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

Yousuke KATSURA,*[,a] Yoshikazu INOUE,[a] Masaaki TOMOI,[b] and Hisashi TAKASUGI[a]

New Drug Research Laboratories[a] and Product Development Laboratories,[b] Fujisawa Pharmaceutical Co., Ltd., 1–6, 2-chome, Kashima, Yodogawa-ku, Osaka 532, Japan. *Received February 19, 1992*

A series of 2-alkylamino-5- or 6-aralkyl-substituted benzazoles were synthesized and tested for histamine H_2-receptor antagonist and anti-stress ulcer activities. These new compounds showed little or no histamine H_2-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 H_2-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 H_2-receptor antagonists (H_2-antagonists) characterized by a semirigid spacer group and a rigid amidino function. Though the structural features of these compounds differ from those of conventional H_2-antagonists originating from cimetidine, several of the derivatives exhibited strong H_2-antagonist activity (Chart 1).

Reports on medicinal chemistry of H_2-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 H_2-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 H_2-antagonists. This paper describes the synthesis and pharmacological activity of several aromatic substituted alkylbenzazoles (II—VI).

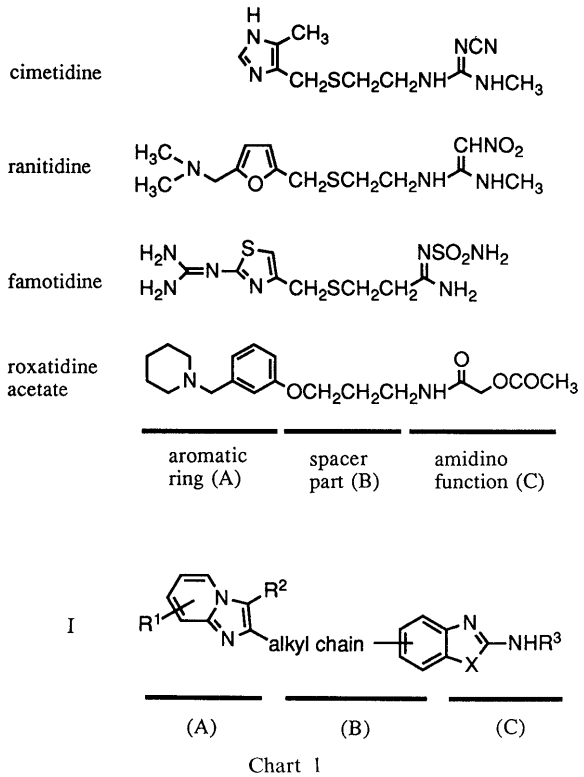

Chart 1

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 $SOCl_2$ 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 NH_4SCN and Br_2 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 Br_2 in $CHCl_3$ 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 NH_4SCN and Br_2 to afford the final compounds (II-**6**—**10**, II-**17** and II-**19**). Treatment of **11** with alkyl isothiocyanate followed by ring closure with Br_2 produced 2-alkylaminobenzothiazoles (II-**5**, II-**14**—**16** and II-**18**). Bromination of II-**6**, II-**7** and II-**9** with Br_2 gave 2-amino-4-bromobenzotiazoles (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 Na_2S 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 NH_4SCN and Br_2 to afford the target compounds (II-**20** and II-**21**) (Chart 4).

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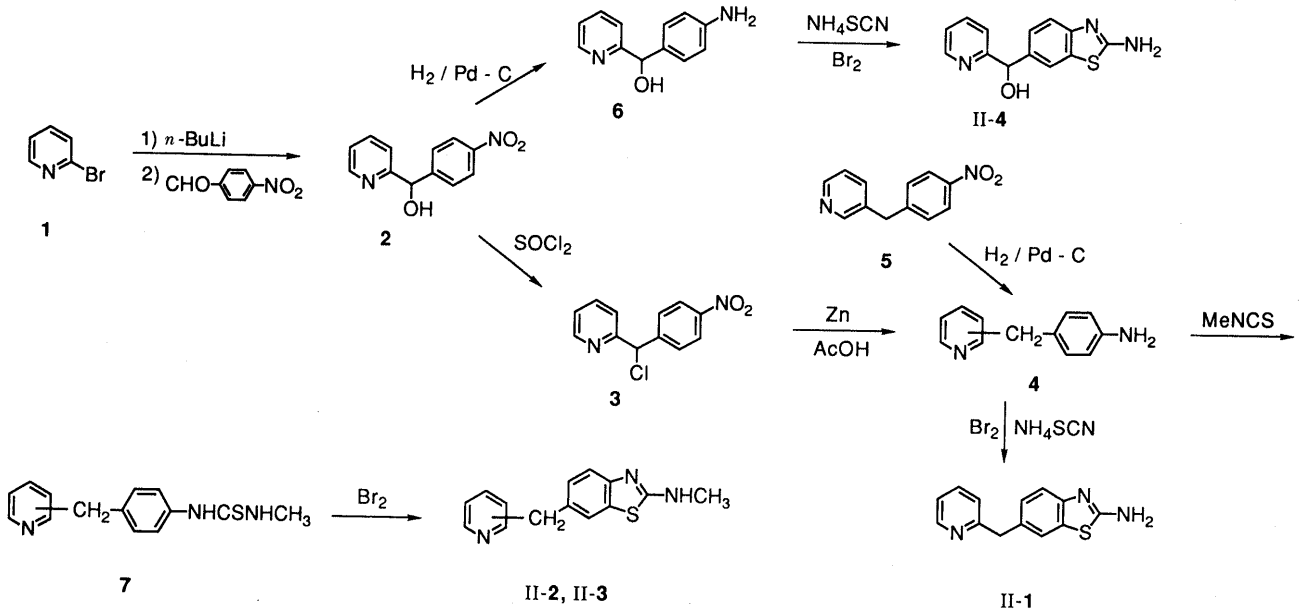

Chart 2

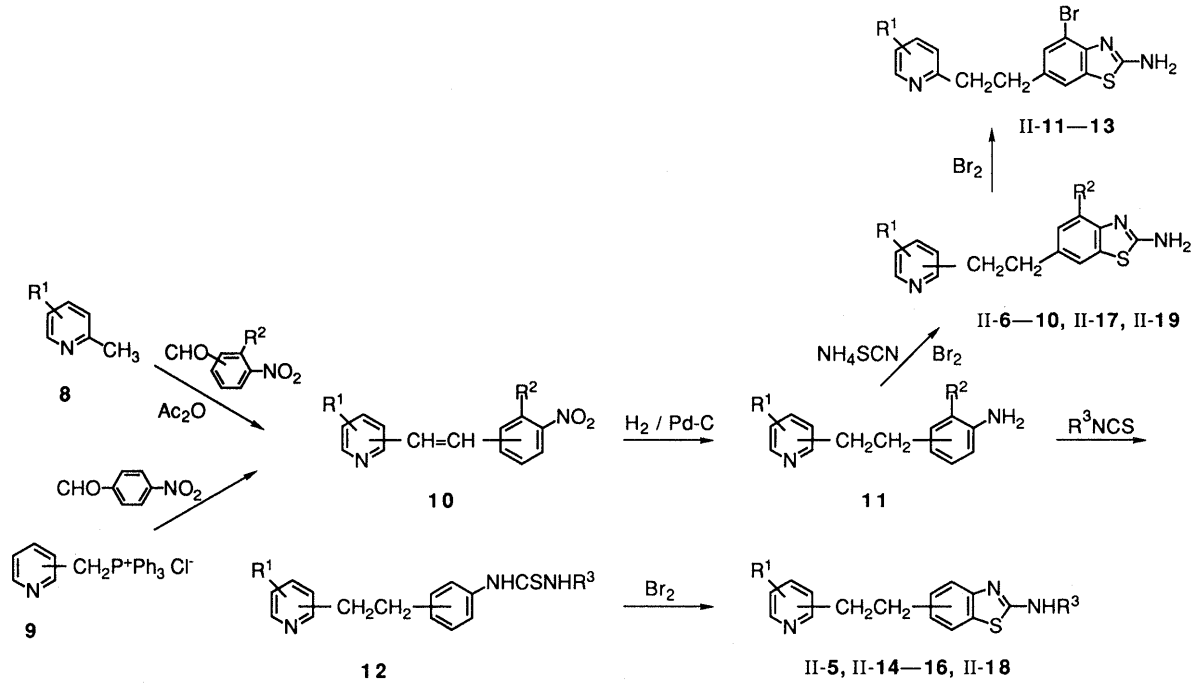

Chart 3

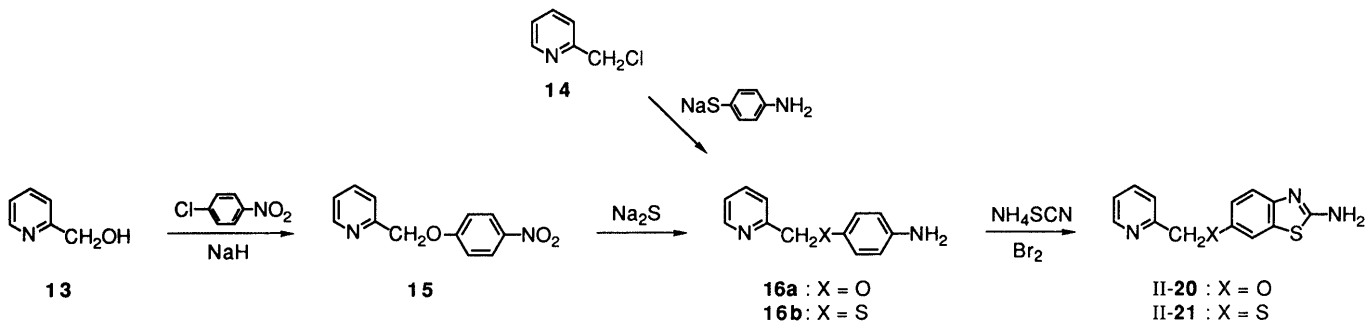

Chart 4

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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-ethylaminobenzoxazoles (II-**24** and II-**25**).

The benzimidazoles (II-**26** and II-**27**) were synthesized as follows. Acetylation of **11** followd 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

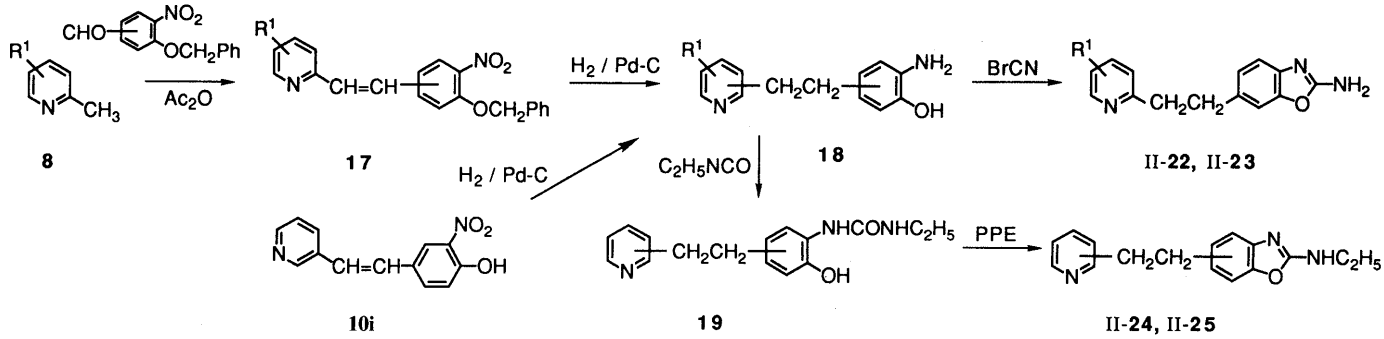

Chart 5

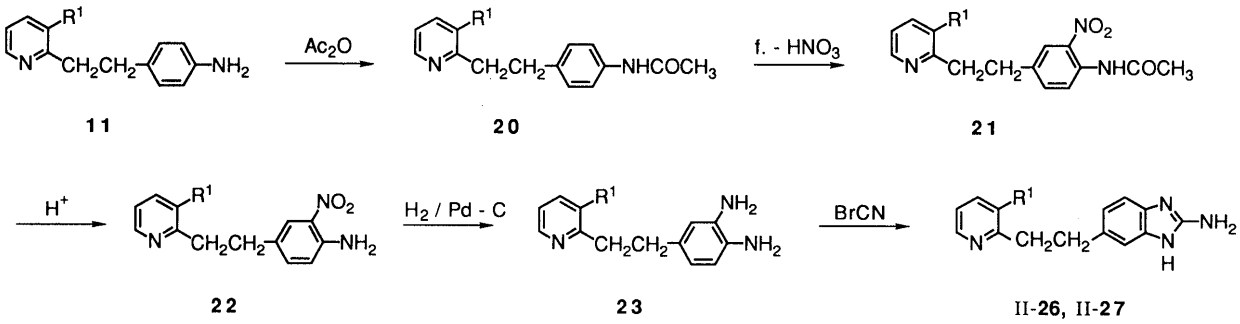

Chart 6

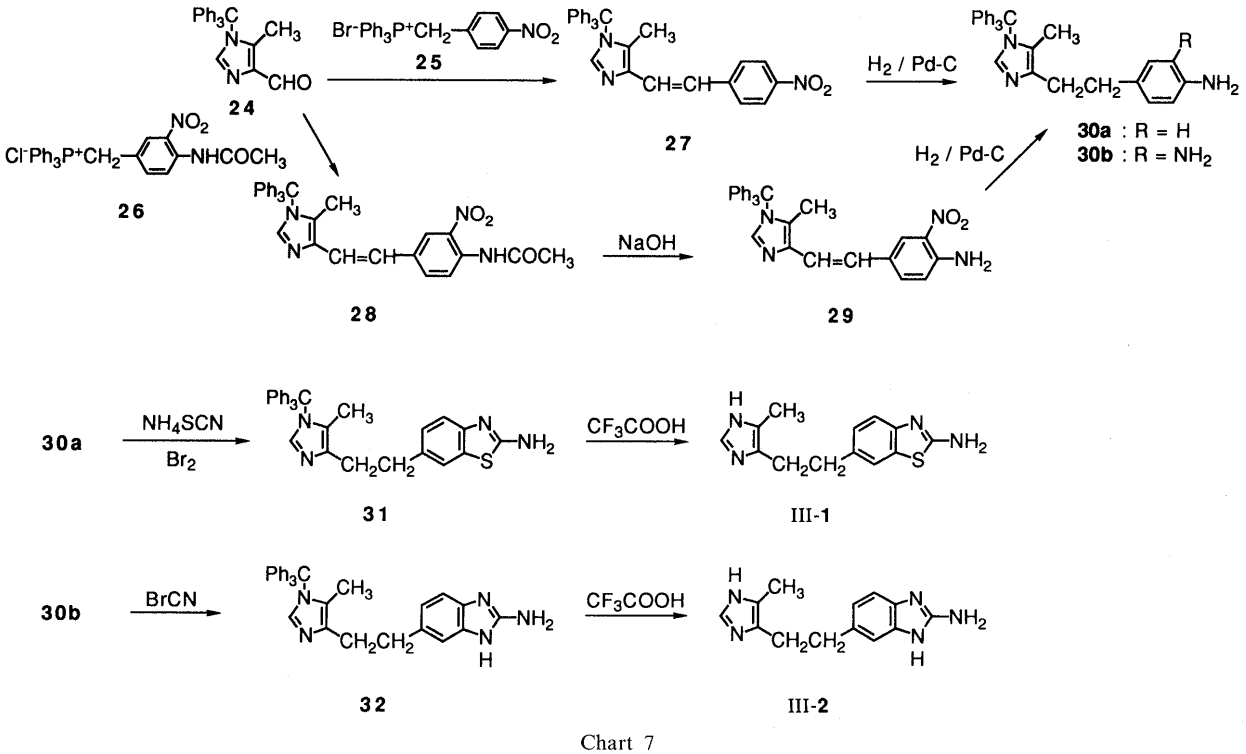

Chart 7

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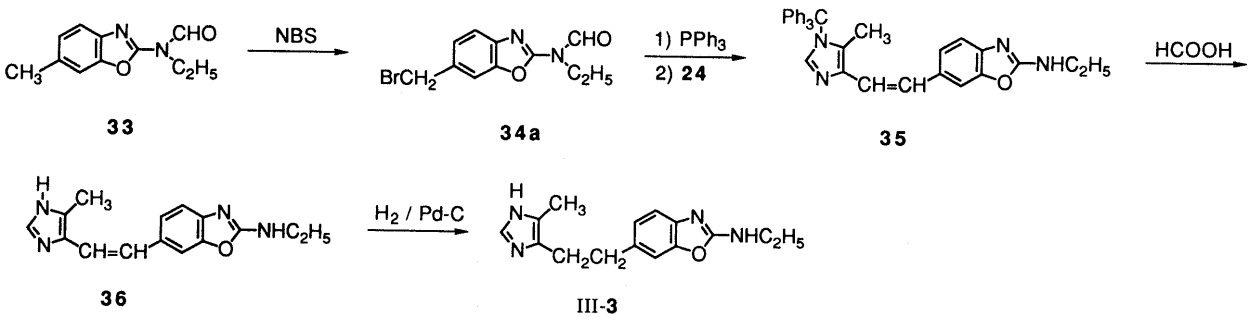

Chart 8

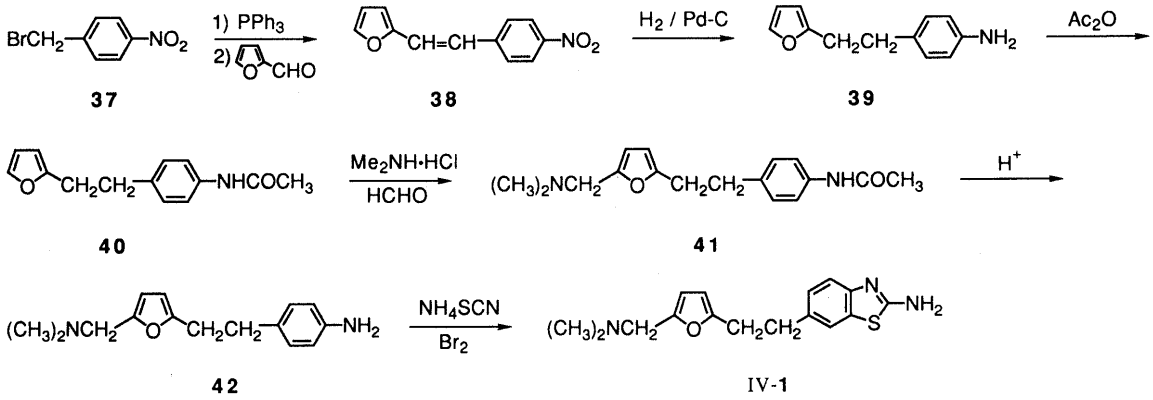

Chart 9

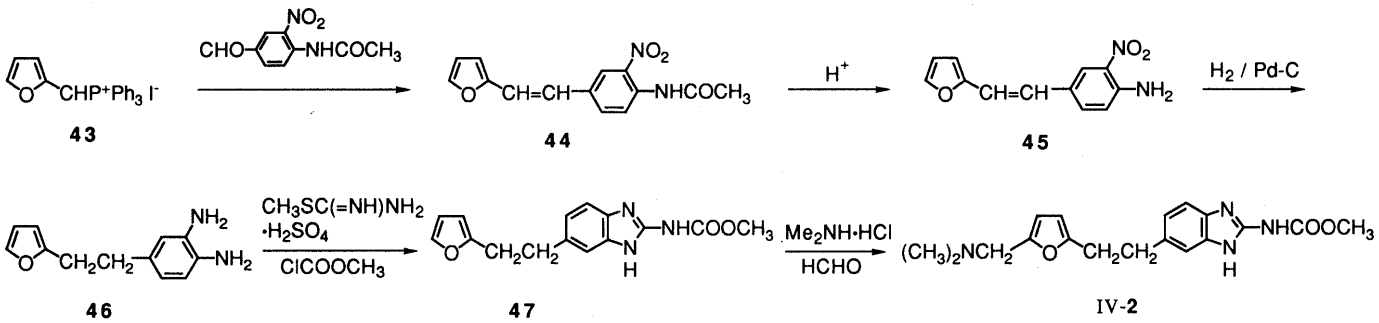

Chart 10

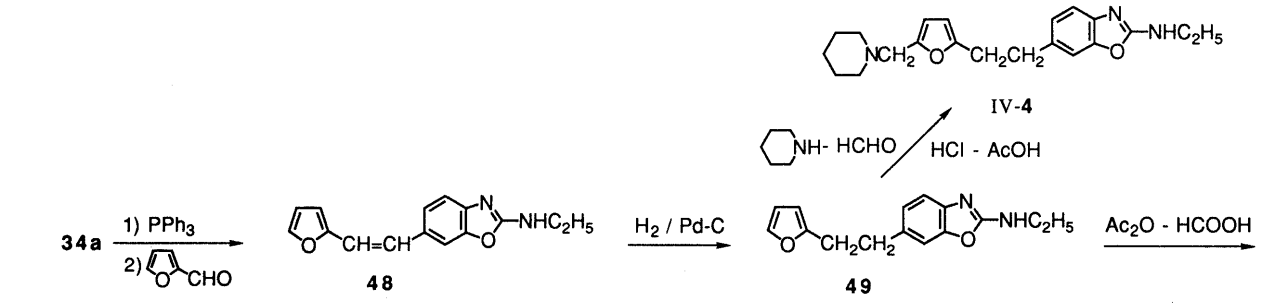

Chart 11

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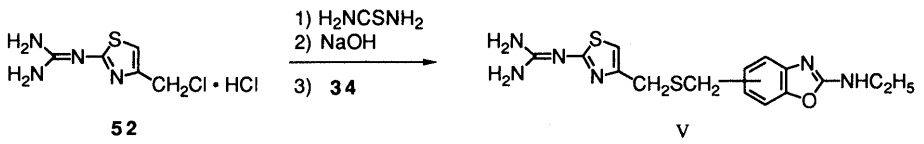

Chart 12

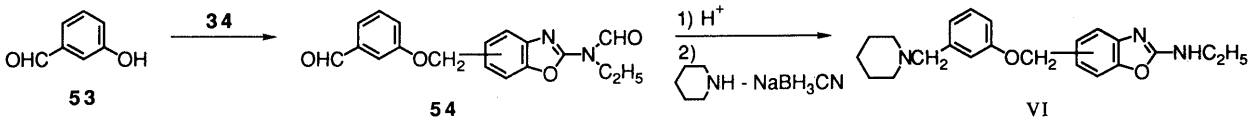

Chart 13

derivatives (**27** and **28**), respectively. After hydrogenation, cyclization of the resultant amino derivatives (**30a** and **30b**) with NH_4SCN–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 $Me_2NH \cdot HCl$ 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 methylisothiouronium 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 furfurylisothiourea (**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.

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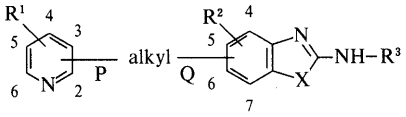
TABLE I. Physical Data of Pyridinylalkylbenzazoles (II)



Compd. No.	R^1	P	Alkyl	Q	R^2	X	R^3	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found)		
											C	H	N
II-1	H	2	CH_2	6	H	S	H	12	182—183 (I–M)	$C_{13}H_{11}N_3S$	64.71 (64.77	4.59 4.47	17.41 17.17)
II-2	H	2	CH_2	6	H	S	CH_3	11	120—122 (I–M)	$C_{14}H_{13}N_3S$	65.85 (65.74	5.13 5.21	16.46 16.39)
II-3	H	3	CH_2	6	H	S	CH_3	18	170—171 (EA–T)	$C_{14}H_{13}N_3S$	65.85 (65.86	5.13 5.04	16.46 16.29)
II-4	H	2	CH(OH)	6	H	S	H	25	187—188 (EA–T)	$C_{13}H_{11}N_3OS$	60.68 (60.92	4.31 4.26	16.33 16.47)
II-5	H	2	CH_2CH_2	4	H	S	C_2H_5	28	106—108 (E–I)	$C_{16}H_{17}N_3S$	67.81 (67.71	6.05 6.08	14.83 14.59)
II-6	H	2	CH_2CH_2	6	H	S	H	63	163—165 (EA)	$C_{14}H_{13}N_3S$	65.85 (65.94	5.13 5.09	16.46 16.44)
II-7	3-CH_3	2	CH_2CH_2	6	H	S	H	67	194—196 (EA–C–M)	$C_{15}H_{15}N_3S$	66.89 (66.61	5.61 5.72	15.60 15.21)
II-8	4-CH_3	2	CH_2CH_2	6	H	S	H	48	195—197 (EA–C–M)	$C_{15}H_{15}N_3S$	66.89 (66.74	5.61 5.49	15.60 15.34)
II-9	5-CH_3	2	CH_2CH_2	6	H	S	H	63	205—207 (EA–T)	$C_{15}H_{15}N_3S$	66.89 (66.92	5.61 5.54	15.60 15.93)
II-10	H	2	CH_2CH_2	6	4-OCH_3	S	H	51	222—224 (EA–T)	$C_{15}H_{15}N_3OS$	63.14 (63.28	5.30 5.39	14.73 14.51)
II-11	H	2	CH_2CH_2	6	4-Br	S	H	53	221—223 (C–E)	$C_{14}H_{12}N_3BrS$	50.31 (50.23	3.62 3.53	12.57 12.55)
II-12	3-CH_3	2	CH_2CH_2	6	4-Br	S	H	52	236—237 (C–E)	$C_{15}H_{14}N_3BrS$	51.74 (51.53	4.05 3.82	12.07 11.89)
II-13	5-CH_3	2	CH_2CH_2	6	4-Br	S	H	52	216—218 (EA–T)	$C_{15}H_{14}N_3BrS$	51.74 (52.06	4.05 4.02	12.07 12.00)
II-14	H	2	CH_2CH_2	6	H	S	CH_3	13	123—124 (EA)	$C_{15}H_{15}N_3S$	66.89 (66.67	5.61 5.57	15.60 15.49)
II-15	H	2	CH_2CH_2	6	H	S	C_2H_5	18	102—104 (EA–I)	$C_{16}H_{17}N_3S$	67.81 (67.68	6.05 5.95	14.83 14.68)
II-16	3-CH_3	2	CH_2CH_2	6	H	S	C_2H_5	9	159—161 (E–EA)	$C_{17}H_{19}N_3S$	68.65 (68.60	6.44 6.50	14.13 13.91)
II-17	H	3	CH_2CH_2	6	H	S	H	45	210—212 (EA–T)	$C_{14}H_{13}N_3S$	65.85 (65.66	5.13 4.99	16.46 16.82)
II-18	H	3	CH_2CH_2	6	H	S	CH_3	17	155—157 (EA)	$C_{15}H_{15}N_3S$	66.89 (66.61	5.61 5.42	15.60 15.24)
II-19	H	4	CH_2CH_2	6	H	S	H	50	187—189 (EA–T)	$C_{14}H_{13}N_3S$	65.85 (65.56	5.13 5.23	16.46 16.26)
II-20	H	2	CH_2O	6	H	S	H	28	169—172 (EA–T)	$C_{13}H_{11}N_3OS$	60.68 (60.34	4.31 4.25	16.33 16.15)
II-21	H	2	CH_2S	6	H	S	H	40	171—172 (EA–T)	$C_{13}H_{11}N_3S_2$	57.12 (56.90	4.06 3.98	15.37 15.10)
II-22	H	2	CH_2CH_2	6	H	O	H	62	203—205 (E–EA)	$C_{14}H_{13}N_3O$	70.27 (69.96	5.48 5.47	17.56 17.45)
II-23	3-CH_3	2	CH_2CH_2	6	H	O	H	70	227—230 (EA–T)	$C_{15}H_{15}N_3O$	71.13 (70.98	5.97 6.09	16.59 16.38)
II-24	H	2	CH_2CH_2	6	H	O	C_2H_5	15	93—94 (EA–H)	$C_{16}H_{17}N_3O$	71.89 (71.80	6.41 6.36	15.72 15.46)
II-25	H	3	CH_2CH_2	5	H	O	C_2H_5	26	230—233 (A–T)	$C_{16}H_{17}N_3O$ ·2HCl	56.48 (56.40	5.63 5.69	12.35 12.23)
II-26	H	2	CH_2CH_2	5(6)	H	NH	H	37	198—200 (A–T)	$C_{14}H_{14}N_4$	70.57 (70.68	5.92 5.89	23.51 23.42)
II-27	3-CH_3	2	CH_2CH_2	5(6)	H	NH	H	34	263—265 (A–T)	$C_{15}H_{16}N_4$ ·2HCl·H_2O	52.49 (52.61	5.87 5.82	16.32 16.30)

a) A, EtOH; C, $CHCl_3$; E, Et_2O; EA, AcOEt; H, *n*-hexane; I, iso-Pr_2O (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 (^{1}H-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 N_2 atmosphere. After being stirred for 1 h, a solution of

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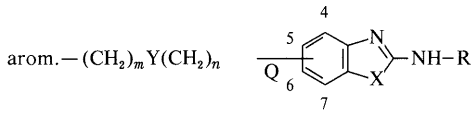
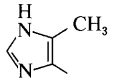
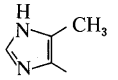
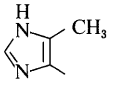
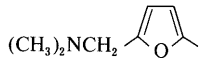
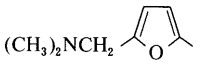
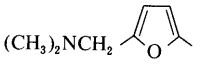
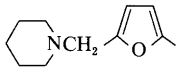
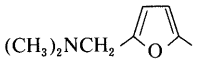
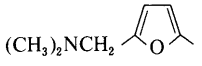
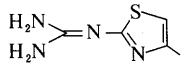
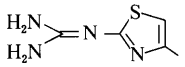
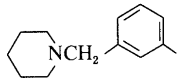
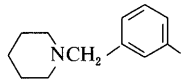
TABLE II. Physical Data of Aralkylbenzazoles (III—VI)



Compd. No.	Arom.	m	Y	n	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)	$C_{13}H_{14}N_4S$	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_2H_5	48	198—201 (E–EA)	$C_{15}H_{18}N_4O$	66.65 (66.59	6.71 6.80	20.73 20.65)
IV-1		1	—	1	6	S	H	22	153—154 (EA–H)	$C_{16}H_{19}N_3OS$	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)	$C_{18}H_{22}N_4O_3$	63.14 (62.88	6.48 6.39	16.36 15.97)
IV-3		1	—	1	6	O	C_2H_5	18	72—73 (EA)	$C_{18}H_{23}N_3O_2 \cdot 3/2C_4H_4O_4$	59.13 (59.18	6.00 6.23	8.62 8.24)
IV-4		1	—	1	6	O	C_2H_5	24	98—100 (A–EA)	$C_{21}H_{27}N_3O_2 \cdot 5/4C_4H_4O_4$	62.64 (62.86	6.47 6.36	8.43 8.64)
IV-5		1	S	1	5	O	C_2H_5	19	100—101 (A–I)	$C_{18}H_{23}N_3O_2S \cdot C_4H_4O_4$	57.25 (57.19	5.90 5.79	9.10 9.06)
IV-6		1	S	1	6	O	C_2H_5	26	181—183 (A–I)	$C_{18}H_{23}N_3O_2S \cdot 2HCl$	51.67 (51.30	6.02 6.33	10.04 9.86)
V-1		1	S	1	5	O	C_2H_5	28	168—169 (A–H)	$C_{15}H_{18}N_6OS_2$	49.70 (49.38	5.01 5.22	23.19 22.95)
V-2		1	S	1	6	O	C_2H_5	19	212—214 (I–M–T)	$C_{15}H_{18}N_6OS_2$	49.70 (49.43	5.01 4.92	23.19 22.86)
VI-1		0	O	1	5	O	C_2H_5	30	132—133 (A–E)	$C_{22}H_{27}N_3O_2 \cdot 2HCl \cdot 1/2H_2O$	59.06 (58.96	6.76 6.96	9.39 9.07)
VI-2		0	O	1	6	O	C_2H_5	15	105—106 (EA–H)	$C_{22}H_{27}N_3O_2$	72.30 (72.53	7.45 7.65	11.50 11.24)

a) A, EtOH; D, *N*,*N*-dimethylformamide (DMF); E, Et_2O; EA, AcOEt; H, *n*-hexane; I, iso-Pr_2O (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)–H_2O (2 l) and the resulting solution was acidified with concentrated HCl. The separated aqueous layer was basified with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$ 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}. ^{1}H-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 $C_{12}H_{10}N_2O_3$: 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 $SOCl_2$ (3.9 g, 33 mmol) in $CHCl_3$ (50 ml) was refluxed for 1 h. The mixture was then poured into H_2O, adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to afford **3** (5.2 g, 96%) as an oil. IR (film): 1525, 1390 cm^{-1}. ^{1}H-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 AcOH (30 ml) was refluxed for 1 h with stirring. After addition of AcOEt–H_2O, an insoluble material was removed by filtration and the resulting solution was adjusted to pH 8 with 20% aqueous K_2CO_3. The separated organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–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}. ^{1}H-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 $C_{12}H_{12}N_2$: 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 H_2. After removal of the

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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 *p.o.*	Compd. No.	Anti-stress ulcer activity (% inhibition) 32 mg/kg *p.o.*
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. ^{1}H-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_2O–DCl	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_2O–DCl	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_2O–DCl	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)
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_2O–DCl	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_2O	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_2O–DCl	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_2O	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_2O–DCl	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_2O–DCl	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_2O–DCl	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, br s)

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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, br s)
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, br s), 11.58 (2H, br s)
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, br s), 11.33 (1H, br s)
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, br s), 11.10 (1H, br s)
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}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 Et_2O–AcOEt to afford **12e** (5.9 g, 96%). *Anal.* Calcd for $C_{15}H_{17}N_3S$: 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 $Na_2S \cdot 9H_2O$ (62 g, 260 mmol) in EtOH (260 ml)–H_2O (50 ml) was refluxed for 2 h. After evaporation of the solvent, the residue was partitioned between AcOEt and H_2O. The obtained organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford **16a** (18 g, 81%) as an oil. IR (Nujol): 3350, 3230, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.60 (2H, br s), 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-pyridyl)methylbenzothiazole (II-1) A solution of **4a** (4.5 g, 24 mmol) and NH_4SCN (3.7 g, 48 mmol) in AcOH (50 ml) was stirred for 1 h at room temperature. After a solution of Br_2 (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–H_2O and adjusted to pH 7.5 with 20% aqueous K_2CO_3. An insoluble material was filtered off and the separated organic layer was washed with brine, dried ($MgSO_4$) 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) Br_2 (3.7 g, 23 mmol) was added dropwise to a solution of **12e** (5.8 g, 21 mmol) in $CHCl_3$ (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–H_2O. The separated aqueous layer was adjusted to pH 7.5 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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 Br_2 (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 H_2O, acidified with 10% HCl and washed with AcOEt. The obtained solution was basified with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from $CHCl_3$–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 Et_2O to afford **19a** (3.2 g, 82%). An analytical sample was obtained by recrystallization from IPE–MeOH. *Anal.* Calcd for $C_{16}H_{19}N_3O_2$: 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–H_2O, the solution was adjusted to pH 8 with 20% aqueous K_2CO_3. The separated organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–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]-1*H*-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–H_2O. The solution was adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with $CHCl_3$–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 H_2O (500 ml). The resulting precipitate was collected by filtration and dissolved in AcOEt–THF–H_2O. The separated organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with Et_2O to afford **28** (6.8 g, 62%). An analytical sample was obtained by recrystallization from IPE–THF. *Anal.* Calcd for $C_{33}H_{28}N_4O_3$: 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 $C_{31}H_{26}N_4O_2$: 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 CF_3COOH (6 ml) was refluxed for 5 h with stirring. After Et_2O (30 ml) was added to the solution, the resulting precipitate was collected by filtration and dissolved in H_2O. The solution was adjusted to pH 9 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from Et_2O–AcOEt to afford **III-1** (0.24 g, 33%). IR (Nujol): 3440, 3280, 1670 cm^{-1}.

5-[2-(2-Furyl)ethyl]-2-methoxycarbonylamino-1*H*-benzimidazole (47) A solution of *S*-methylisothiourea sulfate (2.8 g, 10 mmol) and ClCOOMe (1.5 ml, 20 mmol) in H_2O (10 ml) was adjusted to pH 8 with 5 N NaOH.

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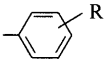
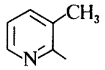
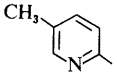
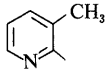
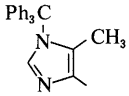
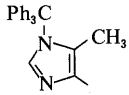
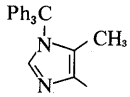
TABLE V. Physical Data of β-Arylstylenes

aryl–CH=CH– 

Compd. No.	Aryl	R	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_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, J=17), 7.83 (2H, d, J=9), 7.63—8.07 (2H, m), 8.30 (2H, d, J=9), 8.33—8.80 (2H, m)[e]
10d		4-NO_2	46	151—152	2.35 (3H, s), 7.17 (1H, d, J=5), 7.46 (1H, s), 7.51 (1H, d, J=16), 7.79 (1H, d, J=16), 7.93 (2H, d, J=9), 8.24 (2H, d, J=9), 8.47 (1H, d, J=5)
10e		4-NO_2	52	179—180	2.73 (3H, s), 7.50 (1H, d, J=17), 7.90 (2H, d, J=9), 7.97 (1H, d, J=17), 7.67—8.67 (3H, m), 8.38 (2H, d, J=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, J=5, 8), 7.42 (1H, d, J=8), 7.57 (1H, d, J=16), 7.59 (1H, d, J=8), 7.62 (1H, s), 7.69 (1H, d, J=16), 7.85 (1H, t, J=8), 7.93 (1H, d, J=8), 8.63 (1H, d, J=5)
10i		3-NO_2, 4-OH	78	Oil	5.29 (1H, s), 6.70 (1H, d, J=12), 6.78 (1H, d, J=12), 7.26—7.46 (3H, m), 7.62 (1H, dd, J=2, 8), 7.73 (1H, d, J=2), 8.43 (1H, d, J=2), 8.44 (1H, dd, J=2, 5)
17a		3-OCH_2Ph, 4-NO_2	92	113—116	5.31 (2H, s), 7.00 (1H, dd, J=2, 8), 7.17—7.65 (11H, m), 7.78 (1H, d, J=8), 8.50 (1H, dd, J=2, 5)
17b		3-OCH_2Ph, 4-NO_2	49	98—100	2.48 (3H, s), 5.42 (2H, s), 7.10—7.83 (11H, m), 7.93 (1H, d, J=8), 8.45 (1H, dd, J=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, J=8), 8.20 (2H, d, J=8)
28		3-NO_2, 4-$NHCOCH_3$	62	203—206	1.38 (3H, s), 2.07 (3H, s), 6.38 (1H, d, J=13), 6.45 (1H, d, J=13), 7.08—7.67 (17H, m), 7.99 (1H, dd, J=2, 8), 8.63 (1H, d, J=2), 10.25 (1H, s)
29		3-NO_2, 4-NH_2	49	188—194	2.25 (3H, s), 6.90 (1H, d, J=13), 7.03 (1H, s), 7.23—8.64 (19H, m)[e]
38		4-NO_2	61	122—125	6.60 (1H, dd, J=2, 4), 6.73 (1H, d, J=4), 7.05 (1H, d, J=16), 7.43 (1H, d, J=16), 7.78 (1H, d, J=2), 7.80 (2H, d, J=8), 8.20 (2H, d, J=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, J=2), 10.30 (1H, s)
45		3-NO_2, 4-NH_2	99	111—114	6.43 (1H, d, J=12), 6.53 (1H, dd, J=2, 3), 6.90 (2H, br s), 7.05 (1H, d, J=12), 7.07 (1H, d, J=8), 7.13 (1H, d, J=3), 7.68 (1H, d, J=2), 7.72 (1H, dd, J=2, 8), 8.10 (1H, d, J=2)

a) Ref. 5*a*. *b*) Ref. 5*b*. *c*) Ref. 5*c*. *d*) Ref. 5*d*. *e*) In CF_3COOH.

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 H_2O and EtOH to afford **47** (1.7 g, 59%). An analytical sample was obtained by recrystallization from DMF–H_2O. *Anal.* Calcd for $C_{15}H_{15}N_3O_3$: 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 PPh_3 (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 $NaHCO_3$ and the mixture was extracted with AcOEt. The extract was dried ($MgSO_4$) 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 $C_{15}H_{14}N_2O_2$: 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

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TABLE VI. Physical Data of Aralkylbenzenes

aryl–$(CH_2)_m$–C$_6$H$_4$–R

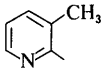
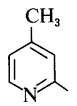
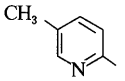
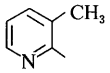
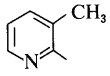
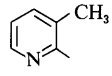
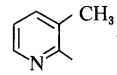
Compd. No.	Aryl	R	m	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6, δ: J=Hz)
7a		4-NHCSNHCH$_3$	1	82	120—122	2.92 (3H, d, J=5), 4.03 (2H, s), 7.08—7.47 (6H, m), 7.51—7.90 (2H, m), 8.52 (1H, dd, J=2, 5), 9.43 (1H, s)
7b		4-NHCSNHCH$_3$	1	95	178—180	2.88 (3H, d, J=5), 3.93 (2H, s), 7.18—7.31 (5H, m), 7.63 (2H, d, J=8), 8.40 (1H, d, J=5), 8.51 (1H, d, J=2), 9.46 (1H, br s)
11a[a]		2-NH$_2$	2			
11b		4-NH$_2$	2	98	Oil	2.75—2.98 (4H, m), 4.83 (2H, br s), 6.49 (2H, d, J=8), 7.14—7.21 (2H, m), 7.65 (1H, dt, J=2, 8), 8.48 (1H, dd, J=2, 5)
11c		4-NH$_2$	2	96	46—48	2.27 (3H, s), 2.90 (4H, s), 4.57 (2H, br s), 6.50 (2H, d, J=8), 6.88 (2H, d, J=8), 7.02 (1H, d, J=8), 7.40 (1H, dd, J=2, 8), 8.32 (1H, d, J=2)
11d		4-NH$_2$	2	91	Oil	2.23 (3H, s), 2.87 (4H, s), 4.78 (2H, br s), 6.53 (2H, d, J=9), 6.80—7.10 (2H, m), 6.90 (2H, d, J=9), 8.33 (1H, d, J=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, J=9), 6.88 (2H, d, J=9), 7.02 (1H, d, J=8), 7.42 (1H, dd, J=2, 8), 8.32 (1H, d, J=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, J=8), 6.85 (2H, d, J=8), 7.25 (2H, dd, J=2, 5), 8.49 (2H, dd, J=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, J=2, 5)
12a		2-NHCSNHC$_2$H$_5$	2	66	118—121	1.07 (3H, t, J=7), 2.95 (4H, s), 3.25—3.72 (2H, m), 6.93—7.80 (8H, m), 8.42 (1H, dd, J=2, 5), 9.07 (1H, s)
12b		4-NHCSNHCH$_3$	2	92	126—129	2.92 (3H, d, J=6), 2.97 (4H, s), 7.00—7.40 (6H, m), 7.40—7.83 (2H, m), 8.43 (1H, dd, J=2, 5), 9.33 (1H, s)
12c		4-NHCSNHC$_2$H$_5$	2	79	124—126	1.08 (3H, t, J=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, J=2, 4), 9.36 (1H, s)
12d		4-NHCSNHC$_2$H$_5$	2	92	124—126	1.10 (3H, t, J=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, J=2, 5), 9.27 (1H, s)
12e		4-NHCSNHCH$_3$	2	96	146—148	2.87 (4H, s), 2.92 (3H, d, J=5), 6.93—7.70 (7H, m), 8.28 (1H, d, J=2, 5), 8.33 (1H, d, J=2), 9.32 (1H, s)
18a		3-OH, 4-NH$_2$	2	86	113—115	2.83 (4H, s), 6.22 (1H, dd, J=2, 8), 6.47 (1H, d, J=2), 6.55 (1H, d, J=8), 7.00—7.33 (2H, m), 7.57 (1H, dt, J=2, 7), 8.45 (1H, dd, J=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, J=5, 7), 7.48 (1H, dd, J=2, 7), 8.28 (1H, dd, J=2, 5)
18c		3-NH$_2$, 4-OH	2	74	Oil	2.78 (4H, s), 6.23 (1H, dd, J=2, 8), 6.52 (1H, d, J=2), 6.60 (1H, d, J=8), 7.32 (1H, d, J=7), 7.60 (1H, dt, J=2, 7), 8.40 (1H, d, J=2), 8.42 (1H, s)
19a		3-OH, 4-NHCONHC$_2$H$_5$	2	82	130—132	1.03 (3H, t, J=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, J=2, 5), 9.87 (1H, s)
19b		3-NHCONHC$_2$H$_5$, 4-OH	2	75	174—175	1.05 (3H, t, J=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, J=8), 7.12 (1H, dd, J=2, 8), 7.40 (2H, d, J=8), 7.55 (1H, dt, J=8, 2), 8.38 (1H, dd, J=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, J=5, 8), 7.08 (2H, d, J=8), 7.45 (1H, dd, J=2, 8), 7.47 (2H, d, J=8), 8.28 (1H, dd, J=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, J=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, J=5, 8), 7.47—7.70 (3H, m), 7.80 (1H, s), 8.35 (1H, dd, J=2, 5), 10.03 (1H, s)

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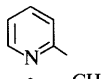
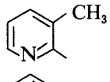
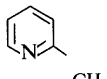
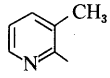
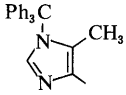
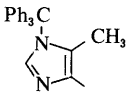
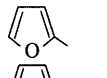
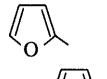
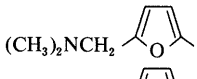
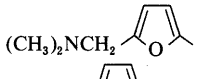
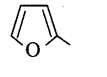
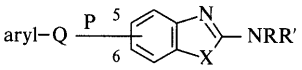
TABLE VI. (continued)

Compd. No.	Aryl	R	*m*	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6, δ: J=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, J=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, J=9), 6.93—7.60 (5H, m), 7.75 (1H, d, J=2), 8.30 (1H, dd, J=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, J=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, J=5, 8), 7.40 (1H, dd, J=2, 8), 8.27 (1H, dd, J=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, J=8), 6.73 (2H, d, J=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)[c]
39		4-NH_2	2	65	38—40	2.77 (4H, s), 4.78 (2H, s), 6.06 (1H, d, J=3), 6.32 (1H, dd, J=2, 3), 6.52 (2H, d, J=8), 6.88 (2H, d, J=8), 7.48 (1H, d, J=2)
40		4-$NHCOCH_3$	2	95	123—125	2.02 (3H, s), 2.86 (4H, s), 6.06 (1H, d, J=3), 6.33 (1H, dd, J=2, 3), 7.12 (2H, d, J=9), 7.50 (1H, d, J=2), 7.51 (2H, d, J=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, J=3), 6.12 (1H, d, J=3), 7.12 (2H, d, J=8), 7.49 (2H, d, J=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, J=3), 6.13 (1H, d, J=3), 6.50 (2H, d, J=8), 6.92 (2H, d, J=8)
46		3,4-NH_2	2	45	79—81	2.57—2.87 (4H, m), 4.26 (4H, s), 6.04 (1H, d, J=3), 6.23 (1H, dd, J=2, 8), 6.32 (1H, dd, J=2, 3), 6.42 (1H, d, J=2), 6.43 (1H, d, J=8), 7.45 (1H, d, J=2)

a) Ref. 5*a*. *b*) Ref. 5*c*. *c*) In D_2O–DCl.

TABLE VII. Physical Data of Several Benzazoles



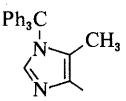
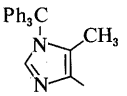
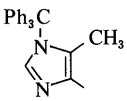
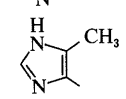
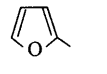
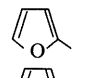
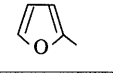
Compd. No.	Aryl	Q	P	X	R	R'	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6, δ: J=Hz)
31		CH_2CH_2	6	S	H	H	43	200—203	2.00 (3H, s), 2.66—2.84 (4H, m), 6.83—7.65 (21H, m)
32		CH_2CH_2	5(6)	NH	H	C_2H_5	54	161—164	1.16 (3H, t, J=7), 1.99 (3H, s), 2.63—2.93 (4H, m), 3.85—4.27 (2H, m), 6.60 (1H, d, J=8), 6.85—7.37 (20H, m)
35		CH=CH	6	O	H	C_2H_5	40	112—114	1.20 (3H, t, J=7), 2.13 (3H, s), 3.19—3.50 (2H, m), 6.18 (1H, d, J=13), 6.46 (1H, d, J=13), 6.86—7.57 (19H, m), 7.86 (1H, t, J=5)
36		CH=CH	6	O	H	C_2H_5	83	197—199	1.19 (3H, t, J=7), 2.06 (3H, s), 3.16—3.48 (2H, m), 6.18 (1H, d, J=13), 6.35 (1H, d, J=13), 6.97 (1H, d, J=8), 7.11 (1H, s), 7.24 (1H, d, J=8), 7.53 (1H, s), 7.79 (1H, t, J=5), 8.10 (1H, s)
47		CH_2CH_2	5(6)	NH	H	$COOCH_3$	59	223—225	2.95 (4H, s), 3.78 (3H, s), 6.09 (1H, d, J=3), 6.35 (1H, dd, J=2, 3), 6.97 (1H, dd, J=2, 8), 7.28 (1H, d, J=2), 7.35 (1H, d, J=8), 7.52 (1H, d, J=3)
48		CH=CH	6	O	H	C_2H_5	76	74—80	1.20 (3H, t, J=7), 3.36 (2H, dq, J=5, 7), 6.17—6.65 (3H, m), 7.02—7.62 (5H, m), 7.93 (1H, t, J=5)
49		CH_2CH_2	6	O	H	C_2H_5	87	76—78	1.20 (3H, t, J=7), 2.93 (4H, s), 3.35 (2H, dq, J=5, 7), 6.03—6.53 (2H, m), 6.85—7.53 (4H, m), 7.75 (1H, t, J=5)

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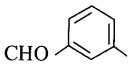
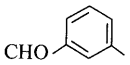
TABLE VII. (continued)

Compd. No.	Aryl	Q	P	X	R	R′	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6, δ: J=Hz)
50		CH_2CH_2	6	O	CHO	C_2H_5	90	57—59	1.20 (3H, t, J=7), 2.93 (4H, s), 3.37 (2H, q, J=7), 6.08 (1H, d, J=3), 6.35 (1H, dd, J=2, 3), 7.00—7.60 (3H, m), 8.15 (1H, s), 9.21 (1H, s)
54a		OCH_2	5	O	CHO	C_2H_5	76	112—114	1.23 (3H, t, J=7), 3.94 (2H, q, J=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_2H_5	84	87—89	1.23 (3H, t, J=7), 3.95 (2H, q, J=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 $NaHCO_3$ and the mixture was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) 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–Et_2O 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-ethylamino-benzoxazole 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 N_2 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)–H_2O (20 ml). The separated organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–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-ethyl-aminobenzoxazole (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)–H_2O (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–H_2O. The separated organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from MeOH–THF–H_2O to afford **V-2** (0.3 g, 19%). IR (Nujol): 3475, 3380, 3260, 1665 cm^{-1}.

2-(*N*-Ethylformamido)-6-(3-formylphenoxymethyl)benzoxazole (54b) A mixture of *m*-hydroxybenzaldehyde (1.0 g, 8.2 mmol), **34a** (2.3 g, 8.3 mmol) and K_2CO_3 (1.3 g, 9.2 mmol) in DMF (10 ml) was stirred for 6 h at room temperature. The reaction mixture was poured into H_2O (50 ml) and extracted with AcOEt. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from IPE–MeOH to afford **54b** (2.2 g, 84%). *Anal.* Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97, N, 8.64. Found: C, 66.99; H, 5.06; N, 8.70.

2-Ethylamino-6-(3-piperidinomethylphenoxymethyl)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 $NaHCO_3$. The separated organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to give an *N*-deformylated product. $NaBH_3CN$ (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 H_2O and the mixture was extracted with AcOEt. The extract was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–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 H_2-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 peper.[2]

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