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Synthesis of Benzylaminopyrimidines and Their Fungicidal Activities against Wheat Brown Rust and Barley Powdery Mildew

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Abstract: Members of a new class of fungicide containing benzylaminopyrimidine as a core structure were synthesized and their fungicidal potencies against wheat brown rust, *Puccinia recondita*, and barley powdery mildew, *Erysiphe graminis*, were assessed. Among these fungicides, *N*-(fluoroalkoxy or fluorophenoxybenzyl)-4-pyrimidinamines showed notable preventive activities. The potency of the new pyrimidines was increased when a difluoromethoxy or tetrafluorophenoxy group was introduced at the 4- or 3-position of the phenyl moiety and a methyl or ethyl group was introduced at the benzyl position. Structure–activity relationships are discussed. © 1998 Society of Chemical Industry

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Key words: benzylaminopyrimidines; wheat brown rust; barley powdery mildew; fungicides

1 INTRODUCTION

A number of fungicides with specific modes of action have been developed. Sterol 14α-demethylation inhibitors (DMIs), including azole fungicides, a type of sterol biosynthesis inhibitor (SBI), are the largest group of modern fungicides.[1]

In the last two decades, the development of resistance to these compounds has severely hampered the chemical control of fungi. Resistance to DMIs is one of the most crucial topics, and compounds with alternative modes of action are sought. For example, amine-type fungicides such as fenpropimorph and fenpropidin are a class of SBI, and their modes of action are different from those of DMIs.[2,3] A new class of carbocation-mimetic ergosterol biosynthesis inhibitor has also been reported.[4] These fungicides can be used as substitutes for DMIs.

We have found *N*-benzyl-4-pyrimidinamines to have a broad spectrum of pesticidal activity.[5] Among them, compounds with a fluoroalkoxy or fluorophenoxy group on the phenyl ring have highly fungicidal activity. Some of them have potent preventive and therapeutic activities against wheat brown rust and barley powdery mildew. Here we describe the synthesis and the structure–activity relationship of this class of fungicides.

2 MATERIALS AND METHODS

2.1 Compounds

The test compounds are listed in Tables 1–4. Their structures were confirmed by 270 MHz-[^{1}H]NMR spectroscopy (GX270, JEOL, Tokyo, Japan) in deuterochloroform using tetramethylsilane as the internal standard or by mass spectroscopy (M-80, Hitachi, Tokyo, Japan). Melting points were measured with a melting

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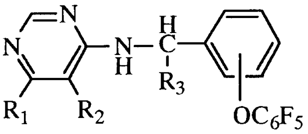
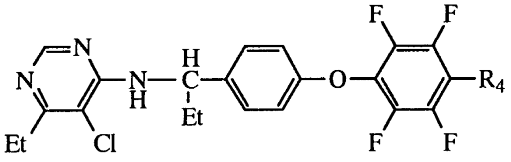
TABLE 1
Effects of Substituents on the Pyrimidine Ring (R_1 and R_2) and at the Benzyl Position (R_3) on Preventive Activities against Wheat Brown Rust and Barley Powdery Mildew



Compound No.	*Substituents*			*Position of OC_6F_5*	*m.p. (°C) or n_D (at °C)*	*pI_4 (M)*	
	R_1	*R_2*	*R_3*			*WBR*[a]	*BPM*[b]
1	Me	F	Me	4	117–119	4·15	4·92
2	Me	F	Et	4	1·5400 (26)	2·93	4·09
3	Me	Cl	H	4	110–115	<3·00[c]	3·46
4	Me	Cl	Me	4	90–91	3·33	4·97
5	Me	Cl	Et	4	118–121	3·35	3·04
6	Et	F	Me	4	88–91	4·93	4·93
7	Et	Cl	Me	4	88–89	4·65	5·35
8	Et	Cl	Et	4	57–59	3·96	4·66
9	Et	Cl	*i*-Pr	4	1·5401 (24)	3·59	4·15
10	Et	Br	Et	4	86–88	3·40	3·40
11	*i*-Pr	Cl	Me	4	62–65	3·16	3·96
12	Cl	Me	H	4	128–132	<3·00[c]	<3·00[d]
13	Cl	Me	Et	4	120–125	<3·00[c]	<3·00[c]
14	Me	Cl	Me	3	1·5580 (22)	3·68	4·09
15	Et	Cl	Me	3	1·5522 (24)	3·95	4·75

[a] Wheat brown rust (*Puccinia recondita*).
[b] Barley powdery mildew (*Erysiphe graminis*).
[c] Rating 0 at the indicated concentration.
[d] Rating 2 at the indicated concentration.

TABLE 2
Effects of *Para* Substituents on the Tetrafluorophenoxy Moiety on Preventive Activities against Wheat Brown Rust and Barley Powdery Mildew



Compound No.	*R_4*	*m.p. (°C) or n_D (at °C)*	*pI_4 (M)*	
			WBR[a]	*BPM*[b]
16	H	1·5518 (22)	4·03	4·04
8	F	57–59	3·96	4·66
17	CHF_2	1·5454 (22)	3·99	4·69
18	CF_3	58–61	3·41	4·23
19	CHO	1·5734 (24)	<3·00[c]	3·51
20	Ac	1·5592 (24)	<3·00[c]	3·38
21	$CH(OCH_2)_2$	1·5589 (24)	<3·00[d]	<3·00[c]
22	CN	1·5677 (24)	<3·00[d]	<3·00[c]
23	NO_2	1·5712 (24)	<3·00[d]	<3·00[d]

[a] Wheat brown rust (*Puccinia recondita*).
[b] Barley powdery mildew (*Erysiphe graminis*).
[c] Rating 2 at the indicated concentration.
[d] Rating 0 at the indicated concentration.

point apparatus (Buchi 535, Flawil, Switzerland). Refractive indexes were measured with a refractometer (3T, Atago-Abbe, Tokyo, Japan). Elemental analyses were in accordance with the proposed structures.

*2.1.1 4-(2,3,5,6-Tetrafluorophenoxy)- and 3- or 4-(pentafluorophenoxy)benzylaminopyrimidines (**1–23**)*

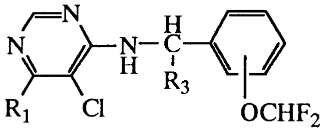
The synthetic routes for compounds **1–23** are shown in Fig. 1. Typical examples of synthetic procedures are described below.

2.1.1.1 α-[RS]*Ethyl-4-hydroxybenzylamine* (***a***; $R_3 = C_2H_5$; *4-OH*). A solution of 4-hydroxypropiophenone (100 g; 0·67 mol), hydroxylamine hydrochloride (55 g; 3·5 mol) and potassium acetate (69 g; 0·7 mol) dissolved in a mixture of ethanol (80 ml) and water (20 ml) was refluxed for 6 h. After cooling, most of the ethanol was removed under reduced pressure. The residual solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. On concentration, 4-hydroxypropiophenone oxime afforded colourless crystals, which was used for the next reaction without further purification. Yield, 45 g (44%).

The oxime (30 g; 0·18 mmol) and 5%-palladium carbon (5 g; N. E. Chemcat. Co., Tokyo, Japan) were

TABLE 3

Effects of Substituents on the Pyrimidine Ring (R_1) and at the Benzyl Position (R_3) and of the Position of the $OCHF_2$ Group on Preventive Activities against Wheat Brown Rust and Barley Powdery Mildew



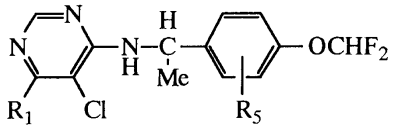
Compound No.	Substituents		Position of $OCHF_2$	m.p. (°C) or n_D (at °C)	pI_4 (*M*)	
	R_1	R_3			WBR[a]	BPM[b]
24	Me	Me	3	1·5538 (23)	4·80	3·36
25	Me	Me	4	56–58	4·20	4·20
26	Et	Me	3	1·5471 (23)	4·82	3·82
27	Et	Me	4	1·5442 (20)	4·82	4·82
28	Me	Et	2	1·5456 (18)	3·05	3·36
29	Me	Et	4	1·5471 (24)	4·54	4·22

[a] Wheat brown rust (*Puccinia recondita*).
[b] Barley powdery mildew (*Erysiphe graminis*).

placed with concentrated hydrochloric acid (5 ml) and ethanol (100 ml) in a 300-ml stainless steel autoclave. Hydrogen gas was introduced into the vessel. The internal pressure was kept at 30 kg cm^{-2} by the introduction of the gas during the reaction. After being maintained at 50°C for 5 h, the mixture was filtered and the filtrate was concentrated *in vacuo*. Distillation of the residue gave 21 g (79% yield) of the desired product as a colourless crystal. M.p. 163–165°C (ref. 6, m.p. 167°C).

TABLE 4

Effects of Substituents on the Pyrimidine (R_1) and Phenyl (R_4) Rings on Preventive Activities against Wheat Brown Rust and Barley Powdery Mildew



Compound No.	Substituents		m.p. (°C) or n_D (at °C)	pI_4 (*M*)	
	R_1	R_5		WBR[a]	BPM[b]
25	Me	H	56–58	4·20	4·20
30	Me	3-Cl	1·5536 (25)	4·24	2·84
31	Me	3-OMe	1·5498 (24)	4·30	3·64
32	Me	3-$OCHF_2$	1·5246 (24)	4·02	4·61
33	Me	3,5-$(Me)_2$	1·5510 (25)	3·36	4·23
34	Me	2-F	71–72	4·82	3·92
27	Et	H	1·5442 (20)	4·82	4·82
35	Et	3-Cl	1·5397 (23)	4·26	2·86
36	Et	3-OMe	1·5458 (24)	4·85	4·55
37	Et	3-$OCHF_2$	1·5218 (24)	4·13	4·64
38	Et	3,5-$(Me)_2$	1·5456 (24)	4·25	4·45
39	Et	2-F	1·5343 (26)	4·84	4·24

[a] Wheat brown rust (*Puccinia recondita*).
[b] Barley powdery mildew (*Erysiphe graminis*).

[^{1}H]NMR (δ ppm): 1·25 (3H, t, $J = 8$ Hz), 2·80 (2H, q, $J = 8$ Hz), 4·20 (1H, m), 6·92 (2H, d, $J = 8$ Hz), 7·52 (2H, d, $J = 8$ Hz), 7·68 (2H, m).

*2.1.1.2 5-Chloro-6-ethyl-*N*-(α-*[RS]*ethyl-4-hydroxybenzyl)pyrimidin-4-amine (**b**; $R_2 = Cl$, $R_1 = R_3 = C_2H_5$; 4-OH).* To a solution of α-[*RS*]ethyl-4-hydroxybenzylamine (5·0 g; 33 mmol), triethylamine (7·3 g; 72 mmol) and 4,5-dichloro-6-ethylpyrimidine[7–10] (7·0 g; 40 mmol) in ethanol (50 ml), a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine was added. The mixture was refluxed for 8 h. After cooling, the ethanol was removed under reduced pressure. The residue was dissolved in toluene (30 ml) and extracted with sodium hydroxide solution (80 g litre^{-1}; 50 ml). The aqueous layer was made neutral by the slow addition of hydrochloric acid (2 M; 50 ml). The solution was extracted with ethyl acetate and dried over sodium sulfate. By removing the solvent under reduced pressure, the desired product (5 g, 52%) was obtained as colourless crystals. M.p. 133–135°C. [^{1}H]NMR (δ ppm): 0·94 (3H, t, $J = 7$ Hz), 1·26 (3H, q, $J = 7$ Hz), 1·92 (2H, m), 2·83 (2H, m), 5·08 (1H, q, $J = 7$ Hz), 5·72 (1H, d, $J = 7$ Hz), 6·81 (1H, m), 7·18 (2H, d, $J = 8$ Hz), 7·32 (2H, d, $J = 8·8$ Hz), 8·40 (1H, m).

*2.1.1.3 5-Chloro-6-ethyl-*N*-[α-*[RS]*ethyl-4-(2,3,5,6-tetrafluorophenoxy)benzyl]pyrimidin-4-amine (**16**).* A solution of 5-chloro-6-ethyl-*N*-(α-[*RS*]ethyl-4-hydroxybenzyl)pyrimidin-4-amine (2·0 g; 6·9 mmol) and potassium hydroxide (0·6 g; 10 mmol) dissolved in *N*,*N*-dimethylformamide (50 ml) was held at 50°C for 30 min under stirring. The solution was allowed to cool to room temperature, pentafluorobenzene (2·3 g; 14 mmol) was added and the mixture held at room temperature

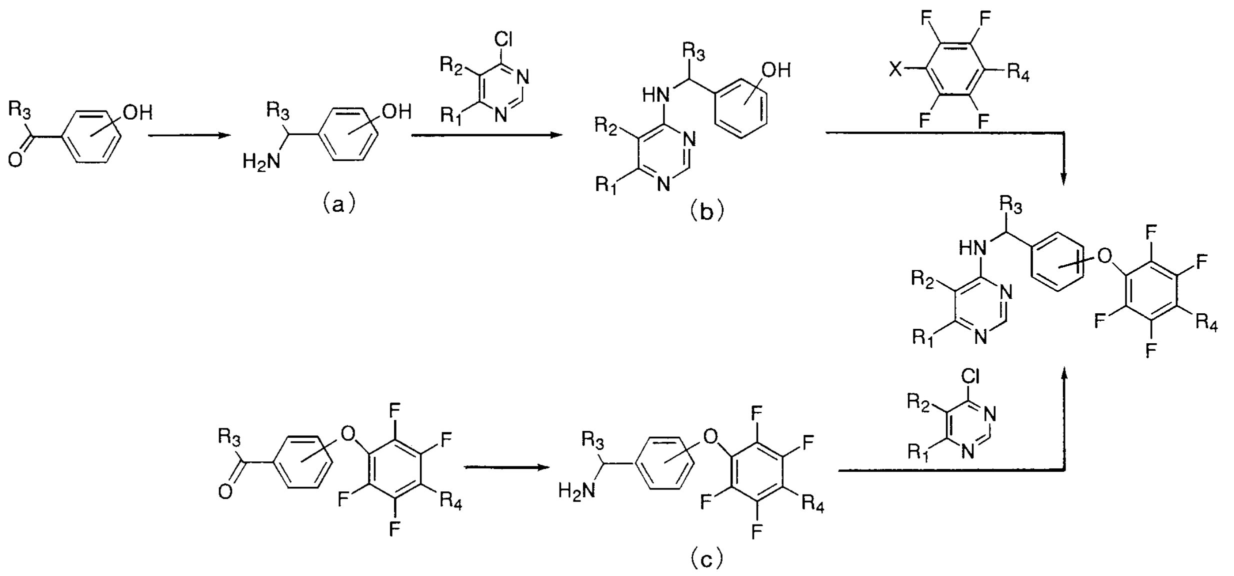


Fig. 1. Synthetic routes for compounds **1**–**23**.

for 4 h. The mixture was poured into water and extracted with toluene. The organic layer was washed with water and dried over anhydrous sodium sulfate. Toluene was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with toluene + ethyl acetate (10 + 1 by volume) to give 1·8 g (60% yield) of light yellow oil. N_D^{22} 1·5518. [^{1}H]NMR (δ ppm): 0·95 (3H, t, J = 8 Hz), 1·24 (3H, t, J = 8 Hz), 1·92 (2H, q, J = 8 Hz), 2·81 (2H, q, J = 8 Hz), 5·14 (1H, q, J = 8 Hz), 5·58 (1H, m), 6·92 (2H, d, J = 8 Hz), 7·15 (1H, m), 7·29 (2H, d, J = 8 Hz), 8·38 (1H, s). [^{19}F]NMR (δ ppm): −153·0 (2F, s), −138·7 (2F, s).

2.1.1.4 α-[RS]*Ethyl-4-pentafluorophenoxybenzylamine* (*c; $R_3 = C_2H_5$; $R_4 = F$; 4-O-PhF$_5$*). A solution of 4-pentafluorophenoxypropiophenone[5] (10 g; 32 mmol), ammonium acetate (15 g; 195 mmol) and sodium cyanoborohydride (1·5 g; 24 mmol) dissolved in ethanol (100 ml) was stirred at 50°C for 5 h. After the solution was cooled, concentrated hydrochloric acid (40 ml) was added and the ethanol was removed under reduced pressure. The residue was made alkaline by the addition of sodium hydroxide solution (80 g litre^{-1}; 250 ml) and was then extracted with toluene. After the removal of the solvent under reduced pressure, the resultant oil was purified by column chromatography (Gel C-200, Wako, Osaka, Japan) with toluene + ethyl acetate + ethanol (5 + 5 + 1 by volume) to give the desired product (4 g, 39% yield) as a colourless oil. CI-MS *m/e:* 318, 301, 273. EI-MS *m/e:* 301, 288.

*2.1.1.5 5-Chloro-6-ethyl-*N-(*α-*[RS]*ethyl-4-pentafluorophenoxybenzyl*)*pyrimidin-4-amine* (***8***). To a solution of 4,5-dichloro-6-ethylpyrimidine (2·1 g; 12 mmol), α-[*RS*] ethyl-4-pentafluorophenoxybenzylamine (3·5 g; 11 mmol) and triethylamine (1·5 g; 15 mmol) in *N*,*N*-dimethylformamide (10 ml), a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine was added. The mixture was refluxed for 8 h. After cooling, the reaction mixture was washed with water, and the organic layer was dried over anhydrous sodium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by column chromatography (Wako Gel C200) using toluene + ethyl acetate (5 + 1 by volume) as an eluent to give 2·0 g (42% yield) of the desired product as colourless crystals. M.p. 57–59°C, [^{1}H]NMR (δ ppm): 0·95 (3H, t, J = 7·6 Hz), 1·25 (3H, q, J = 7·2 Hz), 1·90 (2H, m), 2·78 (2H, q, J = 7·2 Hz), 5·12 (1H, q, J = 7·2 Hz), 5·58 (1H, m), 6·92 (2H, d, J = 8·8 Hz), 7·28 (2H, d, J = 8·8 Hz), 8·37 (1H, s). CI-MS *m/e:* 458, 428.

Compounds **1**–**7**, **9**–**15** and **17**–**23** were prepared by similar procedures. Their physical properties are listed in Tables 1 and 2.

2.1.2 Difluoromethoxybenzylaminopyrimidines (***24***–***39***) The synthetic routes for 4-difluoromethoxybenzylaminopyrimidines are shown in Fig. 2. Typical examples of synthetic procedures are described below.

2.1.2.1 4-Difluoromethoxypropiophenone (*f; $R_3 = C_2H_5$; R_5 = H; 4-OCHF$_2$*). 4-Hydroxypropiophenone (72 g; 480 mmol), chlorodifluoromethane (49·4 g; 571 mmol), potassium carbonate (66 g; 480 mmol) and *N*,*N*-dimethylformamide (120 ml) were placed in a 300 ml-stainless steel autoclave and maintained at 100°C for 3 h while stirring. After cooling, the reaction mixture was poured into water. The mixture was extracted with toluene and the organic layer was washed three times with water. The solution was dried over anhydrous sodium sulfate and concentrated *in vacuo*. Distillation of the residue gave 40 g (42% yield) of the desired product as a colourless oily product, which became solid. M.p. 40·0–41·5°C. [^{1}H]NMR (δ ppm): 1·14 (3H, t, J = 8·0 Hz), 2·80 (2H, q, J = 7·2 Hz),

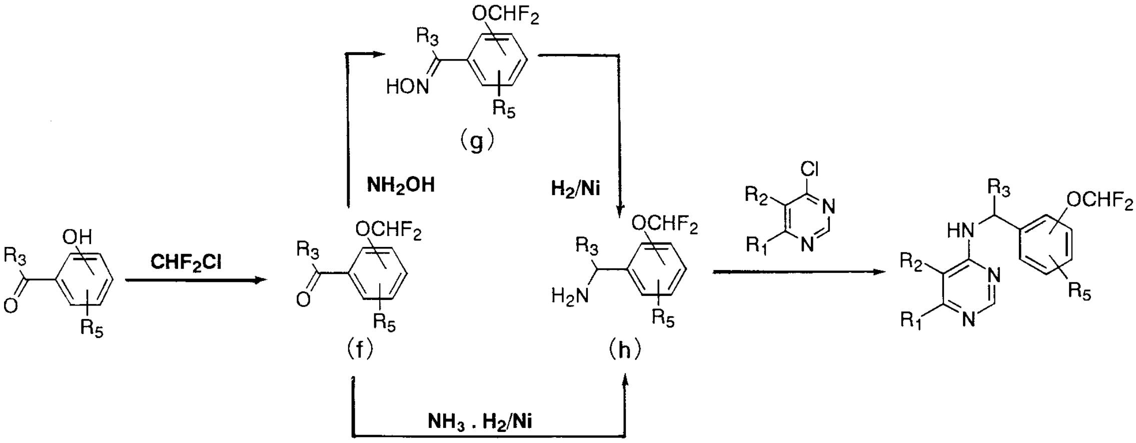


Fig. 2. Synthetic routes for compounds **24**–**39**.

6·49 (1H, t, $J = 74$ Hz), 7·14 (2H, d, $J = 8{\cdot}8$ Hz), 7·34 (2H, d, $J = 8{\cdot}8$ Hz).

2.1.2.2 4-Difluoromethoxypropiophenone oxime (***g***; $R_3 = C_2H_5$; $R_5 = H$; *4-OCHF*$_2$). To a solution of 4-difluoromethoxypropiophenone (400 g; 2·0 mol) and hydroxylamine hydrochloride (222 g; 3·2 mol) dissolved in ethanol (1 litre) and water (240 ml), sodium hydroxide (280 g litre^{-1}; 500 ml) was slowly added. The resulting mixture was stirred at 60°C for 4 h, the ethanol was then removed under reduced pressure, and the residue extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. On concentration, it afforded colourless crystals. They were purified by washing with hexane to give colourless crystals (271 g, 63%). M.p. 78–80°C. [^{1}H]NMR (δ ppm): 1·17 (3H, t, $J = 8{\cdot}0$ Hz), 2·80 (2H, q, $J = 8{\cdot}0$ Hz), 6·53 (1H, t, $J = 73{\cdot}6$ Hz), 7·46 (2H, d, $J = 8{\cdot}8$ Hz), 7·62 (2H, d, $J = 8{\cdot}8$ Hz), 8·64 (1H, m).

2.1.2.3 α-[RS]*Ethyl-4-difluoromethoxybenzylamine* (***h***; $R_3 = C_2H_5$; $R_5 = H$; *4-OCHF*$_2$).

Method 1: 4-Difluoromethoxypropiophenone oxime (910 g; 4·2 mol), Raney nickel (128 g; Kawaken Fine Chem. Co., Tokyo, Japan, NDT-65), ethanol (6 litres), and liquid ammonia (719 g; 42 mol) were placed in a 20-litre stainless steel autoclave. Hydrogen gas was introduced into the vessel, and the internal pressure was kept at 20 kg cm^{-2} by the introduction of further gas during the reaction. After being kept at 100°C for 7 h, the mixture was cooled and filtered, and the filtrate was concentrated *in vacuo*. Distillation of the residue gave 780 g (92% yield) of the desired product as a colourless oil. B.p. 101°C/5 mm Hg. [^{1}H]NMR (δ ppm): 0·85 (3H, t, $J = 7{\cdot}8$ Hz), 1·65 (4H, m), 3·84 (1H, q, $J = 5{\cdot}8$ Hz), 6·48 (1H, t, $J = 72{\cdot}5$ Hz), 7·09 (2H, d, $J = 8{\cdot}7$ Hz), 7·30 (2H, d, $J = 8{\cdot}7$ Hz).

Method 2. Using similar procedures to those of method 1, the desired product was prepared from 4-difluoromethoxypropiophenone (10·8 g; 54 mmol) and liquid ammonia (11·8 g; 700 mmol) in methanol (100 ml) in the presence of Raney nickel (4 g), aluminium hydroxide (6 g; 77 mmol) and hydrogen gas. Yield 2·13 g, 20%.

Method 3. 4-Difluoromethoxypropiophenone (12 g; 60 mmol), liquid ammonia (12 g; 710 mmol), stabilized Raney nickel (12·0 g; Nikki Chem Co., Tokyo, Japan, N-103) and methanol (48 ml) were placed in a 300-ml stainless steel autoclave, and heated with stirring for 3 h at 120°C. Hydrogen gas was then introduced into the vessel to give the pressure of 40 kgf cm^{-2}. The internal pressure was kept constant by the introduction of further hydrogen gas during the reaction. After being stirred at 100°C for 3 h, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in toluene (30 ml) and extracted with hydrochloric acid (2 M, 36 ml). The aqueous layer was made alkaline by the slow addition of sodium hydroxide (3·17 g; 79 mmol). The layer was extracted with toluene. Removal of the solvent under reduced pressure gave the desired product (11·7 g; 97%) as a colourless oily product.

*2.1.2.4 5-Chloro-6-methyl-*N-(α-[RS]*ethyl-4-difluoromethoxybenzyl)pyrimidin-4-amine* (***29***). To a solution of α-[*RS*]ethyl-4-difluoromethoxybenzylamine (1·0 g; 5·0 mmol), triethylamine (0·73 g; 7·2 mmol) and 4,5-dichloro-6-methylpyrimidine[11] (0·9 g; 5·5 mmol) in toluene (20 ml), a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine was added. The mixture was refluxed for 8 h. After cooling, the reaction mixture was washed with water, and the organic layer was dried over anhydrous sodium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by column chromatography (Wako Gel C200) using toluene + ethyl acetate (5 + 1 by volume) as an eluent to give 1·1 g (67% yield) of a colourless oily product. n_D^{24} 1·5518. [^{1}H]NMR (δ ppm): 0·95 (3H, t, $J = 7{\cdot}2$ Hz), 1·25 (2H, q, $J = 7{\cdot}2$ Hz), 2·45 (3H, s), 5·12 (1H, q, $J = 7{\cdot}2$ Hz), 5·59 (1H, d, $J = 7{\cdot}6$ Hz), 6·49 (1H, t, $J = 74$ Hz), 7·08 (2H, d, $J = 8{\cdot}8$ Hz), 7·32 (2H, d, $J = 8{\cdot}8$ Hz), 8·13 (1H, s).

Compounds **24**–**28** and **30**–**39** were prepared by similar procedures. Their physical properties are listed in Tables 3 and 4.

2.2 Biological tests

2.2.1 Preventive activity against wheat brown rust

In a plastic planting pot (6 cm diam. × 10 cm), 10 wheat seedlings (*Triticum aestivum* L.) were grown at 28°C. At the 1·5-leaf stage (on average) aqueous suspensions of wettable powders of the test compounds at given concentration were sprayed over the plants. Two days later, the wheat plants were inoculated by a spore suspension of wheat brown rust, *Puccinia recondita* Rob. ex Desm., at 7×10^4 spores ml^{-1}. One week later, the symptoms of the first leaf were examined. The activity rankings of the test chemicals were defined on a scale of zero to five, corresponding to 0–30, 31–60, 61–80, 81–94, 95–99 and 100% prevention, respectively. The test was done with two pots for each concentration of each compound. When the rankings of the two pots were different, the test was repeated until a reproducible value was obtained. From a concentration-preventive ranking relationship as exemplified in Fig. 3 for compound **31**, the concentration to give the activity ranking 4 was defined as I_4 (M). The pI_4 values, which are reciprocal log values of I_4, are given in Tables 1–4.

2.2.2 Preventive activity against barley powdery mildew

In a plastic planting pot (6 cm diam. × 10 cm), 10 barley seedlings (*Hordeum vulgare* L. var. *vulgare*) were grown at 28°C. At the 1·5-leaf stage (on average) aqueous suspensions of test compounds were sprayed over the plants as before. Two days later, the barley plants were inoculated by conidial spores of barley powdery mildew, *Erysiphe graminis* DC f.sp.*hordei* Marchal. One week later, the symptoms of the first leaf were examined. The activity rankings of the test chemicals were defined in the same way as for the activity against wheat brown rust. The test was done with at least two pots for each concentration of each compound, as for the wheat brown rust. The pI_4 values were calculated as for the wheat brown rust and are listed in Tables 1–4.

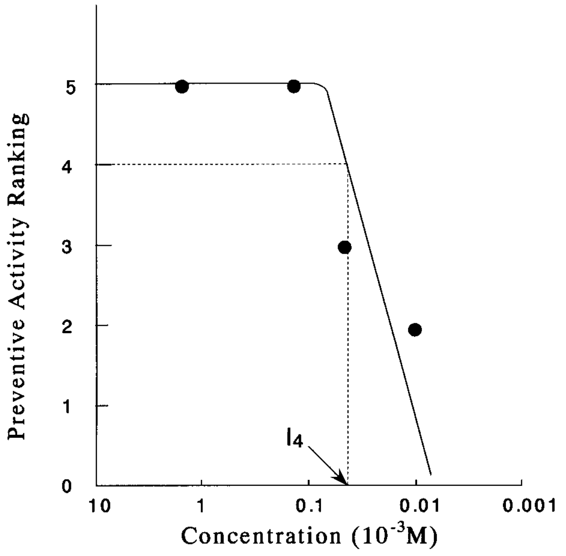


Fig. 3. The preventative activity ranking, I_4, of compound **31** against wheat brown rust.

3 RESULTS AND DISCUSSION

The preventive activities of pentafluorophenoxybenzylaminopyrimidines (**1**–**15**) against wheat brown rust and barley powdery mildew are listed in Table 1. Most of the compounds were more potent against the barley powdery mildew than against the wheat brown rust. Among the position isomers of pentafluorophenoxy derivatives, the 4-position isomers seemed to be more potent than the 3-position isomers (**4** versus **14**; **7** versus **15**), although compound **4** was slightly less active than compound **14** against wheat brown rust.

Among the 4-pentafluorophenoxy derivatives, the methyl analogues on R_3 were more potent than the ethyl analogues (**1** versus **2**; **4** versus **5**; **7** versus **8**). Further enlargement of the alkyl to isopropyl was unfavourable to activity (**9** versus **8**). The unsubstituted compound ($R_3 = H$) was less potent than the methyl analogue (**3** versus **4**). Thus, there seemed to be an optimum size for R_3. One of the most potent congeners listed in Table 1 was compound **7**. The conversion of R_2 from Cl (**7**) to F (**6**) did not significantly affect the potency against either fungus. Conversions of R_1 from ethyl (**7**) to isopropyl (**11**) and of R_2 from Cl (**8**) to Br (**10**) gave less active compounds. Preventive activities varied greatly among the isomers. Compounds **6** and **7** with R_3 = methyl were much more potent than the corresponding isomers **2** and **5** with R_1 = methyl. Another isomer, **13**, of compounds **5** and **7** was very weak and did not give preventive effects at the highest concentration tested.

Even though compound **8** ($R_4 = F$) was not the most potent compound among those listed in Table 1, it was chosen as the target compound to examine the substituent effect. Table 2 shows compound **8** and derivatives **16**–**23** with other substituents at the *para* position of the tetrafluorophenoxy moiety and their preventive activities against wheat brown rust and barley powdery mildew. The CHF_2 derivative (**17**) was as active as compound **8**. Compound **16** ($R_4 = H$) was as active as compound **8** against wheat brown rust, and slightly less active against barley powdery mildew. The introduction of an electron-withdrawing CF_3 group gave a slightly less active compound, **18**. Derivatives **19**–**23** with other electron-withdrawing groups were weak against both fungi.

Table 3 shows the effects of the position of another electron-withdrawing group, $OCHF_2$, on the benzyl-benzene ring and of substituents at R_1 and R_3. Isomers with the $OCHF_2$ group in the 4-position were generally more active than those with that group in the 3-position (**25** versus **24** and **27** versus **26**) or the 2-position (**29** versus **28**). The ethyl derivatives at R_1 were generally more active than the methyl derivatives (**26** versus **24**; **27** versus **25**). The derivative with R_3 = ethyl (**29**) was slightly more potent than the equivalent methyl derivative (**25**) against wheat brown rust, but they showed similar potencies against barley powdery mildew.

The effects of the further introduction of one or two more substituent(s) to the benzene ring of compounds **25** and **27** are summarized in Table 4. The effects were peculiar. The activity of compound **25** against wheat brown rust was increased by the introduction of the 2-F group (**34**) and that against barley powdery mildew was increased by the introduction of the 3-$OCHF_2$ group (**32**). These modifications, however, decreased the activity against the other fungus for each compound. The introduction of 3-Cl (**30**) or 3-OCH_3 (**31**) and the 3,5-$(CH_3)_2$ group (**33**) to compound **25** did not significantly change the activities against wheat brown rust and barley powdery mildew, respectively. However, such modifications decreased the potency against the other fungus. Among the derivatives with R_1 = ethyl (**35**–**39**) further introduction of substituents did not increase activity. The introduction of a 3-OCH_3 (**36**) or 2-F (**39**) group maintained the highest potency against wheat brown rust. These modifications and the introduction of a 3-$OCHF_2$ (**37**) or 3,5-$(CH_3)_2$ (**38**) group, however, slightly decreased the activity against barley powdery mildew.

In summary, benzylaminopyrimidines showed notable preventive activities against wheat brown rust and barley powdery mildew. The preferable combination of substituents on the pyrimidine ring seemed to be a halogen atom and a small alkyl group. The introduction of a small alkyl group at the benzyl position gave potent compounds. Substitution at the 4-position of the benzyl-benzene ring by electron-withdrawing substituents such as $OCHF_2$ and OC_6F_5 gave excellent fungicidal compounds.

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