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Synthesis and Cytoprotective Antiulcer Activity of 2- or 4-(1*H*-Pyrazol-1-yl)pyrimidine Derivatives Related to Mepirizole and Dulcerozine

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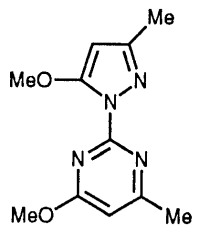
(1*H*-Pyrazol-1-yl)-, (1*H*-imidazol-1-yl)-, and (1*H*-1,2,4-triazol-1-yl)pyrimidines were prepared and evaluated for cytoprotective antiulcer activity. Among them, 4-methoxy-6-methyl-2-(1*H*-pyrazol-1-yl)pyrimidine (18) showed potent inhibition of the HCl–ethanol-induced and water-immersion stress-induced ulcers in rats, as well as low acute toxicity.

Key words mepirizole; dulcerozine; cytoprotective antiulcer activity; 2-(1*H*-pyrazol-1-yl)pyrimidine

Peptic ulcer disease (PUD) is generally believed to result from an imbalance between "aggressive factors," such as acid secretion, pepsin, and bile, and "defensive factors," such as bicarbonate secretion, mucosal secretion, blood flow, and the epithelial cell layer.[1] Much of the available therapy of PUD consists of antiaggressive agents and/or antisecretory drugs such as the H_2-antagonists and the H^+/K^+-ATPase inhibitors. However, despite their efficacy in the short-term healing of PUD, antisecretory drugs do not always provide permanent cures, because relapse occurs in 80—90% of cases within one to two years after cessation of therapy.

One of the authors (S. O.) has recently found that mepirizole (**1**), a non-steroidal anti-inflammatory drug clinically used in Japan,[2,3] and dulcerozine (**2**), a reagent used for preparing experimental ulcers in animals,[4] show a potent cytoprotective effect against HCl–ethanol-induced gastric mucosal damage in rats at an oral dose of less than 10 mg/kg.[5] Using **1** and **2** as lead compounds, we have carried out a systematic search for new cytoprotective antiulcer agents. In this paper we describe the synthesis and the protecting effects against HCl–ethanol lesions in rats of a series of (1*H*-pyrazol-1-yl)-, (1*H*-imidazol-1-yl)-, and (1*H*-1,2,4-triazol-1-yl)pyrimidine derivatives related to **1** and **2**. Although a number of 2-(1*H*-pyrazol-1-yl)pyrimidine[2a,6,7] and 2-(1*H*-imidazol-1-yl)-pyrimidine derivatives[8] have already been synthesized, none of them has been examined for antiulcer action.



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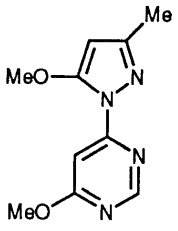

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Chemistry

The compounds related to mepirizole (**1**) were readily synthsized. 2-(5-Methoxy-3-methyl-1*H*-pyrazol-1-yl)pyrimidines **7** and **8** were prepared from the corresponding 2-hydrazinopyrimidines (**3**, **4**)[9] *via* **5** and **6** according to the method used for the synthesis of mepirizole (**1**) (procedure A).[2a]

2-(3-Methyl-1*H*-pyrazol-1-yl)- (**14**—**17**), 2-(1*H*-pyrazol-1-yl)- (**18**—**22**), 2-(1*H*-imidazol-1-yl)- (**23**—**27**), and 2-(1*H*-1,2,4-triazol-1-yl)pyrimidines (**28** and **29**) were synthesized by direct substitution reaction of the corresponding 2-halopyrimidines (**9**—**13**)[10] with 1 eq of 3-methylpyrazole, pyrazole, imidazole, and 1,2,4-triazole in the presence of an equimolar amount of sodium hydride (NaH) in tetrahydrofuran (THF) (procedure B). The structures of the products were confirmed by ^{1}H-NMR spectral analysis (Tables 3 and 4); the assignments of the signals were based on the chemical shifts reported for the 1-arylazoles.[11] In the reaction of 3-methylpyrazole, substitution may take place at either the 1 or 2 position of 3-methylpyrazole. The assigned structures of the products were confirmed by comparison of the ^{1}H-NMR spectra with that of 2-(1*H*-pyrazol-1-yl)pyridine,[12] in which the signals due to H-3′ and H-5′ are known to appear at δ 7.75 and 8.53, respectively. In the ^{1}H-NMR spectra of **14**—**17**, the signal corresponding to H-3′ was absent.

It is of interest to compare the biological activities of **18** and **23** with those of positional isomers (*e.g.*, **31** and **32**). Thus, treatment of 4-chloro-2-methoxy-6-methylpyrimidine (**30**)[13] with 1 eq of sodium pyrazolide or imidazolide gave the expected 4-(1*H*-pyrazol-1-yl)- (**31**) and 4-(1*H*-imidazol-1-yl)pyrimidines (**32**) in 79 and 82% yields, respectively.

The analogues of dulcerozine (**2**) were prepared starting from commercially available 4,6-dichloropyrimidine (**33**). Reaction of **33** with 1 eq of pyrazole in the presence of an equimolar amount of NaH in THF gave 4-chloro-6-(1*H*-pyrazol-1-yl)pyrimidine (**34**) (82%) and 4,6-bis(1*H*-pyrazol-1-yl)pyrimidine (7%).[7] Similar treatment of **33** with imidazole gave 4-chloro-6-(1*H*-imidazol-1-yl)pyrimidine (**35**) (75%) and 4,6-bis(1*H*-imidazol-1-yl)pyrimidine (22%). The reaction of **34** and **35** with various nucleophiles gave the desired compounds **36** and **37** (Chart 2). These results are summarized in Tables 5 and 6. The ^{1}H-NMR spectroscopic data of these compounds are shown in Tables 7 and 8.

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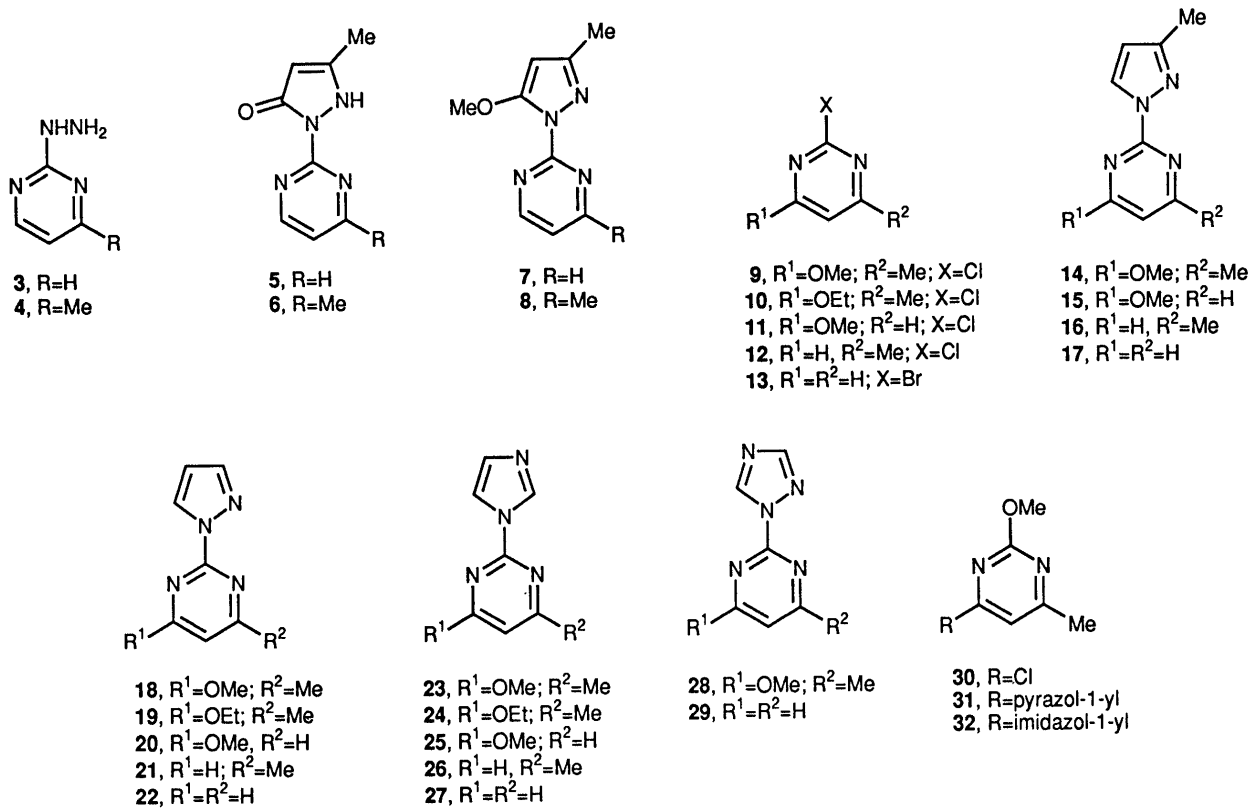

Chart 1

Table 1. Preparation and Antiulcer Effects of 2-(1*H*-Pyrazol-1-yl)pyrimidines (**7**, **8**, and **14**—**22**) and the Related Compound **31**

Compound	Method[a] Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found)			Inhibition (%)		LD_{50} (mg/kg, *p.o.*)
				C	H	N	HEU[c]	SU[d]	
1							91	22	300—1000
7	A (6)	90.5—91.5 (H–A)	$C_{10}H_{12}N_4$	58.81 (58.95	5.92 5.83	27.44 27.21)	70	60	>300
8	A (60)	77—78 (H)	$C_9H_{10}N_4O$	56.83 (56.75	5.31 5.26	29.46 29.20)	78		
14	B (56)	96—98 (H–A)	$C_{10}H_{12}N_4O$	58.81 (58.71	5.92 5.92	27.44 27.34)	85	49	300—1000
15	B (69)	65.5—66.5 (H–A)	$C_9H_{10}N_4O$	56.83 (57.10	5.31 5.19	29.46 29.61)	76	48	>300
16	B (66)	67—68.5 (H)	$C_9H_{10}N_4$	62.04 (62.02	5.80 5.65	32.16 32.23)	95	42	300—1000
17	B (91)	Oil	$C_8H_8N_4$		[e]		70		
18	B (54)	52.5—53 (H)	$C_9H_{10}N_4O$	56.83 (56.94	5.31 5.19	29.46 29.51)	93	80	300—1000
19	B (54)	Oil	$C_{10}H_{12}N_4O$		[f]		78		
20	B (46)	66—68 (H–A)	$C_8H_8N_4O$		[g]		60	40	>300
21	B (61)	Oil	$C_8H_8N_4$		[h]		66		
22	B (45)	73.5—74 (P)	$C_7H_6N_4$		[i]		17		
31	B (79)	47.5—49 (P)	$C_9H_{10}N_4O$	56.83 (56.64	5.30 5.29	29.46 29.56)	27		

a) See text. *b*) A, ethyl acetate; H, hexane; P, petroleum ether. *c*) Inhibitory effect on the HCl–EtOH-induced ulcer in rats at 10 mg/kg, *p.o.* ($N=3$ or 5). Inhibitory effect of irsogladine maleate as a reference agent was 93% at 10 mg/kg. The statistical significance was evaluated by using Student's *t* test ($p<0.05$). *d*) Inhibitory effect on the stress-induced ulcer in rats at 30 mg/kg, *p.o.* ($N=6$). Inhibitory effect of cimetidine as a reference agent was 55% at 100 mg/kg. The statistical significance was evaluated by using Student's *t* test ($p<0.05$). *e*) Characterized as its picrate, mp 135.5—137 °C (from isopropanol). *Anal.* Calcd for $C_{14}H_{11}N_7O_7$: C, 43.19; H, 2.85; N, 25.19. Found: C, 43.33; H, 2.77; N, 25.10. *f*) Characterized as its picrate, mp 151—153 °C (from ethanol). *Anal.* Calcd for $C_{16}H_{15}N_7O_8$: C, 44.35; H, 3.49; N, 22.63. Found: C, 44.54; H, 3.49; N, 22.82. *g*) Exact MS *m/z*: Calcd for $C_8H_8N_4O$; 176.0697. Found: 176.0682. *h*) Characterized as its picrate, mp 109—111 °C (from isopropanol). *Anal.* Calcd for $C_{14}H_{11}N_7O_7$: C, 43.20; H, 2.85; N, 25.19. Found: C, 43.51; H, 2.83; N, 25.07. *i*) Lit.[7] mp 68—70 °C.

Table 2. Preparation and Antiulcer Effects of 2-(1*H*-Imidazol-1-yl)- and 2-(1,2,4-1*H*-Triazol-1-yl)pyrimidines (**23**—**29**) and the Related Compound **32**

Compound	Method[a] Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found)			Inhibition (%)		LD_{50} (mg/kg, *p.o.*)
				C	H	N	HEU[c]	SU[d]	
23	B (51)	53–54 (H)	$C_9H_{10}N_4O$	56.83 (57.29	5.31 5.11	29.46 29.70)	75	72	300—1000
24	B (50)	115—116 (H–A)	$C_{10}H_{12}N_4O$	58.81 (58.86	5.92 5.99	27.44 27.34)	87	51	>300
25	B (66)	78—79 (H–A)	$C_8H_8N_4O$	54.54 (54.77	4.58 4.36	31.80 32.04)	53		
26	B (91)	95—96 (H–A)	$C_8H_8N_4$	59.98 (59.94	5.03 4.85	34.98 34.91)	17		
27	B (81)	115—116 (B)	$C_7H_6N_4$	57.52 (57.22	4.14 3.72	38.34 38.01)	75		
28	B (48)	147—147.5 (I)	$C_8H_9N_5O$	50.25 (50.26	4.74 4.66	36.63 36.65)	41		
29	B (82)	150—150.5 (H)	$C_6H_5N_5$		[e]		7		
32	B (82)	73—74 (H–A)	$C_9H_{10}N_4O$	56.83 (56.79	5.30 5.28	29.46 29.44)	14		

a) See text. *b*) A, ethyl acetate; B, benzene; H, hexane; I, isopropanol. *c*) Inhibitory effect on the HCl–EtOH-induced ulcer in rats at 10 mg/kg, *p.o.* ($N=3$ or 5). Inhibitory effect of irsogladine maleate as a reference agent was 93% at 10 mg/kg. The statistical significance was evaluated by using Student's *t* test ($p<0.05$). *d*) Inhibitory effect on stress-induced ulcer in rats at 30 mg/kg, *p.o.* ($N=6$). Inhibitory effect of cimetidine as a reference agent was 55% at 100 mg/kg. The statistical significance was evaluated by using Student's *t* test ($p<0.05$). *e*) Lit.[5b] mp 154—156 °C.

Table 3. ^{1}H-NMR Spectroscopic Data (60 MHz, $CDCl_3$) for 2-(1*H*-Pyrazol-1-yl)pyrimidines (**1**, **7**, **8**, **14**—**22**), and the Related Compound **31**

Compd.	H-3′	H-4′	H-5′	H-4	H-5	H-6	Others
1	—	5.46 (s)	—	—	6.36 (s)	—	2.28 (3H, s), 2.48 (3H, s), 3.90 (3H, s), 3.98 (3H, s)
7	—	5.53 (s)	—	8.73 (d, 5)	7.12 (t, 5)	8.73 (d, 5)	2.30 (3H, s), 3.95 (3H, s)
8	—	5.52 (s)	—	8.57 (d, 5)	7.00 (d, 5)	—	2.32 (3H, s), 2.60 (3H, s), 3.93 (3H, s)
14	—	6.23 (d, 3)	8.39 (d, 3)	—	6.33 (s)	—	2.40 (3H, s), 2.45 (3H, s), 3.95 (3H, s)
15	—	6.26 (d, 3)	8.43 (d, 3)	8.40 (d, 6)	6.55 (d, 6)	—	2.41 (3H, s), 4.05 (3H, s)
16	—	6.24 (d, 3)	8.46 (d, 3)	8.50 (d, 5)	6.94 (d, 5)	—	2.41 (3H, s), 2.54 (3H, s)
17	—	6.25 (d, 3)	8.44 (d, 3)	8.62 (d, 5)	7.07 (t, 5)	8.62 (d, 5)	2.41 (3H, s)
18	7.84 (br)	[a]	8.63 (d, 3)	—	6.48 (s)	—	2.53 (3H, s), 4.07 (3H, s)
19	7.81 (br)	[a]	8.54 (d, 3)	—	6.42 (s)	—	1.40 (3H, t, 7), 2.48 (3H, s), 4.50 (2H, q, 7)
20	7.76 (br)	6.3—6.5 (m)	8.48 (d, 3)	—	6.55 (d, 6)	8.36 (d, 6)	4.03 (3H, s)
21	7.77 (br)	6.3—6.5 (m)	8.54 (d, 3)	8.47 (d, 5)	6.97 (d, 5)	—	2.55 (3H, s)
22	7.78 (br)	6.3—6.5 (m)	8.53 (d, 3)	8.64 (d, 5)	7.12 (t, 5)	8.64 (d, 5)	
31	7.73 (br)	6.4—6.5 (m)	8.53 (d, 3)	—	7.41 (s)	—	2.52 (3H, s), 4.04 (3H, s)

Chemical shifts in δ and coupling constants in Hz. *a*) Overlapped with the signal of H-5.

Table 4. ^{1}H-NMR Spectroscopic Data (60 MHz, $CDCl_3$) for the 2-(1*H*-Imidazol-1-yl)- and 2-(1*H*-1,2,4-Triazol-1-yl)pyrimidines (**23**—**29**), and the Related Compound **32**

Compd.	H-2′	H-3′	H-4′	H-5′	H-4	H-5	H-6	Others
23	8.53 (br)	—	7.10 (br)	7.8—7.9 (m)	—	6.41 (s)	—	2.44 (3H, s), 4.00 (3H, s)
24	8.56 (br)	—	7.15 (br)	7.8—7.9 (m)	—	6.41 (s)	—	1.43 (3H, t, 7), 2.43 (3H, s), 4.46 (2H, q, 7)
25	8.61 (br)	—	7.14 (br)	7.8—7.9 (m)	—	6.62 (d, 6)	8.36 (d, 6)	4.05 (3H, s)
26	8.57 (br)	—	7.14 (br)	7.8—7.9 (m)	—	6.98 (d, 5)	8.42 (d, 5)	2.48 (3H, s)
27	8.60 (br)	—	[a]	7.8—7.9 (m)	8.67 (d, 5)	7.17 (t, 5)	8.67 (d, 5)	
28	—	8.15 (s)	—	9.19 (s)	—	6.57 (s)	—	2.55 (3H, s), 4.08 (3H, s)
29	—	8.24 (s)	—	9.35 (s)	8.91 (d, 5)	7.44 (t, 5)	8.91 (d, 5)	
32	8.43 (br)	—	7.17 (br)	7.6—7.7 (m)	—	6.86 (s)	—	2.50 (3H, s), 3.98 (3H, s)

Chemical shifts in δ and coupling constants in Hz. *a*) Overlapped with the signal of H-5.

Biology

Compounds **14**—**29**, **31**, **32**, **36a**—**l**, and **37a**—**i** were tested for gastric cytoprotective activity in rats.[14] The test compounds (10 mg/kg) suspended in 1% carboxymethyl cellulose (CMC) or 1% CMC for the control were orally administered 30 min before HCl–ethanol administration. The ulcer lengths of the treated and control groups were compared and the inhibitory rates were calculated.

The antiulcer effects of compounds **14**—**29**, **31**, and **32**, which are related to mepirizole (**1**), are summarized in

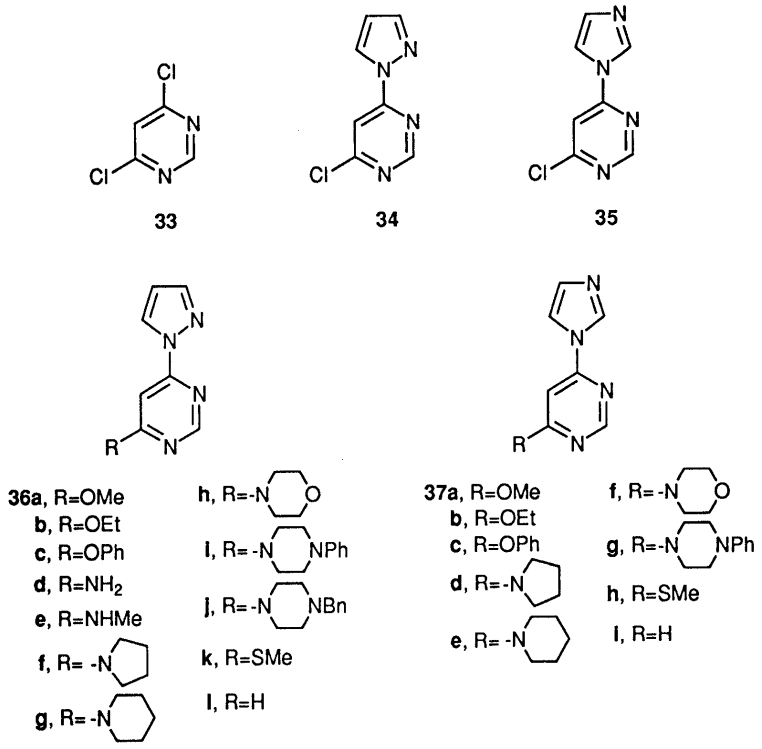

Chart 2

Table 5. Preparation and Antiulcer Effects (*p.o.*) of the 4-(1*H*-Pyrazol-1-yl)pyrimidines (**36**)

Compound No.	Method[a] Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition (%) HEU[c]
2							90
36a	D (75)	108.5—109 (H)	$C_8H_8N_4O$	54.54 (54.97	4.58 4.41	31.80 32.09)	14
36b	D (89)	Oil	$C_9H_{10}N_4O$		[d]		13
36c	E (73)	92.5—93.5 (H)	$C_{13}H_{10}N_4O_4 \cdot 1/5H_2O$	64.56 (64.65	4.33 4.48	23.16 22.88)	29
36d	F (92)	236.5—237 (M)	$C_7H_7N_5$	52.16 (52.61	4.38 4.32	43.46 43.10)	6
36e	G (92)	122—124 (B)	$C_8H_9N_5$	54.84 (55.07	5.18 5.18	39.98 40.27)	62
36f	H (78)	91—92 (H–A)	$C_{11}H_{13}N_5$	61.38 (61.35	6.09 6.09	32.54 31.97)	2
36g	H (95)	Oil			[e]		79
36h	H (70)	99—101 (H–A)	$C_{11}H_{13}N_5O$	57.13 (57.55	5.67 5.65	30.28 30.33)	58
36i	H (71)	151—151.5 (H–A)	$C_{17}H_{18}N_6$	66.65 (66.66	5.92 5.84	27.43 26.80)	−30
36j	H (92)	Oil	$C_{18}H_{20}N_6$	67.48 (67.58	6.29 6.27	26.23 26.02)	82
36k	I (88)	58.5—59.5 (H–A)	$C_8H_9N_5S$	49.98 (50.28	4.19 4.15	29.15 29.30)	59
36l	J (96)	95—95.5[f] (H)	$C_7H_6N_4$	57.52 (57.81	4.14 3.87	38.34 38.58)	37

a) See text. *b*) A, ethyl acetate; B, benzene; H, hexane; M, methanol. *c*) Inhibitory effect on the HCl–EtOH-induced ulcer in rats at 10 mg/kg, *p.o.* ($N=3$ or 5). Inhibitory effect of irsogladine maleate as a reference agent was 93% at 10 mg/kg. The statistical significance was evaluated by using Student's *t* test ($p<0.05$). *d*) Exact MS *m/z*: Calcd for $C_9H_{10}N_4O$: 190.0854. Found: 190.0858. *e*) Characterized as its picrate, mp 172—174 °C (from ethanol): *Anal.* Calcd for $C_{18}H_{18}N_8O_7$: C, 47.16; H, 3.96; N, 24.45. Found: C, 47.41; H, 3.86; N, 24.66. *f*) Lit.[7] mp 94—95 °C.

Tables 1 and 2. The results indicate that (i) the substituents on the pyrazole ring of **1** are not necessarily required, and the 5-methoxy-3-methylpyrazolyl group of **1** can be replaced by a 3-methylpyrazolyl or pyrazolyl group, or even by an imidazolyl group, although the activity of the latter compound is slightly decreased; (ii) the replacement of the pyrazolyl ring of **1** by the 1,2,4-triazolyl ring was not effective; (iii) the substituents on the pyrimidine ring seem to be more important; an alkoxy and/or methyl group at the 4- (and/or 6-) position(s) increased the effect, with

Table 6. Preparation and Antiulcer Effects (*p.o.*) of the 4-(1*H*-Imidazol-1-yl)pyrimidines (**37**)

Compound No.	Method[a] Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition (%) HEU[c]	LD_{50} (mg/kg, *p.o.*)
37a	D (37)	153—154 (H–A)	$C_8H_8N_4O$	54.54 (54.06)	4.58 4.50	31.80 31.41)	48	300—1000
37b	D (41)	82.5—83 (H–A)	$C_9H_{10}N_4O$	56.83 (56.84)	5.31 5.02	29.46 29.52)	84	<300
37c	E (93)	122.5—123 (H–A)	$C_{13}H_{10}N_4O$	65.53 (65.50	4.23 3.86	23.52 23.49)	50	
37d	H (70)	150.5—151 (H–A)	$C_{11}H_{13}N_5$	61.38 (61.53	6.09 6.03	32.54 32.77)	67	
37e	H (85)	107—109 (H–A)	$C_{12}H_{15}N_5$	62.86 (63.14	6.60 6.63	30.55 30.68)	68	
37f	H (68)	154—155 (H–A)	$C_{11}H_{13}N_5O$	57.13 (57.55	5.67 5.52	30.28 30.33)	53	
37g	H (85)	132—133 (H–A)	$C_{17}H_{18}N_6$	66.65 (66.96	5.92 5.90	27.43 27.05)	71	
37h	I (68)	130.5—132 (B)	$C_8H_8N_4S$	49.98 (50.06	4.19 4.05	29.05 29.26)	36	
37i	J (32)	121.5—122.5 (H–A)	$C_7H_6N_4$	57.52 (57.65	4.14 4.00	38.34 38.59)	32	

a) See text. *b*) A, ethyl acetate; B, benzene; H, hexane. *c*) Inhibitory effect on the HCl–EtOH-induced ulcer in rats at 10 mg/kg, *p.o.* ($N=3$ or 5). Inhibitory effect of irsogladine maleate as a reference agent was 93% at 10 mg/kg. The statistical significance was evaluated by using Student's *t* test ($p<0.05$).

Table 7. ^{1}H-NMR Spectroscopic Data (60 MHz, $CDCl_3$) for the 4-(1*H*-Pyrazol-1-yl)pyrimidines (**36**)

Compd.	H-3′	H-4′	H-5′	H-2	H-5	Others
36a	7.73 (br)	6.4—6.6 (m)	8.51 (d, 3)	8.57 (br)	7.24 (s)	4.00 (3H, s)
36b	7.73 (br)	6.4—6.5 (m)	8.52 (d, 3)	8.55 (br)	7.24 (s)	1.40 (3H, t, 7), 4.45 (2H, q, 7)
36c	7.72 (br)	6.4—6.5 (m)	8.52 (d, 3)	8.56 (s)	[a]	7.0—7.6 (6H, m)
36d[b]	7.86 (br)	6.5—6.65 (m)	8.58 (d, 3)	8.38 (s)	7.00 (s)	7.22 (2H, br)
36e	7.68 (br)	6.3—6.5 (m)	8.46 (d, 3)	8.35 (s)	7.00 (s)	3.00 (3H, d, 6), 5.3 (1H, br)
36f	7.72 (br)	6.3—6.5 (m)	8.51 (d, 3)	8.41 (s)	6.81 (s)	1.8—2.2 (4H, m), 3.3—3.7 (4H, br)
36g	7.67 (br)	6.2—6.5 (m)	8.49 (d, 3)	8.38 (s)	7.02 (s)	1.59 (6H, br), 3.5—3.8 (4H, br)
36h	7.68 (br)	6.3—6.5 (m)	8.48 (d, 3)	8.40 (s)	7.05 (s)	3.72 (8H, s)
36i	7.73 (br)	6.3—6.6 (m)	8.54 (d, 3)	8.48 (s)	7.00 (s)	3.1—3.4 (4H, m), 3.75—4.0 (4H, m), 6.8—7.5 (5H, m)
36j	7.70 (br)	6.3—6.5 (m)	8.51 (d, 3)	8.42 (s)	7.08 (s)	2.3—2.6 (4H, m), 3.45 (2H, s), 3.55—3.8 (4H, m), 7.32 (5H, s)
36k	7.73 (br)	6.4—6.55 (m)	8.53 (d, 3)	8.70 (s)	[c]	2.59 (3H, s)
36l	7.75 (br)	6.4—6.6 (m)	8.54 (d, 3)	8.94 (br s)	7.86 (dd, 6, 2)	8.68 (1H, d, 6)

Chemical shifts in δ and coupling constants in Hz. *a*) Overlapped with the signal of the phenyl group. *b*) Taken in dimethyl sulfoxide-d_6. *c*) Overlapped with the signal of H-3′.

Table 8. ^{1}H-NMR Spectroscopic Data (60 MHz, $CDCl_3$) for 4-(1*H*-Imidazol-1-yl)pyrimidines (**37**)

Compd.	H-2′	H-4′	H-5′	H-2	H-5	Others
37a	8.40 (br)	7.18 (br)	7.5—7.7 (m)	8.64 (s)	6.67 (s)	4.03 (3H, s)
37b	8.33 (br)	7.10 (br)	7.4—7.6 (m)	8.50 (s)	6.58 (s)	1.41 (3H, t, 7), 4.43 (2H, q, 7)
37c	8.30 (br)	[b]	7.6—7.7 (m)	8.44 (s)	6.84 (s)	6.9—7.6 (6H, m)
37d	8.32 (br)	7.11 (br)	7.5—7.6 (m)	8.36 (s)	6.12 (s)	1.8—2.2 (4H, m), 3.3—3.7 (4H, m)
37e	8.36 (br)	7.16 (br)	7.55—7.65 (m)	8.43 (s)	6.40 (s)	1.5—1.9 (6H, br), 3.5—3.9 (4H, br)
37f	8.35 (br)	7.16 (br)	7.5—7.6 (m)	8.48 (s)	6.40 (s)	3.5—4.0 (4H, s)
37g	8.35 (s)	[b]	7.5—7.65 (m)	8.45 (s)	6.40 (s)	3.1—3.4 (4H, m), 3.7—3.8 (4H, m)
37h	8.40 (br)	7.15—7.3 (m)	7.55—7.7 (m)	8.79 (s)	7.13 (s)	2.65 (3H, s)
37i	8.42 (br)	7.20 (m)	7.55—7.7 (m)	9.02 (s)	7.28 (dd, 6, 2)	8.74 (1H, d, 6)

Chemical shifts in δ and coupling constants in Hz. *a*) Taken in dimethyl sulfoxide-d_6. *b*) Overlapped with the signal of the phenyl group.

the exception of **26**, which showed unusually low activity (17%); (iv) transposition of the 2-pyrazolyl or 2-imidazolyl group and the 4-methoxy group apparently decreased the effects (27% for **31** and 14% for **32**).

The results obtained for the dulcerozine analogues **36a—l**, and **37a—i** are summarized in Tables 5 and 6. The 4-alkoxy-6-(1*H*-pyrazol-1-yl)pyrimidines (**36a, b**) showed a very weak effect. The 4-alkoxy-6-(1*H*-imidazol-1-yl)-pyrimidines (**37a, b**) showed slightly higher cytoprotective activity, but were still less effective than **2**. Replacement

of the 4-alkoxy group of **36a, b** and **37a, b** by other substituents such as phenoxy, amino, cyclic amino, and methylthio groups or hydrogen decreased the potency, which ranged from moderate to inactive.

Antiulcer activity of some compounds having high protective effects was also examined in the water-immersion stress-induced ulcer model in rats.[15] The compounds were administered orally 5 min before stress and the effect was evaluated in terms of the total length (mm) of each lesion. The results are summarized in Tables 1 and 2.

Of these compounds, 4-methoxy-6-methyl-2-(1*H*-pyrazol-1-yl)pyrimidine (**18**) showed a potent inhibition of both HCl–ethanol-induced (93%) and water-immersion stress-induced ulcers (80%) in rats as well as low acute toxicity (oral LD_{50}, 300—1000 mg/kg in rats). Compound **18** was selected for further biological evaluation.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) spectrometer, using tetramethylsilane as an internal standard. Chemical shifts are recorded in δ values in ppm and coupling constants (J) are given in hertz (Hz); s, d, t, q, sept, m, and br indicate singlet, triplet, quartet, septet, multiplet, and broad, respectively. Column chromatography was performed on Silica gel 60 PF_{254} (Merck) under pressure.

Materials 2-Bromopyrimidine (**13**), 2,4-dichloro-6-methylpyrimidine, and 4,6-dichloropyrimidine (**33**) were obtained commercially. 2-Hydrazino- (**3**) and 2-hydrazino-4-methyl-pyrimidines (**4**),[9] 2-chloro-4-methoxy-6-methyl- (**9**) and 4-chloro-2-methoxy-6-methylpyrimidines (**30**),[9] 2-chloro-4-ethoxy-6-methylpyrimidine (**10**),[16] 2-chloro-4-methoxypyrimidine (**11**),[17] and 2-chloro-4-methylpyrimidine (**12**)[18] were prepared according to the reported procedures.

General Procedure for the Preparation of 2-(5-Methoxy-3-methyl-1*H*-pyrazol-1-yl)pyrimidines (7 and 8) Procedure A: A solution of 2-hydrazinopyrimidine (**3**) (1.1 g, 8.5 mmol) and ethyl acetoacetate (1.3 ml, 10.2 mmol) in methanol (3 ml) was refluxed for 2 h. Then a 3 N sodium hydroxide solution (3.85 ml) was added and the mixture was refluxed for 1 h. The solvent was evaporated off, and the residue was neutralized with acetic acid and extracted with chloroform. The extract was dried (Na_2SO_4) and concentrated. Recrystallization of the residual solid from petroleum benzin gave 2,4-dihydro-5-methyl-2-(2-pyrimidinyl)-3*H*-pyrazol-3-one (**5**) (275 mg, 15%). Dimethyl sulfate (0.39 ml, 4.1 mmol) was added to a solution of **5** (275 mg, 1.56 mmol) and NaOH (155 mg, 3.9 mmol) in methanol (6 ml), and the whole was refluxed for 2.5 h. The methanol was evaporated off, and the residue was dissolved in dichloromethane. The solution was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt; 1 : 2) and then recrystallized from hexane to give **7** (122 mg, 41%).

Similarly, 2-(5-methoxy-3-methyl-1*H*-pyrazol-1-yl)-4-methylpyrimidine (**8**) (178 mg, 6%) was obtained from 2-hydrazino-4-methylpyrimidine (**4**) (1.68 g, 13.5 mmol). The yields of **7** and **8** were not optimized.

General Procedure for the Preparation of 2-(3-Methyl-1*H*-pyrazol-1-yl)- (14—17), 2-(1*H*-Pyrazol-1-yl)- (18—22), 2-(1*H*-Imidazol-1-yl)- (23—27), and 2-(1*H*-1,2,4-Triazol-1-yl)pyrimidines (28 and 29) Procedure B: The following is a typical example. A solution of 3-methylpyrazole (410 mg, 5.0 mmol) in THF (10 ml) was added to a suspension of NaH (200 mg, 60% in oil, washed with pentane, 5.0 mmol) in THF (7 ml) under a nitrogen atmosphere at 0 °C and the mixture was stirred until evolution of hydrogen gas ceased (0.5—1 h). A solution of 2-chloro-4-methylpyrimidine (**12**) (643 mg, 5.0 mmol) in THF (10 ml) was added to the above solution and the whole was stirred at room temperature overnight. The solvent was evaporated off, and the residue was diluted with water and extracted with dichloromethane. The extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 9 : 1). Recrystallization from hexane gave **16** (572 mg, 66%). The results are shown in Tables 1—4.

4-Chloro-6-(1*H*-pyrazol-1-yl)pyrimidine (34) Procedure C: A solution of pyrazole (136 mg, 2.0 mmol) in THF (3 ml) was added to a suspension of NaH (80 mg, 60% in oil, washed with pentane, 2.0 mmol) in THF (2 ml) under a nitrogen atmosphere at 0 °C and the mixture was stirred at room temperature until evolution of hydrogen gas ceased (20 min). A solution of 4,6-dichloropyrimidine (**33**) (298 mg, 2.0 mmol) in THF (3 ml) was added to the above solution and the whole was stirred at room temperature overnight. The solvent was evaporated off, the residue was diluted with water and extracted with dichloromethane. The extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH, 30 : 1). The first eluate gave **34** (296 mg, 82%), as colorless needles, mp 128—129 °C (from hexane). ^{1}H-NMR ($CDCl_3$) δ: 6.4—6.6 (1H, m), 7.80 (1H, br), 7.98 (1H, s), 8.54 (1H, d, J=3 Hz), 8.76 (1H, s). *Anal.* Calcd for $C_7H_5ClN_4$: C, 46.55; H, 2.79; N, 31.02. Found: C, 46.50; H, 2.52 N, 31.42. The second eluate gave 4,6-bis(1*H*-pyrazol-1-yl)pyrimidine (29 mg, 7%), mp 133—133.5 °C (from hexane) (lit.,[7] mp 122 °C). ^{1}H-NMR ($CDCl_3$) δ: 6.4—6.6 (2H, m), 7.78 (2H, br), 8.45 (1H, s), 8.56 (2H, d, J=3 Hz), 8.76 (1H, br s). *Anal.* Calcd for $C_{10}H_8N_6$: C, 56.59; H, 3.80; N, 39.61. Found: C, 56.67; H, 3.76; N, 39.89.

4-Chloro-6-(1*H*-imidazol-1-yl)pyrimidines (35) According to the procedure C, 4,6-dichloropyrimidine (**33**) (298 mg, 2.0 mmol) was treated with imidazole (136 mg, 2.0 mmol) and NaH (80 mg, 60% in oil, 2.0 mmol) to give **35** (283 mg, 79%) and 4,6-bis(1*H*-imidazol-1-yl)-pyrimidine (11 mg, 3%).

Compound **35** has mp 131.5—132 °C (from hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 7.28 (1H, br), 7.43 (1H, s), 7.6—7.8 (1H, m), 8.47 (1H, br s), 8.89 (1H, s). *Anal.* Calcd for $C_7H_5ClN_4$: C, 46.55; H, 2.79; N, 31.02. Found: C, 46.73; H, 2.47; N, 31.17.

4,6-Bis(1*H*-imidazol-1-yl)pyrimidine has mp 243—245 °C (from iso-PrOH). ^{1}H-NMR (DMSO-d_6) δ: 7.24 (2H, br), 8.05—8.15 (2H, m), 8.25 (1H, br), 8.73 (2H, br), 9.00 (1H, s). *Anal.* Calcd for $C_{10}H_8N_6$: C, 56.59; H, 3.80; N, 39.61. Found: C, 56.61; H, 3.76; N, 39.43.

General Procedure for the Preparation of 4-Alkoxy-6-(1*H*-pyrazol-1-yl)- (36a, b) and 6-(1*H*-imidazol-1-yl)pyrimidines (37a, b) Procedure D: The following is a typical example. A solution of **34** (180 mg, 1 mmol) in methanol (2 ml) was added to a solution of sodium methoxide in methanol [prepared from sodium (23 mg, 1 mmol) and absolute methanol (3 ml)] and the whole was stirred at room temperature overnight. Methanol was evaporated off and the residue was dissolved in dichloromethane (20 ml). The solution was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (chloroform) to give 4-methoxy-6-(1*H*-pyrazol-1-yl)pyrimidine (**36a**) (132 mg, 75%).

General Procedure for the Preparation of 4-Phenoxy-6-(1*H*-pyrazol-1-yl)- (36c) and 6-(1*H*-Imidazol-1-yl)pyrimidines (37c) Procedure E: A solution of **34** (180 mg, 1.0 mmol), phenol (175 mg, 1.9 mmol), and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (152 mg, 1.0 mmol) in benzene (10 ml) was refluxed for 7 h. The reaction mixture was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on alumina (hexane–AcOEt, 2 : 1) to give **36c** (175 mg, 73%) as colorless needles. Similarly, **37c** (234 mg, 98%) was obtained from **35** (180 mg, 1.0 mmol) and phenol (175 mg, 1.9 mmol).

4-Amino-6-(1*H*-pyrazol-1-yl)pyrimidine (36d) Procedure F: A mixture of **34** (180 mg, 1.0 mmol) and 30% ammonium hydroxide solution (3 ml) was heated in a sealed tube at 140 °C (bath temperature) for 30 h. After cooling, the precipitated crystals were collected and recrystallized from methanol to give **36d** (148 mg, 92%) as colorless scales.

4-Methylamino-6-(1*H*-pyrazol-1-yl)pyrimidine (36e) Procedure G: Methylamine (0.15 ml, 1.67 mmol) and triethylamine (0.15 ml, 1.11 mmol) were added to a solution of **34** (200 mg, 1.11 mmol) in ethanol (3 ml) and the mixture was refluxed for 2.5 h. The solvent was evaporated off and the residue was dissolved in dichloromethane. The solution was washed with brine, dried ($MgSO_4$), and concentrated. The residual solid was recrystallized from benzene to give **36e** (175 mg, 90%).

General Procedure for the Preparation of 4-(Piperidin-1-yl)-6-(1*H*-pyrazol-1-yl)- (36g) and 4-(1*H*-Imidazol-1-yl)-6-(piperidin-1-yl)pyrimidines (37e) Procedure H: Piperidine (1 ml, 10 mmol) was added dropwise to a solution of **34** (302 mg, 1.68 mmol) in acetone (5 ml) and the mixture was refluxed for 30 min. The solvent was evaporated off and the residue was dissolved in dichloromethane. The solution was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 30 : 1) to give **36g** (365 mg, 95%) as an oil, which formed the picrate, mp 172—174 °C (from ethanol). Similarly, **37e** (327 mg, 85%) was obtained from **35** (303 mg, 1.68 mmol) and piperidine (1 ml, 10 mmol).

General Procedure for the Preparation of 4-Methylthio-6-(1*H*-pyrazol-

1-yl)- (36k) and 4-Methylthio-6-(1*H*-imidazol-1-yl)pyrimidines (37h) Procedure I: A 15% aqueous solution of sodium thiomethoxide (1.4 ml) was added to a solution of **34** (544 mg, 3.0 mmol) in acetone (7 ml) and the solution was stirred at room temperature for 2 h. The whole was concentrated and water was added. The precipitated crystals were collected and dried to give **36k** (510 mg, 88%). Similarly, **37h** (283 mg, 68%) was obtained from **35** (394 mg, 2.2 mmol) and sodium thiomethoxide.

General Procedure for the Preparation of 4-(1*H*-Pyrazol-1-yl)- (36l) and 4-(1*H*-Imidazol-1-yl)pyrimidines (37i) Procedure J: A mixture of **34** (180 mg, 1 mmol), sodium acetate (82 mg, 1 mmol), and 5% palladium-carbon (40 mg) in methanol (40 ml) was stirred under a hydrogen atmosphere at room temperature and an atmospheric pressure overnight. The catalyst was removed in dichloromethane and the solution was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. The residual solid was recrystallized from hexane to give **36l** (141 mg, 96%). Similarly, **37i** (131 mg, 32%) was obtained from **35** (500 mg, 2.77 mmol).

Pharmacological Methods Animals: Male Sprague-Dawley rats (230—270 g, Nihon, Charles-River, Kanagawa, Japan) were used in the experiments. The rats were deprived of food for 24 h beforehand. Drinking water was provided freely for the initial 22 h, but was withheld for 2 h before the start of the experiments.

Effect on HCl–Ethanol Ulcers This test was carried out according to the method of Mizui and Doteuchi.[14] Three or eight rats were used for the control and experimental groups. Gastric mucosal ulcers were induced by giving 1 ml/200 g body wt. of 60% ethanol (v/v) in 150 mM HCl orally, and 1 h later the animals were killed. The stomach was removed, and the gastric contents were expelled through the duodenum by gentle pressure on the gastric wall. The stomach was inflated by injecting 10 ml of 2% formalin to fix the gastric wall, then incised along the greater curvature and examined for lesions. The length (mm) of each lesion was measured under a dissecting microscope (× 10) with a square grid, and lesion severity was expressed as the total length of lesions per stomach. Each test compound (10 mg/kg) suspended in 1% CMC, or 1% CMC alone for the control, was orally administered 30 min before HCl–ethanol administration. The ulcer length of the treated and control groups were compared and the inhibitory effects were evaluated. The results are summarized in Tables 1, 2, 5 and 6.

Effect on Stress Ulceration This experiment was carried out according to the method of Takagi and Okabe.[15] Eight rats were individually immobilized in each compartment of the stress cage. The cage was immersed vertically in a water bath at 22 °C to the height of the xiphoid process of the rats. After 7 h, the rats were killed. The stomachs were removed and incised along the greater curvature. The maximum diameter of each lesion was measured under a dissecting microscope. The total length (mm) of each lesion was used as the ulcer index. Each test compound (30 mg/kg) suspended in 1% CMC or 1% CMC alone as a control was administered orally 5 min before immersion. The ulcer lengths of the treated and control groups were compared and the inhibitory rates were calculated. The results are summarized in Tables 1 and 2.

Acute Toxicity on Oral Administration to Rats A 0.3% CMC–Na suspension of a test compound was orally administered to groups of Slc:Wistar/KY rats (male: 90—120 g), each group consisting of 10 rats. After 72 h, LD_{50} values were calculated by the Probit method.[19]

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References

1) Soll A. H., "Gastrointestinal Disease," ed. by Sleisenger M. H., Fordtran J. S., W. B. Saunders Co., Philadelphia, 1993, pp. 580—679.
2) *a*) Naito T., Yoshikawa T., Kitahara S., Aoki N., *Chem. Pharm. Bull.*, **17**, 1467—1478 (1969); *b*) Akimoto T., Tsukada K., Yamasaki T., Kojima H., Kasahara A., Akashi A., Yamaguchi K., Oshima Y., *Folia Pharmacol. Jpn.*, **65**, 378—409 (91969); *c*) Tsurumi K., Nosaki M., Hiramatsu Y., Hayashi M., Fujimura H., *ibid.*, **65**, 620—642 (1969).
3) A high dose of **1** (200 mg/kg) is known to induce duodenal ulcers in rats. *a*) Okabe S., Ishihara Y., Inoo H., Tanaka H., *Dig. Dis. Sci.*, **27**, 242—249 (1982); *b*) Ishihara Y., Yamada Y., Hata Y., Okabe S., *ibid.*, **28**, 552—558 (1983).
4) *a*) Kurebayashi Y., Asano M., Hashizume T., Akashi A., *Jpn J. Pharmacol.*, **36**, 121—123 (1984); *b*) *Idem*, *Arch Inter. Pharmacodyn. Ther.*, **271**, 155—168 (1984).
5) Tanaka H., Nakagawa M., Takeuchi K., Okabe S., *Dig. Dis. Sci.*, **34**, 238—245 (1989).
6) *a*) Shirakawa K., Tujikawa T., Tsuda T., *Takeda Kenkyusho Nenpo*, **22**, 19—26 (1963); *b*) *Idem*, *ibid.*, **22**, 27—46 (1963).
7) Steel P. J., Constable E. C., *J. Chem. Research (M)*, **1989**, 1601—1611.
8) Del Corona L., Signorelli G., Manzardo S., Pinzetta A., Coppi G., *Eur. J. Med. Chem.*, **26**, 729—733 (1991).
9) *a*) Vanderhaeghe H., Claesen M., *Bull. Soc. Chim. Belg.*, **68**, 30—46 (1959); *b*) Profft E., Raddatz E., *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **295**, 649—662 (1962); *c*) Takagi K., Ueda T., *Chem. Pharm. Bull.*, **11**, 1382—1388 (1963).
10) For a recent review of the reactivity of the 2-halopyrimidines, see Brown D. J., "The Chemistry of Heterocyclic Compounds, The Pyrimidines," Supplement II, ed. by Weissberger A., Taylor E. C., John Wiley & Sons, Inc., New York, 1985, pp. 157—224.
11) Eluguero J., Jacquier R., Mondon S., *Bull. Soc. Chim. Fr.*, **1970**, 1346—1351.
12) Khan M. A., Pinto A. A. A., *J. Heterocycl. Chem.*, **18**, 9—14 (1981).
13) Johnson T. B., Hilbert G. E., *J. Am. Chem. Soc.*, **52**, 2001—2007 (1930).
14) Mizui T., Doteuchi M., *Jpn. J. Pharmacol.*, **33**, 939—945 (1983).
15) Takagi K., Okabe S., *Jpn. J. Pharmacol.*, **18**, 9—18 (1968).
16) Botta M., De Angelis F., Finizia G., Gambacorta A., Nicoletti R., *Synth. Commun.*, **15**, 27—34 (1985).
17) *a*) Kenner G. W., Reise C. B., Todd A. R., *J. Chem. Soc.*, **1955**, 855—859; *b*) Yamanaka H., *Chem. Pharm. Bull.*, **7**, 297—299 (1959).
18) Matsukawa T., Ohta B., *Yakugaku Zasshi*, **70**, 134—137 (1950).
19) Finney D. J., "Probit Analysis," Cambridge University Press, London, 1952, pp. 185—188.