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Original Article

Structure-Activity Relationships of *N*-(1,1,3-Trimethylindan-4-yl)carboxamide Fungicides

Masatsugu ODA, Toshiro SAKAKI, Naoko SASAKI, Nobuyuki NONAKA, Kenji YAMAGISHI and Hirofumi TOMITA

Research Center, Mitsubishi Kasei Corporation, Midori-ku, Yokohama 227, Japan

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A number of *N*-(1,1,3-trimethylindan-4-yl)aryl- or heteroaryl-carboxamides were synthesized and their structure-activity relationships studied. A series of compounds showed potent fungicidal activity against grey mold caused by *Botrytis cinerea*, in addition to rice sheath blight caused by *Rhizoctonia solani*. Pyridine-3-carboxamides substituted by Cl, Br, CH_3 or CF_3 at 2-position exhibited high activity against both diseases. Monosubstituted pyrazine-3-carboxamides, furan-3-carboxamides, pyrazole-4-carboxamides and thiazole-5-carboxamides gave as high activity against both diseases in pot tests and SDC of *Botrytis cinerea* in an enzyme test as the 2-substituted pyridine-3-carboxamides. 2,5-Dimethylfuran-3-carboxamide gave activity against both diseases and SDC as high as 2-methylfuran-3-carboxamide, whereas the activities of 2,4-dimethyl and 2,4,5-trimethylfuran derivatives were extremely low against grey mold in a pot test. Pyrazole-4-carboxamides and thiazole-5-carboxamides showed the same substituent effects as the furan derivatives. Among the compounds of this series, 4-methylthiazole-5-carboxamide (BC340) and 2-chloropyridine-3-carboxamide (BC723) were most potent against both diseases.

INTRODUCTION

Structure-activity relationships of *N*-(substituted-aryl)-2-chloropyridine-3-carboxamides on the fungicidal activity against grey mold caused by *Botrytis cinerea* and rice sheath blight caused by *Rhizoctonia solani* have been reported in our previous papers.[1,2] The studies indicated that alkyl substituents at a position *ortho* to the amino group and molecular hydrophobicity were important factors determining antifungal activity against grey mold, and that the presence of alkyl groups at *meta*-position and the molecular size were significantly influential towards antifungal activity against rice sheath blight. Among the compounds of the series, *N*-(1,1,3-trimethylindan-4-yl)-2-chloropyridine-3-carboxamide (BC723) demonstrated the most potent activity against both diseases. In order to study effects of the carboxylic acid moiety of the compounds on the fungicidal activity, we synthesized various *N*-(1,1,3-trimethylindan-4-yl)aryl- or heteroaryl-carboxamides and evaluated their activities both in pot tests (against grey mold and rice sheath blight) and in enzyme tests (against the mitochondrial succinate dehydrogenase complex, SDC, of *Botrytis cinerea*). This paper reports on the structure-activity relationships of *N*-(1,1,3-trimethylindan-4-yl)aryl- or heteroaryl-carboxamides as fungicides in pot tests against grey mold and rice sheath blight and as inhibitors of the SDC of *Botrytis cinerea*.

MATERIALS AND METHODS

1. *Synthesis of Compounds*

Compounds were prepared by reacting aryl- or heteroaryl-carbonyl chloride (2) with 1,1,3-trimethylindan-4-amine (3)[1] in the presence of a base as shown in Fig. 1. Aryl- or heteroaryl-

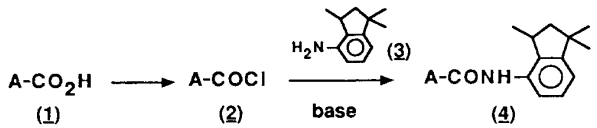


Fig. 1 Synthetic route of *N*-(1,1,3-trimethylindan-4-yl)carboxamide derivatives.

carbonyl chlorides (2) were given by reacting corresponding acids with thionyl chloride. Various acid derivatives (1) were either obtained commercially or synthesized by known methods as follows: 3-Chloro or methylpyridine-2-carboxylic acid was prepared by hydrolysis of corresponding nitril derivatives which had been synthesized from 3-chloro or methylpyridine by known methods.[3,4] 2-Chloropyrazine-3-carboxylic acid was prepared from commercially available 2-aminopyrazine-3-carboxylic acid *via* Sandmeyer reaction.[5,6] 2-Methyl-5, 6-dihydro-1,4-oxathiine-3-carboxylic acid, furan-3-carboxylic acids, pyrazole-4-carboxylic acids, 5-methylisoxazole-4-carboxylic acid, 4-methyl-1,2,3-thiadiazole-5-carboxylic acid, thiazole-5-carboxylic acids and 3-methylisothiazole-4-carboxylic acid were prepared by hydrolysis of corresponding esters which had been synthesized according to the methods described in literature.[7-14] The structures of the compounds were confirmed by IR and ^{1}H NMR spectra. Melting points were measured with a Yanagimoto micromelting point apparatus and uncorrected. Refractive indexes were measured with an Atago Abbe-refractometer IT. The following is an example of typical procedures.

N-(1,1,3-Trimethylindan-4-yl)-4-methylthiazole-5-carboxamide (**29**, *BC340*)

To a solution of 1,1,3-trimethylindan-4-amine (10 g, 57.1 mmol) and triethylamine (6.6 g, 65.3 mmol) in ethyl acetate (50 ml) was added 4-methylthiazole-5-carbonyl chloride (9.3 g, 57.5 mmol) under ice cooling and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with water and brine, and concentrated *in vacuo*. The residue was recrystallized from *n*-hexane and ethyl acetate to yield a white crystalline product (**29**, BC340) (14.6 g, 85.1% yield); mp 104–105°C, Anal. Calcd. for $C_{17}H_{20}N_2OS$: C, 67.97; H, 6.71; N, 9.32%, Found: C, 67.63; H, 6.77; N, 9.26%, ^{1}H NMR ($CDCl_3$) δ ppm: 1.24 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.36 (3H, d, J=6.9 Hz, CH_3), 1.68 (1H, dd, J=14.6 and 5.4 Hz,–CH(H)–), 2.25 (1H, dd, J=14.6 and 8.7 Hz,–CH(H)–), 2.82 (3H, s, CH_3), 3.37 (1H, m, –CH(CH_3)–), 7.00 (1H, d, J=7.8 Hz, Ar-H), 7.26 (1H, t, J=7.8 Hz, Ar-H), 7.41 (1H, bs, NH), 7.74 (1H, d, J=7.8 Hz, Ar-H), 8.76 (1H, s, thiazole-H), IR ν_{max}^{KBr} cm^{-1}: 1660 (CO).

2. Biological Tests and Physicochemical Property (log k')

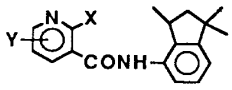
We determined not only preventive activities against grey mold on cucumber and sheath blight on rice in pot tests, but also inhibitory activities against the mitochondrial succinate dehydrogenase complex (SDC; mitochondrial complex II) of *Botrytis cinerea*. All methods used in biological tests have been reported in our previous paper.[1] From the relationships between the protective values and the concentrations in the pot tests, molar EC_{90} (90% prevention) or molar EC_{50} (50% prevention) values were determined. From the relationships between the inhibition values and the inhibitor concentrations in the enzyme tests, molar I_{50} (50% inhibition) values were determined. The results are listed in Tables 1–3, expressed as pEC_{90} (=log $1/EC_{90}$), pEC_{50} (=log $1/EC_{50}$) and pI_{50}(=log $1/I_{50}$), respectively.

The log k' values of compounds were used as the index of hydrophobicity in the study of structure-activity relationships. The capacity factor k' was evaluated from retention time by reversed-phase HPLC. All methods for evaluation of log k' values have been reported in our previous paper.[2] The values are listed in Tables 2 and 3 along with biological activities of the compounds.

RESULTS AND DISCUSSION

Various *N*-(1,1,3-trimethylindan-4-yl)-2-substituted-pyridine-3-carboxamides and their fungicidal activities are summarized in Table 1. Pyridine-3-carboxamides substituted by Br, CH_3 or CF_3 at 2-position (**4**–**6**) showed activity as high as 2-chloropyridine-3-carboxamide (**3**, BC723) against both grey mold and rice sheath blight. 2-Fluoropyridine derivative

Table 1 *N*-(1,1,3-Trimethylindan-4-yl)pyridine-3-carboxamides and their biological activities.



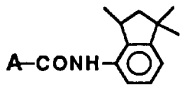
No.	X	Y	mp (°C) or n_D^{25}	Activity against grey mold of *Botrytis cinerea*		Activity against rice sheath blight
				pEC_{90}[a]	pI_{50}[b]	pEC_{50}[c]
1	H	H	136–138	<2.20	5.37	<2.20
2	F	H	1.5685	<2.20	6.00	3.11
3	Cl	H	133–134	4.70	7.39	5.11
4	Br	H	134–135	4.60	7.42	4.44
5	CH_3	H	123.5–124.5	4.40	7.29	4.30
6	CF_3	H	174–175	4.69	7.85	4.68
7	CN	H	144.5–147	3.18	6.12	3.18
8	OH	H	218.5–220	<2.20	—[d]	<2.20
9	OCH_3	H	108–109	<2.20	6.70	2.61
10	$OCHF_2$	H	114.5–115.5	<2.20	6.10	<2.20
11	OCH_2CF_3	H	127–128	<2.20	—[d]	<2.20
12	SH	H	222–224	<2.20	—[d]	<2.20
13	SCH_3	H	134–136	3.00	—[d]	<2.20
14	Cl	6-CH_3	146–147	<2.20	5.38	3.07

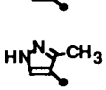
[a] Preventive activity against grey mold in pot tests.
[b] Inhibitory activity against SDC of *Botrytis cinerea* in enzyme tests.
[c] Preventive activity against rice sheath blight in pot tests.
[d] Not tested.

(**2**) were 25-fold less active against the SDC of *Botrytis cinerea* in an enzyme test, inactive against grey mold in a pot test and 100-fold less active against rice sheath blight than the other halide derivatives (**3** and **4**). Pyridine-3-carboxamide derivatives unsubstituted or substituted by CN, OH, OCH_3, $OCHF_2$, SH or SCH_3 (**7**–**13**) were low in activity against both diseases and against the SDC. 2-Chloro-6-methylpyridine-3-carboxamide (**14**), a disubstituted compound, was 100-fold less active against the SDC in an enzyme test and over 100-fold less active against grey mold and rice sheath blight in pot tests than monosubstituted compounds **3**. These effects of substituents in the pyridine ring of *N*-(1,1,3-trimethylindan-4-yl)-pyridine-3-carboxamides on the activity against both diseases were almost the same as those of substituted-phenylcarboxanilides on the activity against rice sheath blight.[15,16]

We then examined biological activities of miscellaneous aryl- or heteroaryl-carboxamides which had been substituted by Cl, CF_3 or alkyl groups at a position *ortho* to the carboxamide group. The results along with the log *k'* of the compounds are summarized in Table 2. 2-Methylfuran-3-carboxamide and 2-methyl-4,5-dihydrofuran-3-carboxamide (**22** and **24**) showed activity as high as 2-chloropyridine-3-carboxamide (**3**, BC723) against both grey mold and rice sheath blight. 2-Ethylfuran derivative (**23**) were 3-, 70- and 10-fold less active respectively against the SDC in an enzyme test, grey mold and rice sheath blight in pot tests than the corresponding 2-methylfuran derivative (**22**). 3-Methylfuran-2-carboxamide (**25**), a geometrical isomer of 2-methylfuran-3-carboxamide (**22**), showed almost 100-fold less activity against grey mold in both pot and enzyme tests and 6-fold less activity against rice sheath blight than compound **22**. In the same way, both 3-chloro and methylpyridine-2-carboxamide (**15** and **16**) exhibited significantly lower activity against both diseases than the corresponding pyridine-3-carboxamides (**3** and **5**). Such drastic varia-

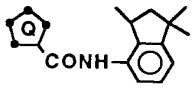
Table 2 *N*-(1,1,3-Trimethylindan-4-yl)aryl- or heteroaryl-carboxamides and their biological activities and physicochemical properties.

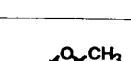
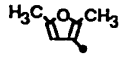
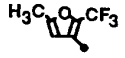
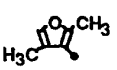
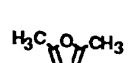
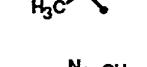
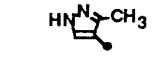
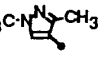
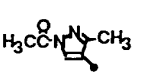
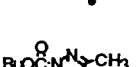
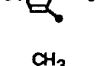
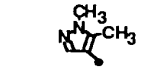
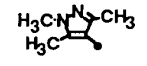
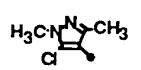
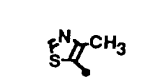


No.	A	mp (°C) or n_D^{25}	log k'[a]	Activity against grey mold or *Botrytis cinerea*		Activity against rice sheath blight
				pEC_{90}[b]	pI_{50}[c]	pEC_{50}[d]
3		133–134	0.181	4.70	7.39	5.11
15		92.5–93.5	0.503	3.35	6.55	4.20
16		1.5805	0.480	<2.20	5.89	3.42
17		124–125	0.319	5.05	8.24	4.10
18		1.5890	0.503	3.90	8.20	5.07
19		145–147	0.227	2.70	5.15	4.20
20		127–128	0.434	<2.20	7.26	5.02
21		159–160	0.457	2.53	7.87	4.91
22		144–145	0.342	4.75	8.09	4 61
23		123–124	0.480	2.90	7.60	3.68
24		103–106	0.319	4.45	7.57	4.15
25		84–86	0.457	2.80	6.40	3.85
26		163–165	0.250	<2.20	5.15	2.63
27		93.5–96	0.227	<2.20	—[e]	3.20
28		76–78	0.227	<2.20	—[e]	<2.20
29		104–105	0.250	4.86	7.97	5.22
30		149–150	0.273	4.16	6.85	4.32
31		98–101	0.135	3.90	7.38	3.97

[a] Capacity factor in HPLC.
[b] Preventive activity against grey mold in pot tests.
[c] Inhibitory activity against SDC of *Botrytis cinerea* in enzyme tests.
[d] Preventive activity against rice sheath blight in pot tests.
[e] Not tested.

Table 3 *N*-(1,1,3-Trimethylindan-4-yl)substituted-furan, pyrazole of thiazolecarboxamides and their biological activities and physicochemical properties.



No.	Q	mp (°C)	log k'[a]	Activity against grey mold or *Botrytis cinerea*		Activity against rice sheath blight
				pEC_{90}[b]	pI_{50}[c]	pEC_{50}[d]
22		144–145	0.342	4.75	8.09	4.61
32		103–104	0.480	4.66	8.15	4.39
33		149–150	0.526	<2.20	7.96	4.59
34		105.5–107	0.411	2.70	8.00	4.34
35		148–149	0.526	<2.20	7.48	4.49
31		98–101	0.135	3.90	7.38	3.97
36		159–161	0.181	4.24	7.34	5.24
37		130–131	0.388	3.81	5.72	3.91
38		115–116	0.618	4.18	5.92	3.98
39		163–165	0.158	2.76	6.65	3.36
40		176.5–178	0.273	<2.20	7.02	5.45
41		132.5–134	0.319	<2.20	6.95	5.21
29		104–105	0.250	4.86	7.97	5.22
42		117–118	0.342	4.35	7.57	5.02
43		258–259	0.158	3.69	7.28	4.58
44		187–188	0.250	3.42	5.89	3.81
45		145–147	0.365	2.86	7.45	4.72

[a] Capacity factor in HPLC.
[b] Preventive activity against grey mold in pot tests.
[c] Inhibitory activity against SDC of *Botrytis cinerea* in enzyme tests.
[d] Preventive activity against rice sheath blight in pot tests.

tions in the activities among the geometrical isomers suggested that the heteroatom in the ring played an important role in the antifungal activities. Phenylcarboxamides (**20** and **21**), derivatives having no heteroatoms in the ring, showed almost the same levels of fungicidal activities against rice sheath blight and inhibitory activity against the SDC of *Botrytis cinerea* as the corresponding pyridine-3-carboxamides (**3** and **6**), whereas their activity against grey mold in a pot test was extremely low. One of the reasons may have been the systemicity of compounds **20** and **21**, because their hydrophobic levels (log k') were relatively high compared with compounds **3**, **17**, **22**, **24** and **29** which were highly active against grey mold as shown in Table 2. 5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxamide (**18**) gave relatively high activity against rice sheath blight and the SDC of *Botrytis cinerea*, whereas the activity against grey mold in a pot test was six times lower than compounds **3**. One of the reasons may have been due to the metabolism of the compound on or in plants or fungi to give a dioxide analogue (**19**), which was low in the activity against grey mold in both pot and enzyme tests. 2-Chloropyrazine-3-carboxamide, 4-methylthiazole-5-carboxamide, 3-methylisothiazole-4-carboxamide and 3-methylpyrazole-4-carboxamide derivatives (**17** and **29**–**31**) were highly active against both diseases in pot tests and the SDC in an enzyme test. Especially a 4-methylthiazole derivative (**29**, BC340) exhibited the same or higher level of activity than a 2-chloropyridine-3-carboxamide derivative (**3**, BC723). On the other hand, 4-methyloxazole-5-carboxamide (**27**), 5-methylisoxazole-4-carboxamide (**26**) and 4-methylthidiazole-5-carboxamide (**28**) were not so active against both diseases. This again suggested that the heteroatom in the ring played some role in the fungicidal activity.

We then examined substituent effects of furan-3-carboxamides, pyrazole-4-carboxamides and thiazole-4-carboxamides which had shown relatively high activity against both diseases among the series of miscellaneous heteroaryl carboxamide compounds. Activities and log k' values of the compounds are given in Table 3. For the following discussion, we commonly numbered the positions of 5-membered-heteroaryl as shown in Fig. 2. 2,4-Dimethyl derivatives of furan-, pyrazole- and thiazole-carboxamides (**32**, **36** and **42**) exhibited as high activity against both diseases in pot tests and SDC in an enzyme test as the corresponding monomethyl derivatives (**22**, **31** and **29**). Thiazole derivatives substituted by amino or mercapto group at 4-positon (**43** or **44**) were relatively low in the activity against both diseases. 2,5-Dimethyl derivative of furancarboxamide (**34**) and 2,4,5-trisubstituted derivatives of furan and pyrazolecarboxamides (**35**, **40** and **41**) were as highly active against rice sheath blight and the SDC of *Botrytis cinerea* as the corresponding 2-methyl derivatives (**22** and **31**), whereas they were extremely inactive against grey mold in a pot test. Furan and thiazole derivatives substituted by CF_3 group at 2-position (**33** and **45**) showed almost the same tendency towards the activities as above. This suggested that both substituents at 5-position and the CF_3 group at 2-position were unfavorable for controlling the fungicidal activity against grey mold in the pot test. The substituent effects may have been due to other factors than the systemicity of compounds because the 2,4-disubstituted (**32** and **36**) and the 2,5- or 2,4,5-substituted derivatives (**34**, **35**, **40** and **41**) and also the 2,4-dimethyl (**32** and **42**) and the 2-CF_3 derivatives (**33** and **45**) had almost the same levels of log k'. The 2,3-dimethyl derivative of pyrazolecarboxamide (**39**) was low in activity against both diseases. Pyrazoles acylated at 4-position (**37** and **38**) showed almost the same levels of fungicidal activity against grey mold and rice sheath blight in pot tests as a deacylated compound (**31**), notwithstanding relatively low activity against the SDC of *Botrytis cinerea* in an enzyme test. This may have been due to the metabolism of the compounds (**37** and **38**) to give a deacylated compound (**31**). Our SAR studies on various 5-membered-heteroarylcarboxamides suggested that 2-methyl or 2,4-

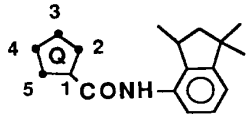


Fig. 2 Numbering of the positions of 5-membered-heteroaryl carboxamides.

dimethyl derivatives had potent fungicidal activity against both diseases as well as the SDC, and that substitution at 5-position was unfavorable towards the activity against grey mold in a pot test. Among the compounds of the series, *N*-(1,1,3-trimethylindan-4-yl)-4-methylthiazole-5-carboxamide (**29**, BC340) and *N*-(1, 1, 3-trimethylindan-4-yl)-2-chloropyridine-3-carboxamide (**3**, BC723) had the most potent activity against both diseases.

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要　　約

N-(1,1,3-トリメチルインダン-4-イル)カルボン酸アミド系殺菌剤の構造活性相関

織田雅次，榊　敏朗，佐々木直子
野仲信行，山岸兼治，富田啓文

N-(1,1,3-トリメチルインダン-4-イル)アリールまたはヘテロアリールカルボン酸アミド誘導体を合成し，その構造活性相関を検討した．本系統には，紋枯病(*Rhizoctonia solani*)のみならず灰色かび病(*Botrytis cinerea*)に対しても高い活性が見られた．2位にCl, Br, CH_3 または CF_3 で置換されたピリジン-3-カルボン酸アミド誘導体は，両病害に対して高い活性を示した．ピラジン-3-カルボン酸アミド，フラン-3-カルボン酸アミド，ピラゾール-4-カルボン酸アミドおよびチアゾール-5-カルボン酸アミド誘導体も，2-置換ピリジン誘導体と同様に高いSDC酵素阻害活性を示し，両病害に対するポット試験でも高い活性を示した．2,5-ジメチルフラン-3-カルボン酸アミドは2-メチルフラン誘導体と同様にSDC酵素阻害に対しても両病害に対しても高い活性を示したが，2,4-ジメチルおよび2,4,5-トリメチル誘導体は灰色かび病に対するポット試験できわめて低い活性しか示さなかった．ピラゾール-4-カルボン酸アミドおよびチアゾール-5-カルボン酸アミド誘導体もフラン誘導体と同様の置換基効果を示した．これらの化合物の中で2-クロロピリジン-3-カルボン酸アミド(BC723)に加えて4-メチルチアゾール-5-カルボン酸アミド(BC340)が，いずれの病害に対しても最も良好な活性を示すことが見出された．