mildew than compound **27**. This indicates that a bulky and hydrophobic substituent at the *ortho* position of the *N*-phenyl ring is necessary to elicit more potent activity against gray mold. Similar effects due to a substituent has been suggested in previous research on BC-723.[6),32)] Furthermore, compounds **28** and **29** exhibited higher activity against wheat brown rust than the *N*-(biphenyl-2-yl) derivative (**15**).

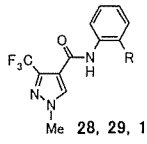
It has been reported that replacement of the benzene ring of the parent compound with the thiophene ring sometimes maintains its biological activity,[33)] and the thiophene ring can be considered a bioisoster of the benzene ring. Hence, we synthesized pyrazole carboxamide derivatives (**30**–**32**) that had 2-substituted-3-thienyl groups on the nitrogen atom of the carbamoyl group and evaluated their activity. As a result, it was found that they exhibited the same activity against gray mold, powdery mildew, and wheat brown rust as that exhibited by the corresponding *N*-phenyl amide derivatives (**15**, **28**, **29**).

Although it was more difficult to synthesize *N*-[(2-substituted)-3-thienyl] carboxamide than *N*-(2-substitued)phenylcarboxamide, *N*-(2-alkyl-3-thienyl)-carboxamide derivatives had structural novelty and high activity and showed a tendency to broaden the fungicidal spectrum. Therefore, we synthesized various *N*-(2-alkyl-3-thienyl)-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamides and examined their fungicidal activity to investigate the effect of the alkyl groups substituted at the 2-position of the thiophene ring on fungicidal

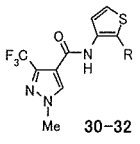
Table 2. Fungicidal activity of *N*-phenyl-3-(trifluoromethyl)pyrazole-4-carboxamide derivatives and *N*-thienyl carboxamide derivatives



27



28, 29, 15



30–32

Compound No.	R	Fungicidal activity			
		Gray mold	Powdery mildew	Brown rust	Blast
27	—	3	0	3	0
28	*iso*-Pr	3	1	3	0
29	*sec*-Bu	3	2	3	0
15	Ph	3	2	1	0
30	*iso*-Pr	3	1	3	0
31	*sec*-Bu	3	2	3	0
32	Ph	3	2	0	0
3 (BC-723)	—	2	0	0	0

Disease (crop): Gray mold (Kidney Beans); Powdery mildew (Cucumber); Brown rust (Wheat); Blast (Rice).

activity.

3. *Various derivatives of N-(2-alkyl-3-thienyl)-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamides*

The fungicidal activity of *N*-(3-thienyl)-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide derivatives that had various alkyl groups at the 2-position of the thiophene ring against four diseases is listed in Table 3. The fungicidal effect of the alkyl group on the thiophene ring against each disease is described as follows.

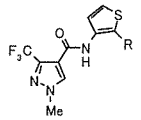
The fungicidal activity against gray mold was dependent on the number of carbon atoms in the branched alkyl group attached at the 2-position of the thiophene ring: Compounds with an alkyl group having 3 to 6 carbon atoms (C_3: **30**, C_4: **31**, C_5: **34–36**, C_6: **1**, **37**, **38**) exhibited high activity against gray mold, whereas compounds with alkyl groups having 2 or 7 carbon atoms did not exhibit high activity (**33**, **39–42**).

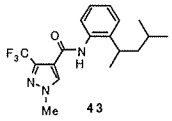
On the other hand, the fungicidal activity against powdery mildew was considered to be affected by the chemical structure of the branched alkyl group: Compounds that have carbon numbers from 4 to 7, and have one methyl group at the α or γ position in their alkyl chains (**31**, **34**, **35**, **37–40**) exhibited moderate or high activity against powdery mildew. Further, compounds having methyl groups at both the α and γ positions in their alkyl chains (**1**, **41**,**42**) exhibited high activity. However, a compound having an ethyl group at the α; position (**36**) showed no activity.

In addition, all the compounds, except for **36**, showed excellent activity against wheat brown rust. On the other hand, only two compounds (**1**, **42**) inhibited rice blast completely, and had a secondary carbon atom at both the α and γ position on their alkyl group.

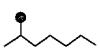
Among these compounds, only compound **1**, which had a 2-(1,3-dimethylbutyl)-2-thienyl group on the nitrogen atom of the carbamoyl group, gave remarkable results at low application rates against four diseases. In addition, we observed that its corresponding phenyl derivative, namely, *N*-[2-(1,3-dimethylbutyl)phenyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-

Table 3. Fungicidal activity of various *N*-(2-alkyl-3-thienyl)-3-(trifluoromethyl)pyrazole-4-carboxamide derivatives





43

Compound No.	Carbon number	R	Fungicidal activity			
			Gray mold	Powdery mildew	Brown rust	Blast
33	2		1	N.T.	N.T.	N.T.
30	3		3	1	3	0
31	4		3	2	3	0
34	5		3	3	3	0
35	5		3	2	3	N.T.
36	5		3	0	2	0
1	6		3	3	3	3
37	6		3	2	3	1
38	6		3	3	3	2
39	7		2	2	3	0
40	7		1	2	3	1
41	7		0	3	3	0
42	7		2	3	3	3
43	6		3	3	3	3

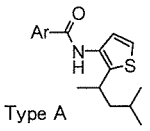
Disease (crop): Gray mold (Kidney Beans); Powdery mildew (Cucumber); Brown rust (Wheat); Blast (Rice). N.T.: not tested.

carboxamide (**43**), exhibited high activity.[31] As a result, 1, 3-dimethylbutyl group, was found to be the most potent alkyl group that can be positioned at the *ortho* position of the *N*-thienyl or *N*-phenyl group.

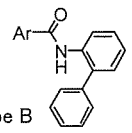
4. N-[2-(1,3-Dimethylbutyl)-3-thienyl] het/aryl carboxamides

Because compound **1**, which had a 2-(1,3-dimethylbutyl)-2-thienyl group on the nitrogen atom of the carbamoyl group, showed excellent fungicidal activity, we synthesized various *N*-[2-(1,3-dimethylbutyl)-3-thienyl] het/aryl carboxamides

Table 4. Fungicidal activity of *N*-[2- (1,3-dimethylbutyl)-3-thienyl]het/aryl carboxamide derivatives (Type A) and corresponding *N*-(biphenyl-2-yl) het/aryl carboxamide derivatives (Type B)



Type A



Type B

Compound No.	R	Type	Fungicidal activity			
			Gray mold	Powdery mildew	Brown rust	Blast
1		A	3	3	3	3
15		B	3	2	1	0
44		A	3	3	3	3
—		B	—	—	—	—
45		A	3	1	3	2
16		B	2	0	N.T.	0
46		A	3	2	3	2
17		B	0	0	0	0
47		A	3	3	3	N.T.
18		B	3	2	N.T.	1
48		A	3	3	3	3
19		B	3	2	0	1
49		A	3	2	3	3
20		B	2	1	N.T.	0
50		A	3	3	3	3
22		B	3	1	0	0
51		A	3	3	3	3
23		B	3	0	1	1
52		A	2	3	N.T.	N.T.
14		B	2	0	N.T.	0
53		A	3	0	3	1
24		B	3	1	0	0
54		A	1	2	3	0
25		B	3	0	N.T.	0
55		A	3	2	3	3
26		B	2	3	2	0
56		A	3	1	3	1
2		B	3	2	0	0

Disease (crop): Gray mold (Kidney Beans); Powdery mildew (Cucumber); Brown rust (Wheat); Blast (Rice). N.T.: not tested.

and evaluated their effect.

The fungicidal activity of *N*-[2-(1,3-dimethylbutyl)-3-thieyl] het/aryl carboxamides (Type A) and *N*-(biphenyl-2-yl) het/aryl carboxamides (Type B) having corresponding het/aryl carboxylic moieties is listed in Table 4.

Type A compounds showed equal or higher activity against gray mold than Type B compounds except for **54**. In addition, all Type A compounds exhibited fungicidal activity against wheat brown rust, whereas Type B compounds exhibited low or no activity. This indicates that the 2-(1,3-dimethylbutyl)-3-thienyl group contributed to fungicidal activity against wheat brown rust. In addition, it was found that five-membered heterocyclic Type A compounds (**1**, **44**–**51**) exhibited higher activity against powdery mildew and rice blast than the corresponding Type B compounds. Further, among six-membered heterocyclic Type A compounds (**52**–**56**), it was found that the pyridine compound (**52**) and pyrane compound (**55**) exhibited high fungicidal activity against powdery mildew and rice blast, respectively.

These results indicates that the introduction of the 2-(1,3-dimethylbutyl)-3-thienyl group to the nitrogen atom on the carbamoyl group not only enhanced fungicidal activity but also broadened the fungicidal spectrum.

Above all, the pyrazole derivatives (**1**, **44**) and thiazole derivative (**48**), which have a CHF_2 or CF_3 group, were the most superior in terms of fungicidal activity and spectrum. In addition, a methyl-substituted thiophene derivative (**50**) and furan derivative (**51**) also exhibited high activity against various diseases.

In view of its residual efficacy in pot tests and phytotoxicity (data not shown), we finally selected compound **1** as the developed compound.

In conclusion, based on BC-723 (**3**) as the lead compound, we synthesized various het/aryl carboxamides and evaluated their fungicidal activity. As a result of the structure-activity relationships, it is considered to be essential for a compound exhibiting activity against various diseases to have both a bulky and hydrophobic alkyl group at the *ortho* position of the *N*-aromatic ring and an *ortho*-substituted het/aryl carboxamide moiety that is the common active structure with Basidiomycetes.[34] Among these compounds, *N*-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide (**1**) showed excellent activity against gray mold, powdery mildew, wheat brown rust and rice blast. Compound **1** was applicable in field tests, and was launched as penthiopyrad in Japan in 2008.

Supplemental Tables S1 and S2 are available in the online publication at http://www.jstage.jst.go.jp/browse/jpestics/.

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英文編掲載報文・短報等の要旨

報　文

カルボキシン関連カルボキサミド系殺菌剤の構造活性相関

吉川幸宏，勝田裕之，貴志淳郎，柳瀬勇次

種々のカルボキサミド化合物を合成し、その構造と殺菌活性の関係を調べた．殺菌活性と殺菌スペクトラムは，アミドの芳香環と窒素原子上の置換基に依存していた．それらの中で，*N*-(ビフェニル-2-イル)-2-クロロピリジン-3-カルボキサミドが灰色かび病に対し高い活性を示し，対応する 1-メチル-3-トリフルオロメチル-ピラゾール-4-カルボキサミドがより高い活性を示した．さらに，*N*-フェニル基上のオルト位に疎水性の分岐アルキルをもつ化合物が，高活性で広い殺菌スペクトラムをもつことがわかった．*N*-フェニル基のベンゼン環は，チオフェン環で代替でき，チオフェン環のアルキル基を最適化することで，種々の病害に対し高い効果を示すペンチオピラド（化合物 **1**，*N*-[(2-(1,3-ジメチルブチル)-3-チエニル)]-1-メチル-3-(トリフルオロメチル)ピラゾール-4-カルボキサミド）を見出した．