Studies on Antiulcer Drugs. III.[1] Synthesis and Antiulcer Activities of Imidazo[1,2-*a*]pyridinylethylbenzoxazoles and Related Compounds. A Novel Class of Histamine H_2-Receptor Antagonists

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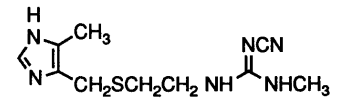
A series of imidazo[1,2-*a*]pyridinylalkylbenzoxazole derivatives was synthesized and tested for histamine H_2-receptor antagonist, gastric antisecretory and antiulcer activities. Some of 2-amino-6-[2-(imidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole derivatives were found to have good pharmacological activities. Among them, 2-amino-6-[2-(7-methoxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-11) and 2-acetamido-6-[2-(7-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-38) showed potent antisecretory and cytoprotective activity. The structure–activity relationships of these compounds are discussed.

Keywords histamine H_2-receptor antagonist; antiulcer activity; cytoprotective activity; antisecretory activity; imidazo[1,2-*a*]pyridinylethylbenzoxazole; structure–activity relationship

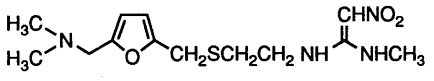
Since the clinical success of cimetidine (**1**),[2] many studies have been performed in the field of histamine H_2-receptor antagonists (H_2-antagonist). As a result, a number of potent compounds (*i.e.*, ranitidine (**2**),[3] nizatidine (**3**),[4] famotidine (**4**),[5] and roxatidine acetate (**5**)[6]) have been marketed. These drugs are very effective in the treatment of peptic ulcers, but it has been observed that the relapse of these ulcers occurs in a high ratio following the cessation of treatment with such antacids. Although no clear reason for this has yet been proven, it is generally considered that the recurrence phenomenon is induced by insufficient gastric mucosal defensive forces. From this point of view, a H_2-antagonist with cytoprotective activity is desirable.

Generally, the structure of H_2-antagonists consists of three fundamental components: (A) a basic heteroaromatic ring or aromatic ring substituted by basic moiety, (B) a four-membered side chain and (C) a urea or amidine equivalent group (Chart 1). In a preceding paper,[1] we reported that 2-amino-5-(imidazo[1,2-*a*]pyridin-2-yl)benzoxazoles (**6**) showed potent cytoprotective activity against ethanol-induced gastric lesions as well as antiulcer activity on stress ulcers in rats. From the structural comparison of these compounds (**6**) with conventional H_2-antagonists (**1**—**5**) we considered that the imidazo[1,2-*a*]pyridine moiety is a basic aromatic ring (A) and the 2-aminobenzoxazole residue is regarded as a bioisostere of the amidine group (C). As a part of continuing search for antiulcer drugs, we designed compounds incorporating an alkyl chain between these two parts in order to find a chemically novel H_2-antagonist with cytoprotective activity (Chart 2). In this paper, we describe the synthesis and pharmacological profiles of 2-amino-6-[2-(imidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazoles and related compounds.

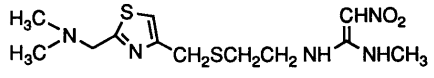
Chemistry The desired compounds listed in Table I were prepared by the routes shown in Charts 3—12. The synthesis of compounds having an ethylene chain was achieved by the route depicted in Chart 3. The key intermediates (**14**—**18** and **20**—**31**) were obtained by three different pathways. Condensation of 3-chloro-2-oxopropyltriphenylphosphoni-



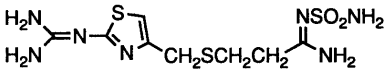
cimetidine (**1**)



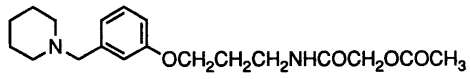
ranitidine (**2**)



nizatidine (**3**)



famotidine (**4**)



roxatidine acetate (**5**)

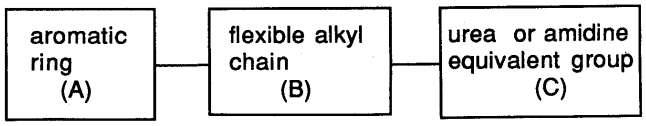


Chart 1

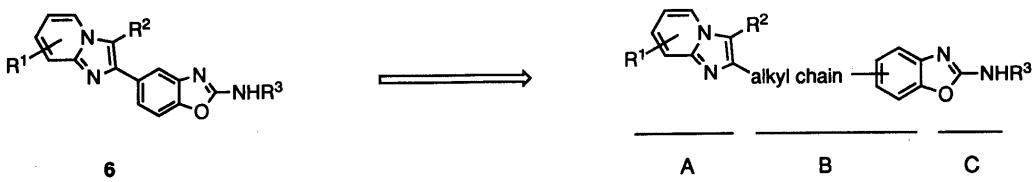
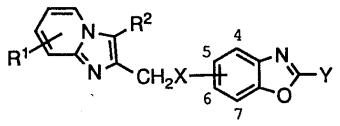


Chart 2

TABLE I. Physical Data of Imidazo[1,2-*a*]pyridinylalkylbenzoxazoles



Compd. No.	R^1	R^2	X	Position	Y	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found)		
									C	H	N
I	7-CH_3	H	CH_2	5	NHC_2H_5	7	114—116 (AN)	$C_{19}H_{20}N_4O$	71.23 (71.14	6.29 6.33	17.49 17.25)
II-1	H	CH_3	CH_2	6	NH_2	72	229—231 (A–I)	$C_{17}H_{16}N_4O$	69.85 (69.71	5.52 5.66	19.16 18.95)
II-2	6-CH_3	CH_3	CH_2	6	NH_2	17	222—223 (E–EA)	$C_{18}H_{18}N_4O \cdot 1/6H_2O$	69.88 (69.89	5.97 5.95	18.28 18.08)
II-3	7-CH_3	H	CH_2	6	NH_2	20	115—117 (EA–I–T)	$C_{17}H_{16}N_4O \cdot 2HCl$	55.90 (55.55	4.97 5.11	15.34 15.13)
II-4	7-CH_3	CH_3	CH_2	6	NH_2	30	269—271 (A–EA)	$C_{18}H_{18}N_4O \cdot 2HCl \cdot 1/2H_2O$	55.68 (55.97	5.45 5.19	14.43 14.46)
II-5	7-CH_3	Cl	CH_2	6	NH_2	42	242—243 (A)	$C_{17}H_{15}ClN_4O$	62.48 (62.65	4.63 4.69	17.14 16.93)
II-6	7-CH_3	CHO	CH_2	6	NH_2	17	260—161 (C–I–M)	$C_{18}H_{16}N_4O_2$	67.49 (67.15	5.03 4.90	17.49 17.16)
II-7	7-CH_3	CH_2OH	CH_2	6	NH_2	26	>200 (dec.) (D–I–M)	$C_{18}H_{18}N_4O_2$	67.07 (66.71	5.63 5.84	17.38 17.50)
II-8	7-C_2H_5	CH_3	CH_2	6	NH_2	49	227—228 (E–EA)	$C_{19}H_{20}N_4O \cdot 1/6H_2O$	70.57 (70.71	6.34 6.16	17.32 17.28)
II-9	7-OH	CH_3	CH_2	6	NH_2	23	230—232 (A–H)	$C_{17}H_{16}N_4O_2 \cdot 3/2H_2O$	60.47 (60.85	5.61 5.44	14.85 14.99)
II-10	7-OCH_3	H	CH_2	6	NH_2	22	251—253 (D–W)	$C_{17}H_{16}N_4O_2 \cdot 4/5H_2O$	63.26 (63.02	5.50 5.56	17.36 17.65)
II-11	7-OCH_3	CH_3	CH_2	6	NH_2	56	248—249 (A–EA)	$C_{18}H_{18}N_4O_2 \cdot 2HCl \cdot 1/2H_2O$	53.47 (53.17	5.24 5.30	13.86 13.85)
II-12	7-OCH_3	Cl	CH_2	6	NH_2	37	229—230 (D–W)	$C_{17}H_{15}ClN_4O_2 \cdot 3/5H_2O$	57.74 (57.60	4.39 4.54	15.85 15.61)
II-13	7-OC_2H_5	CH_3	CH_2	6	NH_2	51	266—268 (A–EA)	$C_{19}H_{20}N_4O_2 \cdot 2HCl \cdot 1/2H_2O$	54.55 (54.68	5.54 5.49	13.39 13.26)
II-14	7-$OCOCH_3$	CH_3	CH_2	6	NH_2	12	197—198 (A–H)	$C_{19}H_{18}N_4O_3 \cdot 3/2H_2O$	60.47 (60.10	5.61 5.63	14.85 14.99)
II-15	7-CH_2OH	CH_3	CH_2	6	NH_2	29	256—257 (A–EA)	$C_{18}H_{18}N_4O_2 \cdot 2HCl \cdot H_2O$	52.31 (52.17	5.36 5.32	13.55 13.48)
II-16	7-CH_2OCH_3	CH_3	CH_2	6	NH_2	49	209—210 (A–EA)	$C_{19}H_{20}N_4O_2 \cdot 1/2H_2O$	66.07 (65.90	6.13 6.22	16.22 16.02)
II-17	7-NH_2	CH_3	CH_2	6	NH_2	35	222—223 (AN–T)	$C_{17}H_{17}N_5O \cdot 2/3H_2O$	63.94 (63.92	5.79 5.60	21.93 21.73)
II-18	7-CH_2NH_2	CH_3	CH_2	6	NH_2	40	223—224 (I–M)	$C_{18}H_{19}N_5O$	67.27 (66.98	5.96 6.04	21.79 21.51)
II-19	7-COOH	CH_3	CH_2	6	NH_2	31	>300 (W)	$C_{18}H_{16}N_4O_3 \cdot 1/3H_2O$	63.15 (63.31	4.91 4.92	16.36 16.37)
II-20	7-$COOCH_3$	CH_3	CH_2	6	NH_2	64	251—252 (A)	$C_{19}H_{18}N_4O_3$	65.13 (64.84	5.18 5.12	15.99 15.72)
II-21	7-$CONH_2$	CH_3	CH_2	6	NH_2	15	>300 (I–M–T)	$C_{18}H_{17}N_5O_2 \cdot 2HCl \cdot 2H_2O$	48.66 (48.54	5.22 5.22	15.76 15.59)
II-22	8-CH_3	CH_3	CH_2	6	NH_2	46	115 (EA–T)	$C_{18}H_{18}N_4O \cdot 1/5H_2O$	69.74 (69.94	6.11 6.22	18.07 17.83)
II-23	8-OH	CH_3	CH_2	6	NH_2	26	232—233 (A–M)	$C_{17}H_{16}N_4O_2$	66.22 (66.07	5.23 5.17	18.17 17.89)
II-24	8-OCH_3	CH_3	CH_2	6	NH_2	37	195—197 (I–M)	$C_{18}H_{18}N_4O_2 \cdot 1/6H_2O$	66.45 (66.51	5.73 5.71	17.21 17.13)
II-25	8-NH_2	CH_3	CH_2	6	NH_2	85	201—202 (A–E–EA)	$C_{17}H_{17}N_5O$	66.43 (66.58	5.57 5.81	22.79 22.49)
II-26	8-$NHCOCH_3$	CH_3	CH_2	6	NH_2	70	220—221 (I–M)	$C_{19}H_{19}N_5O_2$	65.32 (65.65	5.48 5.44	20.04 19.85)
II-27	7-CH_3	CH_3	CH_2	6	$NHCH_3$	20	208—209 (A–H)	$C_{19}H_{20}N_4O \cdot 1/3H_2O$	69.92 (70.16	6.50 6.30	17.17 17.10)
II-28	7-OCH_3	CH_3	CH_2	6	$NHCH_3$	6	244—246 (A–EA)	$C_{19}H_{20}N_4O_2 \cdot 2HCl$	55.75 (55.46	5.42 5.52	13.69 13.34)
II-29	H	CH_3	CH_2	6	NHC_2H_5	27	132—134 (AN)	$C_{19}H_{20}N_4O$	71.23 (70.85	6.29 6.25	17.49 17.35)
II-30	7-CH_3	H	CH_2	6	NHC_2H_5	9	163—164 (AN)	$C_{19}H_{20}N_4O$	71.23 (71.05	6.29 6.49	17.49 17.54)
II-31	7-CH_3	CH_3	CH_2	6	NHC_2H_5	21	189—190 (AN)	$C_{20}H_{22}N_4O$	71.83 (71.54	6.63 6.91	16.75 16.71)
II-32	7-CH_3	Br	CH_2	6	NHC_2H_5	65	190—191 (A–H)	$C_{19}H_{19}BrN_4O$	57.15 (57.46	4.80 4.76	14.03 13.64)

TABLE I. (continued)

Compd. No.	R^1	R^2	X	Position	Y	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found)		
									C	H	N
II-33	7-OCH_3	CH_3	CH_2	6	NHC_2H_5	20	169—171 (A–EA)	$C_{20}H_{22}N_4O_2 \cdot 2HCl$	53.34 (53.27	6.04 6.08	12.44 12.15)
II-34	7-CH_3	CH_3	CH_2	6	NH–iso-C_3H_7	30	139—140 (AN)	$C_{21}H_{24}N_4O$	72.39 (72.58	6.94 6.94	16.08 16.08)
II-35	7-OCH_3	CH_3	CH_2	6	NH–iso-C_3H_7	23	144—145 (A–EA–T)	$C_{21}H_{24}N_4O_2 \cdot 2HCl$	51.33 (51.29	6.56 6.44	11.40 11.15)
II-36	7-CH_3	CH_3	CH_2	6	$NHCH_2CH=CH_2$	10	186—187 (A–H)	$C_{21}H_{22}N_4O$	72.18 (72.38	6.41 6.52	16.03 15.95)
II-37	7-OCH_3	CH_3	CH_2	6	$NHCH_2CH=CH_2$	18	192—193 (A–E–T)	$C_{21}H_{22}N_4O_2 \cdot 2HCl \cdot 5/4H_2O$	55.36 (55.02	5.86 5.78	12.30 11.99)
II-38	7-CH_3	H	CH_2	6	$NHCOCH_3$	58	197—198 (A–E)	$C_{19}H_{18}N_4O_2$	68.25 (68.28	5.43 5.53	16.46 16.62)
II-39	7-CH_3	CH_3	CH_2	6	$NHCOCH_3$	39	205—207 (A–H)	$C_{20}H_{20}N_4O_2$	66.65 (66.78	5.97 5.88	15.55 15.56)
II-40	7-CH_3	Cl	CH_2	6	$NHCOCH_3$	69	200—201 (A–H)	$C_{19}H_{17}ClN_4O_2 \cdot 1/4H_2O$	61.13 (61.09	4.72 4.97	15.01 14.89)
II-41	7-CH_3	$CH_2N(CH_3)_2$	CH_2	6	$NHCOCH_3$	16	184—185 (A–H)	$C_{22}H_{25}N_5O_2 \cdot 2/3H_2O$	67.50 (67.14	6.44 6.62	17.90 17.70)
II-42	7-OH	CH_3	CH_2	6	$NHCOCH_3$	38	210—212 (EA–T–W)	$C_{19}H_{18}N_4O_3 \cdot 3/2H_2O$	60.47 (60.31	5.61 5.42	14.85 14.56)
II-43	7-OCH_3	H	CH_2	6	$NHCOCH_3$	25	181—182 (AN)	$C_{19}H_{18}N_4O_3 \cdot 1/2H_2O$	63.50 (63.74	5.33 5.23	15.59 15.57)
II-44	7-OCH_3	CH_3	CH_3	6	$NHCOCH_3$	58	229—232 (A–H)	$C_{20}H_{20}N_4O_3$	65.92 (65.59	5.53 5.86	15.38 15.19)
II-45	7-$OCOCH_3$	CH_3	CH_2	6	$NHCOCH_3$	64	161—164 (A–H)	$C_{21}H_{20}N_4O_4 \cdot 5/2H_2O$	57.66 (57.39	5.76 5.61	12.80 13.03)
II-46	8-CH_3	CH_3	CH_2	6	$NHCOCH_3$	37	150—152 (A–I)	$C_{20}H_{20}N_4O \cdot 2H_2O$	62.49 (62.87	6.29 6.20	14.57 14.54)
II-47	7-CH_3	H	CH_2	6	$NHCOC_2H_5$	50	196—197 (A–I)	$C_{20}H_{20}N_4O_2$	68.95 (68.85	5.79 5.62	16.08 15.98)
II-48	7-CH_3	H	CH_2	6	NHCO-*n*-C_3H_7	38	200—201 (A–H)	$C_{21}H_{22}N_4O_2$	69.59 (69.84	6.12 6.28	15.46 15.28)
II-49	7-CH_3	H	CH_2	6	NHCO-iso-C_3H_7	62	208—209 (I–M)	$C_{21}H_{22}N_4O_2$	69.59 (69.48	6.12 6.27	15.46 15.30)
II-50	7-CH_3	H	CH_2	6	NHCO-*tert*-C_4H_9	72	201—202 (I–M)	$C_{22}H_{24}N_4O_2$	70.19 (70.58	6.43 6.50	14.88 14.69)
II-51	7-OCH_3	H	CH_2	6	NHCO-*tert*-C_4H_9	26	209—210 (AN)	$C_{22}H_{24}N_4O_3$	67.33 (67.22	6.16 6.19	14.28 14.37)
II-52	7-CH_3	H	CH_2	6	$NHCOCH(C_2H_5)_2$	57	214—215 (A–EA–I)	$C_{23}H_{26}N_4O_2$	70.75 (70.58	6.71 6.68	14.35 14.15)
II-53	7-OCH_3	H	CH_2	6	NH-L-$COCH(CH_3)$-$OCOCH_3$	28	217—218 (I–M)	$C_{22}H_{22}N_4O_4$	64.50 (64.65	5.46 5.59	13.78 13.52)
II-54	7-CH_3	H	CH_2	6	NHCO-cyclo-C_3H_7	31	203—204 (A–H)	$C_{21}H_{20}N_4O_2$	69.98 (69.76	5.59 5.58	15.54 15.51)
II-55	7-CH_3	H	CH_2	6	NHCO-cyclo-C_6H_{11}	41	125—126 (A–EA)	$C_{24}H_{26}N_4O_2$	71.62 (71.39	6.51 6.45	13.92 13.77)
II-56	7-CH_3	CH_3	CH_2	6	$N(CH_3)_2$	9	135—136 (EA–H)	$C_{20}H_{22}N_4O$	71.83 (71.52	6.63 6.77	16.75 16.65)
II-57	7-CH_3	H	CH_2	6	$N=CH-N(CH_3)_2$	14	150—151 (I–M)	$C_{20}H_{21}N_5O$	69.14 (69.20	6.09 5.93	20.16 20.19)
II-58	7-CH_3	CH_3	CH_2	6	$NHC(NH_2)=NH$	33	195—196 (A)	$C_{19}H_{20}N_6O \cdot 4/3H_2O$	61.28 (61.50	6.13 6.30	22.56 22.19)
II-59	7-CH_3	CH_3	CH_2	6	CH_3	28	83—85 (E–EA)	$C_{19}H_{19}N_3O \cdot H_2O$	70.57 (70.86	6.54 6.42	12.99 12.71)
II-60	7-CH_3	CH_3	CH_2	6	C_2H_5	16	115—117 (E–EA)	$C_{20}H_{21}N_3O$	75.21 (74.85	6.63 6.70	13.16 13.04)
II-61	7-CH_3	CH_3	CH_2	6	OH	57	240—243 (I–M)	$C_{18}H_{17}N_3O_2$	70.34 (70.44	5.57 5.56	13.67 13.48)
II-62	7-CH_3	CH_3	CH_2	6	SCH_3	70	106—107 (EA–H)	$C_{19}H_{19}N_3OS$	67.63 (67.81	5.67 5.52	12.45 12.51)
III	7-CH_3	H	O	6	$NHCOCH_3$	10	214—215 (D–I–M)	$C_{18}H_{16}N_4O_3$	64.28 (64.23	4.79 4.97	16.66 16.29)
IV-1	7-CH_3	H	SCH_2	4	NHC_2H_5	66	170—172 (EA)	$C_{19}H_{20}N_4OS$	64.75 (64.47	5.72 5.86	15.90 15.63)
IV-2	7-CH_3	H	SCH_2	5	NHC_2H_5	76	134—136 (EA)	$C_{19}H_{20}N_4OS \cdot 1/3H_2O$	63.66 (63.46	5.81 5.76	15.63 15.40)
IV-3	7-CH_3	H	SCH_2	6	NHC_2H_5	66	149—150 (AN)	$C_{19}H_{20}N_4OS$	64.75 (64.65	5.72 5.68	15.90 15.85)

a) A EtOH; AN MeCN; C CH_2Cl_2; D *N*,*N*-dimethylformamide (DMF); EA AcOEt; H *n*-hexane; I diisopropyl ether (IPE); M MeOH; T tetrahydrofuran (THF); W H_2O.

um chloride (**8**) with 4-substituted-2-aminopyridine,[7] followed by a Wittig reaction with an appropriate benzaldehyde gave ethene derivatives (**14**, **17** and **21**) (method A). Bromination of 2-butanone (**9**) with Br_2 and subsequent reaction with triphenylphosphine provided 3-bromo-2-oxobutylphosphonium bromide (**10**), which was treated with K_2CO_3 to afford phosphorane ylide (**12**). The Wittig reaction of **12** with 3-benzyloxy-4-nitrobenzaldehyde, followed by condensation with appropriate 2-aminopyridines yielded the corresponding ethene derivatives (**25**—**27** and **31**) (method B). The Wittig reaction of 3-chloro-2-oxobutylidenetriphenylphosphorane (**13**) and subsequent condensation also provided the target compounds (**15**, **16**, **18**, **20**, **22**—**24** and **28**—**30**) (method C).

Catalytic hydrogenation of the double bond of **14**—**31** over Pd–C resulted in a concomitant reduction of the nitro group and debenzylation to give the corresponding imidazo[1,2-*a*]pyridinylethyl-*o*-aminophenols (**32**—**50**). Some of them were treated with alkyl isocyanate to yield urea derivatives (**51**—**61**), which were then condensed by means of polyphosphate ester (PPE)[8] as a dehydrating reagent to afford the desired 2-alkylaminobenzoxazoles (I, II-**27**—**31**

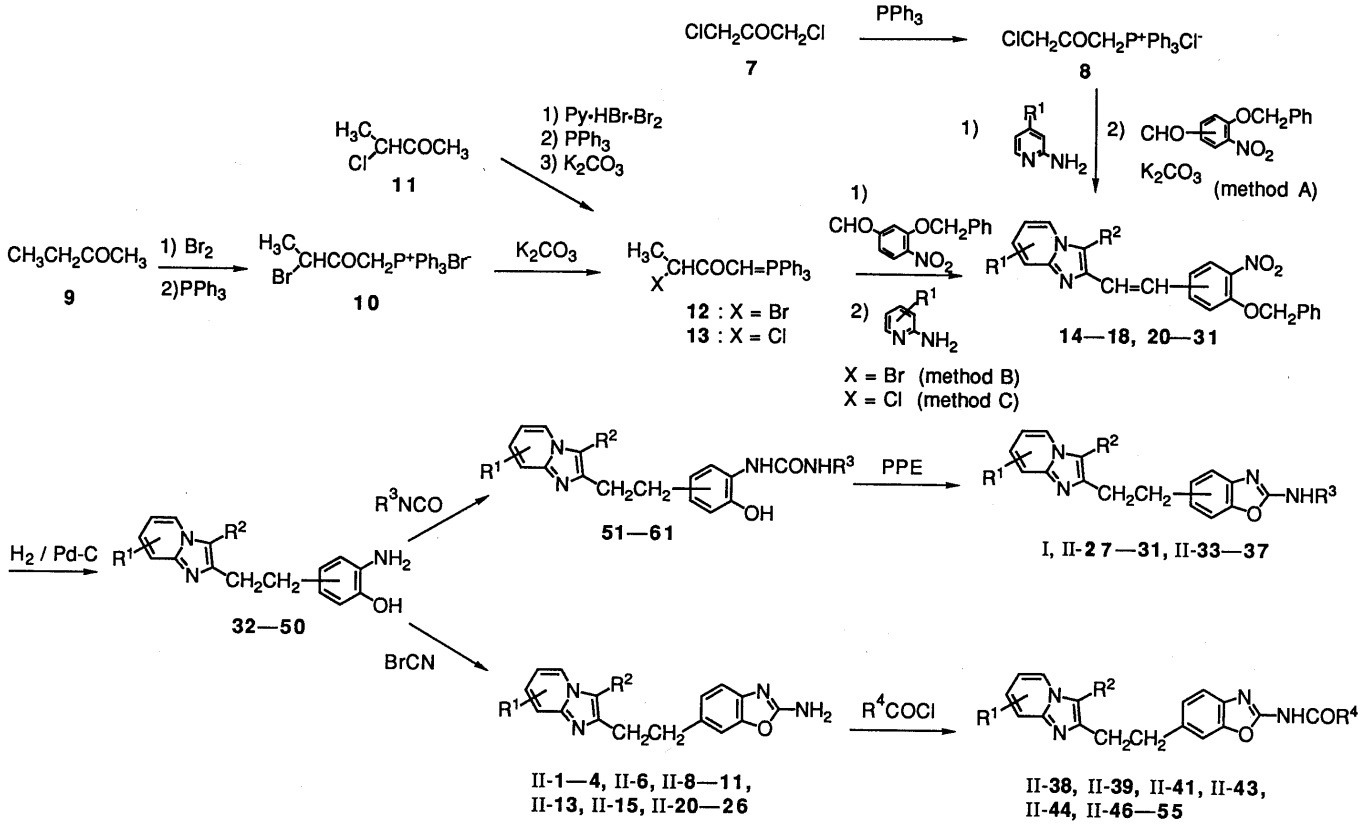


Chart 3

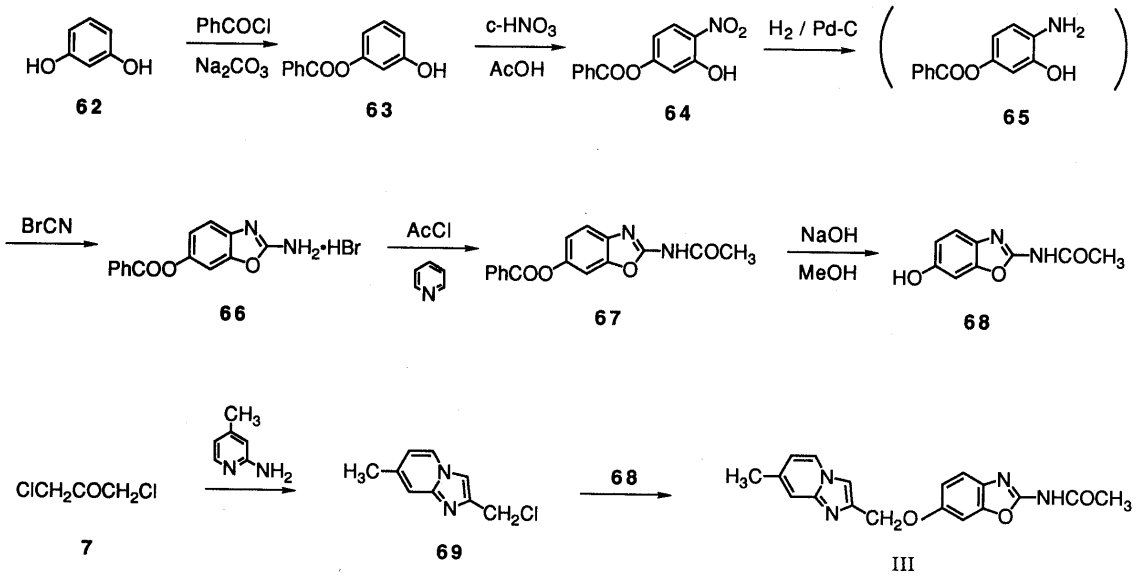


Chart 4

and II-**33**—**37**). 2-Aminobenzoxazole derivatives (II-**1**—**4**, II-**6**, II-**8**—**11**, II-**13**, II-**15** and II-**20**—**26**) were prepared by the cyclization of *o*-aminophenol derivatives with BrCN.[9] Acylation of these products gave the corresponding 2-acylaminobenzoxazoles (II-**38**—**39**, II-**41**, II-**43**, II-**44** and II-**46**—**55**).

Compound III, in which the ethylene chain of II was replaced to the methyloxy group, was prepared from resorcinol (**62**). Monobenzoylation of **62**, followed by nitration, afforded *o*-nitrophenol (**64**).[10] Catalytic reduction of **64** over Pd–C produced *o*-aminophenol (**65**), which was converted, without isolation, to benzoxazole derivative (**66**) with BrCN. Acetylation of **66** and debenzoylation with NaOH provided **68**. The phenol (**68**) was coupled with imidazo[1,2-*a*]pyridinylmethylchloride (**69**), derived from dichloroacetone (**7**) and 2-amino-4-methylpyridine, to afford the final compound (III) (Chart 4).

The compounds possessing a sulfur atom in the alkyl chain were synthesized by the route in Chart 5. Treatment of *o*-aminocresols (**70**—**72**) with ethyl isocyanate, followed by cyclization with PPE, afforded 2-ethylaminobenzoxazoles (**76**—**78**). Formylation of these compounds and successive bromination with *N*-bromosuccinimide (NBS) yielded bromomethylbenzoxazoles (**82**—**84**). The halides were allowed to react with the thiol (**85**), prepared from **69**, to give methylthiomethyl derivatives (**86**—**88**), which were hydrolyzed with acid to yield the desired compounds (IV-**1**—**3**).

Introduction of the various substituents onto the imidazo[1,2-*a*]pyridine ring was carried out as follows. Mannich reaction[7a,b] of II-**38** with formalin and dimethylamine hydrochloride gave II-**41**. Chlorination of II-**3**, II-**10**

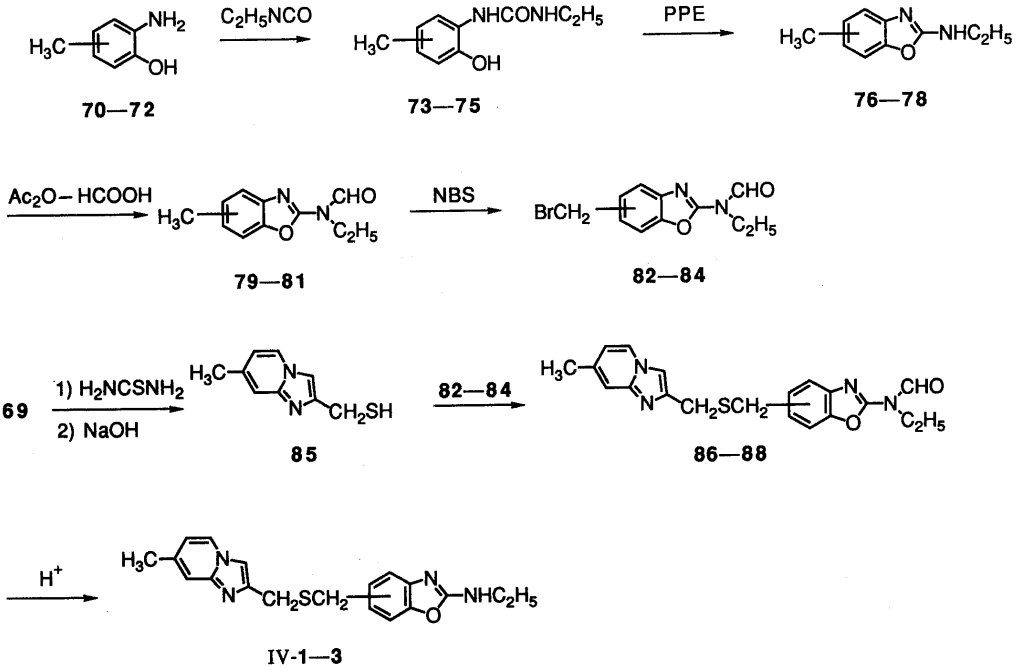


Chart 5

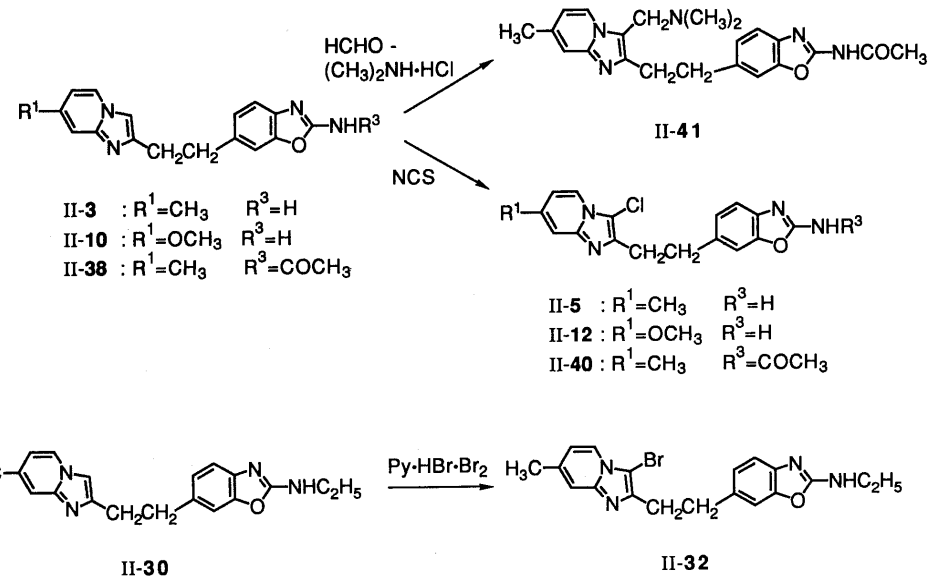
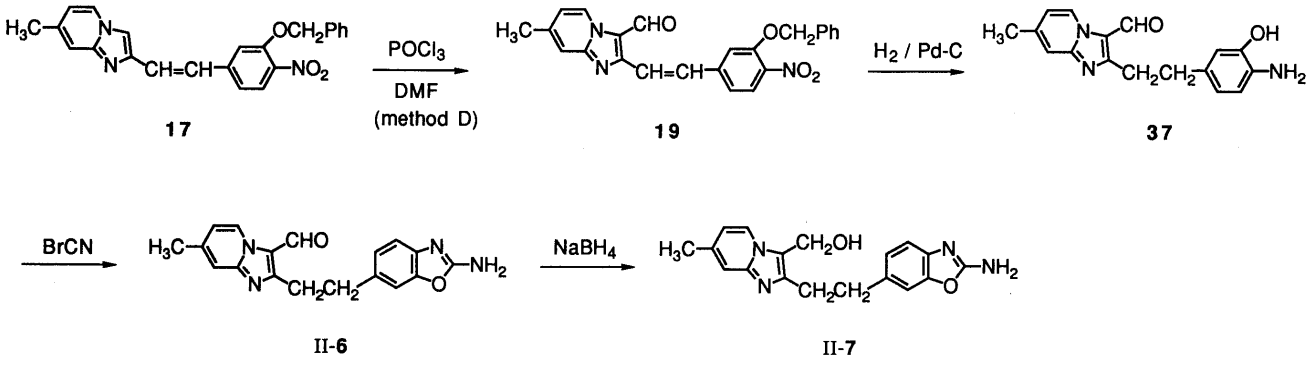


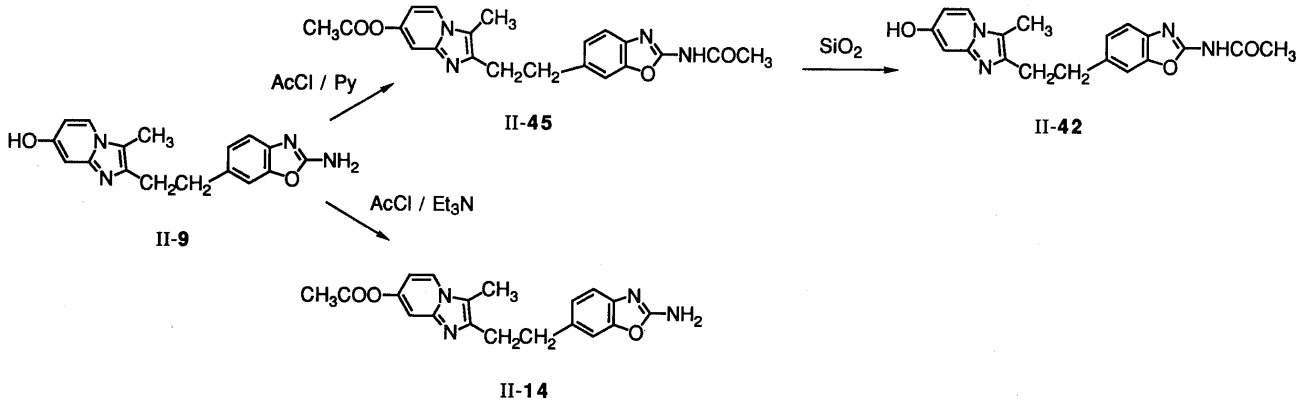
Chart 6

and II-**38** with *N*-chlorosuccinimide (NCS) or bromination of II-**30** with pyridinium bromide perbromide afforded 3-halogenoimidazo[1,2-*a*]pyridine derivatives (II-**5**, II-**12**, II-**40** and II-**32**), respectively (Chart 6). Formylation of **17** with Vilsmeier reagent ($POCl_3$–*N*,*N*-dimethylformamide (DMF)), followed by catalytic reduction over Pd–C and subsequent cyclization with BrCN gave 3-formyl derivative (II-**6**). Reduction of II-**6** with $NaBH_4$ afforded the



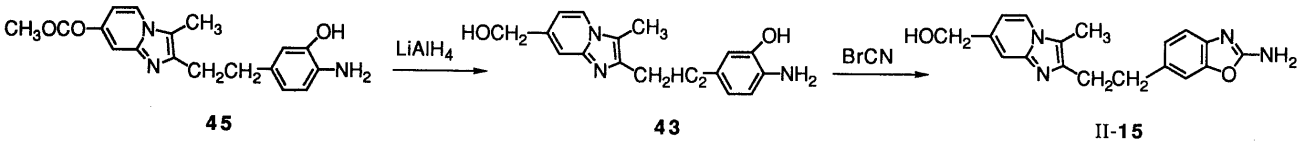
17 **19** **37** II-**6** II-**7**

Chart 7

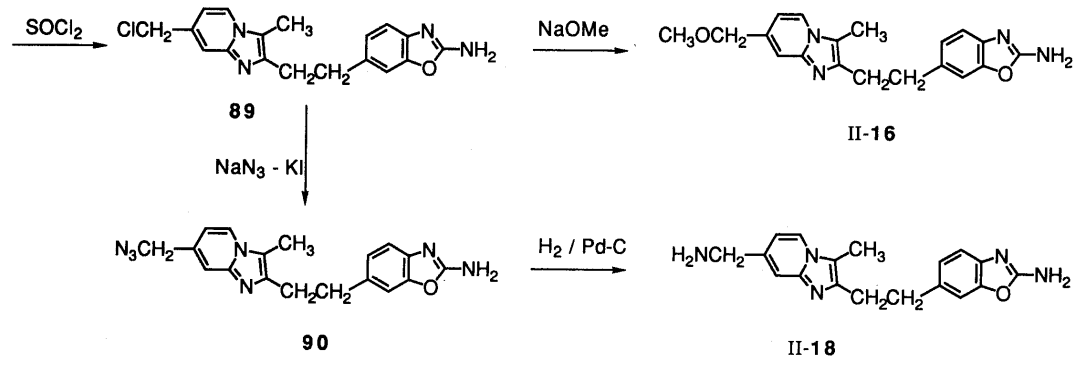


II-**45** II-**42** II-**9** II-**14**

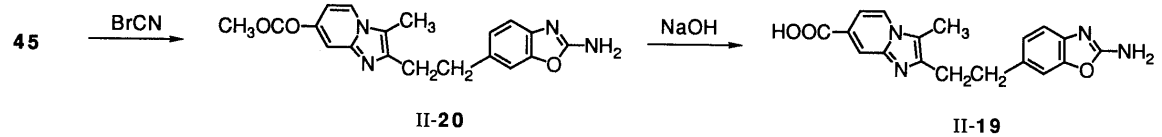
Chart 8



45 **43** II-**15**



89 II-**16** **90** II-**18**

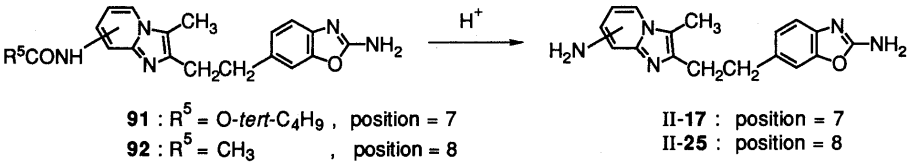


45 II-**20** II-**19**

Chart 9

3-hydroxymethyl derivative (II-**7**) (Chart 7). Acetylation of II-**9** with acetyl chloride produced mono- or diacetyl derivatives (II-**14** and II-**45**) depending on the base used. On treatment with silica gel, the diacetate (II-**45**) was selectively deacetylated to compound II-**42** (Chart 8). Reduction of **45** with $LiAlH_4$ gave **43**, which was cyclized with BrCN to provide II-15. The 7-hydroxymethyl group of II-**15** was converted to the chloromethyl group by means of $SOCl_2$, and the product (**89**) was converted to the methoxymethyl derivative (II-**16**). Reaction of **89** with NaN_3–KI yielded an azide derivative (**90**), which was reduced to the aminomethyl derivative (II-**18**). The 7-methoxycarbonyl derivative (II-**20**) was obtained by the cyclization of **45** with BrCN. Saponification of II-**20** with NaOH gave the carboxylic acid (II-**19**) (Chart 9). 7- and 8-Amino derivatives (II-**17** and II-**25**) were prepared by acidic hydrolysis of the corresponding acylated amino derivatives (**91** and **92**) (Chart 10).

Finally, modification of the substituent on the benzoxazole moiety was done as outlined in Charts 11 and 12. Acylation of the *o*-aminophenol derivative (**36**), followed by ring closure with $POCl_3$ yielded 2-alkylbenzoxazoles (II-**59** and II-**60**). Treatment of **36** with (dichloromethylene)dimethylammonium chloride[11] gave a 2-dimethylaminobenzoxazole derivative (II-**56**). Cyclization of **36** with potassium ethyl xanthogenate[12] afforded the 2-thiobenzoxazole derivative (**95**) as a potassium salt. Methylation of this gave methylthio derivative (II-**62**).



91 : R^5 = O-*tert*-C_4H_9 , position = 7
92 : R^5 = CH_3 , position = 8

II-**17** : position = 7
II-**25** : position = 8

Chart 10

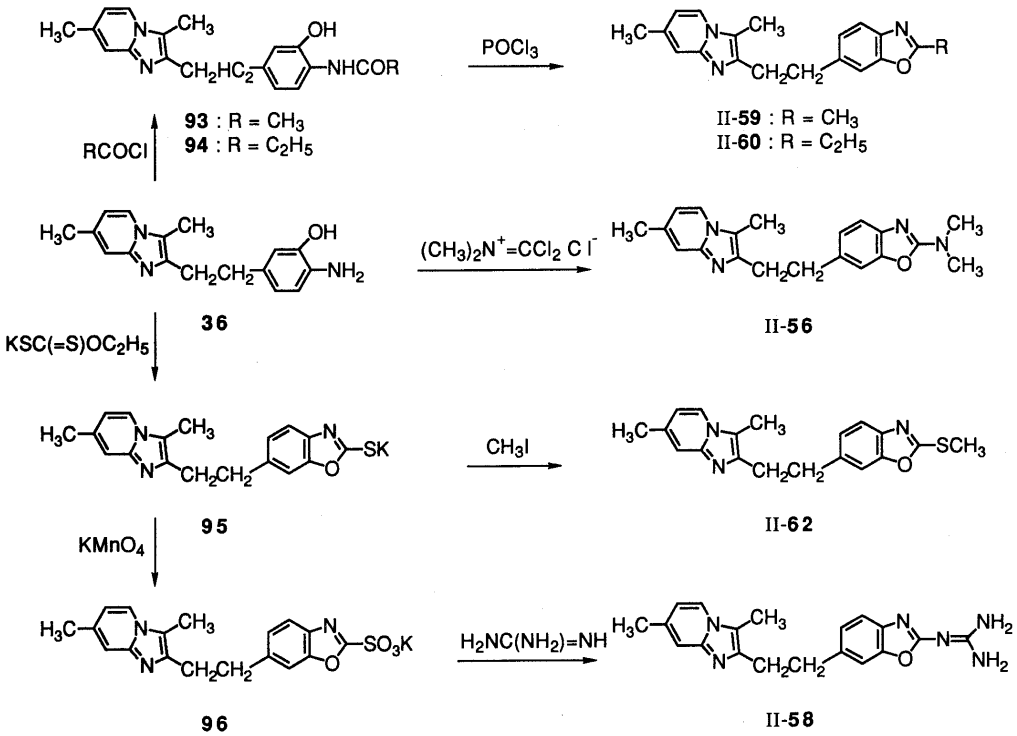


Chart 11

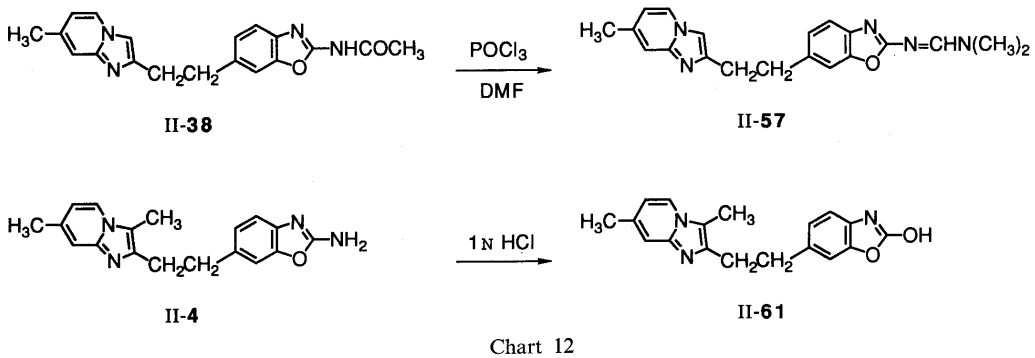


Chart 12

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

Compound No.	H_2-receptor antagonist activity[a] inhibition (%) 1×10^{-6} g/ml	Antisecretory activity[b] inhibition (%) 1 mg/kg i.v.	Antiulcer activity[c] inhibition (%) 32 mg/kg *p.o.*
I	2.6		
II-1	100	NE	78.0
II-2	94.7	NE	81.1
II-3	92.2	73	34.8
II-4	69.1	65	92.9
II-5	76.7	38	75.3
II-6	NE		
II-7	NE		
II-8	88.2	27	97.3
II-9	86.0	91	NE
II-10	93.0	67	42.5
II-11	69.0	59	93.4
II-12	49.3	NE	
II-13	100	59	47.9
II-14	85.7	25	NE
II-15	39.6		
II-16	77.5	NE	50.4
II-17	92.9	70	37.3
II-18	NE		
II-19	NE		
II-20	17.6		
II-21	12.9		
II-22	45.6	67	69.7
II-23	79.5	NE	NE
II-24	19.5		
II-25	67.5	NE	47.5
II-26	NE		
II-27	69.0	48	85.1
II-28	92.5	NE	48.2
II-29	77.4	15	61.8
II-30	90.0	67	84.6
II-31	50.0	59	80.9
II-32	45.2	NE	
II-33	65.9	35	98.6
II-34	76.5	45	62.7
II-35	81.0	23	75.0
II-36	62.9	62	53.7
II-37	74.1	41	61.7
II-38	57.8	53	89.1
II-39	76.7	57	73.8
II-40	53.4	28	50.0
II-41	5.4		
II-42	19.0		
II-43	82.4	57	65.1
II-44	67.3	44	42.5
II-45	55.4	NE	31.3
II-46	60.9	22	52.2
II-47	76.7	68	42.1
II-48	76.2	41	80.1
II-49	100	82	49.4
II-50	78.6	58	83.9
II-51	83.3	40	53.0
II-52	72.3	14	81.1
II-53	53.8	65	79.2
II-54	6.1		
II-55	74.5	NE	62.2
II-56	15.9		
II-57	50.9	56	72.4
II-58	NE		
II-59	NE		
II-60	88.5	NE	59.2
II-61	NE		
II-62	NE		
III	11.9		
IV-1	NE		
IV-2	NE		
IV-3	NE		
Cimetidine	42.9	53	69.4
Ranitidine	43.8	72	81.8

a) H_2-receptor antagonism in isolated guinea pig right atrium. *b*) Inhibition of histamine-stimulated gastric acid secretion in lumen-perfused stomach of the anaesthetized rats ($n=2$). *c*) Inhibitory effect on gastric ulcer induced by water-immersion restraint stress in rats ($n=5$). NE = no effect.

Oxidation of **95** with $KMnO_4$, followed by the reaction with guanidine, afforded the 2-guanidino derivative (**II-58**) (Chart 11). The 2-acetylamino group of **II-38** was converted to dimethylaminomethyleneamino group on treatment with Vilsmeier reagent. Hydrolysis of **II-4** with 1 N HCl yielded the 2-hydroxybenzoxazole derivative (**II-61**) (Chart 12).

Pharmacological Results and Discussion

The biological results of the imidazo[1,2-*a*]pyridine derivatives (I—IV) obtained in this study are listed in Tables II and III. All compounds were evaluated *in vitro* for H_2-antagonist activity using the histamine-stimulated chronotropic response of the guinea pig atrium.[13] Compounds with sufficient potency were assessed according to their *in vivo* pharmacological activities: the inhibition of histamine-stimulated gastric acid secretion in the lumen-perfused anaesthetized rats[14] and antiulcer activity in the restraint and water-immersion stressed rats (stress ulcer).[15]

A comparison of the activities in the compounds incorporating various alkyl chain between the imidazo[1,2-*a*]pyridine moiety and the benzoxazole group indicated that an ethyl chain connected to the 6-position of a benzoxazole group (II) is a determinant of *in vitro* H_2-antagonist activity.

Of the compounds of series II, a number of derivatives showed potent H_2-antagonist activity. In general, methyl, ethyl, methoxy and ethoxy substitution on the imidazo[1,2-*a*]pyridine ring were preferred for this activity. Conversion of these groups with other substitutions (**II-15**, **II-18**—**21**, **II-26** and **II-42**), and the introduction of various functional groups at the 3-position (**II-5**, **II-7**, **II-12**, **II-32**, **II-40** and **II-41**) tended to reduce the activity.

With regard to *in vivo* antisecretory effect, several 7-substituted derivatives, 7-methyl (**II-3**, **II-4**, **II-30**, **II-31**, **II-36**, **II-38**, **II-39**, **II-47**, **II-49**, **II-50** and **II-57**), 7-methoxy (**II-10**, **II-11** and **II-43**), 7-ethoxy (**II-13**), 7-amino (**II-17**) and 7-hydroxy (**II-9**) derivatives, showed potent activity. **II-9** was the most active compound, but had no anti-stress ulcer activity.

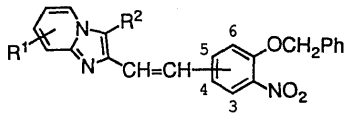
On the other hand, in spite of potent *in vitro* H_2-antagonist activity, 7-unsubstituted (**II-1**), 6-methyl (**II-2**), 7-ethyl (**II-8**), 7-acetoxy (**II-14**), 7-methoxymethyl (**II-16**), 8-hydroxy (**II-23**) and 8-amino (**II-25**) derivatives exhibited a remarkable decrease or a complete loss in activity. These results suggest that no simple correlation exists between the *in vitro* H_2-antagonist activity and the *in vivo* antisecretory

TABLE III. Further Evaluation of **II-4**, **II-11**, **II-30**, **II-38** and the Reference Compounds

Compoumd No.	Acid secretion[a] ED_{50}[c] (mg/kg, i.d.)	Ethanol ulcer[b] ED_{50}[c] (mg/kg, *p.o.*)
II-4	NT	14.1
II-11	21.8	6.1
II-30	NT	11.4
II-38	13.8	4.0
Cimetidine	83.0	>320
Ranitidine	30.5	29.6
Roxatidine acetate	26.9	20.4

a) Gastric antisecretory effect on basal acid secretion in pylorus-ligated rat. *b*) Protective effect on gastric lesion induced by absolute ethanol. *c*) ED_{50} values were estimated from three or four doses. Ten animals were used per dose. NT = not tested.

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



Compd. No.	R^1	R^2	Position	Method	Yield (%)	mp (°C)	^{1}H-NMR	
							Solvent	δ (J=Hz)
14	7-CH_3	H	4	A	25	185—189	DMSO-d_6	2.34 (3H, s), 5.34 (2H, s), 6.70 (1H, dd, J=2, 7), 7.25—7.49 (9H, m), 7.88 (1H, dd, J=2, 8), 7.92 (1H, s), 8.14 (1H, d, J=2), 8.39 (1H, d, J=7)
15	H	CH_3	5	C	23	151—153	DMSO-d_6	2.64 (3H, s), 5.41 (2H, s), 6.43 (1H, t, J=7), 7.23—7.65 (10H, m), 7.73 (1H, s), 7.93 (1H, d, J=8), 8.25 (1H, d, J=7)
16	6-CH_3	CH_3	5	C	20	154—155	DMSO-d_6	2.32 (3H, s), 2.61 (3H, s), 5.42 (2H, s), 7.01—7.79 (11H, m), 7.93 (1H, d, J=8), 8.05 (1H, s)
17	7-CH_3	H	5	A	46	175—176	DMSO-d_6	2.34 (3H, s), 5.40 (2H, s), 6.69 (1H, dd, J=2, 7), 7.17—7.74 (10H, m), 7.89 (1H, d, J=8), 7.98 (1H, s), 8.37 (1H, d, J=7)
18	7-CH_3	CH_3	5	C	26	158—161	DMSO-d_6	2.37 (3H, s), 2.62 (3H, s), 5.45 (2H, s), 6.77 (1H, dd, J=2, 7), 7.22—7.83 (10H, m), 7.97 (1H, d, J=8), 8.13 (1H, d, J=7)
19	7-CH_3	CHO	5	D	53	200—201	DMSO-d_6	2.48 (3H, s), 5.42 (2H, s), 7.13 (1H, dd, J=1.5, 7), 7.30—8.03 (10H, m), 7.40 (1H, d, J=1.5), 9.30 (1H, d, J=7), 10.35 (1H, s)
20	7-C_2H_5	CH_3	5	C	18	142—146	DMSO-d_6	1.23 (3H, t, J=7), 2.61 (3H, s), 2.69 (2H, q, J=7), 5.42 (2H, s), 6.78 (1H, dd, J=2, 7), 7.23—7.83 (10H, m), 7.92 (1H, d, J=8), 8.19 (1H, d, J=7)
21	7-OCH_3	H	5	A	63	121—126	DMSO-d_6	3.80 (3H, s), 5.43 (2H, s), 6.65 (1H, dd, J=2, 7), 7.27—7.75 (10H, m), 7.91 (1H, d, J=8), 7.96 (1H, s), 8.14 (1H, d, J=7)
22	7-OCH_3	CH_3	5	C	25	145—147	CF_3COOH	2.73 (3H, s), 4.12 (3H, s), 5.48 (2H, s), 7.04—7.55 (6H, m), 7.42 (5H, s), 8.10—8.37 (2H, m)
23	7-OC_2H_5	CH_3	5	C	26	153—154	DMSO-d_6	1.39 (3H, t, J=7), 2.60 (3H, s), 4.13 (2H, q, J=7), 5.44 (2H, s), 6.63 (1H, dd, J=2, 7), 6.86 (1H, d, J=2), 7.30—7.97 (10H, m), 8.11 (1H, d, J=7)
24	7-OCH_2Ph	CH_3	5	C	27	168—169	DMSO-d_6	2.59 (3H, s), 5.12 (2H, s), 5.42 (2H, s), 6.71 (1H, dd, J=2, 7), 7.29—7.82 (15H, m), 7.93 (1H, d, J=8), 8.10 (1H, d, J=7)
25	7-NHCOO-*tert*-C_4H_9	CH_3	5	B	46	104—106	DMSO-d_6	1.52 (9H, s), 2.61 (3H, s), 5.45 (2H, s), 7.05 (1H, dd, J=2, 7), 7.22—7.80 (10H, m), 7.95 (1H, d, J=8), 8.16 (1H, d, J=7), 9.67 (1H, s)
26	7-$COOCH_3$	CH_3	5	B	46	167—168	DMSO-d_6	2.61 (3H, s), 3.85 (3H, s), 5.35 (2H, s), 7.23 (1H, dd, J=2, 7), 7.30—7.76 (9H, m), 7.85 (1H, d, J=8), 7.98 (1H, s), 8.23 (1H, d, J=7)
27	7-$CONH_2$	CH_3	5	B	32	>250	DMSO-d_6	2.68 (3H, s), 5.42 (2H, s), 7.35—7.77 (11H, m), 7.94 (1H, d, J=8), 8.08 (1H, s), 8.21 (1H, s), 8.32 (1H, d, J=7)
28	8-CH_3	CH_3	5	C	21	140—142	CF_3COOH	2.78 (3H, s), 2.81 (3H, s), 5.47 (2H, s), 7.08—8.09 (11H, m), 8.23 (1H, d, J=8), 8.33 (1H, d, J=7)
29	8-OCH_3	CH_3	5	C	17	123—125	DMSO-d_6	2.62 (3H, s), 3.97 (3H, s), 5.44 (2H, s), 6.60—7.10 (2H, m), 7.30—8.07 (11H, m)
30	8-OCH_2Ph	CH_3	5	C	66	130—136	DMSO-d_6	2.63 (3H, s), 5.33 (2H, s), 5.41 (2H, s), 6.71—6.93 (2H, m), 7.30—8.08 (16H, m)
31	8-$NHCOCH_3$	CH_3	5	B	39	132—134	DMSO-d_6	2.28 (3H, s), 2.64 (3H, s), 5.46 (2H, s), 6.93 (1H, t, J=7), 7.32—7.82 (9H, m), 7.90—8.11 (3H, m), 9.74 (1H, s)

potency in this series.

Besides good antisecretory effects, compounds II-**4**, II-**11**, II-**30** and II-**38** exhibited potent anti-stress ulcer activity. For these compounds, further evaluation on antisecretory activity against the basal gastric secretion in pylorus-ligated rats[16] and cytoprotective activity against ethanol-induced gastric lesions (ethanol ulcer)[17] were examined. As shown in Table III, the selected compounds revealed potent cytoprotective activity. Of these, compounds II-**11** and II-**38** exhibited considerable antisecretory activity. The activities were superior to those of the reference H_2-antagonists: cimetidine, ranitidine and roxatidine acetate.

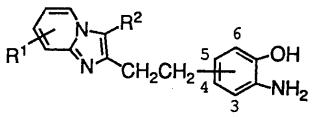
These results indicate that (1): the four-membered flexible alkyl chain of the conventional H_2-antagonists is replaceable with an aralkyl moiety, and (2): rotational freedom of the bond connecting the alkyl chain with the urea (or amidine) equivalent group is not required for expression of the H_2-antagonist activity.

In conclusion, we obtained (imidazo[1,2-*a*]pyridin-2-yl)alkylbenzoxazoles as novel structural H_2-antagonists. Many compounds showed potent *in vitro* H_2-antagonist activity and some of them exhibited good antisecretory activity in *in vivo* tests. Furthermore, compounds II-**11** and II-**38** showed noticeable cytoprotective activity. The potencies were superior to that of the previously reported cytoprotective H_2-antagonist, roxatidine acetate.[18]

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 JMN-PMX60 or a Varian EM-390 spectrometer using tetramethylsilane as an internal standard. Mass spectral

TABLE V. Physical Data of 2-(2-Phenylethyl)imidazo[1,2-*a*]pyridines



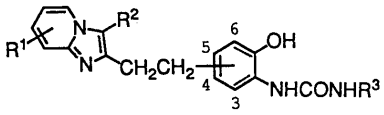
Compd. No.	R^1	R^2	Position	Yield (%)	mp (°C)	^{1}H-NMR	
						Solvent	δ (J=Hz)
32	7-CH_3	H	4	37	187—191	DMSO-d_6	2.34 (3H, s), 2.83 (4H, s), 6.12—6.76 (5H, m), 7.05—7.47 (2H, m), 7.51 (1H, s), 8.26 (1H, d, J=7)
33	H	CH_3	5	71	152—157	DMSO-d_6	2.28 (3H, s), 2.81 (4H, s), 6.35—6.64 (2H, m), 6.67—7.32 (3H, m), 7.49 (1H, dd, J=2, 9), 8.07—8.25 (1H, m)
34	6-CH_3	CH_3	5	100	225—229	CF_3COOH	2.42 (3H, s), 2.58 (3H, s), 3.12—3.38 (4H, m), 6.92 (1H, d, J=8), 7.05 (1H, s), 7.48 (1H, d, J=8), 7.78 (1H, s), 7.80 (1H, d, J=7), 8.15 (1H, d, J=7)
35	7-CH_3	H	5	98	91—97	DMSO-d_6	2.33 (3H, s), 2.78—3.06 (4H, m), 6.42 (1H, dd, J=2, 8), 6.50 (1H, d, J=8), 6.55 (1H, d, J=2), 6.66 (1H, dd, J=2, 7), 7.23 (1H, d, J=2), 7.54 (1H, s), 8.32 (1H, d, J=7)
36	7-CH_3	CH_3	5	72	153—156	DMSO-d_6	2.21 (3H, s), 2.30 (3H, s), 2.74 (4H, s), 6.32 (1H, dd, J=2, 8), 6.46 (1H, d, J=8), 6.47 (1H, d, J=2), 6.61 (1H, dd, J=2, 7), 7.14 (1H, d, J=2), 7.91 (1H, d, J=7)
37	7-CH_3	CHO	5	45	>250	DMSO-d_6	2.43 (3H, s), 2.85—3.18 (4H, m), 6.43—6.53 (3H, m), 7.10 (1H, dd, J=1.5, 7), 7.58 (1H, d, J=1.5), 9.27 (1H, d, J=7), 9.75 (1H, s)
38	7-C_2H_5	CH_3	5	58	134—136	D_2O–DCl	1.36 (3H, t, J=7), 2.24 (3H, s), 2.75—3.32 (6H, m), 6.67 (1H, dd, J=2, 8), 6.76 (1H, d, J=2), 7.12 (1H, d, J=8), 7.32 (1H, dd, J=2, 7), 7.59 (1H, d, J=2), 8.22 (1H, d, J=7)
39	7-OCH_3	H	5	98	94—104	DMSO-d_6	2.79—2.89 (4H, m), 3.81 (3H, s), 6.45 (1H, dd, J=2, 8), 6.53 (1H, d, J=8), 6.55 (1H, dd, J=2, 7), 6.86 (1H, d, J=2), 7.35 (1H, d, J=2), 7.46 (1H, s), 8.30 (1H, d, J=7)
40	7-OCH_3	CH_3	5	79	215—217	D_2O–DCl	2.22 (3H, s), 2.81—3.36 (4H, m), 4.06 (3H, s), 6.70—7.09 (2H, m), 7.00—7.46 (3H, m), 8.21 (1H, d, J=7)
41	7-OC_2H_5	CH_3	5	63	152—154	D_2O–DCl	1.53 (3H, t, J=7), 2.18 (3H, s), 2.87—3.29 (4H, m), 4.28 (2H, q, J=7), 6.77 (1H, dd, J=2, 8), 6.83 (1H, d, J=2), 7.02 (1H, dd, J=2, 7), 7.12 (1H, d, J=2), 7.29 (1H, d, J=8), 8.18 (1H, d, J=7)
42	7-OH	CH_3	5	100	172—176	D_2O–DCl	2.20 (3H, s), 2.80—3.33 (4H, m), 6.83 (1H, dd, J=2, 8), 6.89 (1H, d, J=2), 6.98—7.13 (2H, m), 7.34 (1H, d, J=8), 8.22 (1H, d, J=7)
43	7-CH_2OH	CH_3	5	65	138—145	D_2O–DCl	2.25 (3H, s), 3.13 (4H, s), 4.93 (2H, s), 6.77 (1H, dd, J=2, 8), 6.85 (1H, d, J=2), 7.31 (1H, d, J=7), 7.40 (1H, d, J=8), 7.80 (1H, d, J=2), 8.37 (1H, d, J=7)
44	7-NHCOO-*tert*-C_4H_9	CH_3	5	90	149—153	DMSO-d_6	1.52 (9H, s), 2.23 (3H, s), 2.76 (4H, s), 6.26—6.78 (3H, m), 7.03 (1H, d, J=7), 7.64 (1H, s), 8.05 (1H, d, J=7), 9.61 (1H, s)
45	7-$COOCH_3$	CH_3	5	62	181—183	CF_3COOH	2.57 (3H, s), 3.12—3.54 (4H, m), 4.22 (3H, s), 6.82—7.13 (1H, m), 7.04 (1H, s), 7.45 (1H, d, J=8), 8.12 (1H, d, J=7), 8.49 (1H, d, J=7), 8.67 (1H, s)
46	7-$CONH_2$	CH_3	5	83	76—79	D_2O–DCl	2.34 (3H, s), 3.04—3.34 (4H, m), 6.67—6.94 (2H, m), 7.24—7.47 (1H, m), 7.78 (1H, dd, J=2, 7), 8.29 (1H, d, J=2), 8.55 (1H, d, J=7)
47	8-CH_3	CH_3	5	34	185—188	D_2O–DCl	2.24 (3H, s), 2.64 (3H, s), 3.04—3.31 (4H, m), 6.69—7.00 (1H, m), 6.86 (1H, s), 7.24—7.54 (2H, m), 7.73 (1H, d, J=7), 8.25 (1H, d, J=7)
48	8-OCH_3	CH_3	5	44	85—91	D_2O–DCl	2.23 (3H, s), 2.84—3.37 (4H, m), 4.15 (3H, s), 6.68—6.89 (2H, m), 7.15—7.61 (3H, m), 7.93 (1H, dd, J=2, 7)
49	8-OH	CH_3	5	91	102—107	D_2O–DCl	2.23 (3H, s), 2.96—3.26 (4H, m), 6.79 (1H, dd, J=2, 8), 6.87 (1H, d, J=2), 7.18—7.37 (2H, m), 7.34 (1H, d, J=8), 7.82—8.00 (1H, m)
50	8-$NHCOCH_3$	CH_3	5	89	130—132	DMSO-d_6	2.21 (3H, s), 2.23 (3H, s), 2.58—3.00 (4H, m), 6.32 (1H, d, J=8), 6.41 (1H, s), 6.46 (1H, d, J=7), 6.73 (1H, t, J=7), 7.77 (1H, d, J=7), 7.81 (1H, d, J=8), 9.65 (1H, s)

measurements (MS) were made on either a Hitachi M-80 or a JEOL-D300 mass spectrometer.

2-[2-(3-Benzyloxy-4-nitrophenyl)vinyl]-7-methylimidazo[1,2-*a*]pyridine (17): Method A A mixture of 3-chloro-2-oxopropyltriphenylphosphonium chloride (**8**) (191 g, 0.49 mol) and 2-amino-4-methylpyridine (159 g, 1.5 mol) in MeCN (1.3 l) was refluxed for 5.5 h with stirring. After being ice-cooled, H_2O (400 ml) and 3-benzyloxy-4-nitrobenzaldehyde (63 g, 0.25 mol) were added to the reaction mixture. The mixture was adjusted to pH 9.5 with K_2CO_3 and stirred for 2.5 h while the pH was maintained at 9.5—10 with 20% aqueous K_2CO_3 at room temperature. The reaction mixture was then adjusted to pH 2 with conc. HCl. The precipitate formed was collected by filtration, added to AcOEt–tetrahydrofuran (THF)–H_2O, and adjusted to pH 7 with 20% aqueous K_2CO_3. The separated organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford **17** (43 g, 46%). Recrystallization from EtOH–*n*-hexane gave an analytical sample. IR (Nujol): 1640, 1600, 1590 cm^{-1}. *Anal.* Calcd for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90. Found: C, 71.46; H, 4.87; N, 10.76. MS *m/z*: 385 (M^+).

(3-Bromo-2-oxobutyl)triphenylphosphonium Bromide (10) A solution of Br_2 (71 ml, 1.4 mol) in CH_2Cl_2 (35 ml) was added dropwise to a solution of 2-butanone (**9**) (62 ml, 0.69 mol) in CH_2Cl_2 (500 ml) over 1.5 h at 20—28 °C and the mixture was stirred for 30 min at room temperature. After the solvent was evaporated *in vacuo*, the residue was dissolved in AcOEt (600 ml). PPh_3 (182 g, 0.69 mol) was added to the solution and the mixture was stirred for 2 h at the same temperature. The resulting precipitate was collected by filtration and washed with H_2O–AcOEt to afford **10** (132 g, 39%). mp 193—194 °C [EtOH–diisopropyl ether (IPE)]. *Anal.* Calcd for $C_{22}H_{21}Br_2OP$: C, 53.69; H, 4.30. Found: C, 53.54; H, 4.29. IR (Nujol): 1720 cm^{-1}. ^{1}H-NMR (dimethyl sulfoxide-d_6 (DMSO-d_6)) δ: 1.77 (3H, d, J=7 Hz), 5.06 (1H, q, J=7 Hz), 5.88 (2H, d, J=13 Hz),

TABLE VI. Physical Data of [2-(Imidazo[1,2-*a*]pyridin-2-yl)ethyl]phenylureas



Compd. No.	R^1	R^2	R^3	Position	Yield (%)	mp (°C)	^{1}H-NMR	
							Solvent	δ (J=Hz)
51	7-CH_3	H	C_2H_5	4	95	212—219	DMSO-d_6	1.05 (3H, t, J=7), 2.32 (3H, s), 2.77 (4H, s), 2.99—3.13 (2H, m), 6.64 (1H, d, J=7), 6.68 (1H, d, J=8), 6.79 (1H, t, J=5), 7.22 (1H, d, J=2), 7.49 (1H, s), 7.76 (1H, dd, J=2, 8), 7.84 (1H, s), 8.30 (1H, d, J=7)
52	H	CH_3	C_2H_5	5	69	177—180	CF_3COOH	1.31 (3H, t, J=7), 2.51 (3H, s), 3.22 (4H, m), 3.54 (2H, q, J=7), 6.94—7.72 (4H, m), 7.91—8.22 (2H, m), 8.37—8.58 (1H, m)
53	7-CH_3	H	C_2H_5	5	71	205—206	DMSO-d_6	1.03 (3H, t, J=7), 2.32 (3H, s), 2.85 (4H, s), 3.02—3.15 (2H, m), 6.56—6.73 (4H, m), 7.22 (1H, s), 7.75 (1H, s), 7.67 (1H, d, J=8), 7.77 (1H, s), 8.30 (1H, d, J=7), 9.80 (1H, s)
54	7-CH_3	CH_3	CH_3	5	97	144—149	CF_3COOH	2.44 (3H, s), 2.65 (3H, s), 2.89—3.43 (4H, m), 3.07 (3H, s), 6.92 (1H, d, J=8), 6.99 (1H, s), 7.24 (1H, d, J=8), 7.38 (1H, d, J=7), 7.61 (1H, s), 8.20 (1H, d, J=7)
55	7-CH_3	CH_3	C_2H_5	5	100	188—190	DMSO-d_6	1.04 (3H, t, J=7), 2.22 (3H, s), 2.33 (3H, s), 2.75—3.39 (2H, m), 2.82 (4H, s), 6.42—6.88 (4H, m), 7.23 (1H, s), 7.65 (1H, d, J=8), 7.79 (1H, s), 8.01 (1H, d, J=7), 9.81 (1H, br s)
56	7-CH_3	CH_3	iso-C_3H_7	5	77	197—199	CH_3COOH	1.33 (6H, d, J=6), 2.45 (3H, s), 2.65 (3H, s), 2.91—3.43 (4H, m), 3.99—4.40 (1H, m), 6.94 (1H, d, J=8), 7.02 (1H, s), 7.25 (1H, d, J=8), 7.39 (1H, d, J=7), 7.63 (1H, s), 8.23 (1H, d, J=7)
57	7-CH_3	CH_3	$CH_2CH=CH_2$	5	65	187—189	CF_3COOH	2.44 (3H, s), 2.65 (3H, s), 2.91—3.41 (4H, m), 3.97—4.20 (2H, m), 5.21—5.53 (2H, m), 5.70—6.23 (1H, m), 6.85—7.11 (2H, m), 7.27 (1H, d, J=8), 7.41 (1H, d, J=7), 7.62 (1H, s), 8.22 (1H, d, J=7)
58	7-OCH_3	CH_3	CH_3	5	71	212—213	CF_3COOH	2.42 (3H, s), 2.88—3.44 (7H, m), 4.09 (3H, s), 6.73—7.52 (5H, m), 7.93—8.28 (1H, m)
59	7-OCH_3	CH_3	C_2H_5	5	86	211—213	CF_3COOH	1.11—1.53 (3H, m), 2.44 (3H, s), 3.18 (4H, s), 3.30—3.85 (2H, m), 4.10 (3H, s), 6.67—7.52 (5H, m), 7.90—8.32 (1H, m)
60	7-OCH_3	CH_3	iso-C_3H_7	5	86	207—208	DMSO-d_6	1.07 (6H, d, J=7), 2.21 (3H, s), 2.79 (4H, s), 3.67—3.82 (1H, m), 3.82 (3H, s), 6.53 (1H, dd, J=2, 8), 6.57—6.61 (2H, m), 6.67 (1H,d, J=7), 6.86 (1H, d, J=2), 7.67 (1H, d, J=8), 7.72 (1H, s), 8.03 (1H, d, J=7), 9.76 (1H, br s)
61	7-OCH_3	CH_3	$CH_2CH=CH_2$	5	83	184—186	DMSO-d_6	2.25 (3H, s), 2.86 (4H, s), 3.60—4.00 (2H, m), 3.86 (3H, s), 4.95—5.43 (2H, m), 5.61—6.15 (1H, m), 6.50—6.78 (3H, m), 6.81—7.14 (2H, m), 7.50 (1H, br s), 7.74 (1H, d, J=8), 8.00 (1H, s), 8.06 (1H, d, J=7)

7.57—8.13 (15H, m).

(3-Bromo-2-oxobutylidene)triphenylphosphorane (12) A solution of **10** (30 g, 61 mmol) in AcOEt (150 ml)–THF (150 ml)–H_2O (150 ml) was adjusted to pH 10 with K_2CO_3. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was triturated with IPE to afford **12** (25 g, 97%). mp 152—153 °C (MeCN). *Anal.* Calcd for $C_{22}H_{20}BrOP$: C, 64.25; H, 4.90. Found: C, 64.24; H, 4.92. IR (Nujol): 1550 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.71 (3H, d, J=7 Hz), 4.01 (1H, d, J=24 Hz), 4.65 (1H, q, J=7 Hz), 7.41—8.06 (15H, m).

2-[2-(3-Benzyloxy-4-nitrophenyl)vinyl]-7-methoxycarbonyl-3-methylimidazo[1,2-*a*]pyridine (26): Method B A solution of **12** (5.0 g, 12 mmol) and 3-benzyloxy-4-nitrobenzaldehyde (3.1 g, 12 mmol) in dioxane (50 ml) was refluxed for 4 h. After being concentrated *in vacuo*, 2-amino-4-methoxycarbonylpyridine (4.6 g, 30 mmol) and iso-PrOH (50 ml) were added to the residue and the mixture was refluxed for 4 h, then concentrated to dryness. The residue was dissolved in AcOEt–H_2O and the mixture was acidified with 6 N HCl to pH 6. The resulting precipitate was collected by filtration and dissolved in H_2O. After being adjusted to pH 8 with 20% aqueous K_2CO_3, the mixture was extracted with AcOEt–THF. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with Et_2O to afford **26** (2.5 g, 46%). Recrystallization from MeOH gave an analytical sample. *Anal.* Calcd for $C_{25}H_{21}N_3O_5$: C, 67.71; H, 4.77; N, 9.48. Found: C, 67.41; H, 4.78; N, 9.27. IR (Nujol): 1710, 1580, 1340 cm^{-1}. MS *m/z*: 443 (M^+).

3-Chloro-2-oxobutylidene Triphenyl Phosphorane (13) This compound was prepared from 3-chloro-2-butanone (**11**) in a manner similar to that described for **10** and **12**. Yield 46%, mp 121—122 °C (MeCN). *Anal.* Calcd for $C_{22}H_{20}ClOP$: C, 72.03; H, 5.50. Found: C, 71.96; H, 5.43. IR (Nujol): 1715, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.56 (3H, d, J=7 Hz), 4.05 (1H, d, J=23 Hz), 4.51 (1H, q, J=7 Hz), 7.50—7.78 (15H, m).

2-[2-(3-Benzyloxy-4-nitrophenyl)vinyl]-3,7-dimethylimidazo[1,2-*a*]pyridine (18): Method C A mixture of **13** (100 g, 0.27 mol) and 3-benzyloxy-4-nitrobenzaldehyde (70 g, 0.27 mol) in THF (800 ml) was refluxed for 2 h. The reaction mixture was concentrated to dryness. The residue was heated under reflux with 2-amino-4-methylpyridine (74 g, 0.68 mol) in EtOH (1 l) for 2.5 h. After evaporation of the solvent, the residue was mixed with AcOEt (1 l)–H_2O (1.5 l) and the mixture was adjusted to pH 1 with 6 N HCl under ice-cooling. The resulting precipitate collected was dissolved in H_2O (500 ml). After being adjusted to pH 8 with K_2CO_3, the solution was extracted with AcOEt (600 ml)–THF (500 ml). The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with IPE–Et_2O to afford **18** (28 g, 26%). Recrystallization from EtOH–*n*-hexane gave an analytical sample. *Anal.* Calcd for $C_{24}H_{21}N_3O_3$: C, 69.05; H, 5.55; N, 10.07. Found: C, 69.15; H, 5.62; N, 9.87. IR (Nujol): 1600, 1585 cm^{-1}.

2-[2-(3-Benzyloxy-4-nitrophenyl)vinyl]-3-formyl-7-methylimidazo[1,2-

a]pyridine (19): Method D** A solution of **17** (9.0 g, 23 mmol) in DMF (50 ml) was added dropwise to a solution of $POCl_3$ (6.4 ml, 70 mmol) in DMF (90 ml) at room temperature with stirring. After the mixture was stirred for 6 h, the solvent was evaporated *in vacuo*. The residue was dissolved in H_2O (200 ml)–CH_2Cl_2 (300 ml) and the mixture was made basic with 20% aqueous K_2CO_3. The resulting precipitate was collected, washed with H_2O and crystallized from MeOH–$CHCl_3$–dioxane to afford **19** (5.2 g, 53%). mp 200—201 °C. *Anal.* Calcd for $C_{24}H_{19}N_3O_4$: C, 68.47; H, 4.77; N, 9.95. Found: C, 68.27; H, 4.67; N, 10.17. IR (Nujol): 1630, 1510, 1360 cm^{-1}. MS *m/z*: 413 (M^+).

2-[2-(4-Amino-3-hydroxyphenyl)ethyl]-7-methylimidazo[1,2-*a*]pyridine (35) A solution of **17** (21 g, 79 mmol) in MeOH (300 ml)–THF (300 ml) was hydrogenated over 10% Pd–C (5.0 g) under an atmospheric pressure of H_2 at room temperature. After removal of the catalyst and solvent, the residue was triturated with Et_2O to afford **35** (21 g, 98%), which was not recrystallized because of its instability. *Anal.* Calcd for $C_{16}H_{17}N_3O$: C, 71.88; H, 6.41; N, 15.72. Found: C, 71.65; H, 6.54; N, 15.36. IR (Nujol): 1665, 1590 cm^{-1}. MS *m/z*: 267 (M^+).

2-[2-(4-Amino-3-hydroxyphenyl)ethyl]-7-hydroxymethyl-3-methylimidazo[1,2-*a*]pyridine (43) A solution of 2-[2-(4-amino-3-hydroxyphenyl)ethyl]-7-methoxycarbonyl-3-methylimidazo[1,2-*a*]pyridine (**45**) (2.0 g, 6.2 mmol) in THF (50 ml) was added dropwise to a suspension of $LiAlH_4$ (0.7 g, 18 mmol) in THF (60 ml) at −20 to −10 °C over 30 min and the mixture was stirred at the same temperature for 30 min. An aqueous THF (THF : H_2O = 2 : 1) (30 ml) was slowly added to the reaction mixture, and then 50% aqueous THF (40 ml) and AcOEt (20 ml) were further added. The mixture was adjusted to pH 8 with 6 N HCl and the insoluble material was removed by filtration. The organic layer separated from the filtrate was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with Et_2O–AcOEt to afford **43** (1.2 g, 65%), which was not recrystallized because of its instability. *Anal.* Calcd for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.33; H, 6.48; N, 13.98. IR (Nujol): 3400, 3330, 1640, 1620, 1600, 1580 cm^{-1}. MS *m/z*: 297 (M^+).

2-[2-{4-(3-Ethylureido)-3-hydroxyphenyl}ethyl]-7-methylimidazo[1,2-*a*]pyridine (53) A solution of **35** (20 g, 75 mmol) and EtNCO (7.7 ml, 97 mmol) in THF (200 ml)–MeOH (200 ml) was stirred for 2.5 h at room temperature. After the solvent was evaporated *in vacuo*, the residue was triturated with AcOEt to afford **53** (18 g, 71%). Recrystallization from IPE–MeOH gave an analytical sample. *Anal.* Calcd for $C_{19}H_{22}N_4O_2 \cdot 1/3\ H_2O$: C, 66.26; H, 6.63; N, 16.26. Found: C, 66.17; H, 6.84; N, 16.14. IR (Nujol): 3300, 1645 cm^{-1}. MS *m/z*: 338 (M^+).

2-Amino-6-[2-(7-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-3) A solution of **35** (1.5 g, 5.6 mmol) and BrCN (0.7 g, 6.7 mmol) in EtOH (25 ml) was stirred for 2 h at room temperature. After AcOEt (100 ml) and H_2O (100 ml) were added to the reaction solution, the mixture was adjusted to pH 1 with 10% HCl. The aqueous layer was separated, adjusted to pH 8 with K_2CO_3, and extracted with AcOEt–THF. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by alumina column chromatography eluting with $CHCl_3$–MeOH (19 : 1) to give crystals, which were converted to dihydrochloride in the usual way and recrystallized from AcOEt–IPE–THF to afford II-**3** (0.4 g, 20%). *Anal.* Calcd for $C_{18}H_{17}N_4ClO$: C, 63.44; H, 5.03; N, 16.44. Found: C, 63.14; H, 5.21; N, 16.73. IR (Nujol): 3130, 3070, 1680, 1580 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.32 (3H, s), 2.98 (4H, s), 6.61 (1H, dd, J=2, 7 Hz), 6.93 (1H, dd, J=2, 8 Hz), 7.07 (1H, d, J=8 Hz), 7.10—7.29 (4H, m), 7.51 (1H, s), 8.26 (1H, d, J=7 Hz).

2-Amino-6-[2-(3-chloro-7-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-5) A mixture of II-**3** (0.7 g, 2.4 mmol) and *N*-chlorosuccinimide (NCS) (0.3 g, 2.4 mmol) in dioxane (7 ml)–$CHCl_3$ (7 ml) was stirred for 24 h at room temperature. The resulting precipitate was collected by filtration, washed with dioxane and recrystallized from EtOH to afford II-**5** (0.3 g, 42%). IR (Nujol): 1670 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.38 (3H, s), 3.01 (4H, s), 6.85 (1H, dd, J=2, 7 Hz), 6.93—7.13 (3H, m), 7.21 (2H, s), 7.33 (1H, d, J=2 Hz), 8.09 (1H, d, J=7 Hz).

2-Amino-6-[2-(3-hydroxymethyl-7-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-7) $NaBH_4$ (160 mg, 4.1 mmol) was added in portions to a solution of 2-amino-6-[2-(3-formyl-7-methylimidazo[1,2-*a*]-pyridin-2-yl)ethyl]benzoxazole (II-**6**) (0.65 g, 2.0 mmol) in MeOH (20 ml) under ice-cooling. After being stirred for 23 h at room temperature, the solvent was evaporated *in vacuo*. H_2O was added to the residue and the mixture was neutralized with 1 N HCl. The resulting precipitate was collected, washed with H_2O and recrystallized from MeOH–dioxane–IPE to afford II-**7** (0.17 g, 26%). IR (Nujol): 3340, 3280, 3125, 1680, 1650 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 2.35 (3H, s), 2.96 (4H, s), 4.61 (2H, d, J=4 Hz), 4.96 (1H, t, J=4 Hz), 6.72 (1H, dd, J=2, 7 Hz), 6.91 (1H, dd, J=1.5, 8 Hz), 7.07 (1H, d, J=8 Hz), 7.16 (1H, d, J=1.5 Hz), 7.21 (2H, s), 7.24 (1H, d, J=2 Hz), 8.18 (1H, d, J=7 Hz).

2-Amino-6-[2-(7-chloromethyl-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (89) A mixture of 2-amino-6-[2-(7-hydroxymethyl-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-**15**) (0.50 g, 1.6 mmol) and $SOCl_2$ (5 ml) was stirred for 40 min under ice-cooling. After the reaction mixture was poured into ice-H_2O, the solution was adjusted to pH 8 with 20% aqueous K_2CO_3 and extracted with AcOEt–THF. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with Et_2O to afford **89** (0.42 g, 79%), mp > 300 °C (EtOH–*n*-hexane). *Anal.* Calcd for $C_{18}H_{17}N_4ClO$: C, 63.44; H, 5.03; N, 16.44. Found: C, 63.14; H, 5.21; N, 16.72. IR (Nujol): 1675, 1615, 1570 cm^{-1}. ^{1}H-NMR (D_2O–DCl) δ: 2.31 (3H, s), 3.23 (4H, s), 4.94 (2H, s), 7.21 (1H, d, J=7 Hz), 7.23—7.48 (2H, m), 7.58 (1H, dd, J=2, 7 Hz), 7.95 (1H, s), 8.45 (1H, d, J=7 Hz).

2-Amino-6-[2-(7-methoxymethyl-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-16) A mixture of **89** (0.40 g, 1.2 mmol) and NaOMe (0.13 g. 2.4 mmol) in MeOH (10 ml) was stirred for 3 h at 40—50 °C. The solvent was evaporated *in vacuo* and the residue was dissolved in AcOEt–THF. The solution was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–MeOH (9 : 1) to give crystals which were recrystallized from EtOH–AcOEt to afford II-**16** (0.19 g, 49%). IR (Nujol): 1670, 1570 cm^{-1}. ^{1}H-NMR (D_2O–DCl) δ: 2.26 (3H, s), 3.17 (4H, m), 3.52 (3H, s), 4.73 (2H, s), 7.16 (1H, d, J=8 Hz), 7.19 (1H, d, J=8 Hz), 7.34 (1H, s), 7.36 (1H, dd, J=2, 8 Hz), 7.72 (1H, s), 8.32 (1H, d, J=8 Hz).

2-Amino-6-[2-(7-azidomethyl-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (90) A mixture of **89** (1.3 g, 3.8 mmol), NaN_3 (0.5 g, 7.7 mmol) and KI (1.3 g, 7.8 mmol) in DMF (26 ml) was stirred for 17 h at room temperature. The reaction mixture was poured into H_2O and extracted with AcOEt–THF. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with Et_2O to afford **90** (1.2 g, 92%), mp 207—209 °C (EtOH–*n*-hexane). *Anal.* Calcd for $C_{18}H_{17}N_7O \cdot H_2O$: C, 59.17; H, 5.24; N, 26.83. Found: C, 59.09; H, 5.27; N, 26.70. IR (Nujol): 2100, 1670, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.26 (3H, s), 2.97 (4H, s), 4.49 (2H, s), 6.70—7.02 (2H, m), 7.04 (1H, d, J=8 Hz), 7.12 (1H, s), 7.19 (2H, s), 7.45 (1H, s), 8.11 (1H, d, J=7 Hz). MS *m/z*: 347 (M^+).

2-Amino-6-[2-(7-aminomethyl-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-18) A solution of **90** (1.0 g, 2.9 mmol) in MeOH (100 ml) was hydrogenated over 10% Pd–C (0.3 g) at room temperature under atmospheric pressure of H_2. After removal of the catalyst and solvent, the residue was chromatographed on alumina eluting with $CHCl_3$–MeOH (4 : 1) to give crystals which were recrystallized from IPE–MeOH to afford II-**18** (0.37 g, 40%). IR (Nujol): 1680, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.21 (3H, s), 2.93 (4H, s), 3.72 (2H, s), 6.78 (1H, d, J=7 Hz), 6.83 (1H, d, J=8 Hz), 7.00 (1H, d, J=8 Hz), 7.07 (1H, s), 7.16 (2H, s), 7.30 (1H, s), 7.96 (1H, d, J=7 Hz).

2-Amino-6-[2-(7-amino-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-17) A mixture of 2-amino-6-[2-(3-methyl-7-*tert*-butoxycarbonylaminoimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (0.8 g, 2.0 mmol) and conc. HCl (0.9 ml, 9.8 mmol) in EtOH (20 ml) was refluxed for 1 h with stirring. After the mixture was cooled in an ice bath, the resulting precipitate was collected by filtration, then dissolved in AcOEt–THF, and the mixture was adjusted to pH 8.5 with 20% aqueous K_2CO_3. The separated organic layer was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was triturated with AcOEt to give a product which was recrystallized from MeCN–THF to afford II-**17** (0.21 g, 35%). IR (Nujol): 3370, 3220, 1680, 1650, 1575 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.12 (3H, s), 2.84 (4H, s), 5.47 (2H, br s), 6.18—6.40 (1H, m), 6.29 (1H, s), 6.84 (1H, dd, J=2, 8 Hz), 6.85—7.20 (2H, m), 7.16 (2H, s), 7.71 (1H, d, J=8 Hz).

2-Amino-6-[2-(7-carboxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-19) A mixture of 2-amino-6-[2-(7-methoxycarbonyl-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-**20**) (0.80 g, 2.3 mmol) and 1 N NaOH (6.8 ml, 6.8 mmol) in MeOH (8 ml) was stirred for 20 h at room temperature. After H_2O was added to the reaction mixture, the solution was adjusted to pH 5 with 4 N HCl. The resulting precipitate was collected by filtration to afford II-**19** (0.24 g, 31%). IR (Nujol): 3280, 1690 cm^{-1}. ^{1}H-NMR (CF_3COOH) δ: 2.60 (3H, s), 3.40 (4H, s), 7.21—7.64 (3H, m), 8.16 (1H, d, J=7 Hz), 8.52 (1H, d, J=7 Hz), 8.69 (1H, s).

2-Acetamido-6-[2-(7-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-38) A solution of AcCl (1.9 g, 25 mmol) in CH_2Cl_2 (6 ml) was added dropwise to a solution of 2-amino-6-[2-(7-methylimidazo[1,2-*a*]-

pyridin-2-yl)ethyl]benzoxazole (free base of II-**3**) (6.0 g, 21 mmol) and pyridine (4.9 ml, 62 mmol) in CH_2Cl_2 (60 ml) with stirring at 0 °C. The mixture was stirred for 2 h at the same temperature and a further 22 h at room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and stirred for 1.5 h at 0 °C. The precipitate separated was collected by filtration, washed with H_2O and recrystallized from EtOH–Et_2O to afford II-**38** (4.0 g, 58%). IR (Nujol): 3125, 1700, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 2.33 (3H, s), 3.07 (4H, s), 6.65 (1H, dd, J=2, 7 Hz), 7.08—7.55 (5H, m), 8.29 (1H, d, J=7 Hz), 11.50 (1H, br s).

2-Ethylamino-6-[2-(7-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-30) (1) Cyclization Route: A mixture of **53** (17.5 g, 52 mmol) and PPE (170 g) was stirred at 110 to 120 °C for 1 h. After the reaction mixture was dissolved in AcOEt–THF–H_2O, the solution was adjusted to pH 8 with K_2CO_3. The organic layer separated was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with $CHCl_3$ to give crystals which were recrystallized from MeCN to afford II-**30** (1.3 g, 9%). IR (Nujol): 3150, 1650, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7 Hz), 2.31 (3H, s), 2.97 (4H, s), 3.10—3.51 (2H, m), 6.61 (1H, dd, J=2, 7 Hz), 6.93 (1H, dd, J=2, 7 Hz), 7.10 (1H, d, J=7 Hz), 7.18 (2H, s), 7.50 (1H, s), 7.70 (1H, t, J=5 Hz), 8.26 (1H, d, J=7 Hz).

(II-**30**) (2) Reduction Route: $LiAlH_4$ (40 mg, 1.1 mmol) was added in portions to a solution of II-**38** (700 mg, 2.1 mmol) in THF (14 ml) under cooling in an ice bath. Afterwards, the mixture was stirred for 5 h at room temperature, poured into cold H_2O 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 $CHCl_3$–MeOH (50 : 1) to give crystals which were recrystallized from MeCN to afford II-**30** (350 mg, 52%).

2-[2-(4-Amino-3-hydroxyphenyl)ethyl]-7-hydroxy-3-methylimidazo[1,2-*a*]pyridine (42) This compound was prepared from **24** in a manner similar to that described for **35** and was not recrystallized because of its instability. Yield 100%. An analytical sample was obtained by washing with Et_2O. *Anal.* Calcd for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.92; H, 6.03; N, 14.85. IR (Nujol): 1660, 1640, 1590 cm^{-1}. MS *m/z*: 283 (M^+).

2-Amino-6-[2-(7-hydroxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]-benzoxazole (II-9) This compound was prepared from **42** in a manner similar to that described for II-**3**. Yield 23%. IR (Nujol): 1660, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.16 (3H, s), 2.89 (4H, s), 6.48 (1H, dd, J=2, 7 Hz), 6.57 (1H, s), 6.90 (1H, d, J=8 Hz), 6.90—7.33 (4H, m), 7.92 (1H, d, J=7 Hz).

6-[2-(7-Acetoxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]-2-amino-benzoxazole (II-14) AcCl (1.2 ml, 17 mmol) was added dropwise to a mixture of II-**9** (1.8 g, 5.8 mmol) and Et_3N (2.4 ml, 17 mmol) in CH_2Cl_2 (36 ml) under ice-cooling. After the mixture was stirred for 15 h at room temperature, it was added to AcOEt–THF. The solution was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from EtOH–*n*-hexane to afford II-**14** (0.24 g, 12%). IR (Nujol): 3240, 1755, 1680, 1575 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.26 (3H, s), 2.32 (3H, s), 2.98 (4H, s), 6.80 (1H, dd, J=2, 7 Hz), 6.95—7.43 (4H, m), 7.27 (2H, s), 8.19 (1H, d, J=7 Hz).

2-Acetamido-6-[2-(7-acetoxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]-benzoxazole (II-45) AcCl (1.4 ml, 20 mmol) was added dropwise to a mixture of II-**9** (1.5 g, 4.9 mmol) and pyridine (1.6 ml, 20 mmol) in CH_2Cl_2 (30 ml) under ice-cooling and the mixture was stirred for 24 h at room temperature. The resulting mixture was poured into H_2O, adjusted to pH 8 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 EtOH–*n*-hexane to afford II-**45** (1.2 g, 64%). IR (Nujol): 1770, 1695, 1625, 1575 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 2.25 (3H, s), 2.30 (3H, s), 3.02 (4H, s), 6.75 (1H, dd, J=2, 7 Hz), 7.10 (1H, d, J=8 Hz), 7.23 (1H, d, J=2 Hz), 7.41 (1H, d, J=8 Hz), 7.42 (1H, s), 8.13 (1H, d, J=7 Hz).

2-Acetamido-6-[2-(7-hydroxy-3-methylimidazo[1,2-*a*]pyridin-2-yl)-ethyl]benzoxazole (II-42) Compound II-**45** (0.50 g, 1.3 mmol) was adsorbed on a silica gel (10 g) column. After 15 h, the column was eluted with MeOH–$CHCl_3$ (1 : 9 to 1 : 3). The fractions containing the desired product were concentrated and the residue was dissolved in AcOEt–THF–H_2O. The mixture was adjusted to pH 7.5 with saturated aqueous $NaHCO_3$. The organic layer separated was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crystals which were recrystallized from AcOEt–THF–H_2O to afford II-**42** (0.17 g, 38%). IR (Nujol): 3350 (br), 1725, 1660, 1640, 1580 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.23 (6H, s), 3.06 (4H, s), 6.81 (1H, d, J=7 Hz), 6.88 (1H, s), 7.16 (1H, d, J=8 Hz), 7.48 (1H, d, J=8 Hz), 7.51 (1H, s), 8.18 (1H, d, J=7 Hz).

2-Acetamido-6-[2-(3-dimethylaminomethyl-7-methylimidazo[1,2-*a*]-pyridin-2-yl)ethyl]benzoxazole (II-41) A solution of II-**38** (700 mg, 2.1 mmol), $Me_2NH \cdot HCl$ (205 mg, 2.5 mmol) and 37% aqueous HCHO (0.23 ml, 3.1 mmol) in AcOH (7 ml) was stirred at 50 °C for 15 h. After the solvent was evaporated *in vacuo*, saturated aqueous $NaHCO_3$ was added to the residue and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–MeOH (20 : 1) to give crystals which were recrystallized from EtOH–*n*-hexane to afford II-**41** (130 mg, 16%). IR (Nujol): 1715, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.01 (6H, s), 2.20 (3H, s), 2.34 (3H, s), 2.85—3.11 (4H, m), 3.53 (2H, s), 6.71 (1H, dd, J=2, 7 Hz), 7.08—7.44 (4H, m), 8.14 (1H, d, J=7 Hz).

2-Dimethylamino-6-[2-(3,7-dimethylimidazo[1,2-*a*]pyridin-2-yl)ethyl]-benzoxazole (II-56) A mixture of 2-[2-(4-amino-3-hydroxyphenyl)ethyl]-3,7-dimethylimidazo[1,2-*a*]pyridine (**36**) (2.5 g, 8.9 mmol) and (dichloromethylene)dimethylammonium chloride (1.4 g, 8.9 mmol) in $CHCl_3$ (100 ml) was refluxed for 2.5 h. After H_2O (100 ml) was added to the reaction mixture, the aqueous layer separated was adjusted to pH 8 with K_2CO_3 and extracted with AcOEt–THF. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was extracted with $CHCl_3$ (30 ml) under reflux. The $CHCl_3$ solution was concentrated *in vacuo* to give a crude product which was purified by silica gel column chromatography with $CHCl_3$ and recrystallization from AcOEt–*n*-hexane to afford II-**56** (0.27 g, 9%). IR (Nujol): 1660, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 2.32 (3H, s), 2.93 (4H, s), 3.08 (6H, s), 6.65 (1H, dd, J=2, 7 Hz), 6.89 (1H, dd, J=2, 8 Hz), 7.08 (1H, d, J=8 Hz), 7.08—7.23 (2H, m), 7.95 (1H, d, J=7 Hz).

2-Dimethylaminomethyleneamino-6-[2-(7-methylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-57) Compound II-**38** (2.2 g, 6.6 mmol) was added in small portions to a solution of $POCl_3$ (1.8 ml, 20 mmol) in DMF (20 ml) at room temperature with stirring. After being stirred for 1 h, the mixture was diluted with H_2O (200 ml) and stirred for an additional 30 min. The mixture was basified with 20% aqueous K_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$–MeOH (50 : 1) to give crystals which were recrystallized from MeOH–IPE to afford II-**57** (0.31 g, 14%). IR (Nujol): 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 3.05 (6H, s), 3.18 (4H, s), 6.65 (1H, dd, J=2, 7 Hz), 7.07 (1H, dd, J=1.5, 9 Hz), 7.23—7.37 (3H, m), 7.57 (1H, s), 8.32 (1H, d, J=7 Hz), 8.62 (1H, s).

Potassium 6-[2-(3,7-dimethylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazol-2-thiolate (95) A mixture of **36** (10 g, 36 mmol) and potassium ethylxanthogenate (6.3 g, 39 mmol) in EtOH (80 ml) was refluxed for 3 h with stirring. After cooling, the resulting precipitate was collected by filtration to afford **95** (8.3 g, 65%). mp >300 °C (EtOH–*n*-hexane). *Anal.* Calcd for $C_{18}H_{16}KN_3OS \cdot 1/2H_2O$: C, 58.35; H, 4.62; N, 11.34. Found: C, 58.19; H, 4.60; N, 11.14. IR (Nujol): 1645, 1065 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 2.33 (3H, s), 2.95 (4H, s), 6.70 (1H, dd, J=2, 7 Hz), 6.85 (1H, d, J=2 Hz), 6.88 (1H, d, J=7 Hz), 6.99 (1H, d, J=7 Hz), 7.27 (1H, d, J=2 Hz), 8.01 (1H, d, J=7 Hz).

Potassium 6-[2-(3,7-Dimethylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazol-2-sulfonate (96) A solution of $KMnO_4$ (5.3 g, 33 mmol) in H_2O (123 ml) was added dropwise to a solution of **95** (6.0 g, 17 mmol) in H_2O (80 ml) at 5—10 °C with stirring. After being stirred for 1 h at the same temperature, the mixture was concentrated to one half of the original volume, then mixed with H_2O (50 ml)–CH_2Cl_2 (50 ml). The resulting precipitate was collected by filtration to afford **96** (4.5 g, 65%). mp >300 °C (THF–H_2O). *Anal.* Calcd for $C_{18}H_{16}KN_3O_4S \cdot H_2O$: C, 50.57; H, 4.24; N, 9.83. Found: C, 50.95; H, 4.49; N, 10.14. IR (Nujol): 1635, 1270, 1260, 1250, 1145, 670 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 2.35 (3H, s), 3.07 (4H, s), 6.70 (1H, dd, J=2, 7 Hz), 7.23 (1H, dd, J=2, 7 Hz), 7.25 (1H, d, J=2 Hz), 7.55 (1H, d, J=2 Hz), 7.64 (1H, d, J=7 Hz), 7.99 (1H, d, J=7 Hz).

2-Diaminomethyleneamino-6-[2-(3,7-dimethylimidazo[1,2-*a*]pyridin-2-yl)ethyl]benzoxazole (II-58) A mixture of **95** (1.1 g, 2.7 mmol) and guanidine hydrochloride (0.26 g, 2.7 mmol) in DMF (12 ml) was stirred for 4 h at room temperature. The reaction mixture was poured into H_2O (110 ml)–AcOEt (20 ml). The resulting precipitate was collected by filtration, washed with H_2O and recrystallized from EtOH to afford II-**58** (0.31 g, 33%). IR (Nujol): 3475, 3225, 3125, 1660, 1650, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 2.35 (3H, s), 3.00 (4H, s), 6.70 (1H, dd, J=2, 7 Hz), 6.93 (1H, dd, J=2, 8 Hz), 7.18 (6H, br s), 7.20 (1H, d, J=8 Hz), 8.00 (1H, d, J=7 Hz).

6-[2-(3,7-Dimethylimidazo[1,2-*a*]pyridin-2-yl)ethyl]-2-methylthiobenzoxazole (II-62) MeI (0.38 ml, 6.1 mmol) was added dropwise to a solution of **95** (2.0 g, 5.5 mmol) in MeOH (30 ml) under ice-water cooling. After being stirred for 3 h keeping the temperature below 5 °C, the reaction mixture was concentrated to dryness. The residue was mixed with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from AcOEt–*n*-hexane to afford II-**62** (1.3 g, 70%). IR (Nujol): 1650, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 2.33 (3H, s), 2.75 (3H, s), 2.95—3.10 (4H, m), 6.67 (1H, dd, J=2, 7 Hz), 7.15 (1H, dd, J=2, 7 Hz), 7.23 (1H, d, J=2 Hz), 7.45 (1H, d, J=2 Hz), 7.50 (1H, d, J=8 Hz), 7.98 (1H, d, J=7 Hz).

2-[2-(4-Acetamido-3-hydroxyphenyl)ethyl]-3,7-dimethylimidazo[1,2-*a*]pyridine (93) Acetyl chloride (1.5 ml, 2.1 mmol) was added dropwise to a mixture of **36** (5.0 g, 18 mmol) and $NaHCO_3$ (3.0 g, 36 mmol) in acetone (30 ml)–H_2O (30 ml) for 10 min under ice-cooling. After being stirred for 30 min at the same temperature, AcOEt–THF–H_2O was added to the mixture. The organic layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to afford **93** (3.5 g, 61%). mp 211—213 °C (MeCN). *Anal.* Calcd for $C_{19}H_{21}N_3O_2$: C, 70.56; H, 6.55; N, 13.00. Found: C, 70.70; H, 6.50; N, 12.70. IR (Nujol): 3420, 1675, 1650, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.08 (3H, s), 2.24 (3H, s), 2.34 (3H, s), 2.86 (4H, s), 6.51—6.84 (2H, m), 6.69 (1H, s), 7.24 (1H, s), 7.51 (1H, d, J=8 Hz), 8.02 (1H, d, J=7 Hz), 9.30 (1H, s).

6-[2-(3,7-Dimethylimidazo[1,2-*a*]pyridin-2-yl)ethyl]-2-methylbenzoxazole (II-59) A mixture of **93** (2.5 g, 7.7 mmol) and $POCl_3$ (1.4 ml, 16 mmol) in sulfolane (25 ml) was stirred for 1 h at 100 °C. The reaction mixture was added to H_2O–AcOEt. The aqueous layer separated was adjusted to pH 8 with K_2CO_3 and extracted with AcOEt–THF. The extract 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) to give crystals which were recrystallized from Et_2O–AcOEt to afford II-**59** (0.67 g, 28%). IR (Nujol): 1645, 1615, 1575 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.21 (3H, s), 2.33 (3H, s), 2.57 (3H, s), 3.03 (4H, s), 6.66 (1H, d, J=7 Hz), 7.12 (1H, d, J=8 Hz), 7.21 (1H, s), 7.43 (1H, s), 7.47 (1H, d, J=8 Hz), 7.97 (1H, d, J=7 Hz).

6-[2-(3,7-Dimethylimidazo[1,2-*a*]pyridin-2-yl)ethyl]-2-hydroxybenzoxazole (II-61) A solution of II-**4** (0.60 g, 1.6 mmol) in 1 N HCl (4.8 ml, 4.8 mmol) was refluxed for 40 min with stirring. The resulting precipitate was collected by filtration and suspended in H_2O. After the mixture was adjusted to pH 8, the insoluble material was collected, washed with H_2O and recrystallized from IPE–MeOH to afford II-**61** (0.28 g, 57%). IR (Nujol): 3440, 1790, 1760, 1650 cm^{-1}. ^{1}H-NMR (CF_3COOH) δ: 2.40 (3H, s), 2.68 (3H, s), 3.27 (4H, s), 7.08—7.52 (4H, m), 7.66 (1H, s), 8.22 (1H, d, J=7 Hz), 9.74 (1H, br s).

2-Amino-6-benzoyloxybenzoxazole Hydrobromide (66) A solution of 5-benzoyloxy-2-nitrophenol (**64**)[10] (9.0 g, 35 mmol) in MeOH (180 ml) was hydrogenated over 10% Pd–C (0.9 g) under the atmospheric pressure of H_2 at room temperature. After the catalyst was removed by filtration, BrCN (3.7 g, 35 mmol) was added to the filtrate and the solution was stirred for 7 h at room temperature. The solvent was evaporated *in vacuo* and the residue was recrystallized from IPE–MeOH to afford **66** (5.6 g, 48%). mp 225—226 °C (IPE–MeOH). *Anal.* Calcd for $C_{14}H_{10}N_2O_3 \cdot HBr$: C, 50.17; H, 3.31; N, 8.36. Found: C, 49.95; H, 3.26; N, 8.44. IR (Nujol): 3440, 3350, 3200, 1730, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.27 (1H, dd, J=2, 8 Hz), 7.40 (1H, s), 7.50—7.82 (4H, m), 8.07—8.25 (2H, m). MS m/z: 254 (M^+).

2-Acetamido-6-benzoyloxybenzoxazole (67) AcCl (7.1 ml, 99 mmol) was added dropwise to a solution of **66** (21.1 g, 63 mmol) and pyridine (26.6 ml, 328 mmol) in CH_2Cl_2 (410 ml) under ice-cooling. After the mixture was stirred for 6 h at room temperature, saturated aqueous $NaHCO_3$ (200 ml) and IPE (500 ml) was added to the reaction mixture. The resulting precipitate was collected by filtration to afford **67** (11.5 g, 62%). mp 212—213 °C (IPE–MeOH). *Anal.* Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.88; H, 3.97; N, 9.36. IR (Nujol): 3175, 3140, 1710 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.27 (3H, s), 7.18—8.27 (8H, m), 11.53 (1H, s). MS m/z: 296 (M^+).

2-Acetamido-6-hydroxybenzoxazole (68) A solution of **67** (4.0 g, 14 mmol) and 1 N NaOH (14 ml, 14 mmol) in MeOH (80 ml) was stirred for 2 h at room temperature. The solution was adjusted to pH 7 with 6 N HCl and the resulting precipitate was collected by filtration to afford **68** (1.6 g, 62%). mp 251—252 °C (MeOH–THF). *Anal.* Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.41; H, 3.98; N, 14.43. IR (Nujol): 3255, 3140, 1710, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 6.78 (1H, dd, J=2, 8 Hz), 7.00 (1H, d, J=2 Hz), 7.40 (1H, d, J=8 Hz), 10.00 (1H, br s). MS m/z: 192 (M^+).

2-Chloromethyl-7-methylimidazo[1,2-*a*]pyridine (69) A solution of 1,3-dichloroacetone (30 g, 240 mmol) and 2-amino-4-methylpyridine (64 g, 590 mmol) in MeCN (210 ml) was refluxed for 1 h. After the solvent was evaporated *in vacuo*, the residue was chromatographed on silica gel eluting with CH_2Cl_2–AcOEt (1 : 1) to afford **69** (10 g, 24%). mp 91—93 °C (EtOH–*n*-hexane). *Anal.* Calcd for $C_9H_9ClN_2$: C, 59.84; H, 5.02; N, 15.51. Found: C, 59.55; H, 5.19; N, 15.37. IR (Nujol): 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.34 (3H, s), 4.82 (2H, s), 6.74 (1H, dd, J=2, 7 Hz), 7.30 (1H, s), 7.90 (1H, s), 8.39 (1H, d, J=7 Hz).

2-Acetamido-6-[(7-methylimidazo[1,2-*a*]pyridin-2-yl)methoxy]benzoxazole (III) Methanolic NaOMe (28%, 1.3 g, 6.5 mmol) was added to a solution of **68** (1.3 g, 6.5 mmol) and **69** (1.4 g, 7.8 mmol) in DMF (25 ml). After being stirred at 50 °C for 17 h, the reaction mixture was concentrated to dryness. The residue was added to H_2O 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 $CHCl_3$–MeOH (50 : 1), and the product obtained was recrystallized from dioxane–IPE–MeOH to afford III (0.22 g, 10%). IR (Nujol): 3140, 3075, 1675, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.29 (3H, s), 2.46 (3H, s), 5.17 (2H, s), 6.66 (1H, dd, J=1.5, 7 Hz), 6.78 (1H, dd, J=2, 8 Hz), 6.99 (1H, d, J=2 Hz), 7.20 (1H, d, J=1.5 Hz), 7.43 (1H, d, J=8 Hz), 7.70 (1H, s), 8.32 (1H, d, J=7 Hz), 9.68 (1H, br s).

2-Ethylamino-6-methylbenzoxazole (78) A mixture of 2-(3-ethyl)ureido-5-methylphenol (**75**) (31 g, 16 mmol) and PPE (210 g) was stirred at 120 °C for 2.5 h. Afterwards, the mixture was poured into cold H_2O, 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 triturated with IPE to afford **78** (22 g, 75%). mp 100—101 °C (AcOEt–*n*-hexane). *Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.20; H, 6.88; N, 15.82. IR (Nujol): 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7 Hz), 2.32 (3H, s), 3.10—3.53 (2H, m), 6.87 (1H, dd, J=2, 8 Hz), 7.10 (1H, d, J=8 Hz), 7.12 (1H, d, J=2 Hz), 7.68 (1H, t, J=5 Hz). MS m/z: 176 (M^+).

2-(*N*-Ethylformamido)-6-methylbenzoxazole (81) A solution of Ac_2O (6.4 ml, 68 mmol) and HCOOH (2.6 ml, 68 mmol) was stirred at 50 °C for 30 min. After the solution was cooled in an ice-bath, THF (10 ml) and **78** (4.0 g, 23 mmol) were added and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was poured into H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with IPE to afford **81** (3.0 g, 65%). mp 118—119 °C (IPE–MeOH). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.99; H, 5.98; N, 13.65. IR (Nujol): 1690, 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (3H, t, J=7 Hz), 2.41 (3H, s), 3.92 (2H, q, J=7 Hz), 7.16 (1H, dd, J=2, 8 Hz), 7.42 (1H, d, J=2 Hz), 7.48 (1H, d, J=8 Hz), 9.17 (1H, s).

6-Bromomethyl-2-(*N*-ethylformamido)benzoxazole (84) A mixture of **81** (7.6 g, 37 mmol), NBS (6.6 g, 37 mmol) and benzoyl peroxide (0.20 g, 0.83 mmol) in benzene (150 ml) was refluxed for 70 min. The cooled reaction mixture was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with IPE–*n*-hexane to afford **84** (6.2 g, 59%). mp 98—100 °C (AcOEt–*n*-hexane). *Anal.* Calcd for $C_{11}H_{11}BrN_2O_2$: C, 46.67; H, 3.92; N, 9.89. Found: C, 46.49; H, 4.15; N, 9.77. IR (Nujol): 1705, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7 Hz), 3.95 (2H, q, J=7 Hz), 4.86 (2H, s), 7.34—7.63 (2H, m), 7.77 (1H, d, J=2 Hz), 9.24 (1H, s).

2-Mercaptomethyl-7-methylimidazo[1,2-*a*]pyridine (85) (1) A mixture of **69** (5.0 g, 28 mmol) and thiourea (2.2 g, 28 mmol) in EtOH (10 ml) was refluxed for 20 min. The mixture was added to AcOEt (100 ml) and the resulting precipitate was collected by filtration and washed with AcOEt to give *S*-(7-methylimidazo[1,2-*a*]pyridin-2-ylmethyl)isothiourea hydrochloride (7.1 g, 100%), mp 170—172 °C. IR (Nujol): 1665, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.34 (3H, s), 4.54 (2H, s), 6.66 (1H, dd, J=2, 7 Hz), 7.10 (1H, s), 7.67 (1H, s), 8.02 (1H, d, J=7 Hz).

(2) A mixture of *S*-(7-methylimidazo[1,2-*a*]pyridin-2-ylethyl)isothiourea hydrochloride (7.7 g, 30 mmol) and NaOH (1.2 g, 30 mmol) in H_2O (54 ml) was refluxed for 2 h with stirring. The cooled reaction mixture was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to afford **85** (4.2 g, 79%). mp 176—177 °C. *Anal.* Calcd for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.72. Found: C, 60.74; H, 5.54; N, 15.96. IR (Nujol): 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 4.00 (2H, s), 6.72 (1H, dd, J=2, 7 Hz), 7.28 (1H, s), 7.77 (1H, s), 8.38 (1H, d, J=7 Hz).

2-(*N*-Ethylformamido)-6-[(7-methylimidazo[1,2-*a*]pyridin-2-yl)methylthiomethyl]benzoxazole (88) A mixture of **84** (1.4 g, 4.9 mmol), **85** (0.80 g,

4.5 mmol) and K_2CO_3 (0.50 g, 3.6 mmol) in DMF (8 ml) was stirred for 2 h under ice-cooling. The reaction mixture was poured into H_2O (40 ml) 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 $CHCl_3$–MeOH (39 : 1) to afford **88** (0.78 g, 46%). mp 116—118 °C (IPE–MeOH). *Anal.* Calcd for $C_{20}H_{20}N_4O_2S$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.29; N, 14.52. IR (Nujol): 1695, 1649, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7 Hz), 2.31 (3H, s), 3.70 (2H, s), 3.90 (2H, s), 3.92 (2H, q, J=7 Hz), 6.66 (1H, dd, J=2, 7 Hz), 7.23 (1H, s), 7.31 (1H, dd, J=2, 8 Hz), 7.52 (1H, d, J=8 Hz), 7.59 (1H, s), 7.69 (1H, s), 8.30 (1H, d, J=7 Hz), 9.18 (1H, s).

2-Ethylamino-6-[(7-methylimidazo[1,2-*a*]pyridin-2-yl)methylthiomethyl]benzoxazole (IV-3) A solution of **88** (0.60 g, 1.6 mmol) and conc. HCl (0.70 ml, 7.9 mmol) in MeOH (12 ml) was stirred for 3 h at room temperature. The solvent was evaporated *in vacuo* and the residue was added to AcOEt–THF–H_2O. After the mixture was adjusted to pH 8 with 20% aqueous K_2CO_3, the organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$ to give a product which was triturated with Et_2O, and then recrystallized from MeCN to afford IV-3 (0.37 g, 66%). IR (Nujol): 1665, 1640, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7 Hz), 2.33 (3H, s), 3.13—3.51 (2H, m), 3.69 (2H, s), 3.82 (2H, s), 6.66 (1H, dd, J=2, 7 Hz), 6.98—7.14 (2H, m), 7.14—7.38 (2H, m), 7.69 (1H, s), 7.80 (1H, t, J=5 Hz), 8.29 (1H, d, J=7 Hz).

Biological Test Histamine H_2-Receptor Antagonist Activity[13] The atrial strip isolated from guinea pig was suspended under an initial tension of 0.3 to 0.6 g in an organ bath containing Thyrode solution at 30 °C, and aerated by 95% O_2–5% CO_2 gas. The beating rate and amplitude of contraction of the atrium were recorded by means of a transducer and a polygraph. Histamine hydrochloride (1×10^{-6} g/ml) was added to the bathing fluid and the increase in beating rate after dosing was measured. Addition of test compounds was done 30 min after washing out the histamine hydrochloride. The inhibitory effect of the test compound was calculated by comparing histamine-induced increases in beating rate before and 30 min after dosing with the test compounds.

Gastric Acid Antisecretory Activity (Histamine-Stimulated Acid Secretion)[14] Male Sprague-Dawley rats weighing about 250 g were used. Rats were deprived of food but allowed free access to water for 24 h. The animals were anesthetized with 1.25 g/kg urethane intraperitoneally. The abdomen was opened and the gastric lumen was perfused with saline throughout the experiment. The perfusate was titrated by an autotitrator with 25 mM NaOH as a titrant. Gastric secretion was stimulated by intravenous infusion with histamine (3 mg/kg/h). After reaching a plateau, the test compound (1 mg/kg) was given intravenously. The effect of the drug was expressed as maximal inhibition by acid output.

Gastric Acid Antisecretory Activity (Basal Acid Secretion)[16] Male Sprague-Dawley rats, weighing about 110 g, were deprived of food but had free access to water for 24 h. The pylorus of the stomach was ligated under ether anesthesia. The test compound was administered intraduodenally just after the pyloric ligation. Four hours later, the animals were sacrificed and gastric contents were collected. The volume of samples was measured and the acidity was titrated with 0.1 N NaOH to pH 7.0 using an automatic titrator. Both the volume of gastric fluid and the total gastric acid output in the treated animals were compared with those in the control animals, and the percent inhibition for each dose was calculated.

Antiulcer Activities Restraint and water-immersed stress ulcer (stress ulcer) and ethanol-induced gastric lesion (ethanol ulcer; cytoprotective activity) were evaluated by the methods described in literature,[15,17] and in our previous paper.[19]

The ED_{50} values, the dose required for 50% inhibition of the ulcer index and the gastric acid output, were estimated according to the method of Litchfield and Wilcoxon.[20]

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