

Studies on Antiulcer Drugs. V.¹⁾ Synthesis and Antiulcer Activity of Aralkylbenzazoles

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A series of 2-alkylamino-5- or 6-aralkyl-substituted benzazoles were synthesized and tested for histamine H₂-receptor antagonist and anti-stress ulcer activities. These new compounds showed little or no histamine H₂-receptor antagonist activity in contrast to imidazo[1,2-*a*]pyridine analogues (I). On antiulcer assay, however, some pyridine derivatives (II) exerted higher activity than the reference compounds, sofalcone, sucralfate and cimetidine. The structure-activity relationships of these compounds are discussed.

Keywords aralkylbenzazole; anti-stress ulcer activity; histamine H₂-receptor antagonist; structure-activity relationship; sofalcone; sucralfate; cimetidine

In previous papers^{1,2)} we reported the synthesis and pharmacological evaluation of a series of imidazo[1,2-*a*]pyridinylalkylbenzazoles (I) as a novel class of histamine H₂-receptor antagonists (H₂-antagonists) characterized by a semirigid spacer group and a rigid amidino function. Though the structural features of these compounds differ from those of conventional H₂-antagonists originating from cimetidine, several of the derivatives exhibited strong H₂-antagonist activity (Chart 1).

Reports on medicinal chemistry of H₂-antagonists have described that a replacement of the aromatic ring with an alternative type often caused a change in the pharmacological activity.³⁾ In pursuing our structural system to probe a novel antiulcer agent, it was therefore decided to research the possibility of sustaining the H₂-antagonist and antiulcer activities by changing the aromatic moiety of I. As a surrogate of the imidazo[1,2-*a*]pyridine, we introduced the aromatic ring derived from known H₂-antagonists. This paper describes the synthesis and

pharmacological activity of several aromatic substituted aralkylbenzazoles (II—VI).

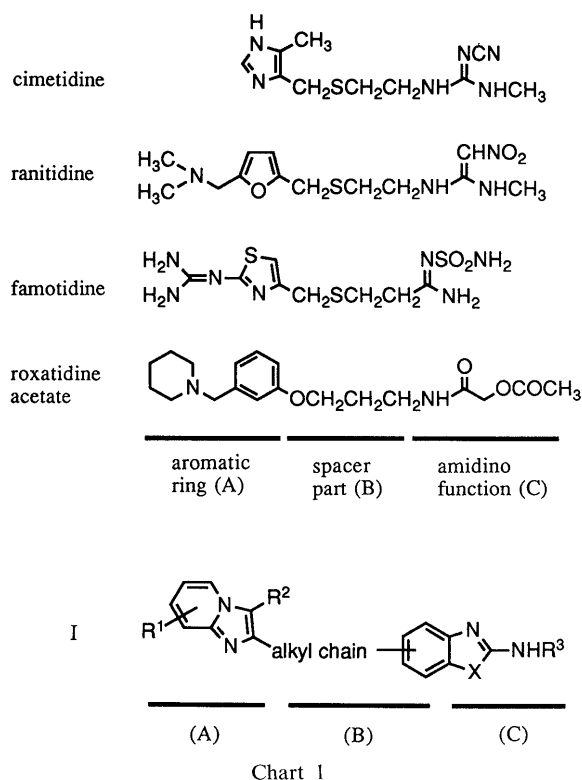
Chemistry

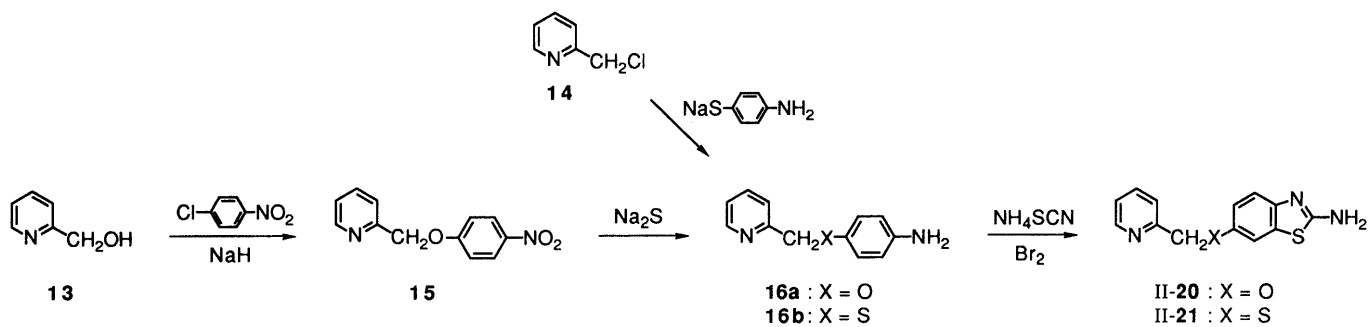
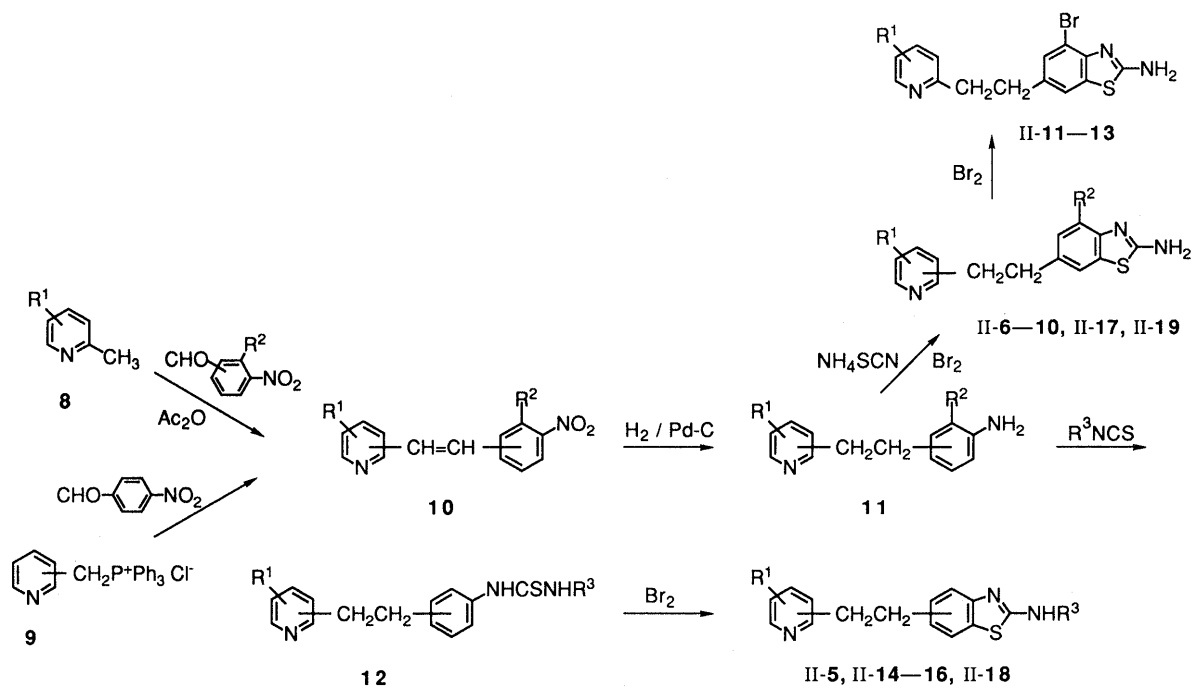
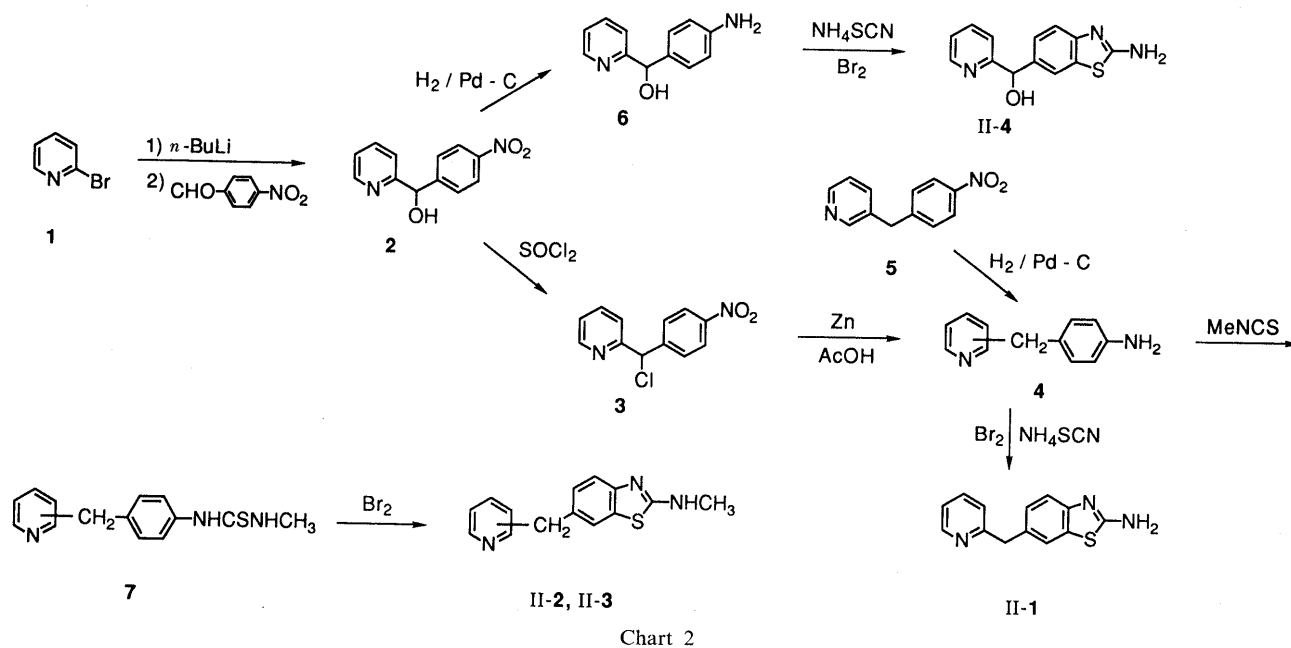
The target compounds listed in Tables I and II were synthesized according to the methods outlined in Charts 2—13.

The pyridinyl derivatives (II) were prepared by the routes shown in Charts 2—6. 2-Lithiopyridine, derived from 2-bromopyridine (1) and *n*-BuLi, was coupled with 4-nitrobenzaldehyde to give 2-(α -hydroxy-4-nitrobenzyl)pyridine (2), which on catalytic reduction yielded the amino derivative (6). Treatment of the alcohol (2) with SOCl₂ provided chloromethylene derivative (3). Dechlorination and simultaneous reduction of the nitro group of 3 with Zn powder in AcOH furnished 2-(4-aminobenzyl)pyridine (4a). 3-Pyridinyl analogue (4b) was obtained by catalytic reduction of 5.⁴⁾ The (4-aminobenzyl)pyridines (4a and 6) were reacted with NH₄SCN and Br₂ to afford the desired 2-aminobenzothiazole derivatives (II-1 and II-4). On treatment of 4 with MeNCS, methylthioureido derivatives (7) were obtained. These compounds (7) were cyclized using Br₂ in CHCl₃ to provide the 2-methylaminobenzothiazoles (II-2 and II-3) (Chart 2).

Compounds 10 having a vinyl linkage between the pyridine ring and nitrobenzene moiety were obtained by the methods described in the literature.⁵⁾ Catalytic reduction of 10 gave the ethylene derivatives (11), which were allowed to react with NH₄SCN and Br₂ to afford the final compounds (II-6—10, II-17 and II-19). Treatment of 11 with alkyl isothiocyanate followed by ring closure with Br₂ produced 2-alkylaminobenzothiazoles (II-5, II-14—16 and II-18). Bromination of II-6, II-7 and II-9 with Br₂ gave 2-amino-4-bromobenzothiazoles (II-11—13) (Chart 3).

Incorporation of a heteroatom into the alkyl linkage was achieved by the modified methods described in the literature. Ullmann type coupling of 2-hydroxymethylpyridine (13) and 4-chloronitrobenzene in the presence of sodium hydride gave 4-nitrophenoxymethylpyridine (15),⁶⁾ which was reduced with Na₂S to yield compound 16a. The thio-analogue (16b) was prepared by condensation of 2-chloromethylpyridine (14) and sodium 4-aminothiophenolate.⁷⁾ These anilines were reacted with NH₄SCN and Br₂ to afford the target compounds (II-20 and II-21) (Chart 4).



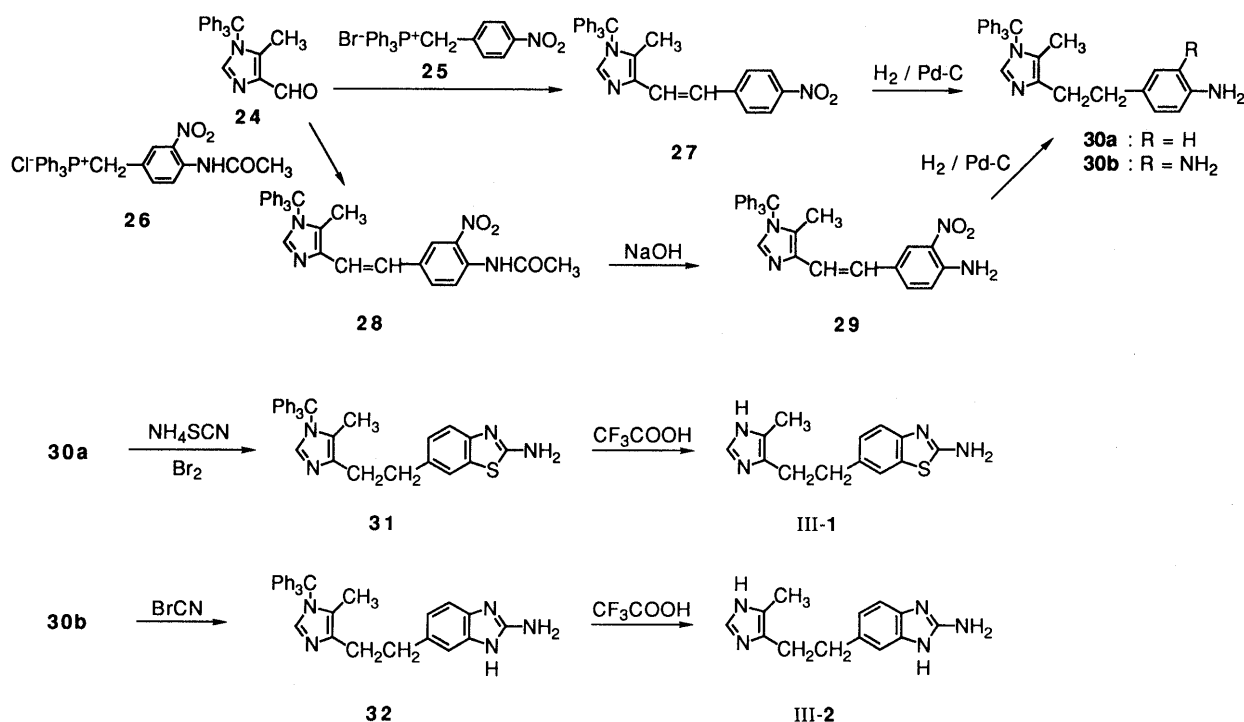
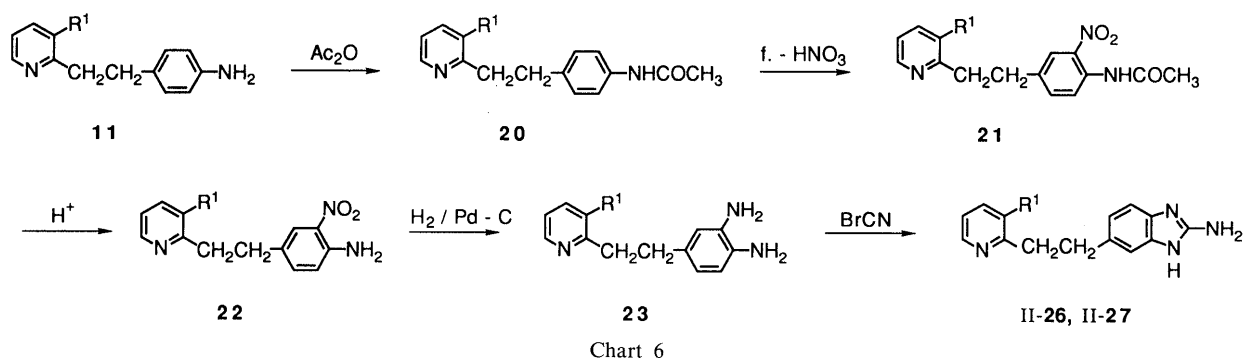
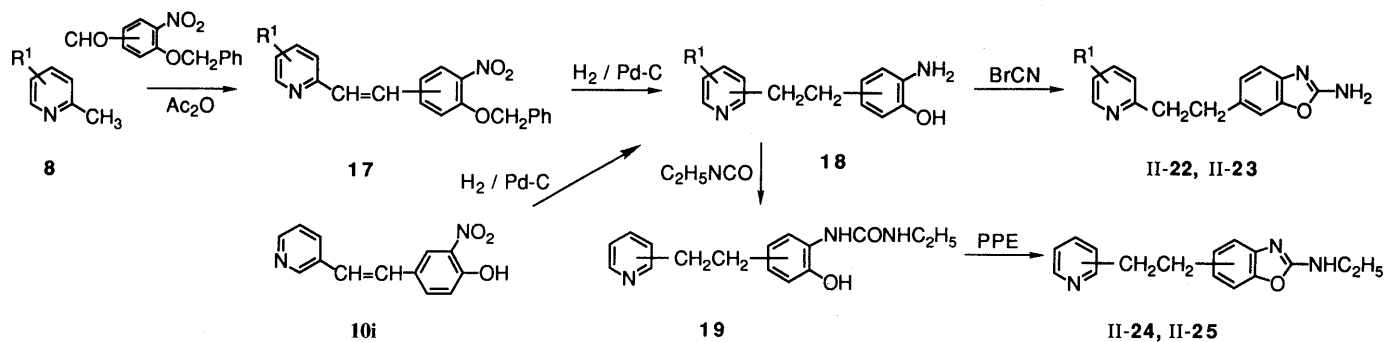


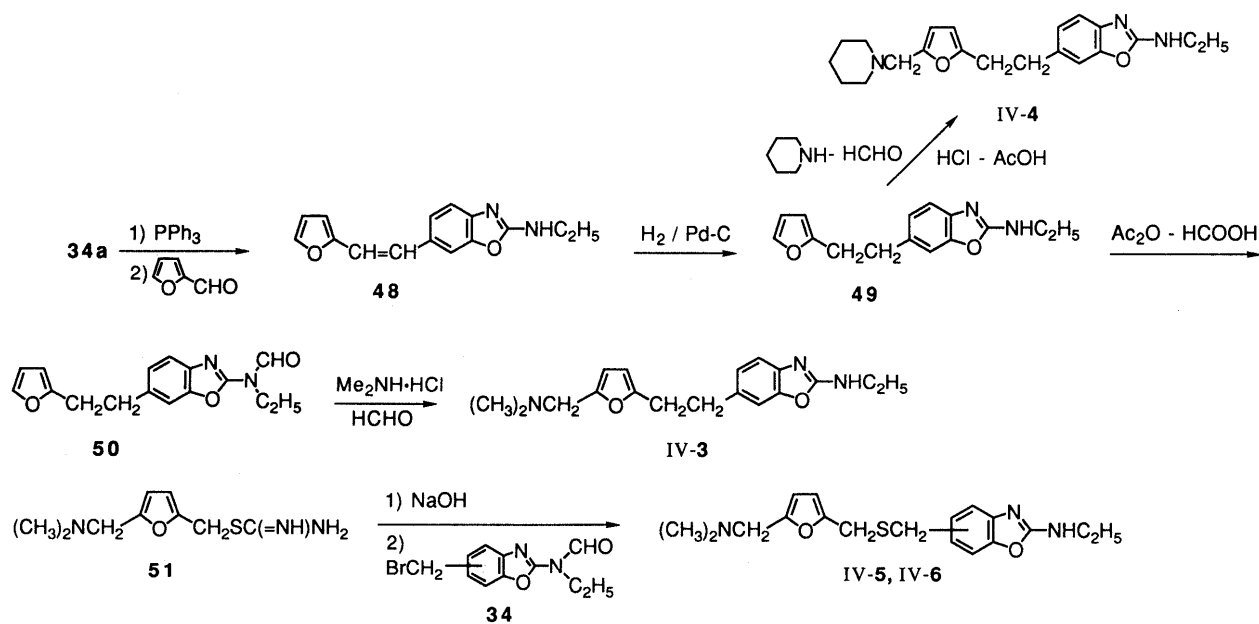
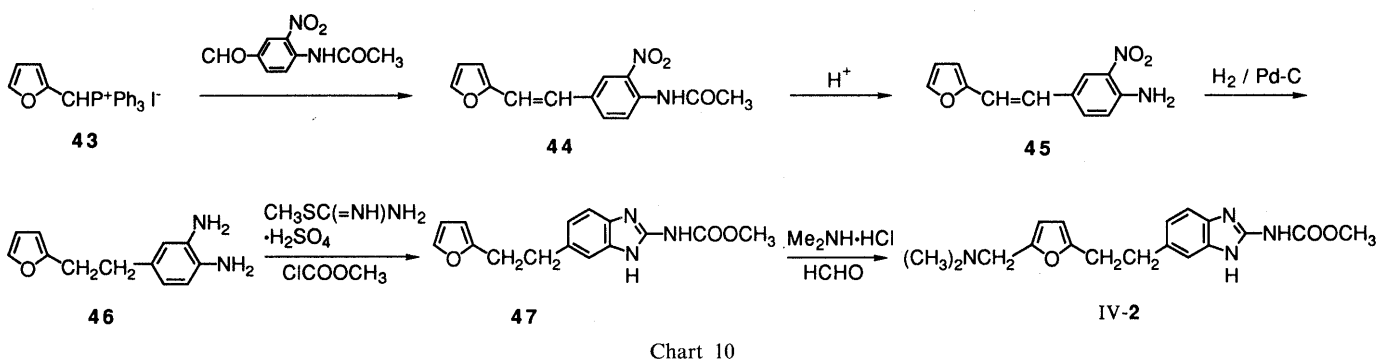
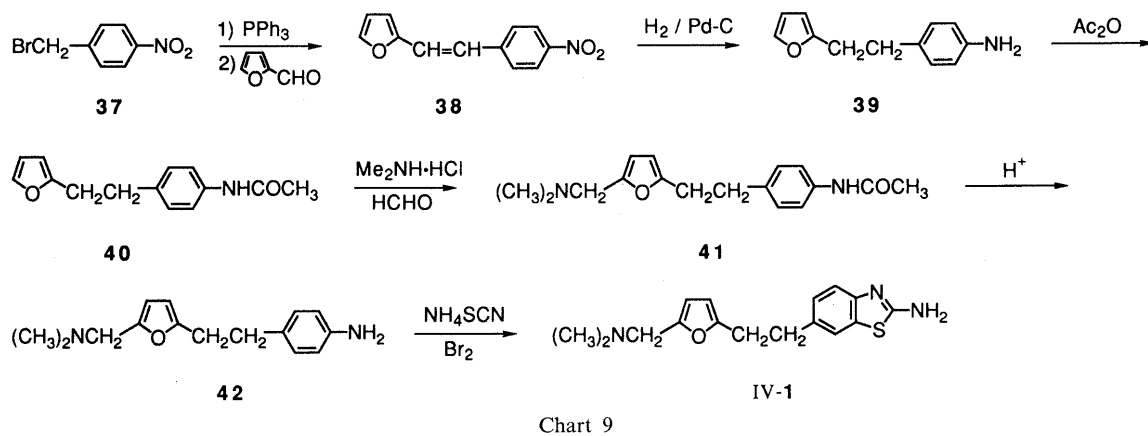
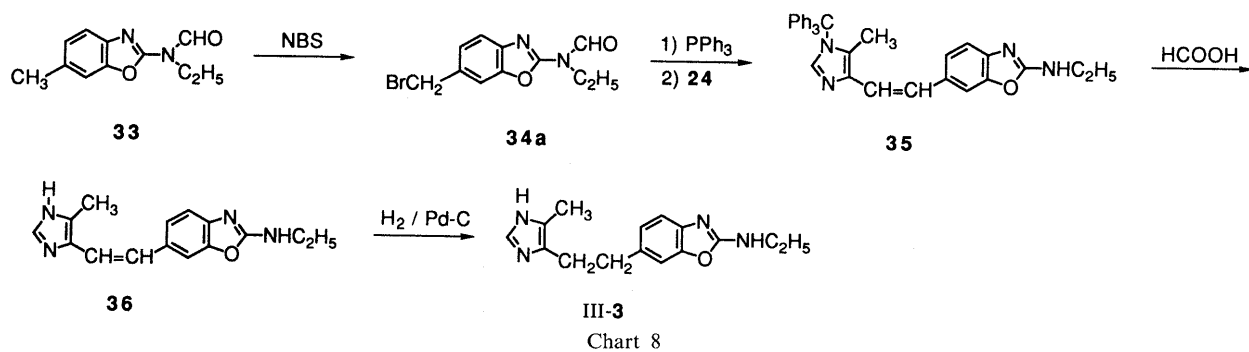
Pyridinylethylbenzoxazoles (II-22—25) were prepared according to the sequence shown in Chart 5. Catalytic hydrogenation of vinyl derivatives (17), obtained by a method similar to that of 10, and subsequent cyclization with BrCN afforded the 2-aminobenzoxazoles (II-22 and II-23). Addition of EtNCO to 18 provided *o*-hydroxyphenylureas (19), which were cyclized in the presence of polyphosphate ester (PPE)⁸ to afford 2-ethylamino-benzoxazoles (II-24 and II-25).

The benzimidazoles (II-26 and II-27) were synthesized

as follows. Acetylation of 11 followed by nitration with fuming nitric acid (*d*=1.50) gave *o*-nitroacetanilides (21), which were hydrolyzed in acidic medium to yield *o*-nitroanilines (22). Catalytic reduction of 22 and subsequent cyclization with BrCN afforded the required compounds (Chart 6).

The synthesis of the imidazolylethyl derivatives (III) was performed through the route given in Charts 7 and 8. Wittig reaction of *N*-protected formylimidazole (24)⁹ with phosphonium bromides (25 and 26) gave the vinyl





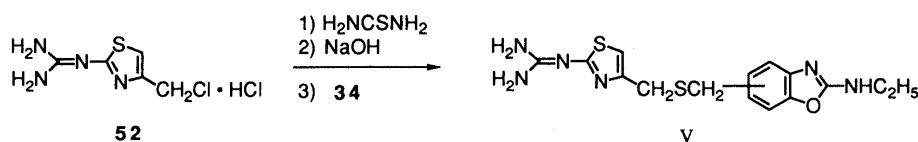


Chart 12

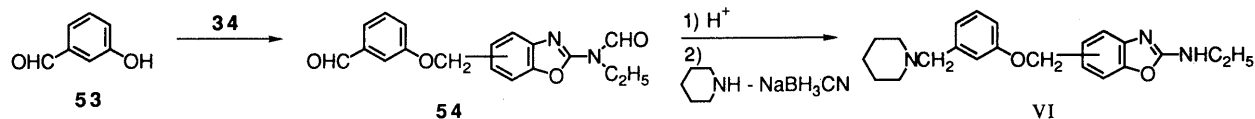


Chart 13

derivatives (**27** and **28**), respectively. After hydrogenation, cyclization of the resultant amino derivatives (**30a** and **30b**) with $\text{NH}_4\text{SCN}-\text{Br}_2$ or BrCN gave the corresponding benzothiazole (**31**) or benzimidazole (**32**), both of which were treated with CF_3COOH to afford the final compounds (**III-1** and **III-2**) (Chart 7). Compound **34a**²⁾ was converted to the phosphonium bromide with PPh_3 and, when reacted with **24**, gave the vinyl derivative (**35**). Treatment of **35** with HCOOH followed by catalytic hydrogenation afforded the target compound (**III-3**) (Chart 8).

The preparation of the furan derivatives (**IV**) was accomplished through the routes in Charts 9–11. Reaction of 4-nitrobenzylbromide (**37**) with PPh_3 , followed by the Wittig reaction of the resulting phosphonium bromide with furfural and then catalytic reduction yielded **39**, which was converted to acetylated derivative (**40**). Mannich reaction of **40** with $\text{Me}_2\text{NH}\cdot\text{HCl}$ and formalin, followed by hydrolysis under acidic condition, and final cyclization with NH_4SCN and Br_2 afforded the benzothiazole derivative (**IV-1**) (Chart 9). The furylethylbenzimidazole derivative (**IV-2**) was obtained by the reaction of phenylene diamine **46**, prepared from phosphonium iodide (**43**) via three steps (Wittig reaction, acid hydrolysis and catalytic reduction), with methylisothiuronium sulfate and methyl chloroformate followed by Mannich reaction (Chart 10). The furylethylbenzoxazole derivatives were prepared by the routes shown in Chart 11. Wittig reaction of phosphonium bromide, derived from **34a** and PPh_3 , with furfural and subsequent hydrogenation produced an ethylene derivative (**49**), which was formylated to give **50**. Mannich reactions of **49** or **50** using piperidine or Me_2NH as a base afforded the final products (**IV-4** and **IV-3**), respectively. After the hydrolysis of furfurylthiourea (**51**) with NaOH ,¹⁰⁾ the resulting thiol was coupled with **34** to provide the products having methylthiomethyl junction (**IV-5** and **IV-6**).

2-Guanidinothiazole derivatives (**V**) and phenoxy derivatives (**VI**) were prepared in a manner similar to that of the furan derivatives (**IV-5** and **IV-6**) (Charts 12 and 13).

Pharmacological Results and Discussion

The compounds listed in Tables I and II were evaluated for antiulcer activity in restraint and water-immersion stressed rats (stress ulcer) and H_2 -antagonist activity using the histamine-stimulated chronotropic response of the isolated guinea pig right atrium.

Contrary to our expectation, all compounds tested

revealed surprisingly poor H_2 -antagonist activity. Moreover, none of the imidazolyl (**III**), furyl (**IV**), or thiazolyl (**V**) or phenyl (**VI**) derivatives possessed notable antiulcer activity (data not shown).

On the other hand, the pyridinyl series (**II**) responded relatively well to antiulcer screening. Compounds in this series having a methylene linkage (**II-1** and **II-2**) showed high activity. Introduction of a hydroxy group (**II-4**) onto the methylene linkage of **II-1** decreased the potency. Compound **II-3**, 3-pyridinyl isomer of **II-2**, also had reduced activity. Elongation of the methylene group of **II-1** to an ethylene chain (**II-6**) exhibited good activity. Substitution of a methyl group at the 3-position (**II-7**) on the pyridine moiety of **II-6** also showed fairly good activity. 4-Methyl (**II-8**) and 5-methyl (**II-9**) isomer of **II-7**, however, revealed marginal activity. Introduction of a substitution at the 4-position on the benzothiazole nuclei (**II-10–12**) caused reduction of the activity in comparison with that of the unsubstituted compounds except for the case of **II-13**. Substitution at the *N*-position on the benzothiazole moiety resulted in a constant (**II-14** and **II-15**) or slight decrease (**II-18**) in activity while introduction of substituents onto two parts (**II-16**) (this position and the pyridine ring) led to marked decreases in activity.

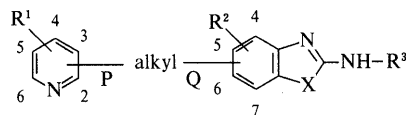
Compound **II-5** which changed the connecting position between the ethylene chain and the benzothiazole nuclei resulted in a fall in the activity. When the position connected to the pyridine ring was converted, 3-pyridinyl derivative (**II-17**) appeared to possess high activity but the activity of the 4-pyridinyl analogue (**II-19**) was low. Insertion of a heteroatom to the alkylchain (**II-20** and **II-21**) conferred reduced activity.

In the series of benzoxazoles and benzimidazoles only compound (**II-26**) revealed activity more potent than that of the corresponding benzothiazole analogues.

In conclusion, we considered the H_2 -antagonist and antiulcer activities of several aralkylbenzazoles (**II–VI**). With respect to their structural features, these compounds seem to possess the necessary conditions for expression of H_2 -antagonist activity; nevertheless, they were devoid of such activity. We deduced from this that an exchange of the aromatic moiety of **I** for another moiety is not as easy as in the case of known H_2 -antagonists.

In contrast, several pyridinyl derivatives (**II**) showed antiulcer activity with potencies superior to that of the reference compounds. Thus, successful replacement of the imidazo[1,2-*a*]pyridine moiety was achieved.

TABLE I. Physical Data of Pyridinylalkylbenzazoles (II)



Compd. No.	R ¹	P	Alkyl	Q	R ²	X	R ³	Yield (%)	mp (°C) (Recryst. solvent) ^{a)}	Formula	Analysis (%)		
											Calcd	(Found)	
II-1	H	2	CH ₂	6	H	S	H	12	182—183 (I-M)	C ₁₃ H ₁₁ N ₃ S	64.71	4.59	17.41
II-2	H	2	CH ₂	6	H	S	CH ₃	11	120—122 (I-M)	C ₁₄ H ₁₃ N ₃ S	65.85	5.13	16.46
II-3	H	3	CH ₂	6	H	S	CH ₃	18	170—171 (EA-T)	C ₁₄ H ₁₃ N ₃ S	65.85	5.13	16.46
II-4	H	2	CH(OH)	6	H	S	H	25	187—188 (EA-T)	C ₁₃ H ₁₁ N ₃ OS	60.68	4.31	16.33
II-5	H	2	CH ₂ CH ₂	4	H	S	C ₂ H ₅	28	106—108 (E-I)	C ₁₆ H ₁₇ N ₃ S	67.81	6.05	14.83
II-6	H	2	CH ₂ CH ₂	6	H	S	H	63	163—165 (EA)	C ₁₄ H ₁₃ N ₃ S	65.85	5.13	16.46
II-7	3-CH ₃	2	CH ₂ CH ₂	6	H	S	H	67	194—196 (EA-C-M)	C ₁₅ H ₁₅ N ₃ S	66.89	5.61	15.60
II-8	4-CH ₃	2	CH ₂ CH ₂	6	H	S	H	48	195—197 (EA-C-M)	C ₁₅ H ₁₅ N ₃ S	66.89	5.61	15.60
II-9	5-CH ₃	2	CH ₂ CH ₂	6	H	S	H	63	205—207 (EA-T)	C ₁₅ H ₁₅ N ₃ S	66.89	5.61	15.60
II-10	H	2	CH ₂ CH ₂	6	4-OCH ₃	S	H	51	222—224 (EA-T)	C ₁₅ H ₁₅ N ₃ OS	63.14	5.30	14.73
II-11	H	2	CH ₂ CH ₂	6	4-Br	S	H	53	221—223 (C-E)	C ₁₄ H ₁₂ N ₃ BrS	50.31	3.62	12.57
II-12	3-CH ₃	2	CH ₂ CH ₂	6	4-Br	S	H	52	236—237 (C-E)	C ₁₅ H ₁₄ N ₃ BrS	51.74	4.05	12.07
II-13	5-CH ₃	2	CH ₂ CH ₂	6	4-Br	S	H	52	216—218 (EA-T)	C ₁₅ H ₁₄ N ₃ BrS	51.74	4.05	12.07
II-14	H	2	CH ₂ CH ₂	6	H	S	CH ₃	13	123—124 (EA)	C ₁₅ H ₁₅ N ₃ S	66.89	5.61	15.60
II-15	H	2	CH ₂ CH ₂	6	H	S	C ₂ H ₅	18	102—104 (EA-I)	C ₁₆ H ₁₇ N ₃ S	67.81	6.05	14.83
II-16	3-CH ₃	2	CH ₂ CH ₂	6	H	S	C ₂ H ₅	9	159—161 (E-EA)	C ₁₇ H ₁₉ N ₃ S	68.65	6.44	14.13
II-17	H	3	CH ₂ CH ₂	6	H	S	H	45	210—212 (EA-T)	C ₁₄ H ₁₃ N ₃ S	65.85	5.13	16.46
II-18	H	3	CH ₂ CH ₂	6	H	S	CH ₃	17	155—157 (EA)	C ₁₅ H ₁₅ N ₃ S	66.89	5.61	15.60
II-19	H	4	CH ₂ CH ₂	6	H	S	H	50	187—189 (EA-T)	C ₁₄ H ₁₃ N ₃ S	65.85	5.13	16.46
II-20	H	2	CH ₂ O	6	H	S	H	28	169—172 (EA-T)	C ₁₃ H ₁₁ N ₃ OS	60.68	4.31	16.33
II-21	H	2	CH ₂ S	6	H	S	H	40	171—172 (EA-T)	C ₁₃ H ₁₁ N ₃ S ₂	57.12	4.06	15.37
II-22	H	2	CH ₂ CH ₂	6	H	O	H	62	203—205 (E-EA)	C ₁₄ H ₁₃ N ₃ O	70.27	5.48	17.56
II-23	3-CH ₃	2	CH ₂ CH ₂	6	H	O	H	70	227—230 (EA-T)	C ₁₅ H ₁₅ N ₃ O	71.13	5.97	16.59
II-24	H	2	CH ₂ CH ₂	6	H	O	C ₂ H ₅	15	93—94 (EA-H)	C ₁₆ H ₁₇ N ₃ O	71.89	6.41	15.72
II-25	H	3	CH ₂ CH ₂	5	H	O	C ₂ H ₅	26	230—233 (A-T)	C ₁₆ H ₁₇ N ₃ O	56.48	5.63	12.35
II-26	H	2	CH ₂ CH ₂	5(6)	H	NH	H	37	198—200 (A-T)	C ₁₄ H ₁₄ N ₄	70.57	5.92	23.51
II-27	3-CH ₃	2	CH ₂ CH ₂	5(6)	H	NH	H	34	263—265 (A-T)	C ₁₅ H ₁₆ N ₄ ·2HCl·H ₂ O	52.49	5.87	16.32

a) A, EtOH; C, CHCl₃; E, Et₂O; EA, AcOEt; H, *n*-hexane; I, iso-Pr₂O (IPE); M, MeOH; T, tetrahydrofuran (THF).

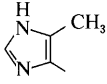
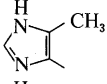
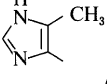
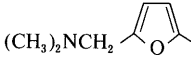
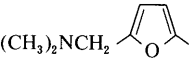
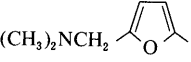
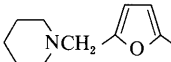
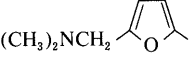
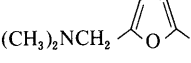
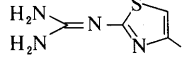
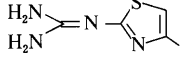
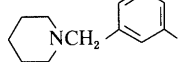
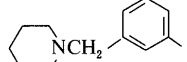
Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were taken with a Hitachi 260-10 spectrometer. Proton nuclear magnetic resonance (¹H-NMR) spectra were recorded with a Varian EM-390 spectrometer

using tetramethylsilane as an internal standard.

2-(α -Hydroxy-4-nitrobenzyl)pyridine (2) A solution of *n*-BuLi in *n*-hexane (10% (w/v), 500 ml, 0.78 mol) was added dropwise to a solution of 2-bromopyridine (**1**) (123 g, 0.78 mol) in tetrahydrofuran (THF) (1 l) at -60°C under N₂ atmosphere. After being stirred for 1 h, a solution of

TABLE II. Physical Data of Aralkylbenzazoles (III—VI)

Compd. No.	Arom.	<i>m</i>	Y	<i>n</i>	Q	X	R	Yield (%)	mp (°C) (Recryst. solvent) ^{a)}	Formula	Analysis (%)		
											Calcd	Found	
											C	H	N
III-1		1	—	1	6	S	H	33	191—193 (E-EA)	C ₁₃ H ₁₄ N ₄ S	60.44 (60.51)	5.46 5.34	21.69 21.79)
III-2		1	—	1	6	NH	H	54	210—213 (E-EA)	C ₁₃ H ₁₅ N ₅	64.71 (64.67)	6.27 6.28	29.02 28.92)
III-3		1	—	1	6	O	C ₂ H ₅	48	198—201 (E-EA)	C ₁₅ H ₁₈ N ₄ O	66.65 (66.59)	6.71 6.80	20.73 20.65)
IV-1		1	—	1	6	S	H	22	153—154 (EA-H)	C ₁₆ H ₁₉ N ₃ OS	63.76 (63.77)	6.35 6.22	13.94 13.69)
IV-2		1	—	1	6	NH	COOCH ₃	58	194—195 (A-D)	C ₁₈ H ₂₂ N ₄ O ₃	63.14 (62.88)	6.48 6.39	16.36 15.97)
IV-3		1	—	1	6	O	C ₂ H ₅	18	72—73 (EA)	C ₁₈ H ₂₃ N ₃ O ₂ · 3/2C ₄ H ₄ O ₄	59.13 (59.18)	6.00 6.23	8.62 8.24)
IV-4		1	—	1	6	O	C ₂ H ₅	24	98—100 (A-EA)	C ₂₁ H ₂₇ N ₃ O ₂ · 5/4C ₄ H ₄ O ₄	62.64 (62.86)	6.47 6.36	8.43 8.64)
IV-5		1	S	1	5	O	C ₂ H ₅	19	100—101 (A-I)	C ₁₈ H ₂₃ N ₃ O ₂ S · C ₄ H ₄ O ₄	57.25 (57.19)	5.90 5.79	9.10 9.06)
IV-6		1	S	1	6	O	C ₂ H ₅	26	181—183 (A-I)	C ₁₈ H ₂₃ N ₃ O ₂ S · 2HCl	51.67 (51.30)	6.02 6.33	10.04 9.86)
V-1		1	S	1	5	O	C ₂ H ₅	28	168—169 (A-H)	C ₁₅ H ₁₈ N ₆ OS ₂	49.70 (49.38)	5.01 5.22	23.19 22.95)
V-2		1	S	1	6	O	C ₂ H ₅	19	212—214 (I-M-T)	C ₁₅ H ₁₈ N ₆ OS ₂	49.70 (49.43)	5.01 4.92	23.19 22.86)
VI-1		0	O	1	5	O	C ₂ H ₅	30	132—133 (A-E)	C ₂₂ H ₂₇ N ₃ O ₂ · 2HCl · 1/2H ₂ O	59.06 (58.96)	6.76 6.96	9.39 9.07)
VI-2		0	O	1	6	O	C ₂ H ₅	15	105—106 (EA-H)	C ₂₂ H ₂₇ N ₃ O ₂	72.30 (72.53)	7.45 7.65	11.50 11.24)

a) A, EtOH; D, *N,N*-dimethylformamide (DMF); E, Et₂O; EA, AcOEt; H, *n*-hexane; I, iso-Pr₂O (IPE); M, MeOH.

4-nitrobenzaldehyde (59 g, 0.39 mol) in THF (600 ml) was slowly added to the mixture, and then the resulting mixture was stirred at the same temperature for 2 h. The reaction suspension was dissolved in AcOEt (2 l)—H₂O (2 l) and the resulting solution was acidified with concentrated HCl. The separated aqueous layer was basified with 20% aqueous K₂CO₃ and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with CHCl₃ to afford **2** (21 g, 24%). An analytical sample was obtained by recrystallization from AcOEt—*n*-hexane, mp 108—109 °C. IR (Nujol): 1520, 1340 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 5.88 (1H, d, *J*=4 Hz), 6.43 (1H, d, *J*=4 Hz), 7.23 (1H, dt, *J*=1, 5 Hz), 7.53—7.93 (2H, m), 7.70 (2H, d, *J*=9 Hz), 8.20 (2H, d, *J*=9 Hz), 8.50 (1H, dd, *J*=1, 5 Hz). Anal. Calcd for C₁₂H₁₀N₂O₃: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.49; H, 4.63; N, 11.97.

2-(α -Chloro-4-nitrobenzyl)pyridine (3) A solution of **2** (5.0 g, 22 mmol) and SOCl₂ (3.9 g, 33 mmol) in CHCl₃ (50 ml) was refluxed for 1 h. The mixture was then poured into H₂O, adjusted to pH 8 with 20% aqueous K₂CO₃ and extracted with AcOEt. The extract was dried (MgSO₄) and concentrated *in vacuo* to afford **3** (5.2 g, 96%) as an oil. IR (film): 1525,

1390 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 6.37 (1H, s), 7.41 (1H, dt, *J*=1, 5 Hz), 7.71—7.96 (2H, m), 7.85 (2H, d, *J*=9 Hz), 8.26 (2H, d, *J*=9 Hz), 8.64 (1H, dd, *J*=1, 5 Hz).

2-(4-Aminobenzyl)pyridine (4a) A mixture of **3** (3.0 g, 12 mmol) and Zn powder (3.9 g, 60 mmol) in AcOEt (30 ml) was refluxed for 1 h with stirring. After addition of AcOEt—H₂O, an insoluble material was removed by filtration and the resulting solution was adjusted to pH 8 with 20% aqueous K₂CO₃. The separated organic layer was dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with CHCl₃—AcOEt (4:1) to afford **4a** (0.9 g, 42%). An analytical sample was obtained by recrystallization from diisopropyl ether (IPE), mp 62—63 °C. IR (Nujol): 3350, 3225 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 3.88 (2H, s), 4.85 (2H, s), 6.68 (2H, d, *J*=8 Hz), 6.93 (2H, d, *J*=8 Hz), 6.97—7.18 (2H, m), 7.63 (1H, dt, *J*=2, 5 Hz), 8.45 (1H, dd, *J*=2, 5 Hz). Anal. Calcd for C₁₂H₁₂N₂: C, 78.23; H, 6.56; N, 15.20. Found: C, 77.93; H, 6.67; N, 14.97.

2-(4-Amino- α -hydroxybenzyl)pyridine (6) A solution of **2** (5.0 g, 22 mmol) in MeOH (30 ml) was hydrogenated over 10% Pd—C (1.0 g) at room temperature under atmospheric pressure of H₂. After removal of the

TABLE III. Antiulcer Activity of Pyridine Derivatives (II) against Restraint and Water-Immersed Stress Ulcer ($n=5$)

Compd. No.	Anti-stress ulcer activity (% inhibition) 32 mg/kg <i>p.o.</i>	Compd. No.	Anti-stress ulcer activity (% inhibition) 32 mg/kg <i>p.o.</i>
II-1	98.2 ^{a)}	II-16	19.4
II-2	87.8 ^{a)}	II-17	94.4 ^{a)}
II-3	54.7	II-18	67.9 ^{b)}
II-4	30.1	II-19	51.9
II-5	64.2	II-20	42.3
II-6	88.5 ^{a)}	II-21	24.0
II-7	72.3 ^{a)}	II-22	74.2 ^{a)}
II-8	62.9	II-23	34.0
II-9	63.7	II-24	55.9
II-10	30.8	II-25	32.2
II-11	50.0	II-26	98.3 ^{a)}
II-12	32.3	II-27	23.5
II-13	63.3 ^{b)}	Sofalcone	33.0 ^{c)}
II-14	72.9 ^{b)}	Sucralfate	45.6 ^{c)}
II-15	83.9 ^{a)}	Cimetidine	69.4 ^{a)}

a) $p < 0.01$. b) $p < 0.05$. c) 100 mg/kg *p.o.*TABLE IV. ¹H-NMR Spectral Data for the Evaluated Compounds (II—VI)

Compd. No.	Solvent	δ (J=Hz)
II-1	DMSO- d_6	4.06 (2H, s), 6.98—7.44 (6H, m), 7.51 (1H, d, $J=2$), 7.66 (1H, dt, $J=2, 8$), 8.46 (1H, d, $J=5$)
II-2	DMSO- d_6	2.92 (3H, d, $J=5$), 4.07 (2H, s), 7.07—7.31 (2H, m), 7.09 (1H, dd, $J=2, 8$), 7.30 (1H, d, $J=8$), 7.53 (1H, d, $J=2$), 7.50—7.80 (1H, m), 7.78 (1H, q, $J=5$), 8.45 (1H, d, $J=5$)
II-3	DMSO- d_6	2.93 (3H, d, $J=5$), 3.96 (2H, s), 7.08 (1H, dd, $J=2, 9$), 7.26 (1H, dd, $J=5, 7$), 7.33 (1H, d, $J=9$), 7.55 (1H, dd, $J=2, 7$), 7.53 (1H, d, $J=2$), 7.80 (1H, q, $J=5$), 8.38 (1H, dd, $J=2, 5$), 8.49 (1H, d, $J=2$)
II-4	DMSO- d_6	5.72 (1H, d, $J=4$), 5.99 (1H, d, $J=4$), 7.06—7.45 (5H, m), 7.55 (1H, d, $J=5$), 7.63 (1H, d, $J=2$), 7.75 (1H, dt, $J=2, 8$), 7.42 (1H, d, $J=5$)
II-5	DMSO- d_6	1.06 (3H, t, $J=7$), 2.98 (4H, s), 2.93—3.30 (2H, m), 6.45 (1H, t, $J=5$), 6.76—7.30 (4H, m), 7.50—7.83 (2H, m), 8.50 (1H, dd, $J=2, 5$)
II-6	DMSO- d_6	3.00 (4H, s), 7.04 (1H, dd, $J=2, 7$), 7.10—7.40 (4H, m), 7.49 (1H, d, $J=2$), 7.49—7.78 (2H, m), 8.48 (1H, d, $J=5$)
II-7	D ₂ O-DCI	2.43 (3H, s), 2.93—3.57 (4H, m), 7.30 (2H, s), 7.48 (1H, s), 7.62 (1H, t, $J=6$), 8.37 (1H, dd, $J=2, 6$), 8.45 (1H, dd, $J=2, 6$)
II-8	D ₂ O-DCI	2.67 (3H, s), 3.27 (4H, s), 7.37 (2H, s), 7.53 (1H, d, $J=2$), 7.73 (1H, s), 7.77 (2H, dd, $J=2, 6$), 8.48 (1H, d, $J=6$)
II-9	D ₂ O-DCI	2.52 (3H, s), 3.00—3.53 (4H, m), 7.28 (2H, s), 7.47 (1H, s), 7.70 (1H, d, $J=8$), 8.25 (1H, dd, $J=2, 8$), 8.38 (1H, d, $J=2$)
II-10	DMSO- d_6	2.94—3.07 (4H, m), 3.78 (3H, s), 6.66 (1H, s), 7.09 (1H, s), 7.17—7.26 (2H, m), 7.30 (2H, s), 7.67 (1H, t, $J=8$), 8.50 (1H, d, $J=4$)
II-11	DMSO- d_6	3.01 (4H, s), 7.17—7.29 (3H, m), 7.52 (1H, s), 7.68 (1H, t, $J=8$), 7.79 (2H, s), 8.50 (1H, d, $J=5$)
II-12	DMSO- d_6	2.24 (3H, s), 2.99 (4H, s), 7.12 (1H, dd, $J=5, 8$), 7.30 (1H, d, $J=2$), 7.50 (1H, dd, $J=2, 8$), 7.54 (1H, d, $J=2$), 7.77 (2H, s), 8.34 (1H, dd, $J=2, 5$)

TABLE IV. (continued)

Compd. No.	Solvent	δ (J=Hz)
II-13	DMSO- d_6	2.25 (3H, s), 2.97 (4H, s), 7.13 (1H, d, $J=8$), 7.28 (1H, d, $J=2$), 7.48 (1H, dd, $J=2, 8$), 7.50 (1H, d, $J=2$), 7.76 (2H, s), 8.33 (1H, d, $J=2$)
II-14	DMSO- d_6	2.94 (3H, d, $J=6$), 3.00 (4H, s), 7.05 (1H, dd, $J=2, 8$), 7.13—7.75 (2H, m), 7.30 (1H, d, $J=8$), 7.48 (1H, d, $J=2$), 7.63 (1H, dt, $J=2, 8$), 7.80 (1H, q, $J=6$), 8.48 (1H, dd, $J=2, 5$)
II-15	DMSO- d_6	1.18 (3H, s), 3.00 (4H, s), 3.29—3.42 (2H, m), 7.04 (1H, dd, $J=2, 8$), 7.16—7.22 (2H, m), 7.26 (1H, d, $J=8$), 7.50 (1H, d, $J=2$), 7.66 (1H, dd, $J=2, 8$), 7.88 (1H, t, $J=6$), 8.50 (1H, dd, $J=2, 5$)
II-16	D ₂ O-DCI	1.42 (3H, t, $J=8$), 2.42 (3H, s), 2.97—3.43 (4H, m), 3.53 (2H, q, $J=8$), 7.30 (1H, s), 7.35 (1H, s), 7.55 (1H, s), 7.90 (1H, q, $J=6$), 8.40 (1H, d, $J=6$), 8.48 (1H, dd, $J=2, 6$)
II-17	DMSO- d_6	2.90 (4H, s), 7.04 (1H, dd, $J=2, 8$), 7.23 (1H, d, $J=8$), 7.28 (1H, dd, $J=5, 8$), 7.38 (2H, s), 7.50 (1H, d, $J=2$), 7.62 (1H, dt, $J=8, 2$), 8.38 (1H, dd, $J=2, 5$), 8.40 (1H, d, $J=2$)
II-18	DMSO- d_6	2.91 (4H, s), 2.95 (3H, d, $J=6$), 7.04 (1H, dd, $J=2, 8$), 7.25 (1H, dd, $J=5, 7$), 7.30 (1H, d, $J=8$), 7.48 (1H, d, $J=2$), 7.60 (1H, dd, $J=2, 7$), 7.80 (1H, q, $J=6$), 8.37 (1H, dd, $J=2, 5$), 8.41 (1H, d, $J=2$)
II-19	DMSO- d_6	2.90 (4H, s), 7.05 (1H, dd, $J=2, 8$), 7.22 (2H, dd, $J=2, 5$), 7.24 (1H, d, $J=8$), 7.38 (2H, s), 8.43 (2H, dd, $J=2, 5$)
II-20	DMSO- d_6	5.14 (2H, s), 6.89 (1H, dd, $J=2, 9$), 7.10—7.41 (5H, m), 7.50 (1H, d, $J=8$), 7.82 (1H, dt, $J=2, 8$), 8.54 (1H, d, $J=5$)
II-21	DMSO- d_6	4.24 (2H, s), 7.15—7.25 (3H, m), 7.30 (1H, d, $J=8$), 7.54 (2H, s), 7.69 (1H, d, $J=2$), 7.70 (1H, t, $J=8$), 8.45 (1H, d, $J=5$)
II-22	DMSO- d_6	3.01 (4H, s), 6.93 (1H, dd, $J=2, 8$), 7.06 (1H, d, $J=8$), 7.17—7.26 (5H, m), 7.66 (1H, dt, $J=2, 8$), 8.49 (1H, dd, $J=2, 5$)
II-23	DMSO- d_6	2.21 (3H, s), 3.00 (4H, s), 6.95 (1H, dd, $J=2, 8$), 7.08 (1H, d, $J=8$), 7.09—7.18 (2H, m), 7.28 (2H, s), 7.49 (1H, d, $J=8$), 8.35 (1H, d, $J=5$)
II-24	DMSO- d_6	1.18 (3H, t, $J=7$), 3.02 (4H, s), 3.24—3.34 (2H, m), 6.94 (1H, dd, $J=2, 8$), 7.10 (1H, d, $J=8$), 7.16—7.24 (3H, m), 7.66 (1H, dt, $J=2, 8$), 7.99 (1H, t, $J=6$), 8.50 (1H, dd, $J=2, 5$)
II-25	D ₂ O	1.43 (3H, t, $J=7$), 3.23 (4H, s), 3.63 (2H, q, $J=7$), 7.14 (1H, dd, $J=2, 8$), 7.28 (1H, d, $J=2$), 7.46 (1H, d, $J=8$), 8.02 (1H, dd, $J=5, 8$), 8.45 (1H, dd, $J=2, 8$), 8.60 (1H, d, $J=2$)
II-26	D ₂ O-DCI	3.13—3.61 (4H, m), 7.10 (1H, d, $J=8$), 7.30 (1H, d, $J=8$), 7.95 (1H, d, $J=8$), 8.07 (1H, d, $J=5$), 8.57 (1H, dd, $J=2, 8$), 8.75 (1H, dd, $J=2, 5$)
II-27	D ₂ O	2.50 (3H, s), 2.85—3.46 (4H, m), 6.80—7.37 (3H, m), 7.92 (1H, dd, $J=5, 7$), 8.47 (1H, d, $J=7$), 8.54 (1H, d, $J=5$)
III-1	D ₂ O-DCI	1.95 (3H, s), 2.95 (4H, s), 7.16 (1H, d, $J=8$), 7.32 (1H, d, $J=8$), 7.42 (1H, s), 8.47 (1H, s)
III-2	D ₂ O-DCI	1.97 (3H, s), 2.91 (4H, s), 6.95 (1H, d, $J=8$), 7.01 (1H, s), 7.19 (1H, d, $J=8$), 8.49 (1H, s)
III-3	D ₂ O-DCI	1.38 (3H, t, $J=7$), 1.96 (3H, s), 3.02 (4H, s), 3.60 (2H, q, $J=7$), 7.11 (1H, d, $J=8$), 7.29 (1H, s), 7.31 (1H, d, $J=8$), 8.48 (1H, s)
IV-1	DMSO- d_6	2.15 (6H, s), 2.89 (4H, s), 3.35 (2H, s), 5.97 (1H, d, $J=3$), 6.12 (1H, d, $J=3$), 7.04 (1H, dd, $J=2, 8$), 7.25 (1H, d, $J=8$), 7.34 (2H, s), 7.47 (1H, d, $J=2$)
IV-2	DMSO- d_6	2.13 (6H, s), 2.91 (4H, s), 3.34 (2H, s), 3.74 (3H, s), 5.96 (1H, d, $J=3$), 6.09 (1H, d, $J=3$), 6.92 (1H, dd, $J=2, 8$), 7.22 (1H, d, $J=2$), 7.28 (1H, d, $J=8$), 11.55 (2H, brs)

TABLE IV. (continued)

Compd. No.	Solvent	δ (J =Hz)
IV-3	DMSO- d_6	1.19 (3H, t, J =7), 2.71 (6H, s), 2.95 (4H, s), 3.20–3.43 (2H, m), 4.29 (2H, s), 6.07 (3H, s), 6.13 (1H, d, J =3), 6.53 (1H, d, J =3), 6.90 (1H, dd, J =2, 8), 7.09 (1H, d, J =8), 7.17 (1H, d, J =2), 7.70 (1H, brs)
IV-4	DMSO- d_6	1.17 (3H, t, J =7), 1.36–1.83 (6H, m), 2.96 (4H, s), 2.96–3.15 (4H, m), 3.15–3.45 (2H, m), 4.26 (2H, s), 6.07 (2.5H, s), 6.15 (1H, d, J =3), 6.53 (1H, d, J =3), 6.93 (1H, dd, J =2, 8), 7.12 (1H, d, J =8), 7.15 (1H, d, J =2), 7.73 (1H, t, J =5)
IV-5	DMSO- d_6	1.20 (3H, t, J =7), 2.37 (6H, s), 3.36 (2H, q, J =7), 3.67 (2H, s), 3.77 (4H, s), 6.26 (1H, d, J =3), 6.38 (1H, d, J =3), 6.62 (2H, s), 6.92 (1H, dd, J =2, 8), 7.18 (1H, d, J =2), 7.28 (1H, d, J =8), 7.83 (1H, brs), 11.58 (2H, brs)
IV-6	DMSO- d_6	1.27 (3H, t, J =7), 2.72 (6H, s), 3.54 (2H, q, J =7), 3.72 (2H, s), 3.90 (2H, s), 4.37 (2H, s), 6.38 (1H, d, J =3), 6.71 (1H, d, J =3), 7.33 (2H, s), 7.55 (1H, s), 10.27 (2H, brs), 11.33 (1H, brs)
V-1	DMSO- d_6	1.19 (3H, t, J =7), 3.18–3.39 (2H, m), 3.50 (2H, s), 3.75 (2H, s), 6.43 (1H, s), 6.82 (4H, s), 6.88 (1H, dd, J =2, 8), 7.13 (1H, d, J =2), 7.20 (1H, d, J =8), 7.79 (1H, t, J =5)
V-2	DMSO- d_6	1.20 (3H, t, J =7), 3.35 (2H, dq, J =6, 7), 3.55 (2H, s), 3.82 (2H, s), 6.48 (1H, s), 6.87 (4H, s), 7.15 (2H, s), 7.30 (1H, s), 7.85 (1H, t, J =6)
VI-1	DMSO- d_6	1.24 (3H, t, J =8), 1.50–2.10 (6H, m), 2.63–3.30 (4H, m), 3.47 (2H, q, J =8), 4.20 (2H, s), 5.22 (2H, s), 7.03–7.56 (7H, m), 9.80 (1H, brs), 11.10 (1H, brs)
VI-2	DMSO- d_6	1.18 (3H, t, J =6.5), 1.35–1.58 (6H, m), 2.17–2.42 (4H, m), 3.33 (2H, dq, J =5, 6.5), 3.37 (2H, s), 5.07 (2H, s), 6.73–7.13 (4H, m), 7.20 (2H, s), 7.40 (1H, s), 7.88 (1H, t, J =5)

catalyst, the solution was concentrated *in vacuo* to afford **6** (3.9 g, 89%) as a semisolid. IR (Nujol): 3350, 3300, 3150, 1630 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ : 4.88 (2H, s), 5.60 (2H, d, J =6 Hz), 6.47 (2H, d, J =8 Hz), 7.00 (2H, d, J =8 Hz), 7.03–7.25 (1H, m), 7.46 (1H, dd, J =2, 7 Hz), 7.73 (1H, dt, J =2, 7 Hz), 8.40 (1H, dd, J =2, 5 Hz).

3-[2-{4-(3-Methylthioureido)phenyl}ethyl]pyridine (12e) A solution of 3-[2-(4-aminophenyl)ethyl]pyridine (**11f**) (4.5 g, 23 mmol) and MeNCS (2.0 g, 27 mmol) in EtOH (60 ml) was refluxed for 1 h with stirring. The solvent was evaporated *in vacuo* and the residue was recrystallized from Et₂O–AcOEt to afford **12e** (5.9 g, 96%). *Anal.* Calcd for C₁₅H₁₇N₃S: C, 66.39; H, 6.31; N, 15.48. Found: C, 66.33; H, 6.58; N, 15.38.

2-(4-Aminophenoxy)methylpyridine (16a) A mixture of 2-(4-nitrophenoxy)methylpyridine (**15**)⁶ (26 g, 110 mmol) and Na₂S·9H₂O (62 g, 260 mmol) in EtOH (260 ml)–H₂O (50 ml) was refluxed for 2 h. After evaporation of the solvent, the residue was partitioned between AcOEt and H₂O. The obtained organic layer was washed with brine, dried (MgSO₄) and concentrated *in vacuo* to afford **16a** (18 g, 81%) as an oil. IR (Nujol): 3350, 3230, 1630 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ : 4.60 (2H, brs), 5.05 (2H, s), 6.53 (2H, d, J =9 Hz), 6.76 (2H, d, J =9 Hz), 7.27 (1H, d, J =5 Hz), 7.43 (1H, d, J =8 Hz), 7.77 (1H, dt, J =2, 8 Hz), 8.53 (1H, dd, J =2, 5 Hz).

2-Amino-6-[2-(2-pyridyl)methyl]benzothiazole (II-1) A solution of **4a** (4.5 g, 24 mmol) and NH₄SCN (3.7 g, 48 mmol) in AcOH (50 ml) was stirred for 1 h at room temperature. After a solution of Br₂ (1.3 ml, 24 mmol) in AcOH (5 ml) was added to the mixture at 10–15 °C, the resulting mixture was stirred for 1 h at this temperature. The reaction mixture was poured into AcOEt–H₂O and adjusted to pH 7.5 with 20% aqueous K₂CO₃. An insoluble material was filtered off and the separated organic layer was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was triturated with AcOEt and recrystallized from IPE–MeOH to afford **II-1** (0.71 g, 12%). IR (Nujol): 1650 cm^{-1} .

2-Methylamino-6-[2-(3-pyridyl)ethyl]benzothiazole (II-18) Br₂ (3.7 g,

23 mmol) was added dropwise to a solution of **12e** (5.8 g, 21 mmol) in CHCl₃ (100 ml) at room temperature with stirring. After being refluxed for 3 h, the reaction solution was concentrated *in vacuo* and the residue was dissolved in AcOEt–H₂O. The separated aqueous layer was adjusted to pH 7.5 with 20% aqueous K₂CO₃ and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was recrystallized from AcOEt to afford **II-18** (0.97 g, 17%). IR (Nujol): 3225 (sh), 1635 cm^{-1} .

2-Amino-4-bromo-6-[2-(2-pyridyl)ethyl]benzothiazole (II-11) A solution of Br₂ (1.4 g, 8.5 mmol) in AcOH (3 ml) was added dropwise to a solution of 2-amino-6-[2-(2-pyridyl)ethyl]benzothiazole (**II-6**) (2.2 g, 8.5 mmol) in AcOH (30 ml) at room temperature with stirring. After being stirred for 4 h, the mixture was poured into H₂O, acidified with 10% HCl and washed with AcOEt. The obtained solution was basified with 20% aqueous K₂CO₃ and extracted with AcOEt. The extract was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was recrystallized from CHCl₃–MeOH to afford **II-11** (1.5 g, 53%). IR (Nujol): 1630 cm^{-1} .

2-[2-{4-(3-Ethylureido)-3-hydroxyphenyl}ethyl]pyridine (19a) A solution of 2-(4-amino-3-hydroxyphenyl)ethylpyridine (**18a**) (2.9 g, 13 mmol) and EtNCO (1.0 ml, 13 mmol) in MeOH (10 ml)–THF (30 ml) was refluxed for 45 min. After evaporation of the solvent, the residue was triturated with Et₂O to afford **19a** (3.2 g, 82%). An analytical sample was obtained by recrystallization from IPE–MeOH. *Anal.* Calcd for C₁₆H₁₉N₃O₂: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.10; H, 6.97; N, 14.65.

2-Ethylamino-6-[2-(2-pyridyl)ethyl]benzoxazole (II-24) A mixture of (**19a**) (3.3 g, 12 mmol) and PPE (30 g) was stirred at 90–100 °C for 1.5 h. After the mixture was poured into AcOEt–THF–H₂O, the solution was adjusted to pH 8 with 20% aqueous K₂CO₃. The separated organic layer was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with CHCl₃–MeOH (39:1) and the product obtained was recrystallized from AcOEt–*n*-hexane to afford **II-24** (0.46 g, 15%). IR (Nujol): 1655, 1590 cm^{-1} .

2-Amino-5-[2-(2-pyridyl)ethyl]-1H-benzimidazole (II-26) A solution of 2-[2-(3,4-diaminophenyl)ethyl]pyridine (**23a**) (1.7 g, 8 mmol) and BrCN (1.3 g, 12 mmol) in EtOH (50 ml) was stirred for 8 h at room temperature. After evaporation of the solvent, the residue was dissolved in AcOEt–H₂O. The solution was adjusted to pH 8 with 20% aqueous K₂CO₃ and extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with CHCl₃–MeOH (92:8) and the product obtained was recrystallized from EtOH–THF to afford **II-26** (0.7 g, 37%). IR (Nujol): 3450, 1700, 1635 cm^{-1} .

4-[2-(4-Acetamido-3-nitrophenyl)vinyl]-5-methyl-1-tritylimidazole (28) A mixture of 4-formyl-5-methyl-1-tritylimidazole (**24**)⁹ (7.3 g, 21 mmol), (4-acetamido-3-nitrobenzyl)triphenylphosphonium chloride (**26**) (10.2 g, 21 mmol) and *tert*-BuOK (2.3 g, 21 mmol) in *N,N*-dimethylformamide (DMF) (70 ml) was stirred for 4 h at room temperature. The reaction mixture was poured into H₂O (500 ml). The resulting precipitate was collected by filtration and dissolved in AcOEt–THF–H₂O. The separated organic layer was dried (MgSO₄) and concentrated *in vacuo*. The residue was triturated with Et₂O to afford **28** (6.8 g, 62%). An analytical sample was obtained by recrystallization from IPE–THF. *Anal.* Calcd for C₃₃H₂₈N₄O₃: C, 74.98; H, 5.34; N, 10.60. Found: C, 74.65; H, 5.56; N, 10.47.

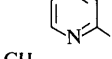
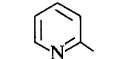
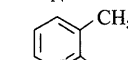
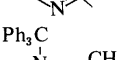
4-[2-(4-Amino-3-nitrophenyl)vinyl]-5-methyl-1-tritylimidazole (29) A solution of **28** (6.3 g, 12 mmol) and 1 N NaOH (24 ml, 24 mmol) in EtOH (60 ml) was refluxed for 1 h. The resulting precipitate was collected by filtration and washed with aqueous EtOH to afford **29** (2.8 g, 49%). An analytical sample was obtained by recrystallization from IPE–MeOH. *Anal.* Calcd for C₃₃H₂₆N₄O₂: C, 76.52; H, 5.39; N, 11.51. Found: C, 76.33; H, 5.42; N, 11.37.

2-Amino-6-[2-(5-methylimidazol-4-yl)ethyl]benzothiazole (III-1) A solution of 2-amino-6-[2-(5-methyl-1-tritylimidazol-4-yl)ethyl]benzothiazole (**31**) (1.4 g, 2.8 mmol) and anisole (1.5 ml, 14 mmol) in CF₃COOH (6 ml) was refluxed for 5 h with stirring. After Et₂O (30 ml) was added to the solution, the resulting precipitate was collected by filtration and dissolved in H₂O. The solution was adjusted to pH 9 with 20% aqueous K₂CO₃ and extracted with AcOEt. The extract was dried (MgSO₄) and concentrated *in vacuo*. The residue was recrystallized from Et₂O–AcOEt to afford **III-1** (0.24 g, 33%). IR (Nujol): 3440, 3280, 1670 cm^{-1} .

5-[2-(2-Furyl)ethyl]-2-methoxycarbonylamino-1H-benzimidazole (47) A solution of *S*-methylisothiourea sulfate (2.8 g, 10 mmol) and ClCOOMe (1.5 ml, 20 mmol) in H₂O (10 ml) was adjusted to pH 8 with 5 N NaOH.

TABLE V. Physical Data of β -Arylstylenes

$\text{aryl}-\text{CH}=\text{CH}-\text{C}_6\text{H}_4-\text{R}$

Compd. No.	Aryl	R	Yield (%)	mp (°C)	¹ H-NMR (DMSO- <i>d</i> ₆ , δ : J=Hz)
10a ^{a)}		2-NO ₂			
10b ^{b)}		4-NO ₂			
10c		4-NO ₂	53	147—150	2.82 (3H, s), 7.50 (1H, d, <i>J</i> =17), 7.83 (2H, d, <i>J</i> =9), 7.63—8.07 (2H, m), 8.30 (2H, d, <i>J</i> =9), 8.33—8.80 (2H, m) ^{e)}
10d		4-NO ₂	46	151—152	2.35 (3H, s), 7.17 (1H, d, <i>J</i> =5), 7.46 (1H, s), 7.51 (1H, d, <i>J</i> =16), 7.79 (1H, d, <i>J</i> =16), 7.93 (2H, d, <i>J</i> =9), 8.24 (2H, d, <i>J</i> =9), 8.47 (1H, d, <i>J</i> =5)
10e		4-NO ₂	52	179—180	2.73 (3H, s), 7.50 (1H, d, <i>J</i> =17), 7.90 (2H, d, <i>J</i> =9), 7.97 (1H, d, <i>J</i> =17), 7.67—8.67 (3H, m), 8.38 (2H, d, <i>J</i> =9) ^{e)}
10f ^{c)}		4-NO ₂			
10g ^{d)}		4-NO ₂			
10h		3-OCH ₃ , 4-NO ₂	98	139—141	4.01 (3H, s), 7.34 (1H, dd, <i>J</i> =5, 8), 7.42 (1H, d, <i>J</i> =8), 7.57 (1H, d, <i>J</i> =16), 7.59 (1H, d, <i>J</i> =8), 7.62 (1H, s), 7.69 (1H, d, <i>J</i> =16), 7.85 (1H, t, <i>J</i> =8), 7.93 (1H, d, <i>J</i> =8), 8.63 (1H, d, <i>J</i> =5)
10i		3-NO ₂ , 4-OH	78	Oil	5.29 (1H, s), 6.70 (1H, d, <i>J</i> =12), 6.78 (1H, d, <i>J</i> =12), 7.26—7.46 (3H, m), 7.62 (1H, dd, <i>J</i> =2, 8), 7.73 (1H, d, <i>J</i> =2), 8.43 (1H, d, <i>J</i> =2), 8.44 (1H, dd, <i>J</i> =2, 5)
17a		3-OCH ₂ Ph, 4-NO ₂	92	113—116	5.31 (2H, s), 7.00 (1H, dd, <i>J</i> =2, 8), 7.17—7.65 (11H, m), 7.78 (1H, d, <i>J</i> =8), 8.50 (1H, dd, <i>J</i> =2, 5)
17b		3-OCH ₂ Ph, 4-NO ₂	49	98—100	2.48 (3H, s), 5.42 (2H, s), 7.10—7.83 (11H, m), 7.93 (1H, d, <i>J</i> =8), 8.45 (1H, dd, <i>J</i> =2, 5)
27		4-NO ₂	63	172—175	1.31 (3H, s), 6.62 (1H, s), 7.05—7.55 (15H, m), 8.01 (2H, d, <i>J</i> =8), 8.20 (2H, d, <i>J</i> =8)
28		3-NO ₂ , 4-NHCOCH ₃	62	203—206	1.38 (3H, s), 2.07 (3H, s), 6.38 (1H, d, <i>J</i> =13), 6.45 (1H, d, <i>J</i> =13), 7.08—7.67 (17H, m), 7.99 (1H, dd, <i>J</i> =2, 8), 8.63 (1H, d, <i>J</i> =2), 10.25 (1H, s)
29		3-NO ₂ , 4-NH ₂	49	188—194	2.25 (3H, s), 6.90 (1H, d, <i>J</i> =13), 7.03 (1H, s), 7.23—8.64 (19H, m) ^{e)}
38		4-NO ₂	61	122—125	6.60 (1H, dd, <i>J</i> =2, 4), 6.73 (1H, d, <i>J</i> =4), 7.05 (1H, d, <i>J</i> =16), 7.43 (1H, d, <i>J</i> =16), 7.78 (1H, d, <i>J</i> =2), 7.80 (2H, d, <i>J</i> =8), 8.20 (2H, d, <i>J</i> =8)
44		3-NO ₂ , 4-NHCOCH ₃	73	74—78	2.13 (3H, s), 6.48—6.60 (4H, m), 7.63—7.77 (3H, m), 8.08 (1H, d, <i>J</i> =2), 10.30 (1H, s)
45		3-NO ₂ , 4-NH ₂	99	111—114	6.43 (1H, d, <i>J</i> =12), 6.53 (1H, dd, <i>J</i> =2, 3), 6.90 (2H, brs), 7.05 (1H, d, <i>J</i> =12), 7.07 (1H, d, <i>J</i> =8), 7.13 (1H, d, <i>J</i> =3), 7.68 (1H, d, <i>J</i> =2), 7.72 (1H, dd, <i>J</i> =2, 8), 8.10 (1H, d, <i>J</i> =2)

a) Ref. 5a. b) Ref. 5b. c) Ref. 5c. d) Ref. 5d. e) In CF₃COOH.

After being stirred for 30 min, the mixture was readjusted to pH 5 with AcOH and added to a solution of 2-[2-(3,4-diaminophenyl)ethyl]furan (46) (2.0 g, 10 mmol) in EtOH (30 ml). After the suspension was stirred for 4 h, the solvent was evaporated *in vacuo*. The residue was washed successively with H₂O and EtOH to afford 47 (1.7 g, 59%). An analytical sample was obtained by recrystallization from DMF-H₂O. *Anal.* Calcd for C₁₅H₁₅N₃O₃: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.99; H, 5.31; N, 14.69.

2-Ethylamino-6-[2-(2-furyl)vinyl]benzoxazole (48) A solution of 6-bromomethyl-2-(*N*-ethylformamido)benzoxazole (34a) (2.9 g, 10 mmol) and PPh₃ (2.6 g, 10 mmol) in DMF (30 ml) was stirred for 2 h at room

temperature. After addition of furfural (1.4 g, 15 mmol) and *tert*-BuOK (1.1 g, 10 mmol), the mixture was stirred for an additional 1 h. Concentrated HCl (4.6 ml, 50 mmol) was added to this mixture and the resulting solution was stirred for 30 min. After evaporation of the solvent, the residue was added to saturated aqueous NaHCO₃ and the mixture was extracted with AcOEt. The extract was dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with AcOEt-toluene (2:8) and the product obtained was recrystallized from AcOEt-*n*-hexane to afford 48 (1.1 g, 76%). *Anal.* Calcd for C₁₅H₁₄N₂O₂: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.55; H, 5.54; N, 10.80.

2-Ethylamino-6-[2-(2-piperidinomethyl)furan-5-yl]ethylbenzoxazole

TABLE VI. Physical Data of Aralkylbenzenes

$\text{aryl}-(\text{CH}_2)_m-\text{C}_6\text{H}_4-\text{R}$

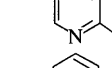
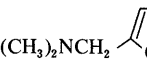
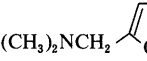
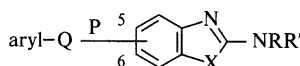
Compd. No.	Aryl	R	<i>m</i>	Yield (%)	mp (°C)	¹ H-NMR (DMSO- <i>d</i> ₆ , δ: <i>J</i> =Hz)
7a		4-NHCSNHCH ₃	1	82	120—122	2.92 (3H, d, <i>J</i> =5), 4.03 (2H, s), 7.08—7.47 (6H, m), 7.51—7.90 (2H, m), 8.52 (1H, dd, <i>J</i> =2, 5), 9.43 (1H, s)
7b		4-NHCSNHCH ₃	1	95	178—180	2.88 (3H, d, <i>J</i> =5), 3.93 (2H, s), 7.18—7.31 (5H, m), 7.63 (2H, d, <i>J</i> =8), 8.40 (1H, d, <i>J</i> =5), 8.51 (1H, d, <i>J</i> =2), 9.46 (1H, brs)
11a ^{a)}		2-NH ₂	2			
11b		4-NH ₂	2	98	Oil	2.75—2.98 (4H, m), 4.83 (2H, brs), 6.49 (2H, d, <i>J</i> =8), 7.14—7.21 (2H, m), 7.65 (1H, dt, <i>J</i> =2, 8), 8.48 (1H, dd, <i>J</i> =2, 5)
11c		4-NH ₂	2	96	46—48	2.27 (3H, s), 2.90 (4H, s), 4.57 (2H, brs), 6.50 (2H, d, <i>J</i> =8), 6.88 (2H, d, <i>J</i> =8), 7.02 (1H, d, <i>J</i> =8), 7.40 (1H, dd, <i>J</i> =2, 8), 8.32 (1H, d, <i>J</i> =2)
11d		4-NH ₂	2	91	Oil	2.23 (3H, s), 2.87 (4H, s), 4.78 (2H, brs), 6.53 (2H, d, <i>J</i> =9), 6.80—7.10 (2H, m), 6.90 (2H, d, <i>J</i> =9), 8.33 (1H, d, <i>J</i> =5)
11e		4-NH ₂	2	94	59—61	2.27 (3H, s), 2.90 (4H, s), 4.57 (2H, s), 6.50 (2H, d, <i>J</i> =9), 6.88 (2H, d, <i>J</i> =9), 7.02 (1H, d, <i>J</i> =8), 7.42 (1H, dd, <i>J</i> =2, 8), 8.32 (1H, d, <i>J</i> =2)
11f ^{b)}		4-NH ₂	2			
11g		4-NH ₂	2	86	99—100	2.70—2.97 (4H, m), 4.87 (2H, s), 6.53 (2H, d, <i>J</i> =8), 6.85 (2H, d, <i>J</i> =8), 7.25 (2H, dd, <i>J</i> =2, 5), 8.49 (2H, dd, <i>J</i> =2, 5)
11h		3-OCH ₃ , 4-NH ₂	2	92	Oil	2.93 (4H, s), 3.70 (3H, s), 4.40 (2H, s), 6.47—6.73 (2H, m), 7.00—7.33 (2H, m), 7.46—7.87 (2H, m), 8.50 (1H, dd, <i>J</i> =2, 5)
12a		2-NHCSNHC ₂ H ₅	2	66	118—121	1.07 (3H, t, <i>J</i> =7), 2.95 (4H, s), 3.25—3.72 (2H, m), 6.93—7.80 (8H, m), 8.42 (1H, dd, <i>J</i> =2, 5), 9.07 (1H, s)
12b		4-NHCSNHCH ₃	2	92	126—129	2.92 (3H, d, <i>J</i> =6), 2.97 (4H, s), 7.00—7.40 (6H, m), 7.40—7.83 (2H, m), 8.43 (1H, dd, <i>J</i> =2, 5), 9.33 (1H, s)
12c		4-NHCSNHC ₂ H ₅	2	79	124—126	1.08 (3H, t, <i>J</i> =6), 3.00 (4H, s), 3.30—3.70 (2H, m), 7.10—7.42 (6H, m), 7.53—7.83 (2H, m), 8.52 (1H, dd, <i>J</i> =2, 4), 9.36 (1H, s)
12d		4-NHCSNHC ₂ H ₅	2	92	124—126	1.10 (3H, t, <i>J</i> =7), 2.23 (3H, s), 2.97 (4H, s), 3.25—4.17 (2H, m), 6.93—7.73 (7H, m), 8.30 (1H, dd, <i>J</i> =2, 5), 9.27 (1H, s)
12e		4-NHCSNHCH ₃	2	96	146—148	2.87 (4H, s), 2.92 (3H, d, <i>J</i> =5), 6.93—7.70 (7H, m), 8.28 (1H, d, <i>J</i> =2, 5), 8.33 (1H, d, <i>J</i> =2), 9.32 (1H, s)
18a		3-OH, 4-NH ₂	2	86	113—115	2.83 (4H, s), 6.22 (1H, dd, <i>J</i> =2, 8), 6.47 (1H, d, <i>J</i> =2), 6.55 (1H, d, <i>J</i> =8), 7.00—7.33 (2H, m), 7.57 (1H, dt, <i>J</i> =2, 7), 8.45 (1H, dd, <i>J</i> =2, 5)
18b		3-OH, 4-NH ₂	2	56	138—140	2.20 (3H, s), 2.70—3.07 (4H, m), 6.40—6.65 (3H, m), 7.08 (1H, dd, <i>J</i> =5, 7), 7.48 (1H, dd, <i>J</i> =2, 7), 8.28 (1H, dd, <i>J</i> =2, 5)
18c		3-NH ₂ , 4-OH	2	74	Oil	2.78 (4H, s), 6.23 (1H, dd, <i>J</i> =2, 8), 6.52 (1H, d, <i>J</i> =2), 6.60 (1H, d, <i>J</i> =8), 7.32 (1H, d, <i>J</i> =7), 7.60 (1H, dt, <i>J</i> =2, 7), 8.40 (1H, d, <i>J</i> =2), 8.42 (1H, s)
19a		3-OH, 4-NHCONHC ₂ H ₅	2	82	130—132	1.03 (3H, t, <i>J</i> =7), 2.72—3.31 (6H, m), 6.50—6.90 (3H, m), 7.13—7.39 (2H, m), 7.53—7.83 (2H, m), 7.87 (1H, s), 8.55 (1H, dd, <i>J</i> =2, 5), 9.87 (1H, s)
19b		3-NHCONHC ₂ H ₅ , 4-OH	2	75	174—175	1.05 (3H, t, <i>J</i> =7), 2.80 (4H, s), 2.95—3.42 (2H, m), 6.05—7.05 (3H, m), 7.17—8.00 (3H, m), 8.40—8.46 (2H, m), 9.70 (1H, s)
20a		4-NHCOCH ₃	2	96	83—85	2.00 (3H, s), 2.93 (4H, s), 6.97—7.07 (1H, m), 7.00 (2H, d, <i>J</i> =8), 7.12 (1H, dd, <i>J</i> =2, 8), 7.40 (2H, d, <i>J</i> =8), 7.55 (1H, dt, <i>J</i> =8, 2), 8.38 (1H, dd, <i>J</i> =2, 5), 9.72 (1H, s)
20b		4-NHCOCH ₃	2	96	90—93	2.07 (3H, s), 2.23 (3H, s), 2.93 (4H, s), 7.03 (1H, dd, <i>J</i> =5, 8), 7.08 (2H, d, <i>J</i> =8), 7.45 (1H, dd, <i>J</i> =2, 8), 7.47 (2H, d, <i>J</i> =8), 8.28 (1H, dd, <i>J</i> =2, 5), 9.75 (1H, s)
21a		3-NO ₂ , 4-NHCOCH ₃	2	87	103—105	2.08 (3H, s), 3.07 (4H, s), 7.03—7.40 (2H, m), 7.50—7.90 (4H, m), 8.50 (1H, dd, <i>J</i> =2, 5), 10.08 (1H, s)
21b		3-NO ₂ , 4-NHCOCH ₃	2	89	127—128	2.10 (3H, s), 2.27 (3H, s), 3.10 (4H, s), 7.17 (1H, dd, <i>J</i> =5, 8), 7.47—7.70 (3H, m), 7.80 (1H, s), 8.35 (1H, dd, <i>J</i> =2, 5), 10.03 (1H, s)

TABLE VI. (continued)

Compd. No.	Aryl	R	<i>m</i>	Yield (%)	mp (°C)	¹ H-NMR (DMSO- <i>d</i> ₆ , δ: <i>J</i> = Hz)
22a		3-NO ₂ , 4-NH ₂	2	96	147—150	2.95 (4H, s), 6.87—7.53 (6H, m), 7.53—7.93 (2H, m), 8.53 (1H, dd, <i>J</i> = 2, 5)
22b		3-NO ₂ , 4-NH ₂	2	90	158—160	2.25 (3H, s), 2.95 (4H, s), 6.95 (1H, d, <i>J</i> = 9), 6.93—7.60 (5H, m), 7.75 (1H, d, <i>J</i> = 2), 8.30 (1H, dd, <i>J</i> = 2, 5)
23a		3,4-NH ₂	2	94	93—95	2.88 (4H, s), 4.30 (4H, br s), 6.17—6.67 (3H, m), 7.03—7.36 (2H, m), 7.50—7.90 (1H, m), 8.50 (1H, dd, <i>J</i> = 2, 5)
23b		3,4-NH ₂	2	89	91—93	2.20 (3H, s), 2.60—3.05 (4H, m), 4.23 (4H, br s), 6.07—6.53 (3H, m), 7.00 (1H, dd, <i>J</i> = 5, 8), 7.40 (1H, dd, <i>J</i> = 2, 8), 8.27 (1H, dd, <i>J</i> = 2, 5)
30a		4-NH ₂	2	50	79—81	1.10 (3H, s), 2.61 (4H, s), 4.83 (2H, br s), 6.47 (2H, d, <i>J</i> = 8), 6.73 (2H, d, <i>J</i> = 8), 6.93—7.67 (16H, m)
30b		3,4-NH ₂	2	66	193—196	1.38 (3H, s), 3.17—3.27 (4H, m), 7.10—7.87 (18H, m), 8.57 (1H, s) ^a
39		4-NH ₂	2	65	38—40	2.77 (4H, s), 4.78 (2H, s), 6.06 (1H, d, <i>J</i> = 3), 6.32 (1H, dd, <i>J</i> = 2, 3), 6.52 (2H, d, <i>J</i> = 8), 6.88 (2H, d, <i>J</i> = 8), 7.48 (1H, d, <i>J</i> = 2)
40		4-NHCOCH ₃	2	95	123—125	2.02 (3H, s), 2.86 (4H, s), 6.06 (1H, d, <i>J</i> = 3), 6.33 (1H, dd, <i>J</i> = 2, 3), 7.12 (2H, d, <i>J</i> = 9), 7.50 (1H, d, <i>J</i> = 2), 7.51 (2H, d, <i>J</i> = 9), 9.87 (1H, s)
41		4-NHCOCH ₃	2	92	Oil	2.01 (3H, s), 2.12 (6H, s), 2.82 (4H, s), 3.35 (2H, s), 5.96 (1H, d, <i>J</i> = 3), 6.12 (1H, d, <i>J</i> = 3), 7.12 (2H, d, <i>J</i> = 8), 7.49 (2H, d, <i>J</i> = 8), 9.86 (1H, s)
42		4-NH ₂	2	77	Oil	2.13 (6H, s), 2.75 (4H, s), 4.63 (2H, br s), 5.95 (1H, d, <i>J</i> = 3), 6.13 (1H, d, <i>J</i> = 3), 6.50 (2H, d, <i>J</i> = 8), 6.92 (2H, d, <i>J</i> = 8)
46		3,4-NH ₂	2	45	79—81	2.57—2.87 (4H, m), 4.26 (4H, s), 6.04 (1H, d, <i>J</i> = 3), 6.23 (1H, dd, <i>J</i> = 2, 8), 6.32 (1H, dd, <i>J</i> = 2, 3), 6.42 (1H, d, <i>J</i> = 2), 6.43 (1H, d, <i>J</i> = 8), 7.45 (1H, d, <i>J</i> = 2)

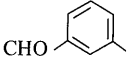
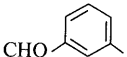
a) Ref. 5a. b) Ref. 5c. c) In D₂O-DCl.

TABLE VII. Physical Data of Several Benzazoles



Compd. No.	Aryl	Q	P	X	R	R'	Yield (%)	mp (°C)	¹ H-NMR (DMSO- <i>d</i> ₆ , δ: <i>J</i> = Hz)
31		CH ₂ CH ₂	6	S	H	H	43	200—203	2.00 (3H, s), 2.66—2.84 (4H, m), 6.83—7.65 (21H, m)
32		CH ₂ CH ₂	5(6)	NH	H	C ₂ H ₅	54	161—164	1.16 (3H, t, <i>J</i> = 7), 1.99 (3H, s), 2.63—2.93 (4H, m), 3.85—4.27 (2H, m), 6.60 (1H, d, <i>J</i> = 8), 6.85—7.37 (20H, m)
35		CH=CH	6	O	H	C ₂ H ₅	40	112—114	1.20 (3H, t, <i>J</i> = 7), 2.13 (3H, s), 3.19—3.50 (2H, m), 6.18 (1H, d, <i>J</i> = 13), 6.46 (1H, d, <i>J</i> = 13), 6.86—7.57 (19H, m), 7.86 (1H, t, <i>J</i> = 5)
36		CH=CH	6	O	H	C ₂ H ₅	83	197—199	1.19 (3H, t, <i>J</i> = 7), 2.06 (3H, s), 3.16—3.48 (2H, m), 6.18 (1H, d, <i>J</i> = 13), 6.35 (1H, d, <i>J</i> = 13), 6.97 (1H, d, <i>J</i> = 8), 7.11 (1H, s), 7.24 (1H, d, <i>J</i> = 8), 7.53 (1H, s), 7.79 (1H, t, <i>J</i> = 5), 8.10 (1H, s)
47		CH ₂ CH ₂	5(6)	NH	H	COOCH ₃	59	223—225	2.95 (4H, s), 3.78 (3H, s), 6.09 (1H, d, <i>J</i> = 3), 6.35 (1H, dd, <i>J</i> = 2, 3), 6.97 (1H, dd, <i>J</i> = 2, 8), 7.28 (1H, d, <i>J</i> = 2), 7.35 (1H, d, <i>J</i> = 8), 7.52 (1H, d, <i>J</i> = 3)
48		CH=CH	6	O	H	C ₂ H ₅	76	74—80	1.20 (3H, t, <i>J</i> = 7), 3.36 (2H, dq, <i>J</i> = 5, 7), 6.17—6.65 (3H, m), 7.02—7.62 (5H, m), 7.93 (1H, t, <i>J</i> = 5)
49		CH ₂ CH ₂	6	O	H	C ₂ H ₅	87	76—78	1.20 (3H, t, <i>J</i> = 7), 2.93 (4H, s), 3.35 (2H, dq, <i>J</i> = 5, 7), 6.03—6.53 (2H, m), 6.85—7.53 (4H, m), 7.75 (1H, t, <i>J</i> = 5)

TABLE VII. (continued)

Compd. No.	Aryl	Q	P	X	R	R'	Yield (%)	mp (°C)	¹ H-NMR (DMSO- <i>d</i> ₆ , δ : <i>J</i> = Hz)
50		CH ₂ CH ₂	6	O	CHO	C ₂ H ₅	90	57–59	1.20 (3H, t, <i>J</i> = 7), 2.93 (4H, s), 3.37 (2H, q, <i>J</i> = 7), 6.08 (1H, d, <i>J</i> = 3), 6.35 (1H, dd, <i>J</i> = 2, 3), 7.00–7.60 (3H, m), 8.15 (1H, s), 9.21 (1H, s)
54a		OCH ₂	5	O	CHO	C ₂ H ₅	76	112–114	1.23 (3H, t, <i>J</i> = 7), 3.94 (2H, q, <i>J</i> = 7), 5.30 (2H, s), 7.29–7.73 (7H, m), 9.28 (1H, s), 10.04 (1H, s)
54b		OCH ₂	6	O	CHO	C ₂ H ₅	84	87–89	1.23 (3H, t, <i>J</i> = 7), 3.95 (2H, q, <i>J</i> = 7), 5.30 (2H, s), 7.27–7.77 (7H, m), 9.23 (1H, s), 10.00 (1H, s)

5/4 Maleate (IV-4) A mixture of 2-ethylamino-6-[2-(2-furyl)ethyl]-benzoxazole (49) (0.93 g, 3.6 mmol), 37% formalin (0.3 ml, 4 mmol), piperidine (0.34 g, 4 mmol) and concentrated HCl (0.35 ml, 4 mmol) in AcOH (10 ml) was stirred at 70 °C for 2 h. After evaporation of the solvent, the residue was added to saturated aqueous NaHCO₃ and the mixture was extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with AcOEt–toluene (2:8). The free base obtained was converted to maleate in the usual manner and the salt was recrystallized from EtOH–Et₂O to afford IV-4 as 5/4 maleate (0.45 g, 24%). IR (Nujol): 1710, 1670, 1620 cm⁻¹.

6-[(2-Dimethylaminomethylfuran-5-yl)methylthiomethyl]-2-ethylaminobenzoxazole Dihydrochloride (IV-6) Ten percent aqueous NaOH (4.6 ml, 12 mmol) was added to a solution of *S*-(2-dimethylaminomethylfuran-5-yl)methylisothiourea dihydrochloride (51)¹⁰ (1.0 g, 4 mmol) in MeOH (10 ml) under N₂ atmosphere at room temperature. After being stirred for 1 h, a solution of 34a (1.1 g, 4 mmol) in MeOH (20 ml)–THF (5 ml) was added dropwise to the mixture at 0 °C and the resulting mixture was stirred for 2 h at this temperature. The solvent was evaporated *in vacuo* and the residue was dissolved in AcOEt (20 ml)–H₂O (20 ml). The separated organic layer was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with CHCl₃–MeOH (20:1). The free base obtained was converted to hydrochloride in the usual manner and the salt was recrystallized from EtOH–IPE to afford IV-6 (0.33 g, 26%) as dihydrochloride. IR (Nujol): 3080, 1695, 1625 cm⁻¹.

6-[(2-Diaminomethyleneaminothiazol-4-yl)methylthiomethyl]-2-ethylaminobenzoxazole (V-2) A solution of 4-chloromethyl-2-guanidinothiazole hydrochloride (52)¹¹ (1.0 g, 4.4 mmol) and thiourea (0.34 g, 4.4 mmol) in EtOH (10 ml)–H₂O (2 ml) was refluxed for 1 h. One *N* NaOH (13.2 ml, 13.2 mmol) was added to that boiling solution and the mixture was refluxed for a further 1 h. After cooling to 0 °C, a solution of 34a (1.3 g, 4.4 mmol) in EtOH (10 ml)–THF (10 ml) was added dropwise to the mixture, and then the resulting mixture was stirred for 4 h at 0–5 °C. The solvent was evaporated *in vacuo* and the residue was dissolved in AcOEt–H₂O. The separated organic layer was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was recrystallized from MeOH–THF–H₂O to afford V-2 (0.3 g, 19%). IR (Nujol): 3475, 3380, 3260, 1665 cm⁻¹.

2-(*N*-Ethylformamido)-6-(3-formylphenoxyethyl)benzoxazole (54b) A mixture of *m*-hydroxybenzaldehyde (1.0 g, 8.2 mmol), 34a (2.3 g, 8.3 mmol) and K₂CO₃ (1.3 g, 9.2 mmol) in DMF (10 ml) was stirred for 6 h at room temperature. The reaction mixture was poured into H₂O (50 ml) and extracted with AcOEt. The extract was dried (MgSO₄) and concentrated *in vacuo*. The residue was recrystallized from IPE–MeOH to afford 54b (2.2 g, 84%). *Anal.* Calcd for C₁₈H₁₆N₂O₄: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.99; H, 5.06; N, 8.70.

2-Ethylamino-6-(3-piperidinomethylphenoxyethyl)benzoxazole (VI-2) A solution of 54b (2.1 g, 6.5 mmol) and concentrated HCl (2.9 ml, 33 mmol) in MeOH (16 ml)–THF (16 ml) was stirred for 1 h at room temperature. After evaporation of the solvent, the residue was dissolved

in AcOEt and saturated aqueous NaHCO₃. The separated organic layer was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo* to give an *N*-deformylated product. NaBH₃CN (0.41 g, 6.4 mmol) was added to a solution of this product (1.9 g, 6.4 mmol), piperidine (0.54 g, 6.4 mmol) and AcOH (1.8 ml, 32 mmol) in MeOH (30 ml)–THF (10 ml) and the mixture was stirred for 6 h. After evaporation of the solvent, the residue was added to H₂O and the mixture was extracted with AcOEt. The extract was washed with saturated aqueous NaHCO₃, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with CHCl₃–MeOH (20:1) and recrystallized from EtOH–*n*-hexane to afford VI-2 (0.36 g, 15%). IR (Nujol): 1690 cm⁻¹.

Biological Tests Histamine H₂-receptor antagonist activity and restraint and water-immersed stress ulcer (stress ulcer) were evaluated by the methods described in the literature^{12,13} and in our previous paper.²⁾

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