J. Pesticide Sci. **13**, 49–55 (1988)

Original Article

Relationship between Antifungal Activities in Greenhouse and *in Vitro* of 1-[1-(Substituted phenyl)vinyl]imidazoles and 1-[2-(Substituted phenyl)allyl]imidazoles

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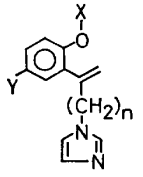
(Received July 8, 1987)

Protective and curative antifungal activities of 16 1-[1-(2-substituted hydroxy-5-substituted phenyl)vinyl]imidazoles and 9 1-[2-(2-substituted hydroxy-5-substituted phenyl)-allyl]imidazoles were measured against *Botrytis cinerea*, a phytopathogenic fungus, under greenhouse conditions. A relationship between their antifungal activity in greenhouse conditions and that *in vitro* was examined quantitatively based on the regression analysis with the aid of physicochemical and structural parameters. The higher the *in vitro* activity, the higher the protective activity in greenhouse conditions. The protective activity was more persistent in the vinylimidazoles than in the corresponding allylimidazoles. The curative activity in greenhouse conditions increased as the activity *in vitro* increased. Substitution of the 2,6-dichlorobenzyloxy group at the 2-position on the benzene ring was favorable to the curative activity. The curative activity does not seem to depend on the hydrophobicity of the molecule, because the positive effect of the log *P* term on the *in vitro* activity and the negative effect on the mobility within the leaf cancel each other.

INTRODUCTION

Recently we have synthesized series of 1-[1-(2-substituted hydroxy-5-substituted phenyl)-vinyl]imidazoles (**I**)[1-3] and 1-[2-(2-substituted hydroxy-5-substituted phenyl)allyl]imidazoles (**II**)[4] which have antifungal activity against *B. cinerea in vitro*. Quantitative structure-activity relationships showed that molecular hydrophobicity as well as certain submolecular steric and structural factors is important in determining variations in the antifungal potency.[4,5] More recently, we have measured their protective and curative antifungal activities against *B. cinerea* under greenhouse conditions. This paper reports the relationships between the antifungal activities of vinylimidazoles **I** and allylimidazoles **II** in greenhouse and *in vitro* conditions with the aid of physicochemical and structural parameters and regression analysis.[6]



I: n=0
II: n=1

MATERIALS AND METHODS

1. *Compounds*

Vinylimidazoles **I** and allylimidazoles **II** used in the present test are listed in Table 1. Compound **3** was newly synthesized using the same method as described in our previous paper.[5]

Table 1 Antifungal activity *in vitro* against *B. cinerea* and physicochemical parameters of vinylimidazoles **I** and allylimidazoles **II** used in the regression analyses.

No.	Compound X[a]	Y	*n*	mp (°C)	Molecular formula	pI_{50}[b]	log *P*[b]	I_{A11}[c]	I_{DC1}[c]
1	$CH_3(CH_2)_2$	CH_3	0	[d]	$C_{15}H_{18}N_2O\cdot(CO_2H)_2$	4.76	3.94	0.0	0.0
2	$CH_3(CH_2)_3$	H	0	[d]	$C_{15}H_{18}N_2O$	5.32	3.82	0.0	0.0
3	$CH_3(CH_2)_4$	Cl	0	129.5–130	$C_{16}H_{19}ClN_2O\cdot(CO_2H)_2$	6.05	5.20	0.0	0.0
4	Bz	Cl	0	[e]	$C_{18}H_{15}ClN_2O\cdot HCl\cdot 1/10H_2O$	5.50	4.85	0.0	0.0
5	2-Cl-Bz	H	0	[d]	$C_{18}H_{15}ClN_2O$	5.81	4.71	0.0	0.0
6	3-Cl-Bz	H	0	[f]	$C_{18}H_{15}ClN_2O\cdot HCl$	5.31	4.71	0.0	0.0
7	4-Cl-Bz	H	0	[d]	$C_{18}H_{15}N_2O\cdot HCl$	5.45	4.71	0.0	0.0
8	2,4-Cl_2-Bz	H	0	[d]	$C_{18}H_{14}Cl_2N_2O$	6.58	5.42	0.0	0.0
9	2,4-Cl_2-Bz	CH_3	0	[d]	$C_{19}H_{16}Cl_2N_2O$	6.02	6.07	0.0	0.0
10	2,4-Cl_2-Bz	F	0	[d]	$C_{18}H_{13}Cl_2FN_2O$	6.52	5.71	0.0	0.0
11	2,4-Cl_2-Bz	Cl	0	[d]	$C_{18}H_{13}Cl_3N_2O$	6.32	6.28	0.0	0.0
12	2,6-Cl_2-Bz	H	0	[d]	$C_{18}H_{14}Cl_2N_2O$	6.39	5.52	0.0	1.0
13	2,6-Cl_2-Bz	CH_3	0	[d]	$C_{19}H_{16}Cl_2N_2O$	6.25	6.07	0.0	1.0
14	2,6-Cl_2-Bz	F	0	[d]	$C_{18}H_{13}Cl_2N_2O$	6.79	5.71	0.0	1.0
15	3,4-Cl_2-Bz	H	0	[e]	$C_{18}H_{14}Cl_2N_2O\cdot HCl$	5.74	5.42	0.0	0.0
16	2-Cl-Thi	H	0	[e]	$C_{16}H_{13}ClN_2OS\cdot HCl$	5.76	4.44	0.0	0.0
17	$CH_3(CH_2)_3$	H	1	[g]	$C_{16}H_{20}N_2O$	5.26	3.84	1.0	0.0
18	$CH_3(CH_2)_7$	H	1	[g]	$C_{20}H_{28}N_2O\cdot(CO_2H)_2$	6.60	5.95	1.0	0.0
19	4-C_6H_5-Bz	H	1	[g]	$C_{25}H_{22}N_2O$	7.26	5.90	1.0	0.0
20	2,4-Cl_2-Bz	H	1	[g]	$C_{19}H_{16}Cl_2N_2O$	7.14	5.44	1.0	0.0
21	2,4-Cl_2-Bz	CH_3	1	[g]	$C_{20}H_{18}Cl_2N_2O\cdot(CO_2H)_2$	6.86	6.09	1.0	0.0
22	2,4-Cl_2-Bz	F	1	[g]	$C_{19}H_{15}Cl_2FN_2O\cdot(CO_2H)_2$	7.19	5.73	1.0	0.0
23	2,6-Cl_2-Bz	F	1	[g]	$C_{19}H_{15}Cl_2FN_2O\cdot(CO_2H)_2$	6.72	5.73	1.0	1.0
24	$C_6H_5(CH_2)_2$	H	1	[g]	$C_{20}H_{20}N_2O\cdot(CO_2H)_2$	5.63	4.35	1.0	0.0
25	$C_6H_5O(CH_2)_2$	H	1	[g]	$C_{20}H_{20}N_2O_2\cdot(CO_2H)_2$	5.54	3.93	1.0	0.0

[a] Symbols Bz and Thi indicate benzyl and thiophen-3-yl groups, respectively.
[b] Compounds **1**, **2** and **4**–**16** are reported in Ref. 5) and compounds **17**–**25** in Ref. 4).
[c] Indicator variables; see text.
[d] Reported in Ref. 5).
[e] Reported in Ref. 2).
[f] Reported in Ref. 1).
[g] Reported in Ref. 4).

The others were the same samples as used in the previous tests.[1,2,4,5]

2. *Biological Tests*

2.1 *Antifungal activity in vitro*

An I_{50} value (molar concentration for 50% inhibition of mycelial growth) of a compound against *B. cinerea* was determined by the agar medium dilution method after 2 days of incubation at 20°C. The activity of the present test compounds, except **3**, was previously reported.[4,5]

2.2 *Protective and curative activities*

Cucumber plant and application of compound: Water-soaked seeds of cucumber (cv., Tsukuba shiroibo) were grown in plastic pots (350 ml in volume) filled with sandy loam soil containing some fertilizers. The pots were kept in a greenhouse. Seedlings in the second-leaf stage were used for the assessment of biological activity. A 50 mg/ml dimethylformamide solution of each compound was diluted with distilled water containing a 20 ppm surfactant to give a concentration of 500 μg/ml. The solution was subsequently diluted (four fold) with distilled water to reach the final concentrations of 500–0.5 μg/ml. Then the water suspension of each compound was

sprayed on the cucumber seedlings, 24 hr before inoculation for the evaluation of protective activity and 24 hr after inoculation for the evaluation of curative activity.

Inoculation of fungus: *B. cinerea* was grown on a potato-sucrose-agar (PSA) medium for 2 days at 20°C to form colonies. Agar disks 4 mm in diameter, including hyphal tips, were cut off at the peripheral regions of fresh colonies. Four disks were inoculated facedown on the leaf surface of a cucumber seedling. The seedlings were incubated for 3 days after the inoculation at 20°C in a humid chamber and the diameters of diseased areas around the four disks were measured and the values were averaged. Potency to inhibit the growth relative to an untreated seedling was expressed by the following equation as percentage inhibition value A.

$$A=\left(1-\frac{\text{The averaged diameter in a treated plot}}{\text{The averaged diameter in a control plot}}\right)\times 100$$

From relationships between the percentage (A) value and concentration in the protective and curative tests, molar EC_{90} (90% protection) and molar EC_{50} (50% cure) concentrations of each test compound were determined, respectively. The results are listed in Table 2, expressed as log $1/EC_{90}$ and log $1/EC_{50}$. The ranges of the experimental errors: EC_{90}; 1–16 %, average 7%: EC_{50}; 4–23%, average 11%.

2.3 Duration of protective activity

Protective activity was evaluated in the

Table 2 Antifungal activities of vinylimidazoles **I** and allylimidazoles **II** against *B. cinerea* in greenhouse conditions.

Compound No.	Protective activity: log $1/EC_{90}$			Curative activity: log $1/EC_{50}$		
	Obsd.	Calcd. by		Obsd.	Calcd. by	
		Eq. (3)	Eq. (4)		Eq. (5)	Eq. (6)
1	2.18	2.14	2.28	3.42	3.24	3.33
2	2.50	2.43	2.48	3.78	3.92	3.85
3	3.08	2.98	2.96	3.54	3.62	3.60
4	2.59	2.64	2.69	3.41	3.32	3.37
5	2.85	2.79	2.80	3.85	3.75	3.70
6	2.18	2.52	2.60	3.13	3.23	3.31
7	2.72	2.60	2.65	3.56	3.37	3.42
8	3.22	3.29	3.20	4.08	4.00	3.89
9	3.18	3.06	3.07	[b]	2.93	3.06
10	3.37	3.29	3.21	3.83	3.72	3.67
11	3.19	3.24	3.21	[b]	3.09	3.17
12	3.31	3.20	3.14	4.34	4.30	4.30
13	3.18	3.18	3.16	3.66	3.73	3.86
14	3.27	3.44	3.32	4.60	4.57	4.50
15	2.83	2.83	2.87	2.92	3.13	3.22
16	2.72	2.74	2.74	3.68	3.90	3.82
17[a]	2.53	2.40	2.28	3.92	3.84	3.79
18[a]	2.99	3.36	3.10	3.71	3.62	3.59
19[a]	3.04	3.71	3.35	3.86	4.34	4.14
20[a]	3.18	3.60	3.24	4.14	4.57	4.32
21[a]	3.13	3.51	3.22	3.96	3.78	3.71
22[a]	3.35	3.66	3.30	4.19	4.40	4.19
23[a]	3.38	3.40	3.12	4.50	4.48	4.44
24[a]	2.77	2.66	2.50	3.83	3.83	3.78
25[a]	2.15	2.56	2.40	3.84	4.06	3.96

[a] Not used in the derivation of Eq. (3) and Eq. (5).

[b] Not determined.

Table 3 Duration of the protective activity of vinylimidazoles **8** and **10**, and allylimidazoles **20** and **22** against *B. cinerea* (spore).

Compound No.	log $1/EC_{90}$		
	Inoculation X day(s) after application		
	$X=8$	$X=1$	Δ[a]
8	4.02	4.84	−0.82
10	4.73	5.13	−0.40
20	3.90	5.72	−1.82
22	4.11	5.65	−1.54

[a] Δ = (log $1/EC_{90}$, 8 days) − (log $1/EC_{90}$, 1 day).

same manner as described above using a spore as an inoculum. Cucumber seedlings were kept in the greenhouse for 1 or 8 days after the application of a compound suspension. The applied seedlings were inoculated with four droplets (10 μl each) of conidia suspension (1×10^5 spores/ml) per leaf. Duration of protective activity was determined by comparing the EC_{90} value of a spore inoculated 8 days after the application with that of a spore inoculated 1 day after the application. The results are listed in Table 3.

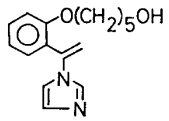
3. Partition Coefficient

A log P (1-octanol/H_2O) value was used to represent molecular hydrophobicity. Log P values of the compounds except compound **3** were reported previously.[4,5] They were estimated by using the CLOGP3 (Ver. 3.3)[7-9] program on a Vax 11/780 computer.

The CLOGP3 program is to calculate a log P value of a compound by summing up the component value (f) assignable to each substructure.[8] Since the f value of 1-N atom of the vinylimidazole ring is not available, an estimated log P value does not represent that of the whole molecule. Since the 1-N atom is common in all vinylimidazoles **I**, the difference between the observed and estimated log P values of compounds **26** and **27** were averaged and −0.52 was taken as the f value of the 1-N.[5] The log P value used in the regression analysis was corrected by the factor as shown in Eq. (1).

$$\log P=\log P_{calcd.}-0.52 \qquad (1)$$

Although compounds were used in free-base form or acid-addition-salt form, hydrophobicity of the free-base was regarded as that of the corresponding salt. The antifungal activity was not affected by adding acid, as described below.



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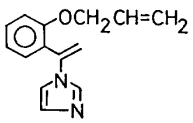

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4. Relationships between Activities in Greenhouse and in Vitro Conditions

Relationships were analyzed on the basis of Eq. (2).[6]

$$\log 1/BA=a\mathrm{pI}_{50}+b(\log P)^2+d\log P+eI_{All}+fI_{DCl}+c \qquad (2)$$

In Eq. (2), BA is biological activity in greenhouse conditions, EC_{90} or EC_{50}, a, b ($\leqq0$), d, e and f are susceptibility constants, and c an intercept. I_{All} and I_{DCl} are indicator variables. The I_{All} takes a value of 1 for allylimidazoles **II** and the I_{DCl} takes a value of 1 for derivatives having two chlorine atoms at the 2- and 6-positions on the benzene ring of the benzyl substituent at the X position. Relevant physicochemical parameters and indicator variables are listed in Table 1. The level of significance of each term was evaluated by F and the student's t tests.

RESULTS AND DISCUSSION

1. Effect of Acid of Acid-addition Salts on Protective and Curative Activities

Our previous reports[4,5] showed that antifungal activities *in vitro* were not influenced by a form of the molecule, a free-base or acid-

Table 4 Protective and curative activities of acid-addition salts of compound **8**[a] against *B. cinerea*.

Acid	log $1/EC_{90}$	log $1/EC_{50}$
HNO_3	3.34	3.66
$(CO_2H)_2$	3.38	3.76
HCl	3.41	3.58
8 (free base)	3.53	3.36

[a] Compounds formulated as 50% wettable powder were used for biological tests.

addition salts. We, therefore, prepared several acid-addition salts of compound **8** as a representative, and determined their protective and curative activities against *B. cinerea*. As shown in Table 4, the antifungal activities of the salts were almost identical with those of free-base **8**, suggesting that the protective and curative activities are not influenced by the counter anions which form the salts.

2. *Relationships between Protective Activity in Greenhouse Conditions and Antifungal Activity in Vitro*

First, we examined the protective activity data on vinylimidazoles **1–16** in Table 2. Equation (3) showed the best correlation.

$$\log 1/EC_{90} = 0.660(\pm 0.130)pI_{50} - 1.00 \quad (3)$$
$$n=16,\ s=0.134,\ r=0.941,\ F_{1,14}=108.7$$

In this and the following equations, n is the number of data used in the correlation, s the standard deviation, r the multiple correlation coefficient, and F_{ν_1,ν_2} the F ratio of the correlation where $\nu_1=m$, and $\nu_2=n-m-1$; m is the number of independent variables used in the correlation. Figures in the parentheses are the 95% confidence intervals. In Eq. (3), all terms were justified above a 99.5% level. The correlation between the protective activity and the activity *in vitro* was excellent.

An addition of log P or I_{DCI} term to Eq. (3) did not afford any significant improvement. Equation (3) indicates that the higher the antifungal activity *in vitro*, the higher the protective activity in greenhouse conditions.

We have suggested[4] that the mode of interaction of vinylimidazoles **I** with a target site is similar to that of allylimidazoles **II**, since the quantitative structure-activity relationship is similar between the vinylimidazoles and the allylimidazoles. We, therefore, estimated the log $1/EC_{90}$ value of the allylimidazoles by Eq. (3). The observed log $1/EC_{90}$ values of allylimidazoles **17–25** were generally lower than those estimated from Eq. (3) (Table 2). We assumed that this could be represented by the indicator variable, I_{All}. What it means will be discussed later. Thus, Eq. (4) was derived for all vinyl- and allyl-imidazoles **1–25**, as shown in Table 2.

$$\log 1/EC_{90} = 0.534(\pm 0.125)pI_{50} - 0.253(\pm 0.175)I_{All} - 0.312 \quad (4)$$
$$n=25,\ s=0.187,\ r=0.887,\ F_{2,22}=40.5$$

In Eq. (4), all terms were justified above a 99.5% level. The addition of log P or I_{DCl} term to Eq. (4) did not afford any significant improvement.

Equation (4) shows that the higher the antifungal activity *in vitro*, the higher the protective activity. The coefficient of the I_{All} term in Eq. (4) is negative, indicating that the protective activity of compound **II** is lower than that of compound **I** although their pI_{50} values are the same. The term I_{All} was not a necessary factor to determine the curative activity of imidazoles **I** and **II**, however. For the evaluation of protective activity, a compound was applied to the seedlings 24 hr before inoculation, while for the evaluation of curative activity, the compound was applied 24 hr after inoculation. We, therefore, examined the persistency of their protective activity. Table 3 shows that the duration of the protective activity was longer in vinylimidazoles **I** than in allylimidazoles **II**. The I_{All} term would suggest a difference in a rate of decomposition or metabolism on or within the leaf between **I** and **II**.

3. *Relationships between Curative Activity in Greenhouse Conditions and Antifungal Activity in Vitro*

First, we analyzed the curative activity data on vinylimidazoles, **1–8**, **10**, and **12–16** in Table 2. Equation (5) showed the best correlation.

$$\log 1/EC_{50} = 1.04(\pm 0.309)pI_{50} - 0.764\ (\pm 0.277)\log P + 0.569\ (\pm 0.284)\ I_{DCl} + 1.31 \quad (5)$$
$$n=14,\ s=0.155,\ r=0.952,\ F_{3,10}=32.2$$

In Eq. (5), all terms were justified above a 99.5% level. The correlation of the curative activity with pI_{50}, log P, and I_{DCl} was excellent. An addition of $(\log P)^2$ term to Eq. (5) did not afford any significant improvement.

Equation (5) shows that the higher the antifungal activity *in vitro*, the higher the curative

Table 5 Development of Eq. (6)[a].

pI_{50}	log P	I_{DCl}	Intercept	r[b]	s[c]	F_{ν_1,ν_2}[d]	F of difference between Eqs.[f]	Eq. No.
0.344 (±0.199)			1.71	0.616	0.321	$F_{1,21}=12.8$		(7)
0.281 (±0.187)		0.410[e] (±0.345)	2.03	0.724	0.288	$F_{2,20}=11.0$	$F_{1,20}=6.09$[g]	(8)
0.714 (±0.335)	−0.407[e] (±0.313)		1.53	0.739	0.281	$F_{2,20}=12.0$	$F_{1,20}=7.38$[h]	(9)
0.791 (±0.203)	−0.597 (±0.200)	0.621 (±0.215)	1.92	0.919	0.173	$F_{3,19}=24.4$	$F_{1,19}=38.2$,[i] 35.6[j]	(6)

[a] Figures in the parentheses are the 95% confidence intervals. All terms are justified above a 99.5% level by the t-test unless noted otherwise.
[b] Multiple correlation coefficient.
[c] Standard deviation.
[d] F value of the correlation. $\nu_1=m$, $\nu_2=n-m-1$, n and m are the number of data and independent variables used in the correlation, respectively.
[e] Justified at a level between 99.5 and 95%.
[f] $F_{1,20,0.025}=5.87$, $F_{1,19,0.005}=10.1$.
[g] Eqs. (7) and (8).
[h] Eqs. (7) and (9).
[i] Eqs. (8) and (6).
[j] Eqs. (9) and (6).

activity. The coefficient of term I_{DCl} was positive. Substitution of the 2,6-dichlorobenzyloxy group at the 2-position on the benzene ring was favorable to the curative activity although the physicochemical meaning has not yet been clarified. The log P term will be discussed in detail later.

Next, we analyzed the curative activity data in Table 2 including those on the allylimidazoles, and obtained Eq. (6), which almost is equivalent to Eq. (5).

$$\log 1/EC_{50}=0.791(\pm0.203)pI_{50} -0.597(\pm0.215)\log P +0.621(\pm0.215)I_{DCl} +1.92 \quad (6)$$
$$n=23,\ s=0.173,\ r=0.919,\ F_{3,19}=24.4$$

In Eq. (6), all terms were justified above a 99.5% level. Tables 5 and 6 show the development of Eq. (6) and the internal correlation of independent variables, respectively. Although a squared correlation coefficient between variables pI_{50} and log P was relatively high ($r^2=0.724$), the addition of log P term to Eq. (8) to give Eq. (6) was statistically significant since the F value[10] of 38.2, a difference between Eqs. (8) and (6), was larger than the critical F value of 10.1 at a 99.5% level, as shown in Table 5.

Table 6 Squared correlation matrix of the variables used in Eq. (6).

	pI_{50}	log P	I_{DCl}
pI_{50}	1.000	0.724	0.081
log P		1.000	0.166
I_{DCl}			1.000

Edgington[11] reported that one of chemical requisites for the mobility of the xenobiotics within plants is their log P value. In the region where the log P value is higher than 2, the mobility decreases as the log P value increases. The log P value for the present series of imidazoles **I** and **II** remains in the range of 3.82–6.09. In Eqs. (5) and (6), therefore, the log P term may indicate an effect on the mobility of the molecule within the leaf. As the curative activity was assessed by the application of a compound to the leaf inoculated 24 hr before, the mobility of the molecule within the leaf may be important in determining the activity. As the protective activity was assessed by the application of the compound to the leaf 24 hr before the inoculation, however, the

mobility may be less important.

In Eqs. (5) and (6), the pI_{50} and the $\log P$ terms statistically contributed to the curative activity. Since hydrophobicity ($\log P$) is most important in determining the *in vitro* activity (pI_{50}) of **I** and **II**,[4,5] the curative activity does not seem to depend on the $\log P$ term, because the positive effect of the $\log P$ term on the pI_{50} value and the negative effect on the mobility cancel each other in Eqs. (5) and (6); the coefficient of the $\log P$ term in Eqs. (5) or (6) is -0.764 and -0.597, respectively, and that of the pI_{50} is 0.55–0.67.[4,5]

The relationship between the curative and *in vitro* activities of vinylimidazoles **I** and the relationship between those of allylimidazoles **II** were combined by Eq. (6). The combination shows that the difference in the rate of decomposition on or within the leaves between **I** and **II** might be relatively small, when imidazoles **I** and **II** were applied to the leaf inoculated 24 hr before.

ACKNOWLEDGMENTS

We wish to express our thanks to Professor Toshio Fujita of Kyoto University for his invaluable suggestions and to Dr. Yoshiyuki Hayashi, Director of the Aburahi Laboratories of Shionogi & Co., Ltd., for his encouragement and permission to publish this work. We also wish to express our thanks to Drs. Takashi Maeda, Ichiro Ishizuka, Yoshio Hayase, and Michio Masuko for their invaluable discussion and encouragement. We are also indebted to Mr. Hiroyuki Kai and Mmes. Kinuko Kumano, Kaoru Hirooka, and Etsuko Seko for their expert technical assistances.

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要　　約

1-[1-(置換フェニル)ビニル]イミダゾール類と1-[2-(置換フェニル)アリル]イミダゾール類の温室内での防除効果と *in vitro* の抗菌活性との相関関係

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16個の1-[1-(2-置換ヒドロキシ-5-置換フェニル)ビニル]イミダゾール類と9個の1-[2-(2-置換ヒドロキシ-5-置換フェニル)アリル]イミダゾール類の，温室内ポット試験条件下での灰色カビ病菌（*Botrytis cinerea*）に対する予防効果と治療効果を測定した．ポット試験の効果と先に報告した *in vitro* の殺菌活性との間の関係を，物理化学的および構造パラメータを用いて重回帰分析により定量的に解析した．その結果 *in vitro* の活性が高くなればなるほど予防効果は高くなることがわかった．ビニルイミダゾール類の予防効果は対応するアリルイミダゾール類のそれに比べて持続性があった．また，ポット試験の治療効果は *in vitro* の活性が高くなるほど高くなることと，ベンゼン環の2位に2，6-ジクロロベンジルオキシ基が存在すると，治療効果にとり好ましいことが明らかになった．さらに分子の疎水性の効果については，*in vitro* 活性に対する正の効果と葉内での浸透移行性に対する負の効果とが互いに相殺されることにより，治療効果は分子の疎水性には依存しないと考えられた．