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

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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 H_2-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 H_2-receptor antagonist; anti-stress ulcer activity; antisecretory activity; imidazo[1,2-*a*]pyridinylethylbenzothiazole; imidazo[1,2-*a*]pyridinylethylbenzimidazole; structure–activity relationship

In a previous paper[1] 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 comparsion with the conventional histamine H_2-receptor antagonists (H_2- 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 H_2-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.

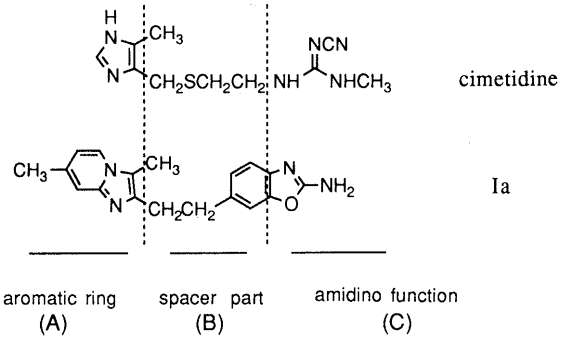


Chart 1

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-aminopyridines 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 (IId). Acetylation of IIa and IIc with acetyl chloride in the presence of pyridine furnished 2-acetylaminobenzothiazole derivatives (IIe and IIf) (Chart 2).

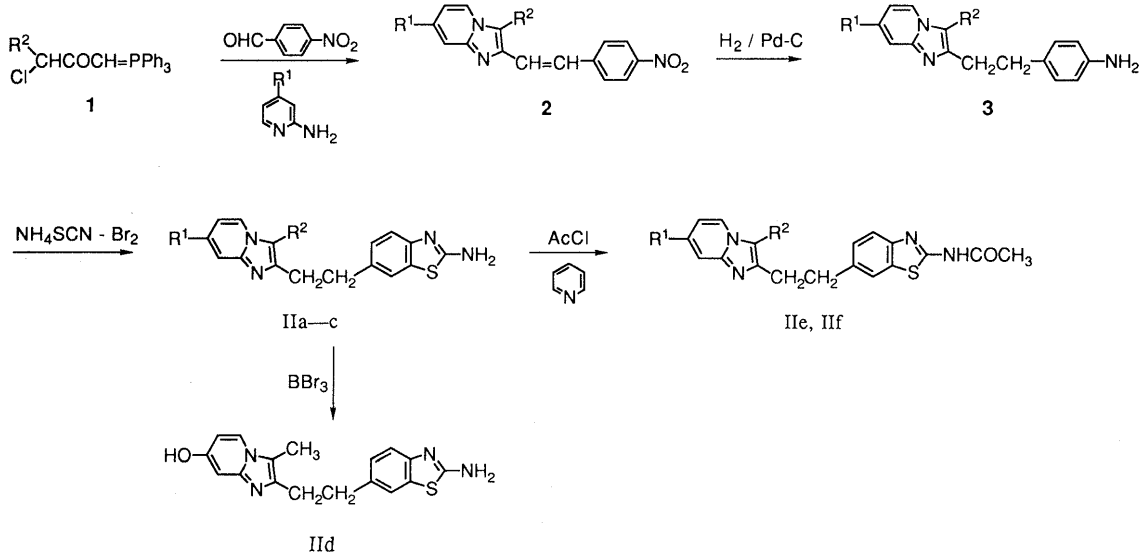


Chart 2

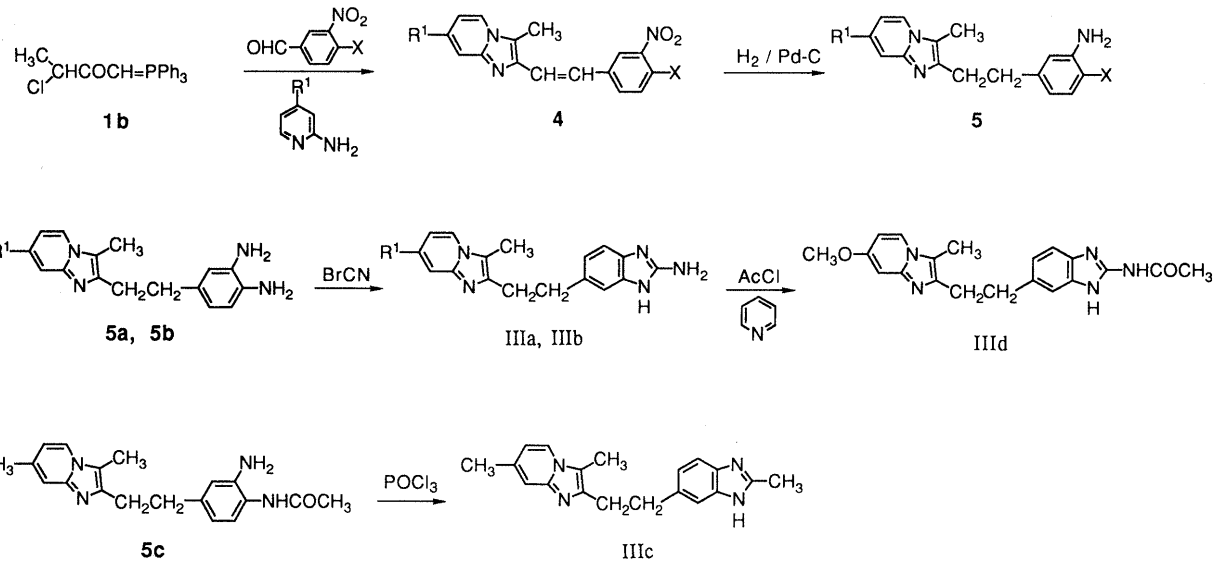
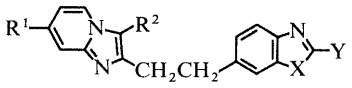


Chart 3

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)		
								C	H	N
IIa	CH_3	H	S	NH_2	14	245—246 (D–W)	$C_{17}H_{16}N_4S$	66.23 (66.36)	5.23 5.14	18.17 17.88)
IIb	CH_3	CH_3	S	NH_2	27	285—286 (I–M)	$C_{18}H_{18}N_4S \cdot 2HCl \cdot 6/5H_2O$	51.85 (51.60)	5.41 5.63	13.44 13.31)
IIc	OCH_3	CH_3	S	NH_2	14	223—225 (I–M)	$C_{18}H_{18}N_4OS \cdot 3/2H_2O$	59.16 (59.19)	5.79 5.64	15.33 15.20)
IId	OH	CH_3	S	NH_2	10	265—266 (A–E)	$C_{17}H_{16}N_4OS \cdot 2HCl \cdot 2H_2O$	47.12 (46.85	5.12 4.91	12.93 12.62)
IIe	CH_3	H	S	$NHCOCH_3$	27	259—260 (A–H)	$C_{19}H_{18}N_4OS \cdot 1/2H_2O$	63.49 (63.54	5.33 5.26	15.59 15.72)
IIf	OCH_3	CH_3	S	$NHCOCH_3$	35	240—242 (A–EA–I)	$C_{20}H_{20}N_4O_2S$	63.14 (62.88	5.30 5.17	14.73 14.82)
IIIa	CH_3	CH_3	NH	NH_2	19	296—298 (EA–T)	$C_{18}H_{19}N_5$	70.80 (70.63	6.27 6.31	22.93 22.84)
IIIb	OCH_3	CH_3	NH	NH_2	21	244—246 (I–M)	$C_{18}H_{19}N_5O \cdot 2HCl \cdot 5/2H_2O$	49.20 (49.40	5.96 5.96	15.94 15.93)
IIIc	CH_3	CH_3	NH	CH_3	54	151—153 (AN)	$C_{19}H_{20}N_4$	74.97 (74.72	6.62 6.72	18.41 18.17)
IIId	OCH_3	CH_3	NH	$NHCOCH_3$	41	235—237 (A–T)	$C_{20}H_{21}N_5O_2 \cdot H_2O$	62.98 (62.70	6.08 6.19	18.36 18.05)

a) A, EtOH; AN, MeCN; D, *N*,*N*-dimethylformamide (DMF); E, Et_2O; EA, AcOEt; H, *n*-hexane; I, isopropyl ether (IPE); M, MeOH; T, tetrahydrofuran (THF); W, H_2O.

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 IIe and IIf (Chart 3).

Pharmacological Results and Discussion The imidazo[1,2-*a*]pyridines obtained in this study were tested *in vitro* for histamine H_2-receptor antagonist (H_2-antagonist) activity using the histamine-stimulated chronotropic response 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 rats[3] and anti-ulcer activity was measured in water-immersion stressed rats.[4] These biological results are presented in Table II.

In the H_2-antagonist assay, 3,7-dimethyl- and 3-methoxy-7-methylimidazo[1,2-*a*]pyridinyl derivatives of benzothiazole (IIb and IIc) 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, IIf and IIId) of IIb, IIc and IIIb, however, resulted in remarkable decrease or total disappearence 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 H_2-antagonist activity. Accordingly, an additional experiment was carried out to explore the discrepancy of IIb between *in vitro* H_2-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 rabbit[5] 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 H_2-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 (%)] *in vitro*[b] 1×10^{-5} g/ml	*in vivo*[c] 1 mg/kg i.v.	Antiulcer activity[d] [inhibition (%)] 32 mg/kg *p.o.*
Ia	93.1	65.9	65	92.9
IIa	NT			
IIb	84.6	50.0	NE	85.4
IIc	68.6		47	75.0
IId	42.9			
IIe	10.6			
IIf	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

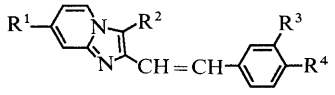
a) H_2-receptor antagonism in the isolated guinea pig right atrium. *b*) Antisecretory activity in the isolated rabbit gastric gland. *c*) Inhibition of histamine-stimulated gastric acid secretion in the lumen-perfused stomach of the anaesthetized rats ($n=2$). *d*) Inhibitory effect on gastric ulcer 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 (^{1}H-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.

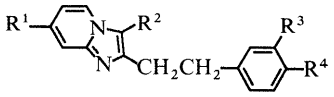
7-Methoxy-3-methyl-2-[2-(4-nitrophenyl)vinyl]imidazo[1,2-*a*]-pyridine (2c) A mixture of 3-chloro-2-oxobutylidenetriphenylphosphorane (**1**) (23.6 g, 64 mmol) and 4-nitrobenzaldehyde (9.7 g, 64 mmol) in dioxane

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	^{1}H-NMR δ (J=Hz)
2a	CH_3	H	H	NO_2	56	237—238	DMSO-d_6	2.36 (3H, s), 6.74 (1H, dd, J=2, 7), 7.30 (1H, d, J=2), 7.49 (1H, d, J=16), 7.59 (1H, d, J=16), 7.87 (2H, d, J=8), 8.03 (1H, s), 8.21 (2H, d, J=8), 8.42 (1H, d, J=7)
2b	CH_3	CH_3	H	NO_2	26	207—208	DMSO-d_6	2.36 (3H, s), 2.57 (3H, s), 6.73 (1H, dd, J=2, 7), 7.27 (1H, d, J=2), 7.44 (1H, d, J=16), 7.55 (1H, d, J=16), 7.86 (2H, d, J=9), 8.15 (1H, d, J=7), 8.18 (2H, d, J=9)
2c	OCH_3	CH_3	H	NO_2	31	213—214	DMSO-d_6	2.59 (3H, s), 3.85 (3H, s), 6.65 (1H, dd, J=2, 7), 6.87 (1H, d, J=2), 7.43 (1H, d, J=16), 7.55 (1H, d, J=16), 7.91 (2H, d, J=9), 8.15 (1H, d, J=7), 8.20 (2H, d, J=9)
4a	CH_3	CH_3	NO_2	NO_2	46	234—236	DMSO-d_6	2.36 (3H, s), 2.71 (3H, s), 6.77 (1H, dd, J=2, 7), 7.27 (1H, d, J=2), 7.50 (1H, d, J=16), 7.86 (1H, d, J=16), 8.12 (1H, d, J=9), 8.15 (1H, d, J=7), 8.23 (1H, d, J=9), 8.54 (1H, s)
4b	OCH_3	CH_3	NO_2	NH_2	100	260—261	CF_3COOH	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-d_6	2.08 (3H, s), 2.37 (3H, s), 2.57 (3H, s), 6.74 (1H, dd, J=2, 7), 7.26 (1H, d, J=2), 7.39 (1H, d, J=16), 7.53 (1H, d, J=16), 7.58 (1H, d, J=8), 7.97 (1H, dd, J=2, 8), 8.12 (1H, d, J=7), 8.21 (1H, d, J=2), 10.26 (1H, s)
4d	OCH_3	CH_3	NO_2	$NHCOCH_3$	31	227—230	CF_3COOH	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)	^{1}H-NMR Solvent	^{1}H-NMR δ (J=Hz)
3a	CH_3	H	H	NH_2	96	144—148	DMSO-d_6	2.31 (3H, s), 2.83 (4H, s), 4.76 (2H, s), 6.47 (2H, d, J=8), 6.64 (1H, dd, J=2, 7), 6.86 (2H, d, J=8), 7.21 (1H, d, J=2), 7.52 (1H, s), 8.30 (1H, d, J=7)
3b	CH_3	CH_3	H	NH_2	89	79—80	DMSO-d_6	2.21 (3H, s), 2.33 (3H, s), 2.80 (4H, s), 6.47 (2H, d, J=8), 6.68 (1H, dd, J=2, 7), 6.84 (2H, d, J=8), 7.22 (1H, d, J=2), 8.07 (1H, d, J=7)
3c	OCH_3	CH_3	H	NH_2	63	114—116	DMSO-d_6	2.21 (3H, s), 2.80 (4H, s), 3.83 (3H, s), 6.51 (2H, d, J=8), 6.58 (1H, dd, J=2, 7), 6.89 (1H, d, J=2), 6.90 (2H, d, J=8), 8.00 (1H, d, J=7)
5a	CH_3	CH_3	NH_2	NH_2	52	112—114	DMSO-d_6	2.24 (3H, s), 2.33 (3H, s), 2.81 (4H, s), 4.06 (4H, s), 6.23 (1H, dd, J=2, 7), 6.40 (1H, d, J=2), 6.41 (1H, d, J=8), 6.69 (1H, dd, J=2, 8), 7.21 (1H, d, J=2), 8.02 (1H, d, J=7)
5b	OCH_3	CH_3	NH_2	NH_2	84	205—208	DCl-D_2O	2.61 (3H, s), 3.18 (4H, s), 4.03 (3H, s), 7.10 (1H, d, J=2, 8), 7.22 (1H, s), 7.47—7.82 (3H, m), 8.26 (1H, d, J=7)
5c	CH_3	CH_3	NH_2	$NHCOCH_3$	81	168—173	DMSO-d_6	2.04 (3H, s), 2.29 (3H, s), 2.36 (3H, s), 2.85 (4H, s), 6.43 (1H, dd, J=2, 8), 6.63 (1H, d, J=2), 6.73 (1H, dd, J=2, 7), 7.10 (1H, d, J=8), 7.27 (1H, d, J=2), 8.06 (1H, d, J=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)–H_2O (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)–H_2O (120 ml). After the mixture was adjusted to pH 8, the organic layer separated was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with AcOEt–iso-Pr_2O (IPE) to afford **2c** (6.1 g, 31%). mp 213—214 °C (THF). *Anal.* Calcd for $C_{17}H_{15}N_3O_3$: 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 H_2 at 40—60 °C. After removal of the solvent and catalyst, the residue was triturated with Et_2O to afford **3c** (3.4 g, 63%). mp 114—116 °C (IPE–MeOH). *Anal.* Calcd for $C_{17}H_{19}N_3O$: 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 NH_4SCN (1.2 g, 16 mmol) in AcOH (22 ml) was stirred at room temperature for 1 h. A solution of Br_2 (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–H_2O and the pH of the solution was adjusted to 8 with 20% aqueous K_2CO_3. The organic layer separated was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with $CHCl_3$–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}. ^{1}H-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 (IId) BBr_3 (17 g, 68 mmol) was added dropwise to a suspension of IIc (2.3 g, 6.8 mmol) in $CHCl_3$ (115 ml) at room temperature with stirring. After being stirred for 20 h, the solvent was evaporated *in vacuo*. The residue was added to H_2O (100 ml) and the solution was adjusted to pH 7.5 with 20% aqueous K_2CO_3. The resulting precipitate was collected and dissolved in AcOEt–THF–H_2O. The organic layer separated was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with $CHCl_3$–MeOH (9 : 1) to give a product which was converted to the dihydrochloride in the usual way and the salt was recrystallized from EtOH–Et_2O to afford IId (0.27 g, 10%). IR (Nujol): 1670, 1655, 1605, 1580 cm^{-1}. ^{1}H-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 (IIf) 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 CH_2Cl_2 (10 ml) with stirring at 0 °C. After being stirred for 2 h at room temperature, the mixture was added to H_2O (10 ml) and adjusted to pH 8 with 20% aqueous K_2CO_3. The organic layer separated was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from EtOH–AcOEt–IPE to afford IIf (0.39 g, 35%). IR (Nujol): 1685, 1650, 1610, 1545 cm^{-1}. ^{1}H-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]-1*H*-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 H_2O (20 ml) was adjusted to pH 9 with 20% aqueous K_2CO_3 and extracted with AcOEt–THF. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from AcOEt–THF to afford IIIa (0.33 g, 19%). IR (Nujol): 1640, 1560 cm^{-1}. ^{1}H-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-1*H*-benzimidazole (IIIc) A solution of 2-[2-(4-acetylamino-3-aminophenyl)-ethyl]imidazo[1,2-*a*]pyridine (**5c**) (1.5 g, 4.7 mmol) and $POCl_3$ (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–H_2O. The aqueous layer separated was added to AcOEt–THF and the mixture was adjusted to pH 8 with 20% aqueous K_2CO_3. The organic layer obtained was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–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}. ^{1}H-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 accumlation was performed according to the method of Sack and Spenney.[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 accumlation 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 antisecretory and anti-stress ulcer activity were evaluated by the methods described in the literature[2-4] 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

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