

Studies on Antiulcer Drugs. IV.¹⁾ Synthesis and Antiulcer Activities of Imidazo[1,2-*a*]pyridinylethylbenzothiazoles and -benzimidazoles

Yousuke KATSURA,*^a Yoshikazu INOUE,^a Shigetaka NISHINO,^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 January 16, 1992

A series of 6-[2-(imidazo[1,2-*a*]pyridin-2-yl)ethyl]benzothiazoles (II) and benzimidazole analogues (III) was synthesized and tested for histamine H₂-receptor antagonist, gastric antisecretory and anti-stress ulcer activity. A benzimidazole derivative (IIIa) exhibited strong antisecretory activity, whereas the corresponding benzothiazole derivative (IIb) lacked this potency in *in vivo* test. In contrast to compound IIIa, however, compound IIb demonstrated good inhibition against stress induced ulcer. The structure-activity relationships of these compounds are discussed.

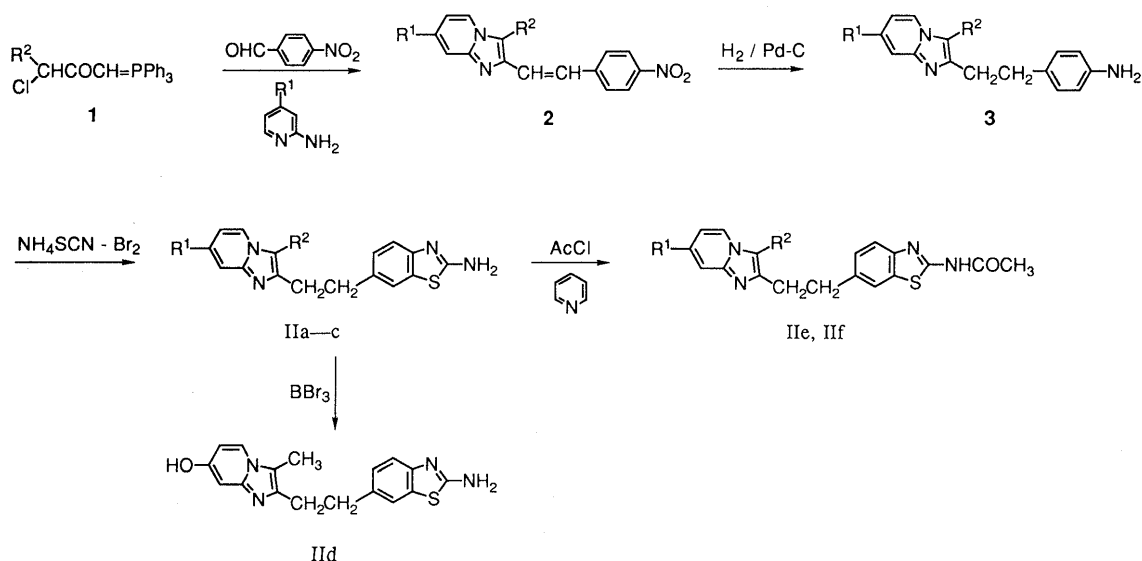
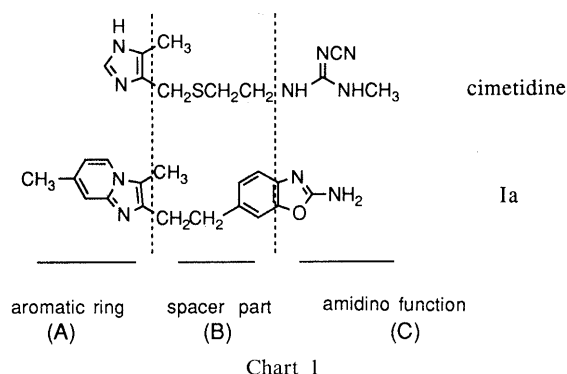
Keywords histamine H₂-receptor antagonist; anti-stress ulcer activity; antisecretory activity; imidazo[1,2-*a*]pyridinylethylbenzothiazole; imidazo[1,2-*a*]pyridinylethylbenzimidazole; structure-activity relationship

In a previous paper¹⁾ we reported the synthesis and pharmacological activities of a series of imidazo[1,2-*a*]pyridinylethylbenzoxazoles (I) and related compounds, which were structurally characterized by a rigid amidino function and a partially restricted spacer part in comparison with the conventional histamine H₂-receptor antagonists (H₂- antagonists) (Chart 1). The biological observation of these compounds revealed that the introduction of such a system could be successful approach for the exploration of a novel class of H₂-antagonists. As part of a continued

program aimed at obtaining novel antiulcer drugs, it is of interest to investigate some modifications of this system. This paper describes the synthesis and pharmacological evaluation of a number of 6-[2-(imidazo[1,2-*a*]pyridin-2-yl)ethyl]benzothiazoles and benzimidazole analogues.

Chemistry The synthesis of the target compounds (II and III) listed in Table I was achieved by the routes illustrated in Charts 2 and 3. The imidazo[1,2-*a*]pyridinylethylanilines (3) and phenylenediamines (5), key intermediates in the synthesis of the desired compounds, were prepared using the method described.¹⁾ Namely, Wittig reaction of the haloketones (1) with a corresponding benzaldehyde and subsequent condensation with an appropriate 2-amino-pyridines gave vinyl derivatives (2 and 4). Catalytic hydrogenation of these compounds over 10% palladium on carbon afforded the expected compounds (3 and 5).

Treatment of 3 with ammonium thiocyanate in the presence of bromine gave the requisite benzothiazole derivatives (IIa—c). Demethylation at the 7-methoxy group on the imidazo[1,2-*a*]pyridine moiety of IIc with boron tribromide provided the 7-hydroxy derivative (IIId). Acetylation of IIa and IIc with acetyl chloride in the presence of pyridine furnished 2-acetylaminobenzothiazole derivatives (IIe and IIf) (Chart 2).



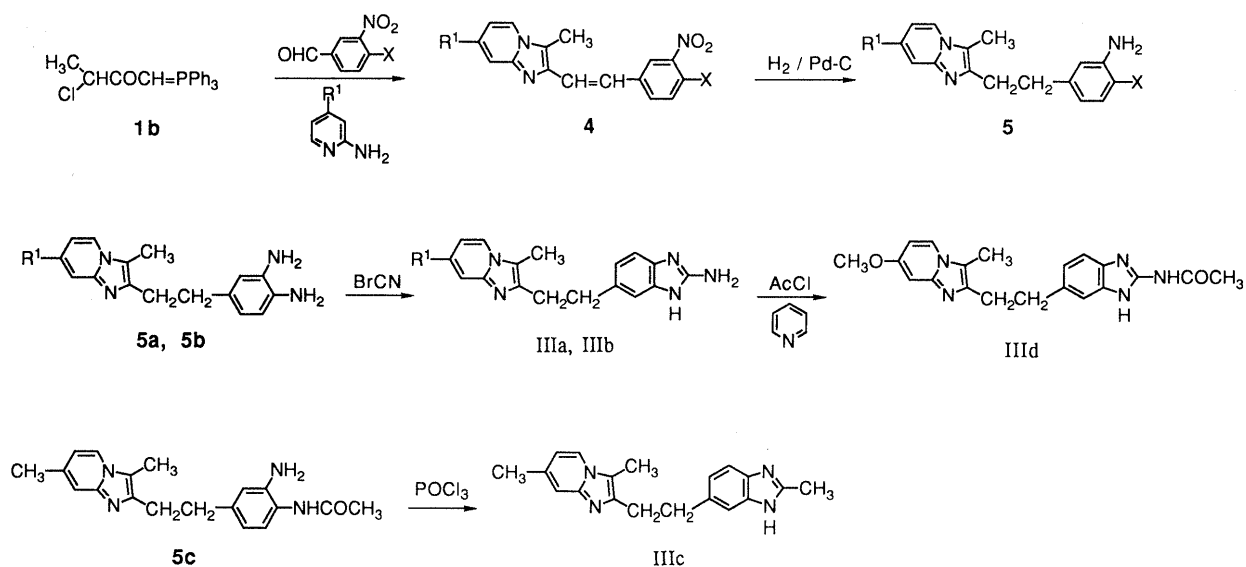


Chart 3

TABLE I. Physical Data of 6-[2-(Imidazo[1,2-*a*]pyridin-2-yl)ethyl]benzothiazoles (II) and benzimidazoles (III)

Compd. No.	R ¹	R ²	X	Y	Yield (%)	mp (°C) (Recryst. solvent) ^{a)}	Formula	Analysis (%)		
								Calcd	Found	
IIa	CH ₃	H	S	NH ₂	14	245–246 (D–W)	C ₁₇ H ₁₆ N ₄ S	66.23	5.23	18.17
IIb	CH ₃	CH ₃	S	NH ₂	27	285–286 (I–M)	C ₁₈ H ₁₈ N ₄ S	66.36	5.14	17.88
IIc	OCH ₃	CH ₃	S	NH ₂	14	223–225 (I–M)	C ₁₈ H ₁₈ N ₄ OS	51.85	5.41	13.44
IId	OH	CH ₃	S	NH ₂	10	265–266 (A–E)	C ₁₇ H ₁₆ N ₄ OS	51.60	5.63	13.31
IIf	CH ₃	H	S	NHCOCH ₃	27	259–260 (A–H)	C ₁₉ H ₁₈ N ₄ OS	59.16	5.79	15.33
IIIa	CH ₃	CH ₃	NH	NH ₂	19	240–242 (EA–I)	C ₂₀ H ₂₀ N ₄ O ₂ S	59.19	5.64	15.20
IIIb	OCH ₃	CH ₃	NH	NH ₂	21	296–298 (EA–T)	C ₁₈ H ₁₉ N ₅	47.12	5.12	12.93
IIIc	CH ₃	CH ₃	NH	CH ₃	54	151–153 (AN)	C ₁₉ H ₂₀ N ₄	46.85	4.91	12.62
IIId	OCH ₃	CH ₃	NH	NHCOCH ₃	41	235–237 (A–T)	C ₂₀ H ₂₁ N ₅ O ₂ ·H ₂ O	63.49	5.33	15.59

a) A, EtOH; AN, MeCN; D, *N,N*-dimethylformamide (DMF); E, Et₂O; EA, AcOEt; H, *n*-hexane; I, isopropyl ether (IPE); M, MeOH; T, tetrahydrofuran (THF); W, H₂O.

2-Aminobenzimidazole derivatives (IIIa and IIIb) were obtained by cyclization of the phenylenediamines (5a and 5b) with cyanogen bromide. Ring closure of the *N*-monoacetylphenylenediamine derivative (5c) with phosphorus oxychloride afforded 2-methylbenzimidazole derivative (IIIc). 2-Acetylaminobenzimidazole derivative (IIId) was prepared in a manner similar to that of IIf and IIf (Chart 3).

Pharmacological Results and Discussion The imidazo[1,2-*a*]pyridines obtained in this study were tested *in vitro* for histamine H₂-receptor antagonist (H₂-antagonist) activity using the histamine-stimulated chronotropic re-

sponse of the guinea pig right atrium.²⁾ Compounds with sufficient potency were then evaluated for *in vivo* models. Gastric antisecretory activity was assessed in histamine-stimulated lumen-perfusion anaesthetized rats³⁾ and anti-ulcer activity was measured in water-immersion stressed rats.⁴⁾ These biological results are presented in Table II.

In the H₂-antagonist assay, 3,7-dimethyl- and 3-methoxy-7-methylimidazo[1,2-*a*]pyridinyl derivatives of benzothiazole (IIb and IIf) and benzimidazole (IIIa and IIIb) exhibited very potent or fairly good activity. Conversion of the 7-substitution on the imidazo[1,2-*a*]pyridine nuclei of IIb to a hydroxy group (IId) reduced the activity.

Replacement of the amino group of IIIa with a methyl group (IIIc) in the 2-position on the benzazole moiety resulted in moderate activity. Acetylated derivative (IIe, IIc and IIId) of IIb, IIc and IIb, however, resulted in remarkable decrease or total disappearance of the activity in the screening dose, respectively.

With respect to *in vivo* antisecretory assay, the benzimidazole derivative (IIIa) revealed noticeable antisecretory activity and the potency was superior to that of ranitidine, while the corresponding benzothiazole derivative (IIb) was found to be inactive in this screening in spite of high H₂-antagonist activity. Accordingly, an additional

experiment was carried out to explore the discrepancy of IIb between *in vitro* H₂-antagonist potency and *in vivo* antisecretory activity.

To confirm the affinity at the gastric site, the *in vitro* antisecretory activity of IIb, IIIa and the corresponding benzoxazole derivative (Ia), which structurally differ by only one atom in the benzazole moiety, was determined in the gastric gland preparation of the rabbit⁵⁾ and compared with those of the reference compounds. The good activity of IIb on this assay demonstrates that this compound possesses the ability to interact on the receptor existing on the gastric gland. It is therefore conceivable that the deficiency of the *in vivo* antisecretory activity in IIb is due to insufficient concentration on the effector site.

The benzothiazole derivatives (IIb and IIc) responded well in antiulcer screening, and the potencies were comparable to that of ranitidine and cimetidine, respectively. The benzimidazole derivatives (IIIa—c), however, did not show a significant activity.

In conclusion, the benzimidazoles (III) revealed relatively good antisecretory activity, with that of compound IIIa being notable in response to high H₂-antagonist activity. In antiulcer action, the benzothiazoles (II) were more effective than the benzimidazoles.

TABLE II. Pharmacological Activities of 6-[2-(Imidazo[1,2-*a*]pyridin-2-yl)ethyl]benzothiazoles (II) and Benzimidazoles (III)

Compd. No.	H ₂ -antagonist activity ^{a)} [inhibition (%)] 3.2 × 10 ⁻⁶ g/ml	Antisecretory activity [inhibition (%)]		Antiulcer activity ^{d)} [inhibition (%)] 32 mg/kg <i>p.o.</i>
		<i>in vitro</i> ^{b)} 1 × 10 ⁻⁵ g/ml	<i>in vivo</i> ^{c)} 1 mg/kg i.v.	
Ia	93.1	65.9	65	92.9
IIa	NT			
IIb	84.6	50.0	NE	85.4
IIc	68.6		47	75.0
IIId	42.9			
IIf	10.6			
IIIa	27.5			
IIIa	100	86.4	90	10.0
IIIb	88.7		59	47.9
IIIc	57.9		64	NE
IIId	NE			
Cimetidine	56.6	36.0	53	69.4
Ranitidine	74.0	58.2	72	81.8

a) H₂-receptor antagonism in the isolated guinea pig right atrium. b) Antisecretory activity in the isolated rabbit gastric gland. c) Inhibition of histamine-stimulated gastric acid secretion in the lumen-perfused stomach of the anaesthetized rats (*n*=2). d) Inhibitory effect on gastric ulcer induced by water-immersion restraint stress in the rats (*n*=5). NT=not tested. NE=no effect.

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. Mass spectral measurements (MS) were made on a JEOL JMS D-300 mass spectrometer.

7-Methoxy-3-methyl-2-[2-(4-nitrophenyl)vinyl]imidazo[1,2-*a*]-pyridine (2c) A mixture of 3-chloro-2-oxobutylidene triphenylphosphorane (1) (23.6 g, 64 mmol) and 4-nitrobenzaldehyde (9.7 g, 64 mmol) in dioxane

TABLE III. Physical Data of 2-(2-Phenylvinyl)imidazo[1,2-*a*]pyridines (2 and 4)

Compd. No.	R ¹	R ²	R ³	R ⁴	Yield (%)	mp (°C)	¹ H-NMR	
							Solvent	δ (<i>J</i> =Hz)
2a	CH ₃	H	H	NO ₂	56	237—238	DMSO- <i>d</i> ₆	2.36 (3H, s), 6.74 (1H, dd, <i>J</i> =2, 7), 7.30 (1H, d, <i>J</i> =2), 7.49 (1H, d, <i>J</i> =16), 7.59 (1H, d, <i>J</i> =16), 7.87 (2H, d, <i>J</i> =8), 8.03 (1H, s), 8.21 (2H, d, <i>J</i> =8), 8.42 (1H, d, <i>J</i> =7)
2b	CH ₃	CH ₃	H	NO ₂	26	207—208	DMSO- <i>d</i> ₆	2.36 (3H, s), 2.57 (3H, s), 6.73 (1H, dd, <i>J</i> =2, 7), 7.27 (1H, d, <i>J</i> =2), 7.44 (1H, d, <i>J</i> =16), 7.55 (1H, d, <i>J</i> =16), 7.86 (2H, d, <i>J</i> =9), 8.15 (1H, d, <i>J</i> =7), 8.18 (2H, d, <i>J</i> =9)
2c	OCH ₃	CH ₃	H	NO ₂	31	213—214	DMSO- <i>d</i> ₆	2.59 (3H, s), 3.85 (3H, s), 6.65 (1H, dd, <i>J</i> =2, 7), 6.87 (1H, d, <i>J</i> =2), 7.43 (1H, d, <i>J</i> =16), 7.55 (1H, d, <i>J</i> =16), 7.91 (2H, d, <i>J</i> =9), 8.15 (1H, d, <i>J</i> =7), 8.20 (2H, d, <i>J</i> =9)
4a	CH ₃	CH ₃	NO ₂	NO ₂	46	234—236	DMSO- <i>d</i> ₆	2.36 (3H, s), 2.71 (3H, s), 6.77 (1H, dd, <i>J</i> =2, 7), 7.27 (1H, d, <i>J</i> =2), 7.50 (1H, d, <i>J</i> =16), 7.86 (1H, d, <i>J</i> =16), 8.12 (1H, d, <i>J</i> =9), 8.15 (1H, d, <i>J</i> =7), 8.23 (1H, d, <i>J</i> =9), 8.54 (1H, s)
4b	OCH ₃	CH ₃	NO ₂	NH ₂	100	260—261	CF ₃ COOH	2.77 (3H, s), 4.15 (3H, s), 7.11—7.61 (4H, m), 7.83—8.44 (3H, m), 8.71 (1H, s)
4c	CH ₃	CH ₃	NO ₂	NHCOCH ₃	8	245—246	DMSO- <i>d</i> ₆	2.08 (3H, s), 2.37 (3H, s), 2.57 (3H, s), 6.74 (1H, dd, <i>J</i> =2, 7), 7.26 (1H, d, <i>J</i> =2), 7.39 (1H, d, <i>J</i> =16), 7.53 (1H, d, <i>J</i> =16), 7.58 (1H, d, <i>J</i> =8), 7.97 (1H, dd, <i>J</i> =2, 8), 8.12 (1H, d, <i>J</i> =7), 8.21 (1H, d, <i>J</i> =2), 10.26 (1H, s)
4d	OCH ₃	CH ₃	NO ₂	NHCOCH ₃	31	227—230	CF ₃ COOH	2.56 (3H, s), 2.76 (3H, s), 4.14 (3H, s), 7.10—7.46 (4H, m), 7.90—8.39 (2H, m), 8.43—8.73 (2H, m)

TABLE IV. Physical Data of 2-(2-Phenylethyl)imidazo[1,2-*a*]pyridines (3 and 5)

Compd. No.	R ¹	R ²	R ³	R ⁴	Yield (%)	mp (°C)	Solvent	¹ H-NMR
								δ (J = Hz)
3a	CH ₃	H	H	NH ₂	96	144–148	DMSO- <i>d</i> ₆	2.31 (3H, s), 2.83 (4H, s), 4.76 (2H, s), 6.47 (2H, d, <i>J</i> = 8), 6.64 (1H, dd, <i>J</i> = 2, 7), 6.86 (2H, d, <i>J</i> = 8), 7.21 (1H, d, <i>J</i> = 2), 7.52 (1H, s), 8.30 (1H, d, <i>J</i> = 7)
3b	CH ₃	CH ₃	H	NH ₂	89	79–80	DMSO- <i>d</i> ₆	2.21 (3H, s), 2.33 (3H, s), 2.80 (4H, s), 6.47 (2H, d, <i>J</i> = 8), 6.68 (1H, dd, <i>J</i> = 2, 7), 6.84 (2H, d, <i>J</i> = 8), 7.22 (1H, d, <i>J</i> = 2), 8.07 (1H, d, <i>J</i> = 7)
3c	OCH ₃	CH ₃	H	NH ₂	63	114–116	DMSO- <i>d</i> ₆	2.21 (3H, s), 2.80 (4H, s), 3.83 (3H, s), 6.51 (2H, d, <i>J</i> = 8), 6.58 (1H, dd, <i>J</i> = 2, 7), 6.89 (1H, d, <i>J</i> = 2), 6.90 (2H, d, <i>J</i> = 8), 8.00 (1H, d, <i>J</i> = 7)
5a	CH ₃	CH ₃	NH ₂	NH ₂	52	112–114	DMSO- <i>d</i> ₆	2.24 (3H, s), 2.33 (3H, s), 2.81 (4H, s), 4.06 (4H, s), 6.23 (1H, dd, <i>J</i> = 2, 7), 6.40 (1H, d, <i>J</i> = 2), 6.41 (1H, d, <i>J</i> = 8), 6.69 (1H, dd, <i>J</i> = 2, 8), 7.21 (1H, d, <i>J</i> = 2), 8.02 (1H, d, <i>J</i> = 7)
5b	OCH ₃	CH ₃	NH ₂	NH ₂	84	205–208	DCI-D ₂ O	2.61 (3H, s), 3.18 (4H, s), 4.03 (3H, s), 7.10 (1H, d, <i>J</i> = 2, 8), 7.22 (1H, s), 7.47–7.82 (3H, m), 8.26 (1H, d, <i>J</i> = 7)
5c	CH ₃	CH ₃	NH ₂	NHCOCH ₃	81	168–173	DMSO- <i>d</i> ₆	2.04 (3H, s), 2.29 (3H, s), 2.36 (3H, s), 2.85 (4H, s), 6.43 (1H, dd, <i>J</i> = 2, 8), 6.63 (1H, d, <i>J</i> = 2), 6.73 (1H, dd, <i>J</i> = 2, 7), 7.10 (1H, d, <i>J</i> = 8), 7.27 (1H, d, <i>J</i> = 2), 8.06 (1H, d, <i>J</i> = 7)

(240 ml) was refluxed for 2 h. The solvent was evaporated *in vacuo*. The residue and 2-amino-4-methoxypyridine (20.0 g, 161 mmol) were dissolved in iso-PrOH (240 ml) and the solution was refluxed for 2 h. After evaporation of the solvent, the residue was suspended in AcOEt (120 ml)–H₂O (120 ml) and the mixture was adjusted to pH 1 with 6 N HCl. The resulting precipitate was collected by filtration and added to tetrahydrofuran (THF, 120 ml)–AcOEt (120 ml)–H₂O (120 ml). After the mixture was adjusted to pH 8, the organic layer separated was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was triturated with AcOEt–iso-Pr₂O (IPE) to afford **2c** (6.1 g, 31%). mp 213–214 °C (THF). *Anal.* Calcd for C₁₇H₁₅N₃O₃: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.90; H, 4.81; N, 13.20. IR (Nujol) 1650, 1630, 1585, 1330 cm⁻¹. MS *m/z*: 309 (M⁺).

2-[2-(4-Aminophenyl)ethyl]-7-methoxy-3-methylimidazo[1,2-*a*]pyridine (3c) A solution of **2c** (6.0 g, 19 mmol) in *N,N*-dimethylformamide (DMF) (120 ml) was hydrogenated over 10% Pd–C (2.0 g) under atmospheric pressure of H₂ at 40–60 °C. After removal of the solvent and catalyst, the residue was triturated with Et₂O to afford **3c** (3.4 g, 63%). mp 114–116 °C (IPE–MeOH). *Anal.* Calcd for C₁₇H₁₉N₃O: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.29; H, 6.94; N, 14.75. IR (Nujol): 3360, 3300, 3140, 1640, 1605 cm⁻¹. MS *m/z*: 281 (M⁺).

2-Amino-6-[2-(7-methoxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)-ethyl]-benzothiazole (IIc) A mixture of **3c** (2.2 g, 7.8 mmol) and NH₄SCN (1.2 g, 16 mmol) in AcOH (22 ml) was stirred at room temperature for 1 h. A solution of Br₂ (0.40 ml, 7.8 mmol) in AcOH (4 ml) was added dropwise to the mixture at 10–15 °C. After being stirred for 1.5 h at room temperature, the reaction mixture was poured into AcOEt–THF–H₂O and the pH of the solution was adjusted to 8 with 20% aqueous K₂CO₃. The organic layer separated was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with CHCl₃–MeOH (19:1) to give a product which was recrystallized from IPE–MeOH to afford **IIc** (0.38 g, 14%). IR (Nujol): 1650, 1635, 1535 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 2.20 (3H, s), 2.90 (4H, s), 3.81 (3H, s), 6.56 (1H, dd, *J* = 2, 7 Hz), 6.86 (1H, d, *J* = 2 Hz), 7.03 (1H, dd, *J* = 2, 8 Hz), 7.21 (1H, d, *J* = 8 Hz), 7.34 (2H, s), 7.48 (1H, d, *J* = 2 Hz), 7.99 (1H, d, *J* = 7 Hz).

2-Amino-6-[2-(7-hydroxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)-ethyl]-benzothiazole Dihydrochloride (IIId) BBr₃ (17 g, 68 mmol) was added dropwise to a suspension of **IIc** (2.3 g, 6.8 mmol) in CHCl₃ (115 ml) at room temperature with stirring. After being stirred for 20 h, the solvent was evaporated *in vacuo*. The residue was added to H₂O (100 ml) and the solution was adjusted to pH 7.5 with 20% aqueous K₂CO₃. The resulting precipitate was collected and dissolved in AcOEt–THF–H₂O. The organic

layer separated was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with CHCl₃–MeOH (9:1) to give a product which was converted to the dihydrochloride in the usual way and the salt was recrystallized from EtOH–Et₂O to afford **IIId** (0.27 g, 10%). IR (Nujol): 1670, 1655, 1605, 1580 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (3H, s), 3.04 (4H, s), 7.07 (1H, dd, *J* = 2, 7 Hz), 7.15 (1H, dd, *J* = 2 Hz), 7.29 (1H, d, *J* = 8 Hz), 7.44 (1H, d, *J* = 8 Hz), 7.72 (1H, s), 8.42 (1H, d, *J* = 7 Hz), 9.72 (2H, br s).

2-Acetamido-6-[2-(7-methoxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)-ethyl]-benzothiazole (IIIf) AcCl (6.3 ml 3.6 mmol) was added dropwise to a solution of **IIc** (1.0 g, 3.0 mmol) and pyridine (0.7 g, 9.0 mmol) in CH₂Cl₂ (10 ml) with stirring at 0 °C. After being stirred for 2 h at room temperature, the mixture was added to H₂O (10 ml) and adjusted to pH 8 with 20% aqueous K₂CO₃. The organic layer separated was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was recrystallized from EtOH–AcOEt–IPE to afford **IIIf** (0.39 g, 35%). IR (Nujol): 1685, 1650, 1610, 1545 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 2.20 (6H, s), 2.94–3.04 (4H, m), 3.82 (3H, s), 6.57 (1H, dd, *J* = 2, 7 Hz), 6.86 (1H, d, *J* = 2 Hz), 7.25 (1H, dd, *J* = 2, 8 Hz), 7.61 (1H, d, *J* = 8 Hz), 7.78 (1H, d, *J* = 2 Hz), 7.99 (1H, d, *J* = 7 Hz).

2-Amino-6-[2-(3,7-dimethylimidazo[1,2-*a*]pyridin-2-yl)-ethyl]-1H-benzimidazole (IIIa) A solution of 2-[2-(3,4-diaminophenyl)-ethyl]-3,7-dimethylimidazo[1,2-*a*]pyridine (**5a**) (1.6 g, 5.7 mmol) and BrCN (0.73 g, 6.9 mmol) in EtOH (30 ml) was stirred for 3 h at room temperature and the resulting precipitate was collected by filtration. A suspension of the material in H₂O (20 ml) was adjusted to pH 9 with 20% aqueous K₂CO₃ and extracted with AcOEt–THF. The extract was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was recrystallized from AcOEt–THF to afford **IIIa** (0.33 g, 19%). IR (Nujol): 1640, 1560 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 2.19 (3H, s), 2.30 (3H, s), 2.89 (4H, s), 5.93 (2H, s), 6.63 (1H, dd, *J* = 2, 7 Hz), 6.75 (1H, d, *J* = 9 Hz), 6.87 (1H, d, *J* = 2 Hz), 6.92 (1H, d, *J* = 9 Hz), 7.15 (1H, s), 7.93 (1H, d, *J* = 7 Hz).

6-[2-(3,7-Dimethylimidazo[1,2-*a*]pyridin-2-yl)-ethyl]-2-methyl-1H-benzimidazole (IIIc) A solution of 2-[2-(4-acetylaminophenyl)-ethyl]imidazo[1,2-*a*]pyridine (**5c**) (1.5 g, 4.7 mmol) and POCl₃ (0.5 ml, 5.6 mmol) in sulfolane (15 ml) was stirred for 2 h at 100 °C. The reaction mixture was poured into AcOEt–H₂O. The aqueous layer separated was added to AcOEt–THF and the mixture was adjusted to pH 8 with 20% aqueous K₂CO₃. The organic layer obtained was washed with H₂O, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with CHCl₃–MeOH (19:1) to give a product which was recrystallized from MeCN to afford **IIIc** (0.77 g, 54%). IR (Nujol): 1645, 1590 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 2.19 (3H, s), 2.34 (3H, s), 2.46

(3H, s), 2.95—3.02 (4H, m), 6.69 (1H, d, $J=7$ Hz), 6.95 (1H, d, $J=8$ Hz), 7.24 (2H, s), 7.33 (1H, d, $J=8$ Hz), 8.00 (1H, d, $J=7$ Hz).

Biological Test. Antagonism of Gastric Acid Secretion *in Vitro* The gastric glands were prepared following the procedure of Berglindh *et al.*,^{5a)} and aminopyrine accumulation was performed according to the method of Sack and Spenny.^{5b)} The corpus mucosa from a rabbit was subjected to collagenase digestion and gastric glands were isolated. Acid secretion from the glands was assayed by aminopyrine accumulation method. An assay medium contained gland suspension, histamine (10^{-4} M), test drug (10^{-5} M) and [14 C]aminopyrine (total volume was 1 ml). In the control experiment, buffer was added instead of a test drug. The glands were incubated at 37°C for 30 min, and the radioactivity accumulated in the glands, which is considered to be an appropriate index of acid secretion, was then measured. The inhibitory effect of the drug was calculated by comparing with control value.

Histamine H_2 -receptor antagonist activity using guinea pig right atrium, gastric acid antiseecretory and anti-stress ulcer activity were evaluated by the

methods described in the literature²⁻⁴⁾ and in our previous paper.¹⁾

Acknowledgements The authors are indebted to Mr. H. Itoh, Mr. H. Ishikawa and Mr. H. Yamakuni for carrying out the biological testing. Thanks are also due to the staff members of our analytical division for elemental analysis and measurement of spectral data.

References and Notes

- 1) Part III: Y. Katsura, Y. Inoue, S. Nishino, M. Tomoi, H. Itoh, and H. Takasugi, *Chem. Pharm. Bull.*, **40**, 1424 (1992).
- 2) J. W. Black, W. A. M. Duncan, C. J. Durant, C. R. Ganellin, and E. M. Parsons, *Nature* (London) **236**, 385 (1972).
- 3) M. N. Ghosh and M. O. Schild, *Br. J. Pharmacol.*, **13**, 54 (1958).
- 4) K. Takagi and S. Okabe, *Jpn. J. Pharmacol.*, **18**, 9 (1968).
- 5) a) T. Berglindh, H. F. Helander, and K. J. Öbrink, *Acta Physiol. Scand.*, **97**, 401 (1976); b) J. Sack and J. G. Spenny, *Am. J. Physiol.*, **243**, G313 (1982).