Nicotinamide Derivatives as a New Class of Gastric (H^+/K^+)-ATPase Inhibitors. III.[1,2] Synthesis and Gastric Antisecretory Activity of 2-[(2- and 4-Aminobenzyl, and α-methylbenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides

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A new series of 2-[(2-aminobenzyl, 4-aminobenzyl, and α-methylbenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides was synthesized and evaluated for gastric antisecretory activities. Several of the compounds synthesized exhibited potent inhibitory activities against [^{14}C]aminopyrine accumulation stimulated by dibutyryl cyclic AMP in isolated rabbit parietal cells and histamine-induced gastric acid secretion in pylorus-ligated rats by intraduodenal administration. In particular, the more polar diastereoisomer of 2-[(4-methoxy-α-methylbenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamide (13b) showed *in vivo* inhibitory activity equivalent or superior to that of omeprazole and was a more selective (H^+/K^+)-ATPase inhibitor than omeprazole.

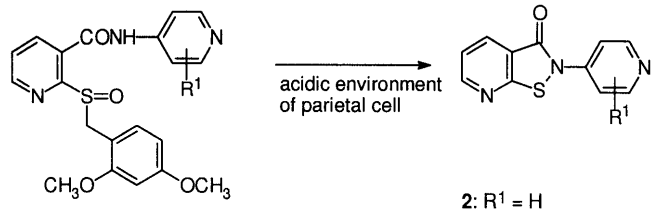
Key words (H^+/K^+)-ATPase inhibitor; antisecretory activity; *N*-(4-pyridinyl)-2-sulfinyl-3-pyridinecarboxamide

The 2-[(2-pyridinylmethyl)sulfinyl]benzimidazoles (PSBs),[3-7] represented by omeprazole,[3] have been found to cause complete suppression of gastric acid secretion. Among them, omeprazole,[3] lansoprazole,[4] and pantoprazole[5] have been introduced as clinically useful antiulcer agents. It is well known that the PSBs act as prodrugs, being chemically transformed to active forms in an acidic environment such as the apical membrane of the parietal cell and irreversibly inhibiting gastric (H^+/K^+)-ATPase, which plays a major role in gastric acid secretion.[8]

We have found a new class of irreversible and potent (H^+/K^+)-ATPase inhibitors, 2-[(2,4-dimethoxybenzyl)-sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides **1**, as reported previously.[1,2] In particular, 2-[(2,4-dimethoxybenzyl)sulfinyl]-*N*-(2,5-dimethyl-4-pyridinyl)-3-pyridinecarboxamide (**1a**, AD-9161) and 2-[(2,4-dimethoxybenzyl)sulfinyl]-*N*-(2,6-dimethyl-4-pyridinyl)-3-pyridinecarboxamide (**1b**, AD-8717) have inhibitory activities equivalent or superior to those of omeprazole against both the histamine-induced gastric acid secretion in pylorus-ligated rats by intraduodenal (i.d.) administration and [^{14}C]aminopyrine (AP) accumulation stimulated by dibutyryl cyclic AMP (dbcAMP) in isolated rabbit parietal cells.[2] Upon acid activation in the acidic environment of the parietal cell, **1** may be converted to the active forms, *N*-(4-pyridinyl)-2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridines **3** and **4**, which irreversibly inhibit gastric (H^+/K^+)-ATPase (Chart 1). Additionally, most of **1** are much more stable at neutral and weakly acidic pH than omeprazole. It follows that they are more selective (H^+/K^+)-ATPase inhibitors than omeprazole.

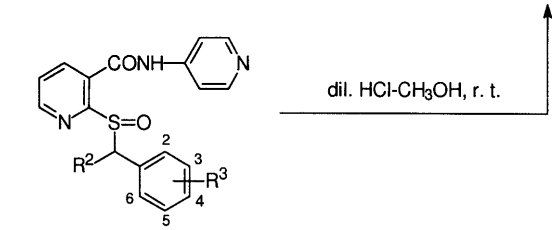
In our previous paper,[9] we reported that not only the carboxamides (**1**) bearing a 2,4-dimethoxybenzyl[1] group on the sulfur atom, but also carboxamides bearing a 2-(methylamino)benzyl (**6a**), 2-(dimethylamino)benzyl (**7a**), 2,5-difluoro-4-(dimethylamino)benzyl (**9a**), 2-methoxy-α-methylbenzyl (**11a**) or 4-methoxy-α-methylbenzyl (**13b**) group were readily converted into the isothiazolopyridine **2** in high yields at room temperature in a dilute hydrochloric acid–methanol solution. Hence, these carboxamides **6a**, **7a**, **9a**, **11a**, and **13b**, were expected to have potent *in vivo* gastric antisecretory activity, like **1**. We were also interested in the chemical stability of these compounds in acidic conditions.

The present study was focused on finding a new series of potent gastric (H^+/K^+)-ATPase inhibitors which would possess *in vivo* gastric antisecretory activity and desirable chemical profiles similar to that of the 3-pyridinecarbox-



1a (AD-9161): R^1 = 2-CH_3, 5-CH_3
1b (AD-8717): R^1 = 2-CH_3, 6-CH_3

2: R^1 = H
3: R^1 = 2-CH_3, 5-CH_3
4: R^1 = 2-CH_3, 6-CH_3



6a: R^2 = H; R^3 = 2-$NHCH_3$
7a: R^2 = H; R^3 = 2-$N(CH_3)_2$
9a: R^2 = H; R^3 = 2-F, 4-$N(CH_3)_2$, 5-F
11a: R^2 = CH_3; R^3 = 2-OCH_3
13b: R^2 = CH_3; R^3 = 4-OCH_3

Chart 1

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amides **1**. This paper deals with the synthesis, chemical stability, and antisecretory activities of 2-[(2-aminobenzyl, 4-aminobenzyl, and α-methylbenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides.

Chemistry

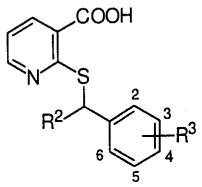
The requisite 3-pyridinecarboxylic acids **15**—**27** (Table 1) were prepared by condensation of 2-mercapto-3-pyridinecarboxylic acid (**14**) with the corresponding benzyl or α-methylbenzyl chlorides according to the method reported previously (Chart 2).[1,9] Syntheses of the carboxamides **6a**, **7a**, **9a**, **11a**, and **13b** (Table 2) were previously reported.[9] The carboxamides **6b, c**, **7b—d**, **8a, b**, **9b, c**, **10**, and **12b** listed in Table 2 were prepared by condensation of the corresponding carboxylic acids **15**—**27** with 4-aminopyridine by the use of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, followed by oxidation with *m*-chloroperbenzoic acid (*m*CPBA) as reported previously[1,9] (Chart 2). A carboxamide **5** was prepared *via* the 2-nitrobenzyl derivative obtained by condensation of the carboxylic acid **15** with 4-aminopyridine by the use of oxalyl chloride, followed by catalytic reduction and subsequent oxidation. An attempt to prepare a carboxamide **29** by oxidation of the corresponding sulfide **28** derived from the carboxylic acid **23** by the use of *m*CPBA was unsuccessful (Chart 3). Each diastereoisomer, **11a, b**, **12b**, and **13a, b**, was isolated by chromatographic purification and recrystallization of the respective diastereoisomeric mixtures obtained by oxidation of the corresponding sulfides[9] with *m*CPBA. The less polar isomer (**12a**) of **12**, however, could not be isolated in a pure form.

Pharmacological Results and Discussion

Compounds **5**—**13** were evaluated for the ability to inhibit the histamine-induced gastric acid secretion in pylorus-ligated rats by i.d. administration, as well as the AP accumulation stimulated by dbcAMP in isolated rabbit parietal cells. The results and the half-lives of conversion to the active form **2** at pH 1.0, 3.0, and 5.0 are summarized in Table 3 in comparison with those of **1b** and omeprazole.

The 2-[(2- and 4-aminobenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides **5**—**9** were initially evaluated. As expected, compounds bearing a 2-(methylamino)benzyl (**6a**), 2-(dimethylamino)benzyl (**7a**), or 2,5-difluoro-4-(dimethylamino)benzyl (**9a**) group on the sulfur atom exhibited potent *in vitro* and *in vivo* inhibitory activities. In particular, **7a** exhibited *in vitro* and *in vivo* activities equivalent to those of omeprazole. Compound **5** bearing an amino group at the 2-position of the phenyl ring did not inhibit the AP accumulation. Substitution by the bulkier alkylamino groups such as *n*-propylamino (**6b**),

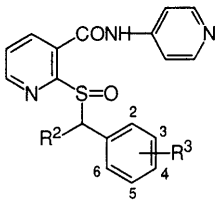
Table 1. 3-Pyridinecarboxylic Acids **15**—**27**



Compd.	R^2	R^3	mp (°C) (Recryst. solvent[a])	Yield (%)	Formula	Analysis (%) Calcd (Found)				
						C	H	Halogen	N	S
15	H	2-NO_2	224—226 (G)	64	$C_{13}H_{10}N_2O_4S$	53.79 (53.71	3.47 3.54		9.65 9.60	11.05 10.78)
16	H	2-NH(*n*-C_3H_7)	Oil[b]	80	$C_{16}H_{18}N_2O_2S$					
17	H	2-NH(iso-C_4H_9)	159—161 (A)	63	$C_{17}H_{20}N_2O_2S$	64.53 (64.50	6.37 6.27		8.85 8.90	10.13 9.95)
18	H	2-$N(CH_3)C_2H_5$	118—121 (A)	79	$C_{16}H_{18}N_2O_2S$	63.55 (63.45	6.00 5.80		9.26 9.27	10.60 10.39)
19	H	2-$N(CH_3)$*n*-C_3H_7	Oil[c]	78	$C_{17}H_{20}N_2O_2S$					
20	H	2-$N(CH_3)$iso-C_4H_9	117—120 (D-E)	68	$C_{18}H_{22}N_2O_2S$	65.43 (65.15	6.71 6.57		8.48 8.45	9.70 9.64)
21	H	2-$N(CH_3)_2$, 4-Cl	143—147 (A)	98	$C_{15}H_{15}ClN_2O_2S$	55.81 (55.68	4.68 4.53	10.98 10.85	8.68 8.57	9.93 9.83)
22	H	2-$N(CH_3)_2$, 3-Br, 5-Br	196—197 (B)	78	$C_{15}H_{14}Br_2N_2O_2S$	40.38 (40.54	3.16 3.19	35.82 35.51	6.28 6.21	7.19 7.05)
23	H	4-$N(CH_3)_2$	195—199 (B)	50	$C_{15}H_{16}N_2O_2S$	62.48 (62.54	5.59 5.51		9.71 9.68	11.12 11.05)
24	H	2-F, 3-F, 4-$N(CH_3)_2$, 5-F	187—188 (A)	58	$C_{15}H_{13}F_3N_2O_2S$	52.63 (52.38	3.83 3.70	16.65 16.68	8.18 8.28	9.37 9.22)
25	H	2-F, 4-$N(CH_3)_2$, 5-F, 6-F	204—205 (F)	97	$C_{15}H_{13}F_3N_2O_2S$	52.63 (52.76	3.83 3.74	16.65 16.72	8.18 8.20	9.37 9.38)
26	CH_3	H	147—151 (A)	84	$C_{14}H_{13}NO_2S$	64.84 (64.60	5.05 4.96		5.40 5.58	12.36 12.41)
27	CH_3	3-OCH_3	115—117 (A)	56	$C_{15}H_{15}NO_3S \cdot 1/5H_2O$	61.50 (61.80	5.30 5.05		4.78 4.93	10.94 11.03)

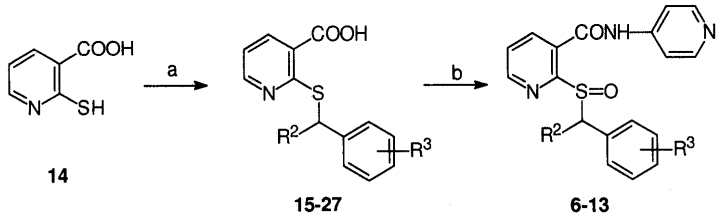
a) A = CH_3CN, B = acetone, C = $CHCl_3$, D = $(C_2H_5)_2O$, E = *n*-hexane, F = CH_3OH, G = $CH_3COOC_2H_5$, H = toluene, I = $(C_2H_5)_2O$. *b*) Mass spectrum (APCIMS) *m/z*: 303 (MH^+). *c*) Mass spectrum (APCIMS) *m/z*: 317 (MH^+).

Table 2. 3-Pyridinecarboxamides **5**—**13**



Compd.	R^2	R^3	mp (°C) (Recryst. solvent[a])	Yield (%)	Formula	Analysis (%) Calcd (Found)				
						C	H	Halogen	N	S
5	H	2-NH_2	208—210 (A)	7	$C_{18}H_{16}N_4O_2S\cdot 1/4H_2O$	60.57 (60.80	4.66 4.62		15.70 15.79	8.98 8.84)
6a[b]	H	2-$NHCH_3$	154—156 (A)	17	$C_{19}H_{17}N_4O_2S\cdot 1/4H_2O$					
6b	H	2-NH(*n*-C_3H_7)	178—181 (A)	18	$C_{19}H_{17}N_3O_2S\cdot 1/2H_2O$	62.51 (62.64	5.75 5.51		13.89 13.83	7.95 7.82)
6c	H	2-NH(iso-C_4H_9)	194—198 (F–C)	10	$C_{22}H_{24}N_4O_2S\cdot 1/4H_2O$	63.98 (63.76	5.98 5.88		13.57 13.38	7.76 7.75)
7a[b]	H	2-$N(CH_3)_2$	162—166 (A)	42	$C_{15}H_{16}N_2O_2S\cdot 1/4H_2O$					
7b	H	2-$N(CH_3)C_2H_5$	178—180 (A)	42	$C_{21}H_{22}N_4O_2S$	63.94 (63.81	5.62 5.62		14.20 14.23	8.13 8.10)
7c	H	2-$N(CH_3)$*n*-C_3H_7	155—158 (A)	28	$C_{22}H_{24}N_4O_2S\cdot 1/4H_2O$	63.98 (64.24	5.98 5.88		13.57 13.90	7.76 7.48)
7d	H	2-$N(CH_3)$iso-C_4H_9	145—147 (A)	49	$C_{23}H_{26}N_4O_2S$	65.38 (65.34	6.20 6.16		13.26 13.22	7.59 7.66)
8a	H	2-$N(CH_3)_2$, 4-Cl	187—190 (A)	64	$C_{20}H_{19}ClN_4O_2S$	57.90 (57.87	4.62 4.50	8.54 8.55	13.50 13.44	7.73 7.74)
8b	H	2-$N(CH_3)_2$, 3-Br, 5-Br	250—251 (F–C)	44	$C_{20}H_{18}Br_2N_4O_2S$	44.63 (44.51	3.37 3.15	29.69 29.99	10.41 10.24	5.96 5.98)
9a[b]	H	2-F, 4-$N(CH_3)_2$, 5-F	176—178 (A)	18	$C_{20}H_{18}F_2N_4O_2S$					
9b	H	2-F, 3-F, 4-$N(CH_3)_2$, 5-F	183—185 (A)	61	$C_{20}H_{17}F_3N_4O_2S$	55.29 (54.99	3.94 3.80	13.12 12.89	12.90 12.76	7.38 7.23)
9c	H	2-F, 4-$N(CH_3)_2$, 5-F, 6-F	221—224 (B–F)	47	$C_{20}H_{17}F_3N_4O_2S$	55.29 (55.07	3.94 3.94	13.12 13.05	12.90 12.79	7.38 7.20)
10	CH_3	H	236—238 (A)	64	$C_{19}H_{17}N_3O_2S$	64.94 (64.66	4.88 4.83		11.96 12.02	9.12 8.99)
11a[b,c]	CH_3	2-OCH_3	219—221 (A)	17	$C_{20}H_{19}N_3O_3S$					
11b[d]	CH_3	2-OCH_3	239—241 (A)	11	$C_{20}H_{19}N_3O_3S$	62.97 (62.60	5.02 5.00		11.02 11.16	8.41 8.29)
12b[d]	CH_3	3-OCH_3	233—236 (H)	25	$C_{20}H_{19}N_3O_3S$	62.97 (63.00	5.02 4.95		11.02 10.96	8.41 8.29)
13a[c]	CH_3	4-OCH_3	219—221 (A)	33	$C_{20}H_{19}N_3O_3S\cdot 1/4H_2O$	62.24 (61.98	5.09 4.75		10.89 10.86	8.31 8.35)
13b[b,d]	CH_3	4-OCH_3	240—243 (I)	28	$C_{20}H_{19}N_3O_3S$					

a) See footnote *a*) in Table 1. *b*) These compounds were previously prepared.[9] *c*) Less polar diastereoisomer. *d*) More polar diastereoisomer.



14 **15-27** **6-13**

a) corresponding chloride, $N(C_2H_5)_3$; b) 1) 4-aminopyridine, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide. 2) *m*CPBA

Chart 2

isobutylamino (**6c**), ethylmethylamino (**7b**), methylpropylamino (**7c**), and isobutylmethylamino (**7d**) groups, reduced the *in vivo* activity compared with that of **7a**. The conversion of **5**, **6a**—**c**, **7a**—**d**, and **9a** into **2**, however, was not so pH-dependent as that of **1b**; they were readily converted even at neutral or weakly acidic pH. Their ready conversions are considered undesirable because the formed **2** may react with thiol groups of other enzymes. Therefore, we attempted to increase the stability of **7a** and **9a**. Since the conversion rate may depend on the stability of the carbonium ions of the leaving group, as suggested previously,[9] we expected that introduction of an electronegative substituent such as halogen into the phenyl ring of the benzyl group of **7a** and **9a** would increase their stability.

The effect of introduction of chlorine (**8a**) and bromine (**8b**) into the phenyl ring of **7a**, and fluorine (**9b, c**) into the phenyl ring of **9a** on the chemical stability, as well as on the activities, was then examined. Compounds bearing chlorine at the 4-position (**8a**) and fluorines at the 2,5,6-positions (**9c**) did not show increased stability, whereas 3,5-dibromide **8b** and 2,3,5-trifluoride **9b** had considerably increased stability. The introduction of halogens had little effect on *in vitro* activity: In spite of having a much longer half-life at pH 1 than that of **7a**, unexpectedly, **8b** exhibited potent *in vitro* activity. As a matter of course, **8b** itself did not inhibit the (H^+/K^+)-ATPase ($IC_{50} > 100\,\mu M$). We speculate that the potent *in vitro* activity of **8b** might be due to its high membrane permeability. Compounds **8b** and **9b**, however, did not exhibit *in vivo* activity. The lack of correlation between the *in vitro* and *in vivo* assay may be due to a disparity in the ability of the compounds to reach the parietal cells. As a consequence of the study on compounds **5**—**9**, it appeared that increasing the hydrophobicity of **6a**, **7a**, and **9a** seemed to decrease the *in vivo* activity, as reported previously.[1]

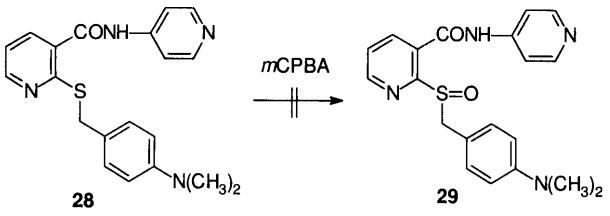


Chart 3

Next, 2-[(α-methylbenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides **10**—**13** were evaluated. Compounds **11a, b** bearing a 2-methoxy-α-methylbenzyl group on the sulfur atom and the 4-methoxy isomers **13a, b** exhibited potent *in vitro* and *in vivo* activities, like **6a**, **7a**, and **9a**. In particular, **13b** exhibited *in vivo* activity equivalent or superior to that of **1b**. On the other hand, compounds **10** and **12b**, having much longer half-lives at pH 1 than those of **11** and **13**, did not significantly inhibit the AP accumulation. Compounds **11** and **13** were converted into the isothiazolopyridine **2** with marked dependence on pH, but the half-lives at pH 3 and 5 differed considerably, depending on the compounds. Although **13b** was converted into **2** immediately at pH 1, it was very stable at both neutral and weakly acidic pH (pH 5.0). The stability of **13b** was not as high as that of **1b**, but it was much higher than that of omeprazole. Consequently, **13b** was expected to be a more selective inhibitor than omeprazole.

As a result of the present study, several 2-[(2-aminobenzyl, 4-aminobenzyl, and α-methylbenzyl)sulfinyl]-*N*-

Table 3. Antisecretory Activities and Half-Lives of Conversion of 3-Pyridinecarboxamides **5**—**13**

Compound	[^{14}C]AP-accumulation[a] IC_{50}[b] or % inhibn (μM)	Inhibn of gastric acid secretion pylorus-ligated rats[a] ED_{50}[c] or % inhibn (i.d. dose mg/kg)[d]	Half-lives of conversion (h)[a,e]		
			pH 1.0	pH 3.0	pH 5.0
5	>10 (−3.2%)		<0.02	0.11	0.58
6a	1.1	7.3 [1.2—42.7]	<0.02	<0.02	0.09
6b	1.8	12.9% (10)		<0.02	0.10
6c	0.29	14.6% (100)		<0.02	0.16
7a	0.38	4.1 [1.1—15.2]	<0.02	0.14	0.22
7b	2.4	51.2% (10)[f]	<0.02	0.38	0.62
		11.3% (3)			
7c	2.9	22.8% (10)	<0.02	0.28	0.44
7d	0.40	35.2% (10)[g]	<0.02	0.11	0.39
8a	0.27	9.1 [1.9—45.2]		<0.05	0.56
8b	0.74	−16.4% (100)	5.51		
9a	0.35	8.9 [1.4—58.9]		<0.02	0.12
9b	0.23	28.1% (10)	0.08	1.88	>50
9c	0.99	16.7% (100)	<0.02	<0.02	0.73
10	>10 (−7.3%)		12.83		
11a	0.49	6.1 [0.7—56.0]	<0.02	14.44	57.76
11b	0.28	4.7 [0.4—48.3]	<0.02	3.72	8.88
12b	>10 (2.9%)		23.10		
13a	0.17	5.4 [2.1—14.1]	<0.02	0.05	1.42
13b	0.46	1.9 [0.7—4.6]	<0.02	0.11	3.55
1b	0.27	2.7 [1.0—6.8]	<0.02	0.50	28.88
Omeprazole	0.37	4.1 [1.5—10.9]		<0.05	0.32

a) See Experimental. *b*) IC_{50} values were calculated from the regression lines. *c*) ED_{50} values were calculated from the regression lines (95% confidence limits in brackets). *d*) $n=4$—8 at each dose. *e*) Half-lives of conversion for **7a**, **13b** and omeprazole at pH 7 were 1.74, 144.41, and 10.50 h, respectively. *f*) $p<0.01$. *g*) $0.01<p<0.05$.

(4-pyridinyl)-3-pyridinecarboxamides were found to have potent inhibitory activities against histamine-induced gastric acid secretion in pylorus-ligated rats and against AP accumulation. In particular, **13b** showed *in vivo* activity equivalent or superior to **1b**, and was a selective inhibitor, like most of **1**. Therefore, this compound seems to be a promising candidate as an agent for treating acid-related gastrointestinal disorders.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8200PC spectrophotometer. ^{1}H-NMR spectra were taken at 200 MHz with a Varian Gemini-200 spectrometer in $(CH_3)_2SO$-d_6. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained on a Hitachi M-80-B mass spectrometer for secondary ion mass spectra (SIMS), or a Hitachi M-1000 LC API mass spectrometer for atmospheric pressure chemical ionization mass spectra (APCIMS). The HPLC was carried out on a Shimadzu LC-10A system. Organic extracts were dried over anhydrous $MgSO_4$.

The following known intermediates were prepared according to the literature: 2-(isobutylamino)benzyl chloride[10]; 2-(isobutylmethylamino)-benzyl chloride.[11]

2-(*n*-Propylamino)benzyl Chloride Hydrochloride This compound was prepared from methyl anthranilate in a manner similar to that described in the literature.[10] The overall yield was 84%.

2-(Ethylmethylamino)benzyl Chloride Hydrochloride and 2-(*n*-Propylmethylamino)benzyl Chloride Hydrochloride These compounds were prepared from methyl anthranilate in a manner similar to that described in the literature.[11] The overall yields were 68% and 58%, respectively.

4-Chloro-2-(dimethylamino)benzyl Chloride Hydrochloride and 3,5-Dibromo-2-(dimethylamino)benzyl Chloride Hydrochloride These compounds were prepared from methyl 4-chloroanthranilate and methyl 3,5-dibromoanthranilate, respectively, in a manner similar to that described in the literature.[12] The overall yields were 50% and 94%, respectively.

4-(Dimethylamino)-2,3,5-trifluorobenzyl Chloride Hydrochloride and 4-(Dimethylamino)-2,5,6-trifluorobenzyl Chloride Hydrochloride These compounds were prepared from 2,3,4,5-tetrafluorobenzoic acid and 2,4,5,6-tetrafluorobenzoic acid, respectively, in a manner similar to that described previously.[9] The overall yields were 41% and 44%, respectively.

3-Pyridinecarboxylic Acids 15—27 (Table 1) Typical Procedure: 2-[[3,5-Dibromo-2-(dimethylamino)benzyl]thio]-3-pyridinecarboxylic Acid (22) This compound was prepared from 2-mercapto-3-pyridinecarboxylic acid (**14**) and 3,5-dibromo-2-(dimethylamino)benzyl chloride hydrochloride in a manner similar to that described previously:[1,9] ^{1}H-NMR δ: 2.81 (6H, s), 4.43 (2H, s), 7.27 (1H, dd, J=4.8, 8.1 Hz), 7.64 (1H, d, J=2.3 Hz), 7.71 (1H, d, J=2.3 Hz), 8.23 (1H, dd, J=2.2, 8.1 Hz), 8.66 (1H, dd, J=2.2, 4.8 Hz), 13.48 (1H, br). APCIMS m/z: 447 (MH^+). IR (KBr) cm^{-1}: 1678 (C=O).

2-[(2-Aminobenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides 5-9 and 2-[(α-Methylbenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides 10—13 (Table 2) Typical Procedure 2-[[3,5-Dibromo-2-(dimethylamino)benzyl]sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamide (8b) Crude 2-[[3,5-dibromo-2-(dimethylamino)benzyl]thio]-*N*-(4-pyridinyl)-3-pyridinecarboxamide was derived from 2-[[3,5-dibromo-2-(dimethylamino)benzyl]thio]-3-pyridinecarboxylic acid (**22**) in 81% yield by condensation with 4-aminopyridine by the use of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride in a manner similar to that described previously:[1,9] ^{1}H-NMR δ: 2.80 (6H, s), 4.49 (2H, s), 7.32 (1H, dd, J=4.9, 7.2 Hz), 8.00 (1H, dd, J=2.0, 7.2 Hz), 8.48 (2H, m), 8.64 (1H, dd, J=2.0, 4.9 Hz), 10.82 (1H, s). APCIMS m/z: 523 (MH^+).

Compound **8b** was derived from the crude 2-[[3,5-dibromo-2-(dimethylamino)benzyl]thio]-*N*-(4-pyridinyl)-3-pyridinecarboxamide in 54% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,2,9] ^{1}H-NMR δ: 2.71 (6H, s), 4.30 (1H, d, J=12.1 Hz), 4.56 (1H, d, J=12.1 Hz), 7.36 (1H, d, J=2.3 Hz), 7.67 (2H, m), 8.27 (1H, dd, J=1.8, 8.0 Hz), 8.51 (2H, m), 8.91 (1H, dd, J=1.8, 5.1 Hz), 11.06 (1H, br). APCIMS m/z: 539 (MH^+). IR (KBr) cm^{-1}: 1044 (S=O), 1671 (C=O).

2-[(2-Aminobenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamide (5) 2-[(2-Nitrobenzyl)thio]-*N*-(4-pyridinyl)-3-pyridinecarboxamide was derived from 2-[(2-nitrobenzyl)thio]-3-pyridinecarboxylic acid (**15**) in 64% yield by condensation with 4-aminopyridine by the use of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride in a manner similar to that described previously:[1,2,9] ^{1}H-NMR δ: 4.72 (2H, s), 7.31 (1H, dd, J=4.7, 7.5 Hz), 7.47 (1H, m), 7.77 (1H, dd, J=1.6, 7.2 Hz), 7.94 (1H, dd, J=1.3, 8.1 Hz), 8.02 (1H, dd, J=1.9, 7.5 Hz), 8.49 (2H, m), 8.54 (1H, dd, J=1.9, 4.9 Hz), 10.81 (1H, s). APCIMS m/z: 367 (MH^+). *Anal.* Calcd for $C_{18}H_{14}N_4O_3S$: C, 59.01; H, 3.85; N, 15.29; S, 8.75. Found: C, 58.89; H, 3.67; N, 15.03; S, 8.64.

2-[(2-Nitrobenzyl)thio]-*N*-(4-pyridinyl)-3-pyridinecarboxamide (4.5 g, 12 mmol) was hydrogenated in 300 ml of C_2H_5OH containing 0.05 g of 5% Pd–C at room temperature under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (20:1) as the eluent to give 1.2 g (29%) of crude 2-[(2-aminobenzyl)thio]-*N*-(4-pyridinyl)-3-pyridinecarboxamide. SIMS m/z: 337 (MH^+).

Compound **5** was derived from the crude 2-[(2-aminobenzyl)thio]-*N*-(4-pyridinyl)-3-pyridinecarboxamide in 37% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,2,9] ^{1}H-NMR δ: 4.13 (1H, d, J=12.7 Hz), 4.35 (1H, d, J=12.7 Hz), 5.34 (2H, s), 6.53 (1H, m), 6.71 (1H, m), 7.69 (2H, m), 7.76 (1H, dd, J=4.7, 7.9 Hz), 8.36 (1H, dd, J=1.6, 7.9 Hz), 8.52 (2H, m), 8.92 (1H, dd, J=1.6, 4.7 Hz), 11.13 (1H, s). APCIMS m/z: 353 (MH^+). IR (KBr) cm^{-1}: 1034 (S=O), 1664 (C=O).

The Less Polar Diastereoisomer of 2-[(4-Methoxy-α-methylbenzyl)sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides (13a) A solution of 2-[(4-methoxy-α-methylbenzyl)thio]-*N*-(4-pyridinyl)-3-pyridinecarboxamide[9] (6.7 g, 18 mmol) in CH_2Cl_2 (100 ml) was treated dropwise with 70% *m*CPBA (4.3 g, 17 mmol) in CH_2Cl_2 (50 ml) at −40 °C under stirring. The resulting mixture was stirred at the same temperature for 30 min, washed with saturated aqueous $NaHCO_3$ (30 ml), and dried. The solvent was removed by distillation *in vacuo* and the residue was chromatographed on silica gel. Elution with $CHCl_3$–CH_3OH (25:1) followed by recrystallization of the product from CH_3CN gave the less polar isomer **13a**. Elution with $CHCl_3$–CH_3OH (10:1) followed by recrystallization from diethyl ether gave the more polar isomer **13b**.[9]

13a: ^{1}H-NMR δ: 1.43 (3H, d, J=7.5 Hz), 3.72 (3H, s), 4.53 (1H, q, J=7.5 Hz), 6.81 (2H, m), 7.06 (2H, m), 8.23 (1H, dd, J=1.6, 7.9 Hz), 8.51 (2H, m), 8.78 (1H, dd, J=1.6, 4.7 Hz), 11.01 (1H, s). APCIMS m/z: 382 (MH^+). IR (KBr) cm^{-1}: 1026 (S=O), 1678 (C=O).

Physical and spectral data for the more polar isomer **13b** were reported previously.[9]

The More Polar Diastereoisomer of 2-[(2-Methoxy-α-methylbenzyl)-sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides (11b) Compound **11b** was prepared in a manner similar to that described above: ^{1}H-NMR δ: 1.48 (3H, d, J=7.3 Hz), 3.35 (3H, s), 5.07 (1H, q, J=7.3 Hz), 6.75 (1H, m), 6.90 (1H, m), 8.28 (1H, dd, J=1.6, 7.9 Hz), 8.52 (2H, m), 8.66 (1H, dd, J=1.6, 4.9 Hz), 10.96 (1H, s). APCIMS m/z: 382 (MH^+). IR (KBr) cm^{-1}: 1045 (S=O), 1682 (C=O).

Physical and spectral data for the less polar isomer **11a** were reported previously.[9]

The More Polar Diastereoisomer of 2-[(3-Methoxy-α-methylbenzyl)-sulfinyl]-*N*-(4-pyridinyl)-3-pyridinecarboxamides (12b) Compound **12b** was prepared in a manner similar to that described above. The less polar isomer (**12a**) could not be isolated in a pure form by recrystallization or chromatographic purification: ^{1}H-NMR δ: 1.43 (3H, d, J=7.2 Hz), 3.78 (3H, s), 4.55 (1H, q, J=7.2 Hz), 6.85 (3H, m), 7.22 (1H, m), 7.66 (2H, m), 7.71 (1H, dd, J=4.8, 8.1 Hz), 8.22 (1H, dd, J=1.8, 8.1 Hz), 8.51 (2H, m), 8.87 (1H, dd, J=1.8, 4.8 Hz), 10.88 (1H, s). SIMS m/z: 382 (MH^+). IR (KBr) cm^{-1}: 1041 (S=O), 1674 (C=O).

Determination of the Diastereoisomeric Purity of 11a, b, 12b, and 13a, b The diastereoisomeric purity of sulfoxides was measured by HPLC under the following conditions: CAPCELL PACK C_{18} SG120 4.6—250 mm, 25% CH_3CN–10 mM phosphate buffer (pH 7.0), 1 ml/min, detector UV at 254 nm. The diastereoisomeric purity of **11a, b**, **12b**, and **13a, b** was determined to be >99%.

pH-Dependent Chemical Stability of 5—13 and Omeprazole The half-lives of each compound were determined in 100 mM HCl (pH 1) and McIlvaine buffer[13] (pH 3—7) which had been adjusted to the appropriate

pH. Each compound was dissolved in $(CH_3)_2SO$ at a concentration of 10 μM. Then 20 μl of the prepared solution was added to 1.96 ml of the appropriate buffer and 0.02 ml of 1% Triton solution. The mixture was incubated at 37 °C for various periods of time, and 20 μl of this solution was injected into the HPLC column (CAPCELL PACK C_{18} SG120 4.6—250 mm, CH_3CN/10 mM phosphate buffer (pH 7.0), 1 ml/min, UV detector at 254 nm). On the basis of peak area, the amounts of the 3-pyridinecarboxamides and the reference compound were estimated, and the half-life of each compound in different media was determined from the linear regression of the logarithm of the concentration *vs.* time.

Reference Compounds Omeprazole was extracted from commercially available Omepral® tablets (Fujisawa Pharmaceutical Co., Ltd.).

Acid Formation in Isolated Rabbit Parietal Cells Rabbit parietal cells were isolated as described by Fryklund *et al.*[14] Acid formation in the parietal cells was assessed in terms of accumulation of [^{14}C]AP.[15] The parietal cell-rich fraction (1—2 × 10^7 cells/300 μl) was suspended in 1.5 ml of Earle's balanced salt solution containing 5.6 kBq of [^{14}C]AP, 25 mM HEPES–NaOH buffer, pH 7.4, 0.2% bovine serum albumin, and test compound. Dibutyryl cAMP (1 mM) was added, and the reaction mixture was incubated at 37 °C for 30 min under an atmosphere of 95% O_2 and 5% CO_2. The cells were separated from the medium by brief centrifugation and digested with tissue solubilizer. A liquid scintillator was added, and radioactivity was counted using a liquid scintillation counter. The radioactivity accumulated by the cells in the presence of 0.1 mM dinitrophenol was subtracted from all data to correct for trapped [^{14}C]AP.

Histamine-Induced Gastric Acid Secretion in Pylorus-Ligated Rats[4] Male Stranded: Wistar rats weighing about 200 g were used. Rats were deprived of food but allowed free access to water for 24 h prior to experiments. Each experiment was performed using 4—7 rats/group. Under urethane anesthesia (1 g/kg), a midline laparotomy was performed and a ligature was tightly secured around the pylorus. Either vehicle or drug was administered intraduodenally immediately after ligation of the pylorus, and the abdominal incision was closed. Thirty minutes later, histamine (30 mg/kg) was injected s.c. Three hours later, the stomach was removed, and the gastric contents were collected. The volume of gastric juice was measured, and the acid concentration of 1.0 ml aliquots was determined by automatic titration to pH 7 with 0.01 N NaOH. The product of the gastric volume and acid concentration was used to calculate the total acid output. Total acid output during a 3-h period was compared with that obtained in control animals and results were expressed as percent inhibition.

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