Synthesis of 2-[[(4-Fluoroalkoxy-2-pyridyl)methyl]sulfinyl]-1*H*-benzimidazoles as Antiulcer Agents

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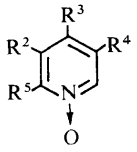
Many 2-[[(4-fluoroalkoxy-2-pyridyl)methyl]sulfinyl]-1*H*-benzimidazoles were synthesized and tested for antisecretory, antiulcer, and cytoprotective activities. Most of these compounds were superior to omeprazole in antisecretory and antiulcer potencies, and especially in protecting the gastric mucosa from ethanol-induced damage. Among these compounds, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole, AG-1749 (lansoprazole) (6f), was selected for further development and clinical evaluation.

Keywords 2-[[(4-fluoroalkoxy-2-pyridyl)methyl]sulfinyl]-1*H*-benzimidazole; 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole; AG-1749; lansoprazole; antisecretory activity; antiulcer activity; cytoprotective activity; $(H^+ + K^+)$-ATPase inhibitor

Peptic ulcers are generally thought to result from an imbalance in the aggressive forces of acid and pepsin and the defensive forces of resistance. Consequently, antiulcer therapy has been directed towards these two factors. Since the clinical success of the histamine H_2 receptor antagonist cimetidine, endeavors have been made to synthesize more potent antisecretory drugs. Recent investigations have revealed that a seires of benzimidazole derivatives, such as omeprazole, exert antisecretory activity by inhibiting $(H^+ + K^+)$-adenosine triphosphatase (ATPase) which plays an important role as a proton pump in the parietal cell.[1] $(H^+ + K^+)$-ATPase inhibitors therefore seem to be attractive drugs for the treatment of peptic ulcer diseases.[2]

Preliminary studies revealed that the $(H^+ + K^+)$-ATPase inhibitors synthesized in our laboratories were relatively unstable irrespective of their good biological activities. Also, as it is known[3] that the introduction of fluorine into a molecule increases both thermal and oxidative stability, alters chemical reactivity, and/or enhances the rate of absorption and transport, we investigated $(H^+ + K^+)$-

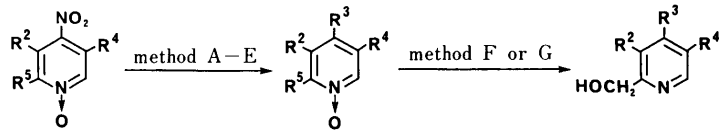
TABLE I. Pyridine *N*-Oxides



2

Compd. No.	R^2	R^3	R^4	R^5	Method[a]	Yield (%)	mp (°C) Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
2a	H	CF_3CH_2O	H	Me	A	66	148—150 MeOH–$CHCl_3$	$C_8H_8F_3NO_2$	46.39 (46.17)	3.89 4.06	6.76 6.58)
2b	Me	CF_3CH_2O	H	Me	A	94	131—132 AcOEt–hexane	$C_9H_{10}F_3NO_2$	48.87 (49.06)	4.56 4.53	6.33 6.28)
2c	H	CF_3CH_2O	Me	Me	B	54	153—154 Et_2O–hexane	$C_9H_{10}F_3NO_2$	48.87 (48.93)	4.56 4.65	6.33 6.29)
2d	Me	CF_3CH_2O	Me	H	A	90	138—139 AcOEt–hexane	$C_9H_{10}F_3NO_2$	48.87 (48.95)	4.56 4.54	6.33 6.44)
2e	H	$C_2F_5CH_2O$	H	Me	C	51	79—81 Et_2O–hexane	$C_9H_8F_5NO_2$	42.24 (42.27)	3.14 3.14	5.45 5.40)
2f	Me	$C_2F_5CH_2O$	H	Me	D	74	148—149 AcOEt–hexane	$C_{10}H_{10}F_5NO_2$	44.29 (44.27)	3.72 3.54	5.16 5.25)
2g	H	$C_2F_5CH_2O$	Me	Me	D	48	140—142 Et_2O–hexane	$C_{10}H_{10}F_5NO_2$	44.29 (44.32)	3.72 3.72	5.16 5.11)
2h	Me	$C_2F_5CH_2O$	Me	H	A	81	89—91 Et_2O–hexane	$C_{10}H_{10}F_5NO_2$	44.29 (44.19)	3.72 3.98	5.16 5.16)
2i	H	$H(CF_2)_2CH_2O$	H	Me	D	80	Oil[b]				
2j	Me	$H(CF_2)_2CH_2O$	H	Me	A	86	138—139 AcOEt–hexane	$C_{10}H_{11}F_4NO_2$	47.44 (47.33)	4.38 4.22	5.53 5.50)
2k	H	$H(CF_2)_2CH_2O$	Me	Me	B	70	143.5—144.5 AcOEt–hexane	$C_{10}H_{11}F_4NO_2$	47.44 (47.41)	4.38 4.32	5.53 5.44)
2l	Me	$F(CF_2)_3CH_2O$	H	Me	B	73	119—120 iso-Pr_2O	$C_{11}H_{10}F_7NO_2$	41.13 (41.02)	3.14 3.03	4.36 4.20)
2m	Me	$H(CF_2)_4CH_2O$	H	Me	B	81	Oil[b]				
2n	H	CCl_3CH_2O	H	Me	E	66	Oil[b]				

a) A: R^3H, *tert*-BuOK; B: R^3H, K_2CO_3, MeCN; C: R^3H, *tert*-BuOK, pyridine; D: R^3H, K_2CO_3, HMPA, MeCOEt; E: K_2CO_3, R^3H. *b*) Oily compounds were used without further purification.



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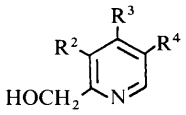
method A: *tert*-BuOK, R^3H B: K_2CO_3, R^3H, MeCN C: *tert*-BuOK, R^3H, pyridine
D: K_2CO_3, HMPA, R^3H, MeCOEt E: K_2CO_3, R^3H F: 1)Ac_2O, conc. H_2SO_4
2) aq. NaOH G: 1) Me_2SO_4 2) $(NH_4)_2S_2O_4$, MeOH–H_2O

Chart 1

TABLE II. 2-Hydroxymethylpyridines



3

Compd. No.	R^2	R^3	R^4	Method[a]	Yield (%)	mp (°C) Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
3a	H	CF_3CH_2O	H	F	89	Oil[b]				
3b	Me	CF_3CH_2O	H	F	66	93—94 iso-Pr_2O–hexane	$C_9H_{10}F_3NO_2$	48.87 (49.01	4.56 4.55	6.33 6.29)
3c	H	CF_3CH_2O	Me	F	44	117—119 Et_2O–hexane	$C_9H_{10}F_3NO_2$	48.87 (48.75	4.56 4.43	6.33 6.44)
3d	Me	CF_3CH_2O	Me	G	18	62—63 iso-Pr_2O–hexane	$C_9H_{10}F_3NO_2$	51.07 (51.14	5.14 5.23	5.96 5.98)
3e	H	$C_2F_5CH_2O$	H	F	75	Oil[b]				
3f	Me	$C_2F_5CH_2O$	H	F	64	Oil[b]				
3g	H	$C_2F_5CH_2O$	Me	F	50	87—89 iso-Pr_2O	$C_{10}H_{10}F_5NO_2$	44.29 (44.35	3.72 3.75	5.16 5.18)
3h	Me	$C_2F_5CH_2O$	Me	G	84	Oil[b]				
3i	H	$H(CF_2)_2CH_2O$	H	F	68	88—89 iso-Pr_2O	$C_9H_9F_4NO_2$	45.20 (45.24	3.79 3.71	5.86 5.87)
3j	Me	$H(CF_2)_2CH_2O$	H	F	62	67—68 iso-Pr_2O	$C_{10}H_{11}F_4NO_2$	47.44 (47.55	4.38 4.42	5.53 5.52)
3k	H	$H(CF_2)_2CH_2O$	Me	F	71	98—99 iso-Pr_2O	$C_{10}H_{11}F_4NO_2$	47.44 (47.52	4.38 4.36	5.53 5.41)
3l	Me	$F(CF_2)_3CH_2O$	H	F	64	Oil[b]				
3m	Me	$H(CF_2)_4CH_2O$	H	F	65	Oil[b]				
3n	H	CCl_3CH_2O	H	F	55	Oil[b]				

a) F: 1) Ac_2O, conc. H_2SO_4, 2) aq. NaOH; G: 1) Me_2SO_4, 2) $(NH_4)_2S_2O_4$, MeOH–H_2O. *b*) Oily compounds were used without further purification.

ATPase inhibitors containing fluorine in an attempt to find inhibitors with increased stability and improved activity. We describe in this paper the synthesis and biological activities of 2-[[(4-fluoroalkoxy-2-pyridyl)methyl]sulfinyl]-1*H*-benzimidazoles.

Synthesis As shown in Chart 1, 4-fluoroalkoxypyridine *N*-oxides (**2**) were synthesized from 4-nitropyridine *N*-oxides (**1**)[4] by methods A—E. Usually, substitution of the nitro group with a fluorinated alcohol was carried out in the presence of potassium *tert*-butoxide. However, in the case of 2,3-dimethyl-4-nitropyridine *N*-oxide and 2,2,3,3,3-pentafluoropropanol, the nitro compound was immediately decomposed by the base to give the substituted product in a poor yield. After examining several bases and solvents, a combination of potassium carbonate (K_2CO_3) and acetonitrile (CH_3CN) was found to be the best.

4-Fluoroalkoxy-2-(hydroxymethyl)pyridines (**3**) were prepared by method F or G. 4-Fluoroalkoxy-2-methylpyridine *N*-oxides (**2**: R^5 = Me) reacted with acetic anhydride (Ac_2O) to give 2-acetoxy derivatives, which were hydrolyzed with sodium hydroxide (NaOH) (method F). 2-Unsubstituted-4-fluoroalkoxypyridine *N*-oxides (**2**: R^5 = H) were treated with dimethyl sulfate (Me_2SO_4) to give *N*-methoxypyridinium salts, which were hydroxymethylated with ammonium persulfate ($(NH_4)_2S_2O_4$) in aqueous methanol (MeOH) to give **3** (method G) (Chart 1, Tables I, II).

The 2-(hydroxymethyl)pyridines (**3**) were chlorinated with thionyl chloride and then condensed with 2-mercaptobenzimidazoles (**4**)[5] to give the corresponding sulfides (**5**). The desired sulfoxides (**6**) were obtained by oxidation of the sulfides (**5**) with *m*-chloroperbenzoic acid (MCPBA) (Chart 2, Tables III, IV).

Most 2-mercaptobenzimidazoles were prepared according to previously reported methods.[5] 2-Mercapto-5-methylsulfonyl-1*H*-benzimidazole (**4**: $R^1 = MeSO_2$) was obtained from 4-methylthio-2-nitroaniline (**7**)[6] as shown in Chart 3. The nitroaniline (**7**) was oxidized with MCPBA to the sulfone (**8**), which was reduced with sodium hydro-

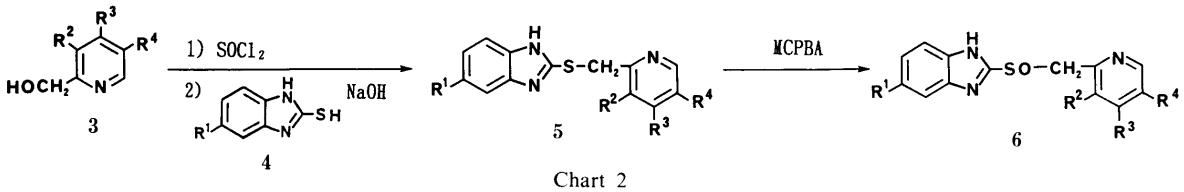
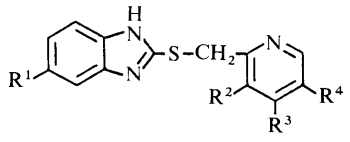


Chart 2

TABLE III. 2-[[(2-Pyridyl)methyl]thio]-1*H*-benzimidazoles



5

Compd. No.	R^1	R^2	R^3	R^4	Yield (%)	mp (°C) Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
5a	H	H	CF_3CH_2O	H	77	138—139 AcOEt–hexane	$C_{15}H_{12}F_3N_3OS$	53.09 (53.13	3.56 3.58	12.38 12.40)
5b	F	H	CF_3CH_2O	H	50	135—136 AcOEt–hexane	$C_{15}H_{11}F_4N_3OS$	50.42 (50.60	3.10 3.12	11.76 11.67)
5c	MeO	H	CF_3CH_2O	H	64	152—153 AcOEt–hexane	$C_{16}H_{14}F_3N_3O_2S$	52.03 (52.21	3.82 3.84	11.38 11.17)
5d	EtO	H	CF_3CH_2O	H	72	103—104 iso-Pr_2O	$C_{17}H_{16}F_3N_3O_2S$	53.26 (53.54	4.21 4.32	10.96 10.79)
5e	PrO	H	CF_3CH_2O	H	66	102—103 iso-Pr_2O–hexane	$C_{18}H_{18}F_3N_3O_2S$	54.40 (54.39	4.57 4.65	10.57 10.32)
5f	H	Me	CF_3CH_2O	H	96	149—150 AcOEt–hexane	$C_{16}H_{14}F_3N_3OS$	54.39 (54.44	3.99 3.88	11.89 11.98)
5g	$MeSO_2$	Me	CF_3CH_2O	H	77	124—127 AcOEt–hexane	$C_{17}H_{16}F_3N_3O_3S_2 \cdot H_2O$	45.43 (45.71	4.04 4.10	9.35 9.24)
5h	CF_3	Me	CF_3CH_2O	H	91	92—93 AcOEt–hexane	$C_{17}H_{13}F_6N_3OS \cdot H_2O$	46.47 (46.34	3.44 3.33	9.56 9.43)
5i	MeO	Me	CF_3CH_2O	H	96	159—160 AcOEt–hexane	$C_{17}H_{16}F_3N_3O_2S$	53.26 (53.31	4.21 4.29	10.96 10.96)
5j	H	H	CF_3CH_2O	Me	71	168—170 Et_2O	$C_{16}H_{14}F_3N_3OS$	54.39 (54.43	3.99 4.00	11.89 11.76)
5k	H	Me	CF_3CH_2O	Me	56	151—152 AcOEt–hexane	$C_{17}H_{16}F_3N_3OS$	55.58 (55.56	4.39 4.36	11.44 11.33)
5l	H	H	$C_2F_5CH_2O$	H	57	125—126 Et_2O–hexane	$C_{16}H_{12}F_5N_3OS$	49.33 (49.50	3.11 3.05	10.79 10.79)
5m	H	Me	$C_2F_5CH_2O$	H	80	144—145 AcOEt–hexane	$C_{17}H_{14}F_5N_3OS$	50.62 (50.62	3.50 3.58	10.42 10.26)
5n	H	H	$C_2F_5CH_2O$	Me	86	151—152 AcOEt–hexane	$C_{17}H_{14}F_5N_3OS$	50.62 (50.64	3.50 3.47	10.42 10.36)
5o	H	Me	$C_2F_5CH_2O$	Me	65	158—160 AcOEt–hexane	$C_{18}H_{16}F_5N_3OS$	51.79 (51.71	3.86 3.84	10.07 10.01)
5p	H	H	$H(CF_2)_2CH_2O$	H	80	Oil[a]				
5q	H	Me	$H(CF_2)_2CH_2O$	H	82	134—135 AcOEt–hexane	$C_{17}H_{15}F_4N_3OS$	52.98 (53.08	3.92 3.96	10.90 10.89)
5r	H	H	$H(CF_2)_2CH_2O$	Me	84	148—149 AcOEt–hexane	$C_{17}H_{15}F_4N_3OS$	52.98 (53.22	3.92 3.86	10.90 10.52)
5s	H	Me	$F(CF_2)_2CH_2O$	H	94	130—131 AcOEt–iso-Pr_2O	$C_{18}H_{14}F_7N_3OS$	47.69 (47.68	3.11 3.05	9.27 9.05)
5t	H	Me	$H(CF_2)_4CH_2O$	H	77	90—92 CCl_4	$C_{19}H_{15}F_8N_3OS \cdot 1/2H_2O$	46.15 (46.14	3.26 3.25	8.50 8.42)
5u	H	H	CCl_3CH_2O	H	66	Oil[a]				

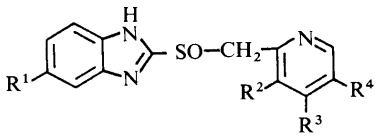
a) Oily compounds were used without further purification.

sulfide to give the phenylenediamine (**9**). Cyclization of the phenylenediamine (**9**) with potassium ethyl xanthate afforded the desired 2-mercaptobenzimidazole (**4**: $R^1 = MeSO_2$) (Chart 3).

Biological Results

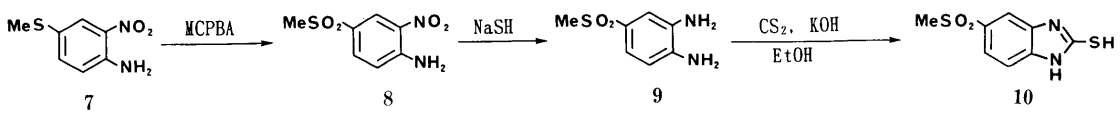
The biological activities of the 2-[[(4-fluoroalkoxy-2-pyridyl)methyl]sulfinyl]-1*H*-benzimidazoles (**6**) synthesized here were evaluated using the three assay methods described under "Experimental." They showed remarkable antisecretory, antiulcer, and cytoprotective activities. In addition, as expected, they showed significantly improved stability in the solid state as compared to the corresponding alkoxy analogues. Representative compounds and their

TABLE IV. 2-[[(2-Pyridyl)methyl]sulfinyl]-1*H*-benzimidazoles



6

Compd. No.	R^1	R^2	R^3	R^4	Yield (%)	mp (°C) Recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
6a	H	H	CF_3CH_2O	H	67	176—177 AcOEt–hexane	$C_{15}H_{12}F_3N_3O_2S$	50.70 (50.59)	3.40 3.24	11.83 11.86)
6b	F	H	CF_3CH_2O	H	53	187—189 (d) AcOEt–hexane	$C_{15}H_{11}F_4N_3O_2S$	48.26 (48.35)	2.97 2.89	11.26 11.16)
6c	MeO	H	CF_3CH_2O	H	90	162—163 (d) AcOEt–Et_2O–hexane	$C_{16}H_{14}F_3N_3O_3S$	49.87 (49.97)	3.66 3.63	10.90 10.76)
6d	EtO	H	CF_3CH_2O	H	57	58—60	$C_{17}H_{16}F_3N_3O_3S \cdot 0.4H_2O$	50.22 (50.25)	4.16 3.95	10.33 10.42)
6e	PrO	H	CF_3CH_2O	H	71	48—53	$C_{18}H_{18}F_3N_3O_3S \cdot 0.4H_2O$	51.40 (51.53)	4.50 4.27	9.99 10.08)
6f	H	Me	CF_3CH_2O	H	45	168—170 (d) Acetone–Et_2O–hexane	$C_{16}H_{14}F_3N_3O_2S$	52.03 (52.13)	3.82 3.77	11.38 11.38)
6g	$MeSO_2$	Me	CF_3CH_2O	H	54	173—175 Acetone	$C_{17}H_{16}F_3N_3O_4S_2$	45.63 (45.47)	3.60 3.46	9.39 9.15)
6h	CF_3	Me	CF_3CH_2O	H	74	161—162 (d) Acetone–Et_2O–hexane	$C_{17}H_{13}F_6N_3O_2S$	46.69 (46.54)	3.00 2.85	9.61 9.80)
6i	MeO	Me	CF_3CH_2O	H	81	141—142 (d) Acetone–Et_2O–hexane	$C_{17}H_{16}F_3N_3O_3S$	51.13 (51.13)	4.04 3.99	10.51 10.35)
6j	H	H	CF_3CH_2O	Me	71	175—177 Acetone–Et_2O–hexane	$C_{16}H_{14}F_3N_3O_2S$	52.03 (51.97)	3.82 3.79	11.38 11.20)
6k	H	Me	CF_3CH_2O	Me	76	178—179 (d) Acetone–Et_2O–hexane	$C_{17}H_{16}F_3N_3O_2S$	53.26 (53.33)	4.21 4.21	10.96 10.92)
6l	H	H	$C_2F_5CH_2O$	H	86	148—150 Et_2O–hexane	$C_{16}H_{12}F_5N_3O_2S$	47.38 (47.62)	2.98 2.99	10.37 10.30)
6m	H	Me	$C_2F_5CH_2O$	H	78	161—163 (d) Acetone–iso-Pr_2O	$C_{17}H_{14}F_5N_3O_2S$	48.69 (48.49)	3.36 3.34	10.02 9.91)
6n	H	H	$C_2F_5CH_2O$	Me	73	145—148 Acetone–Et_2O–hexane	$C_{17}H_{14}F_5N_3O_2S$	48.69 (48.48)	3.36 3.56	10.02 10.24)
6o	H	Me	$C_2F_5CH_2O$	Me	51	157—159 Acetone–Et_2O–hexane	$C_{18}H_{16}F_5N_3O_2S$	49.88 (49.80)	3.72 3.70	9.70 9.62)
6p	H	H	$H(CF_2)_2CH_2O$	H	73	132—133 Acetone–Et_2O–hexane	$C_{16}H_{13}F_4N_3O_2S$	49.61 (49.62)	3.38 3.37	10.85 10.86)
6q	H	Me	$H(CF_2)_2CH_2O$	H	75	147—148 (d) Acetone–Et_2O–hexane	$C_{17}H_{15}F_4N_3O_2S$	50.87 (50.92)	3.77 3.66	10.47 10.31)
6r	H	H	$H(CF_2)_2CH_2O$	Me	74	136—139 (d) Acetone–Et_2O–hexane	$C_{17}H_{15}F_4N_3O_2S$	50.87 (50.64)	3.77 3.65	10.47 10.34)
6s	H	Me	$F(CF_2)_2CH_2O$	H	54	162—164 (d) Acetone–Et_2O–hexane	$C_{18}H_{14}F_7N_3O_2S$	46.06 (46.12)	3.01 3.03	8.90 8.95)
6t	H	Me	$H(CF_2)_4CH_2O$	H	84	130—132 (d) Acetone–Et_2O–hexane	$C_{19}H_{15}F_8N_3O_2S$	45.51 (45.21)	3.02 2.97	8.38 8.21)
6u	H	H	CCl_3CH_2O	H	62	173—175 (d) Acetone–Et_2O–hexane	$C_{15}H_{12}Cl_3N_3O_2S$	44.52 (44.81)	2.99 2.96	10.38 10.45)



7 8 9 10

Chart 3

biological activities are shown in Table V. Most of these compounds were superior to omeprazole in antisecretory and antiulcer potencies, and especially in protecting the gastric mucosa from ethanol (EtOH)-induced damage.

After examining the pharmacological and toxicological properties of these compounds, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridy]methyl]sulfinyl]-1*H*-benzimidazole, AG-1749 (lansoprazole) (**6f**), was selected as a promising antiulcer agent. The antisecretory and antiulcer activities and possible mechanism for the inhibition of $(H^+ + K^+)$-ATPase of AG-1749 have been described in detail.[7] Further development and clinical evaluation of AG-1749 are in progress.

TABLE V. Antisecretory, Antiulcer, and Cytoprotective Activities of 2-[[(4-Fluoroalkoxy-2-pyridyl)methyl]sulfinyl]-1*H*-bemzimidazoles

Compd.	ED_{50} value (mg/kg)		
	Antisecretory activity	Antiulcer activity	Cytoprotective activity
6a	0.6	2.0[a]	4.2[a]
6f	1.6	2.4	8.5
6m	2.7	5.1[a]	5.3
6q	3.5[a]	1.2[a]	3.7
Omeprazole	3.3	7.0	15.3

a) ED_{50} values were calculated from the dose-inhibition relationships for 6—12 rats by the method of least squares or graphically.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Hitachi 215 grating infrared spectrophotometer. The nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a Varian EM-390 spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard, and coupling constants (J) are given in Hz. Column chromatography was performed using silica gel (Wakogel C-300 or Merck Art9385).

Pyridine *N*-Oxides (2) Method A: A solution of potassium *tert*-butoxide (5.7 g, 50 mmol) in 2,2,2-trifluoroethanol (5 ml) was added to an ice-cooled solution of 2,3-dimethyl-4-nitropyridine *N*-oxide (5.0 g, 30 mmol). The reaction mixture was stirred at 50—60 °C for 42 h. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 10 : 1). Recrystallization from AcOEt–hexane gave 2,3-dimethyl-4-(2,2,2-trifluoroethoxy)pyridine *N*-oxide (**2b**) (6.2 g, 94%) as colorless needles, mp 131—132 °C. NMR δ: 2.24 (3H, s), 2.53 (3H, s), 4.39 (2H, q, J=8), 6.31 (1H, d, J=7.5), 8.15 (1H, d, J=7.5). IR (KBr): 2960, 1615, 1490, 1460, 1390, 1310, 1270, 1250, 1220, 1190, 1170, 1110, 1025, 980, 880, 855, 810, 780 cm^{-1}.

Compounds **2a**, **d**, **h**, **j** were obtained by a procedure similar to that described for **2b**; the yields, melting points and elemental analysis data are given in Table I.

Method B: A mixture of 2,3-dimethyl-4-nitropyridine *N*-oxide (2.0 g, 12 mmol), 2,2,3,3,4,4,4-heptafluorobutanol (2.3 ml, 18 mmol), and K_2CO_3 (4.9 g, 35 mmol) in acetonitrile (20 ml) was stirred at 90—100 °C for 41 h. The reaction mixture was poured into water and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 10 : 1) and recrystallized from isopropyl ether to give 2,3-dimethyl-4-(2,2,3,3,4,4,4-heptafluorobutoxy)pyridine *N*-oxide (**2l**) (2.8 g, 73%) as colorless needles, mp 119—120 °C. NMR δ: 2.23 (3H, s), 2.53 (3H, s), 4.47 (2H, tt, J=1.5, 12), 6.63 (1H, d, J=7.5), 8.15 (1H, d, J=7.5). IR (KBr): 1445, 1355, 1300, 1250, 1220, 1175, 1110, 1070, 1015, 960, 910, 810, 780, 760 cm^{-1}.

Compounds **2c**, **k**, **m** were obtained by a procedure similar to that described for **2l**; the yields, melting points and elemental analysis data are given in Table I.

Method C: Potassium *tert*-butoxide (7.6 g, 66 mmol) was added portionwise to a solution of 2-methyl-4-nitropyridine *N*-oxide (6.8 g, 44 mmol) and 2,2,3,3,3-pentafluoropropanol (20 g, 132 mmol) in pyridine (80 ml). Afrer being stirred at room temperature for 2 d, the solvent was removed *in vacuo*. The residue was purified by column chromatography (AcOEt : MeOH = 10 : 1) and recrystallized from ether–hexane to give 2-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine *N*-oxide (**2e**) (5.8 g, 51%) as colorless crystals, mp 79—81 °C. NMR δ: 2.35 (3H, s), 4.87 (2H, t, J=12), 7.05 (1H, dd, J=3, 7.5), 7.26 (1H, d, J=3), 8.19 (1H, d, J=7.5). IR (KBr): 3060, 1481, 1310, 1178, 1023, 835 cm^{-1}.

Method D: A mixture of 2,3-dimethyl-4-nitropyridine *N*-oxide (2.0 g, 12 mmol), 2,2,3,3,3-pentafluoropropanol (3.1 ml, 30 mmol), hexamethylphosphoramide (HMPA) (2.1 ml, 12 mmol), and K_2CO_3 (3.2 g, 24 mmol) in 2-butanone (30 ml) was stirred at 70—80 °C for 4.5 d. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was diluted with water and extracted with AcOEt. The extract was dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was purified by column chromatography ($CHCl_3$: MeOH = 10 : 1) and recrystallized from AcOEt–hexane to give 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine *N*-oxide (**2f**) (2.4 g, 74%) as colorless needles, mp 148—149 °C. NMR δ: 2.21 (3H, s), 2.53 (3H, s), 4.44 (2H, t, J=12), 6.61 (1H, d, J=7), 8.16 (1H, d, J=7). IR (KBr): 1455, 1390, 1300, 1270, 1250, 1200, 1155, 1120, 1100, 955, 805, 790, 770 cm^{-1}.

Compounds **2g, i** were obtained by a procedure similar to that described for **2f**; the yields, melting points and elemental analysis data are given in Table I.

Method E: A mixture of 2-methyl-4-nitropyridine *N*-oxide (2.0 g, 13 mmol) and K_2CO_3 in 2,2,2-trichloroethanol (10 ml) was stirred at 90—110 °C for 2.5 h. The mixture was poured into water and extracted with AcOEt. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatogtaphy ($CHCl_3$: MeOH = 10 : 1) to give 2-methyl-4-(2,2,2-trichloroethoxy)pyridine *N*-oxide (**2n**) (2.2 g, 66%) as a reddish oil. NMR δ: 2.54 (3H, s), 4.63 (2H, s), 6.75—7.0 (2H, m), 8.22 (1H, d, J=6.5). IR (neat): 3600—2600, 1630, 1475, 1310, 1235, 1210, 1180, 1055, 835, 820, 800, 745, 725 cm^{-1}.

2-Hydroxymethylpyridines (3) Method F: A mixture of 2,3-dimethyl-4-(2,2,2-trifluoroethoxy)pyridine *N*-oxide (**2b**) (6.2 g, 28 mmol), Ac_2O (15 ml), and conc. H_2SO_4 (3 drops) was stirred at 100—120 °C for 5 h. After removal of Ac_2O *in vacuo*, the residue was dissolved in a solution of NaOH (2.4 g, 84 mmol) in MeOH (30 ml)–H_2O (8 ml). The mixture was stirred at room temperature for 3 h. After removal of MeOH, the residue was extracted with AcOEt. The extract was washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography (AcOEt) and recrystallized from isopropyl ether–hexane to give 2-hydroxymethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (**3b**) (4.4 g, 66%) as pale brown plates, mp 93—94 °C. NMR δ: 2.09 (3H, s), 4.43 (2H, q, J=8), 4.67 (3H, brs), 6.69 (1H, d, J=5.5), 8.37 (1H, d, J=5.5). IR (KBr): 3200, 1580, 1480, 1445, 1310, 1290, 1265, 1250, 1160, 1120, 1040, 1010, 970, 900, 860, 840, 830, 820, 730, 670 cm^{-1}.

Compounds **3a**, **c**, **e—g, i—n** were obtained by a procedure similar to that described for **3b**; the yields, melting points and elemental analysis data are given in Table II.

Method G: A mixture of 3,5-dimethyl-4-(2,2,2-trifluoroethoxy)pyridine *N*-oxide (**2d**) (10 g, 46 mmol) and dimethyl sulfate (6.1 ml, 48 mmol) was stirred at 110—120 °C for 30 min. The reaction mixture was diluted with MeOH (150 ml) and refluxed for 1 h. A solution of ammonium persulfate (11 g, 48 mmol) in water (15 ml) was added dropwise over 1 h to the reaction mixture under refluxing, and refluxing was further continued for 1 h. The cooled mixture was made basic with conc. aqueous NaOH, and the precipitate was filtered off. The filtrate was extracted with $CHCl_3$, and the extract was dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromtography ($CHCl_3$: MeOH = 10 : 1) and recrystallized from isopropyl ether–hexane to give 3,5-dimethyl-2-hydroxymethyl-4-(2,2,2-tirfluoroethoxy)pyridine (**3d**) (2.0, 18%) as colorless plates, mp 62—63 °C. NMR δ: 2.13 (3H, s), 2.27 (3H, s), 4.22 (2H, q, J=8), 4.63 (2H, s), 8.23 (1H, brs). IR (KBr): 3170, 1570, 1280, 1250, 1160, 1110, 1040, 1030, 965 cm^{-1}.

2-[[(2-Pyridyl)methyl]thio]-1*H*-benzimidazoles (5) A Typical Procedure: Thionyl chloride (1 ml, 14 mmol) was added to a solution of 2-hydroxymethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (**3b**) (1.5 g, 6.8 mmol) in $CHCl_3$ (30 ml), and the mixture was refluxed for 20 min. After removal of the solvent, the residue was dissolved in MeOH (10 ml) and added to a solution of 2-mercaptobenzimidazole (1.0 g, 6.8 mmol) and 5.2 M MeONa/MeOH (5 ml, 26 mmol) in MeOH (20 ml). The mixture was refluxed for 1 h and then concentrated *in vacuo*. The residue was diluted with water and extracted with AcOEt. The extract was washed with aqueous NaOH and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane) and recrystallized from AcOEt–hexane to give 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]-1*H*-benzimidazole (**5f**) (2.3 g, 96%) as colorless crystals, mp 149—150 °C. NMR δ: 2.30 (3H, s), 4.39 (2H, q, J=7.5), 4.40 (2H, s), 6.68 (1H, d, J=6), 7.05—7.25 (2H, m), 7.35—7.65 (2H, m), 8.38 (1H, d, J=6). IR (KBr): 3300—2500, 1585, 1480, 1440, 1425, 1310, 1280, 1270, 1260, 1230, 1160, 1115, 975, 760, 750 cm^{-1}.

Compounds **5a—e**, **g—u** were obtained by a procedure similar to that described for **5f**; the yields, melting points and elemental analysis data are given in Table III.

2-[[(2-Pyridyl)methyl]sulfinyl]-1*H*-benzimidazoles (6) A Typical Procedure: A solution of MCPBA (1.5 g, 6.2 mmol) in $CHCl_3$ (15 ml) was added dropwise to an ice-cooled solution of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]-1*H*-benzimidazole (**5f**) (2.2 g, 6.2 mmol) in $CHCl_3$ (30 ml). The solution was washed with a saturated $NaHCO_3$ solution and dried ($MgSO_4$). After removal of the solvent, the

residue was purified by column chromatography (AcOEt) and recrystallized from acetone–ether–hexane to give 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (**6f**) (1.0 g, 45%) as colorless crystals, mp 168—170 °C (dec.). NMR δ: 2.18 (3H, s), 4.33 (2H, q, J=7.5), 4.77 (2H, m), 6.63 (1H, d, J=6), 7.15—7.9 (4H, m), 8.32 (1H, d, J=6). IR (KBr): 3325—2700, 1580, 1475, 1450, 1400, 1280, 1265, 1250, 1170, 1115, 1040, 970, 860, 815, 750 cm^{-1}.

Compound **6a—e**, **g—u** were obtained by a procedure similar to that described for **6f**; the yields, melting points and elemental analysis data are given in Table IV.

4-Methylsulfonyl-2-nitroaniline (7) A solution of MCPBA (29 g, 0.16 mol) in $CHCl_3$ (300 ml) was added to an ice-cooled solution of 4-methylthio-2-nitroaniline[6] (5.1 g, 28 mmol) in $CHCl_3$ (250 ml), and the mixture was stirred for 30 min. The mixture was concentrated to *ca.* 200—300 ml, and ice-water and aqueous $NaHCO_3$ were added to the mixture. The precipitate was collected by filtration and recrystallized from AcOEt to give **7** (5.3 g, 89%) as colorless crystals, mp 201—203 °C. NMR δ (DMSO-d_6): 3.07 (3H, s), 7.10 (1H, d), 7.70 (1H, q), 7.92 (2H, br), 8.40 (1H, d). IR (KBr): 3500, 3380, 3030, 1630, 1300, 1150, 973, 835, 780 cm^{-1}. *Anal.* Calcd for $C_7H_8N_2O_4S$: C, 38.88; H, 3.73; N, 12.96. Found: C, 39.09; H, 3.81; N, 12.95.

4-Methylsulfonyl-1,2-diaminobenzene (9) 4-Methylsulfonyl-2-nitroaniline (**7**) (4.4 g, 24 mmol) was added to a solution of sodium hydrosulfide hydrate (12 g) in water (40 ml) and MeOH (200 ml) at 60 °C. The mixture was stirred for 2.5 h and concentrated *in vacuo*. The residue was extracted with AcOEt. The extract was washed with brine and dried (Na_2SO_4). After removal of the solvent, the residue was recrystallized from AcOEt to give **9** (3.3 g, 88%) as colorless crystals, mp 156—158 °C. NMR δ (DMSO-d_6): 2.92 (3H, s), 5.10 (4H, br), 6.59 (1H, d), 6.91 (1H, q), 6.99 (1H, d). IR (KBr): 3410, 3350, 1585, 1505, 1280, 1135, 965, 765 cm^{-1}. *Anal.* Calcd for $C_7H_{10}N_2O_2S$: C, 45.12; H, 5.37; N, 15.04. Found: C, 45.28; H, 5.48; N, 14.92.

2-Mercapto-5(6)-methylsulfonyl-1*H*-benzimidazole (10) A solution of 4-methylsulfonyl-1,2-diaminobenzene (**9**) (1.3 g, 7.0 mmol) in EtOH (26 ml) was added to a mixture of KOH (0.80 g, 14 mmol), carbon disulfide (2.9 g, 38 mmol), water (5 ml), and EtOH (25 ml). The reaction mixture was refluxed for 15 h and concentrated. The pH of the residual solution was adjusted to 5—6 with AcOH. The precipitate was collected by filtration and recrystallized from acetone–hexane to give **10** (2.9 g, 70%) as colorless crystals, mp >300 °C. NMR δ(DMSO-d_6): 3.15 (3H, s), 3.90 (2H, br), 7.29 (1H, d), 7.56 (1H, d), 7.65 (1H, q). *Anal.* Calcd for $C_8H_8N_2O_2S_2$: C, 42.09; H, 3.53; N, 12.27. Found: C, 41.91; H, 3.39; N, 11.91.

Assay Seven-week old male Jcl:Sprague-Dawley rats weighing 190 to 230 g were used. The animals were fasted for 24 h but had free access to water.

Antisecretory Activity The pylorus was ligated under anesthetization with urethane (1.2 g/kg i.p.), and the abdomen was closed. A compound or vehicle was given intraduodenally just after the pylorus was ligated. Thirty minutes later, histamine (30 mg/kg) was given s.c. The stomach was removed 3 h after the secretagogue was administered, and the gastric contents were collected and centrifuged at 3000 rpm for 10 min. The volume of each sample was measured, the acid concentration was determined by automatic titration to pH 7.0 with 0.1 N NaOH, and the total acid output during the 3-h period was calculated.

Antiulcer Activity Water-immersion stress ulcers were induced as described by Takagi and Okabe.[8] The animals were given a compound or the vehicle *p.o.* and 30 min later were placed in a stress cage and were immersed vertically to the level of the xiphoid process in a water bath maintained at 23 °C. Five hours later, each animal was taken out of its cage and sacrificed by CO_2 asphyxiation. The length (millimeters) of individual lesions in the corpus was measured, and the sum of the length of all lesions in each stomach was used as the lesion index.

Cytoprotective Activity A compound or vehicle was administered *p.o.* 30 min before 1 ml of absolute EtOH was administered *p.o.* The animals were sacrificed 1 h after receiving the EtOH, and the stomach was removed and examined for lesions.

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