Nicotinamide Derivatives as a New Class of Gastric (H^+/K^+)-ATPase Inhibitors. II.[1] Synthesis and Structure–Activity Relationships of 2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamides

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Members of a new series of 2-[(2,4-dimethoxybenzyl)sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamides were synthesized and evaluated for their gastric antisecretory activity and the ability to inhibit cytochrome P450-dependent *O*-dealkylation of 7-ethoxycoumarin (7-EC) in rat liver microsomes. Several of the compounds synthesized exhibited potent inhibitory activities against both [^{14}C]aminopyrine accumulation stimulated by dibutyryl cyclic AMP in isolated rabbit parietal cells and histamine-induced gastric acid secretion in pylorus-ligated rats when administered intraduodenally; their inhibitory activities were equivalent to or superior to those of the parent compound [2-[(2,4-dimethoxybenzyl)sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamide] and omeprazole. Among the compounds having potent antisecretory activity *in vitro* and *in vivo*, 2-[(2,4-dimethoxybenzyl)sulfinyl]-*N*-(2,5-dimethyl-4-pyridinyl)pyridine-3-carboxamide and 2-[(2,4-dimethoxybenzyl)sulfinyl]-*N*-(2,6-dimethyl-4-pyridinyl)pyridine-3-carboxamide in particular showed lower inhibitory activity against the 7-EC deethylase than omeprazole. It seems probable that, unlike omeprazole, these compounds do not interact with a metabolism of other drugs *in vivo*. These compounds, therefore, are considered to be more promising candidate agents for treating acid-related gastrointestinal disorders than the parent compound reported previously.

Key words (H^+/K^+)-ATPase inhibitor; 7-ethoxycoumarin deethylase; antisecretory activity; 2-[(2,4-dimethoxybenzyl)-sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamide

The inhibition of gastric acid secretion has been proven to be a powerful therapeutic principle in the treatment of gastric and duodenal ulcer diseases. In particular, inhibitors of gastric (H^+/K^+)-ATPase, which is located in the apical membrane of the parietal cell and plays a major role in gastric acid secretion, seems to have great potential. Among the (H^+/K^+)-ATPase inhibitors, 2-[(2-pyridinylmethyl)sulfinyl]benzimidazoles (PSBs)[2–6] have been found to have superior properties, causing complete suppression of gastric acid secretion. Omeprazole,[2] lansoprazole,[3] and pantoprazole[4] have recently been introduced for clinical use. The PSBs act as prodrugs, being chemically transformed into active forms in an acidic environment, such as that of the apical membrane of the parietal cell, and inhibiting gastric (H^+/K^+)-ATPase irreversibly.[7] Many PSB analogues[8–15] have been found to possess desirable preclinical biological properties, and proposed as candidate orally active antiulcer agents.

We have found a new class of irreversible and potent (H^+/K^+)-ATPase inhibitors represented by 2-[(2,4-dimethoxybenzyl)sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamide (**1**), as reported previously.[1] Upon acid activation in the acidic environment of the parietal cell, **1** may be converted into its active form, *N*-(4-pyridinyl)-2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridine (**2**), which irreversibly inhibits gastric (H^+/K^+)-ATPase (Chart 1). Its inhibitory activities against [^{14}C]aminopyrine (AP) accumulation stimulated by dibutyryl cyclic AMP (dbcAMP) in isolated rabbit parietal cells and histamine-induced gastric acid secretion in pylorus-ligated rats in the case of intraduodenal (i.d.) administration are comparable to those of omeprazole. Additionally, **1** is much more stable at neutral and weakly acidic pH than omeprazole. It follows from these that **1** is a more selective (H^+/K^+)-ATPase inhibitor than omeprazole. However, **1** is expected to influence the metabolism of other drugs, because it shows potent inhibitory activity against cytochrome P450-dependent *O*-deethylation of 7-ethoxycoumarin (7-EC) in rat microsomes ($IC_{50}=4.5\ \mu M$); this assay was carried out for initial screening of drug interaction. Its potency was higher than that of omeprazole, which is known to influence the metabolism of other drugs *in vitro* and *in vivo*.[16] Thus, we attempted to reduce the 7-EC deethylase-inhibitory activity by modifying **1**.

Kobayashi *et al.*[17] reported that 3- or 4-benzylpyridine potently inhibited cytochrome P450-dependent *N*-demethylation of aminopyrine in rat microsomes, whereas 2-benzylpyridine had little effect. They suggested that the

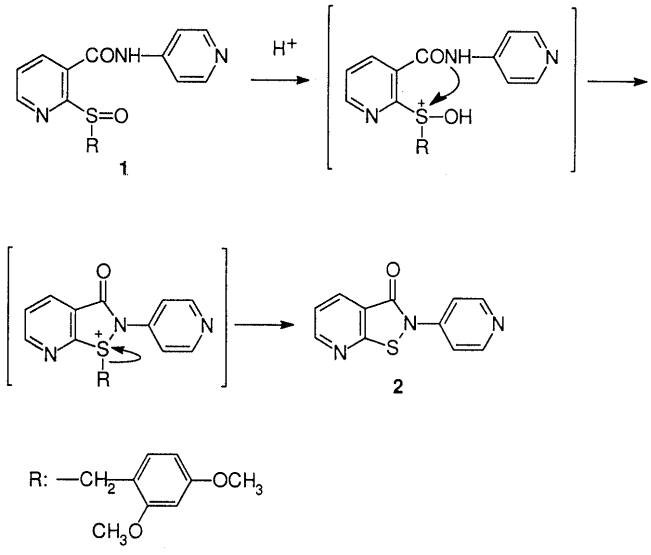

Chart 1

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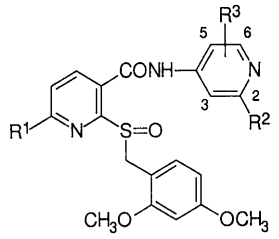
Table 1. 2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamides **3**—**22**



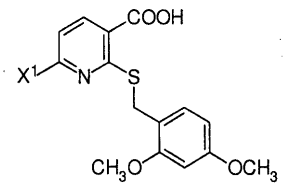
Compd.	R^1	R^2	R^3	Procedure[a]	mp (°C) (Recryst. solvent[b])	Yield (%)	Formula	Analysis (%) Calcd (Found)			
								C	H	N	S
3	H	H	3-CH_3	B	151—154 (C)	14	$C_{21}H_{21}N_3O_4S \cdot 9/20C_2H_5OH$	60.86 (60.56	5.53 5.13	9.72 9.50	7.42 7.03)
4a	H	CH_3	H	B	200—204 (A)	30	$C_{21}H_{21}N_3O_4S$	61.30 (61.15	5.14 5.13	10.21 10.13	7.79 7.46)
4b	H	CH_3	3-CH_3	B	207—210 (C)	17	$C_{22}H_{23}N_3O_4S$	62.10 (61.99	5.45 5.34	9.88 9.71	7.54 7.36)
4c	H	CH_3	5-CH_3	B	195—197 (C)	38	$C_{22}H_{23}N_3O_4S \cdot 1/4H_2O$	61.45 (61.61	5.51 5.51	9.77 9.55	7.46 7.08)
4d	H	CH_3	6-CH_3	B	213—215 (A)	60	$C_{22}H_{23}N_3O_4S \cdot 1/4H_2O$	61.45 (61.26	5.51 5.57	9.77 9.74	7.46 7.36)
4e	$N(CH_3)_2$	CH_3	6-CH_3	B	171—173 (A)	25	$C_{25}H_{27}N_3O_6S \cdot 1/4H_2O$	60.93 (60.82	6.07 5.98	11.84 11.88	6.78 6.68)
5	H	C_2H_5	H	A	183—185 (A)	21	$C_{22}H_{23}N_3O_4S$	62.10 (61.84	5.45 5.42	9.88 9.76	7.54 7.33)
6	H	nC_3H_7	H	B	160—162 (C)	30	$C_{23}H_{25}N_3O_4S \cdot 1/2H_2O$	61.59 (61.36	5.84 5.85	9.37 9.27	7.15 7.02)
7a	H	CH_2OH	H	D	201—203 (B)	16	$C_{21}H_{21}N_3O_5S \cdot 1/4H_2O$	58.39 (58.61	5.02 4.83	9.73 9.64	7.42 7.27)
7b	H	CH_2OH	3-CH_3	D	174—176 (B)	31	$C_{22}H_{23}N_3O_5S$	59.85 (59.47	5.25 5.21	9.52 9.43	7.26 6.99)
7c	H	CH_2OH	5-CH_3	D	157—159 (B)	12	$C_{22}H_{23}N_3O_5S \cdot 1/10H_2O$	57.73 (57.69	5.46 5.12	9.18 9.07	7.01 6.61)
7d	H	CH_2OH	6-CH_3	D	131—134 (A)	36	$C_{22}H_{23}N_3O_5S \cdot 3/2H_2O$	56.40 (56.22	5.59 5.21	8.97 8.80	6.84 6.61)
8a	H	CH_2OCOCH_3	H	C	169—171 (A–F)	23	$C_{23}H_{23}N_3O_6S$	58.84 (58.60	4.94 4.99	8.95 8.93	6.83 6.78)
8b	H	CH_2OCOCH_3	3-CH_3	C	171—173 (E)	42	$C_{24}H_{25}N_3O_6S$	59.61 (59.58	5.21 5.19	8.69 8.50	6.63 6.40)
8c	H	CH_2OCOCH_3	5-CH_3	C	197—199 (I)	57	$C_{24}H_{25}N_3O_6S \cdot 1/4H_2O$	59.06 (59.07	5.27 5.19	8.61 8.55	6.57 6.28)
8d	H	CH_2OCOCH_3	6-CH_3	C	189—191 (A)	55	$C_{24}H_{25}N_3O_6S \cdot 1/10H_2O$	59.72 (59.39	5.24 5.23	8.71 8.66	6.61 6.22)
9	$N(CH_3)_2$	CH_2OCOCH_3	H	C	110—115 (A)	20	$C_{25}H_{28}N_4O_6S \cdot 5/4H_2O$	56.12 (56.16	5.75 5.64	10.47 10.45	5.99 5.84)
10	H	$CH_2OCOC_2H_5$	H	E	136—138 (C)	31	$C_{24}H_{25}N_3O_6S$	59.61 (59.32	5.21 5.27	8.69 8.62	6.63 6.57)
11	H	$CH_2OCOC_2H_5$	6-CH_3	C	178—180 (A)	51	$C_{25}H_{27}N_3O_6S$	60.35 (60.12	5.47 5.37	8.45 8.49	6.44 6.31)
12	H	$CH_2OCOnC_3H_7$	H	E	145—147 (C)	39	$C_{25}H_{27}N_3O_6S \cdot 1/4H_2O$	59.81 (59.89	5.52 5.61	8.37 8.37	6.39 6.26)
13	H	$CH_2OCOnC_4H_9$	H	E	134—136 (C)	46	$C_{26}H_{29}N_3O_6S \cdot 1/4H_2O$	60.51 (60.49	5.76 5.76	8.14 8.14	6.21 6.08)
14a	H	NH_2	H	F	212—215 (B)	30	$C_{20}H_{20}N_4O_4S$	58.24 (58.14	4.89 4.80	13.58 13.45	7.77 7.50)
14b	H	$NHCH_3$	H	F	215—218 (A)	27	$C_{21}H_{22}N_4O_4S$	59.14 (59.00	5.20 5.16	13.14 13.26	7.52 7.29)
15a	H	$N(CH_3)_2$	H	A	191—193 (A)	46	$C_{22}H_{24}N_4O_4S$	59.98 (59.83	5.49 5.43	12.72 12.61	7.28 7.15)
15b	H	$N(CH_3)_2$	3-CH_3	A	197—200 (A)	30	$C_{23}H_{26}N_4O_4S$	60.77 (60.53	5.77 5.75	12.33 12.29	7.05 6.79)
15c	H	$N(CH_3)_2$	5-CH_3	A	200—202 (C)	19	$C_{23}H_{26}N_4O_4S$	60.77 (61.06	5.77 5.80	12.33 12.34	7.05 6.90)
15d	H	$N(CH_3)_2$	6-CH_3	A	105—108 (C)	39	$C_{23}H_{26}N_4O_4S \cdot 1/2H_2O$	59.59 (59.38	5.87 5.84	12.09 11.90	6.92 6.84)
15e	H	$N(C_2H_5)_2$	H	A	173—175 (B)	6	$C_{24}H_{28}N_4O_4S$	61.52 (61.26	6.02 6.06	11.96 11.80	6.84 6.60)

Table 1. (continued)

Compd.	R^1	R^2	R^3	Procedure[a]	mp (°C) (Recryst. solvent[b])	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S
16a	H	$NH(CH_2)_2OH$	H	F	164—172 (B)	5	$C_{22}H_{24}N_4O_6S$	56.76 (56.94	5.41 5.34	12.04 11.85	6.89 6.54)
16b	H	$NCH_3(CH_2)_2OH$	H	F	170—174 (A)	11	$C_{23}H_{26}N_4O_5S$	58.71 (58.50	5.57 5.57	11.91 11.84	6.81 6.56)
16c	H	4-methyl-1-piperazinyl	H	F	153—154 (A)	15	$C_{25}H_{29}N_5O_4S\cdot 3/4H_2O$	58.98 (59.19	6.04 5.81	13.76 13.77	6.30 5.93)
17	H	4-hydroxy-1-piperidinyl	H	A	135—137 (C)	31	$C_{25}H_{28}N_4O_5S\cdot 1/4H_2O$	59.92 (59.98	5.73 5.64	11.18 11.01	6.40 6.13)
18	CH_3	H	H	A	197—200 (A)	23	$C_{21}H_{21}N_3O_4S$	61.30 (61.12	5.14 5.02	10.21 9.98	7.79 7.68)
19a	iso-C_3H_7	H	H	H	204—205 (A)	24	$C_{23}H_{25}N_3O_4S$	62.85 (62.74	5.73 5.64	9.56 9.65	7.30 7.03)
19b	iso-C_4H_9	H	H	H	205—207 (B–D–H)	22	$C_{24}H_{27}N_3O_4S$	63.56 (63.32	6.00 5.92	9.26 9.06	7.07 6.79)
19c	iso-Pen	H	H	H	183—186 (A)	53	$C_{25}H_{29}N_3O_4S\cdot H_2O$	61.84 (61.69	6.43 6.05	8.65 8.52	6.60 6.43)
20	phenyl	H	H	A	209—212 (A)	34	$C_{26}H_{23}N_3O_4S\cdot 1/4H_2O$	65.79 (65.41	4.95 4.85	9.41 9.26	6.63 6.56)
21a	$NHCH_3$	H	H	G	153—157 (A)	56	$C_{21}H_{22}N_4O_4S\cdot 1/4H_2O$	58.52 (58.49	5.26 5.30	13.00 12.93	7.44 7.28)
21b	$N(CH_3)_2$	H	H	G	178—180 (A)	42	$C_{22}H_{24}N_4O_4S$	59.98 (59.76	5.49 5.45	12.72 12.86	7.28 7.29)
21c	$NCH_3(CH_2)_2OH$	H	H	G	169—171 (A)	32	$C_{23}H_{26}N_4O_5S$	58.71 (58.42	5.57 5.54	11.91 12.75	6.81 6.74)
21d	4-methyl-1-piperazinyl	H	H	G	172—174 (A)	24	$C_{25}H_{29}N_5O_4S\cdot 1/2H_2O$	59.51 (59.57	5.99 5.86	13.88 14.04	6.35 6.27)
21e	4-hydroxyl-1-piperidinyl	H	H	G	199—201 (A)	42	$C_{25}H_{28}N_4O_5S$	60.47 (60.36	5.68 5.65	11.28 11.33	6.46 6.37)
22	$N(CH_3)_2$	$N(CH_3)_2$	H	G	195—197 (A)	16	$C_{24}H_{29}N_5O_4S$	59.61 (59.34	6.04 5.94	14.48 14.36	6.63 6.39)

a) Capital letters refer to the procedures described in the Experimental. *b*) A=CH_3CN, B=CH_3OH, C=acetone, D=$CHCl_3$, E=toluene, F=$(C_2H_5)_2O$, G=C_2H_5OH, H=*n*-hexane, I=$(iso\text{-}C_3H_7)_2O$.

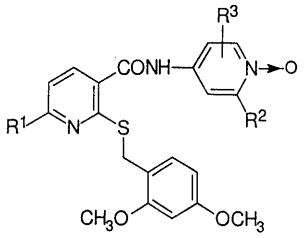
Table 2. 2-[(2,4-Dimethoxybenzyl)thio]pyridine-3-carboxylic Acids **23**—**27**



Compd.	X^1	mp (°C) (Recryst. solvent[a])	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Halogen
23[b]	H	189—192 (B)	96	$C_{15}H_{15}NO_4S$					
24	CH_3	164—166 (B)	82	$C_{16}H_{17}NO_4S$	60.17 (59.88	5.37 5.28	4.39 4.27	10.04 9.93)	
25	C_6H_5	231—233 (C)	62	$C_{21}H_{19}NO_4S$	66.12 (66.08	5.02 5.01	3.67 3.72	8.41 8.33)	
26	Cl	187—190 (C)	52	$C_{15}H_{14}ClNO_4S$	53.02 (53.02	4.15 3.92	4.12 4.08	9.44 9.41	10.43 10.18)
27	F	200—203 (C)	54	$C_{15}H_{14}FNO_4S$	55.72 (55.98	4.36 4.26	4.33 4.29	9.92 9.83	5.88 5.58)

a) See footnote *b* in Table 1. *b*) This compound was previously prepared.[18]

Table 3. 4-[2-[(2,4-Dimethoxybenzyl)thio]-3-pyridinecarbonylamino]pyridine 1-Oxides **28**—**31**



Compd.	R^1	R^2	R^3	mp (°C) (Recryst. solvent[a])	Yield (%)	Formula	Analysis (%) Calcd (Found)			
							C	H	N	S
28	H	H	3-CH_3	200—223 (B)	32	$C_{21}H_{21}N_3O_4S\cdot 1/4H_2O$	60.64 (60.79	5.21 5.05	10.10 10.14	7.71 7.49)
29a	H	CH_3	H	234—236 (B)	35	$C_{21}H_{21}N_3O_4S\cdot 1/4H_2O$	60.64 (60.83	5.21 5.05	10.10 10.07	7.71 7.48)
29b	H	CH_3	3-CH_3	150—152 (C)	69	$C_{22}H_{23}N_3O_4S$	62.10 (62.00	5.45 5.38	9.88 9.72	7.54 7.21)
29c	H	CH_3	5-CH_3	134—136 (A)	63	$C_{22}H_{23}N_3O_4S\cdot 3/5H_2O$	60.56 (60.70	5.59 5.48	9.63 9.48	7.35 7.07)
29d	H	CH_3	6-CH_3	241—244 (B)	32	$C_{22}H_{23}N_3O_4S\cdot 1/4H_2O$	61.45 (61.59	5.51 5.33	9.77 9.65	7.46 7.20)
29e	$N(CH_3)_2$	CH_3	6-CH_3	174—178 (B)	24	$C_{24}H_{28}N_4O_4S\cdot 3/4H_2O$	59.80 (60.14	6.17 6.07	11.62 11.63	6.65 6.50)
30	H	n-C_3H_7	H	Oil[b]	57	$C_{23}H_{25}N_3O_4S$				
31	$N(CH_3)_2$	CH_3	H	202—204 (B)	88	$C_{23}H_{26}N_4O_4S\cdot 3/4H_2O$	59.02 (59.17	5.92 5.79	11.97 11.94	6.85 6.64)

a) See footnote *b* in Table 1. *b*) Mass spectrum (APCIMS) *m/z*: 440 (MH^+).

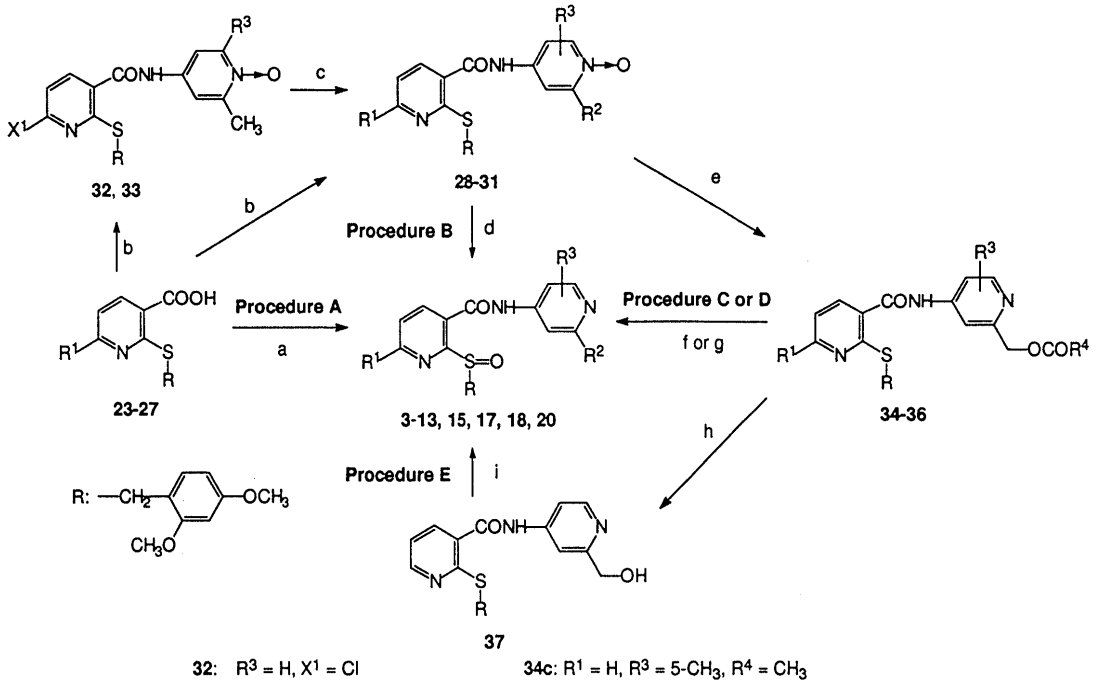
aminopyrine *N*-demethylase inhibition exhibited by 3- or 4-benzylpyridine was a the result of high-affinity binding of the nitrogen atom of the pyridine ring to the heme moiety of the cytochrome P450 molecule. Since the nitrogen atom of the pyridine ring may be hindered from binding to the heme moiety by introduction of a benzyl group into the α-position, we expected that introduction of a substituent into the α-position of the pyridine ring on the nitrogen atom of the carbamoyl moiety of **1** would result in a decrease in the 7-EC-deethylase inhibitory activity.

The present study was focused on not only enhancing the inhibitory activities of **1** against histamine-induced gastric acid secretion and AP accumulation, but also decreasing the inhibitory activity of **1** against the 7-EC deethylase. The present paper deals with the synthesis and pharmacological activities of 2-[(2,4-dimethoxybenzyl)-sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamides.

Chemistry

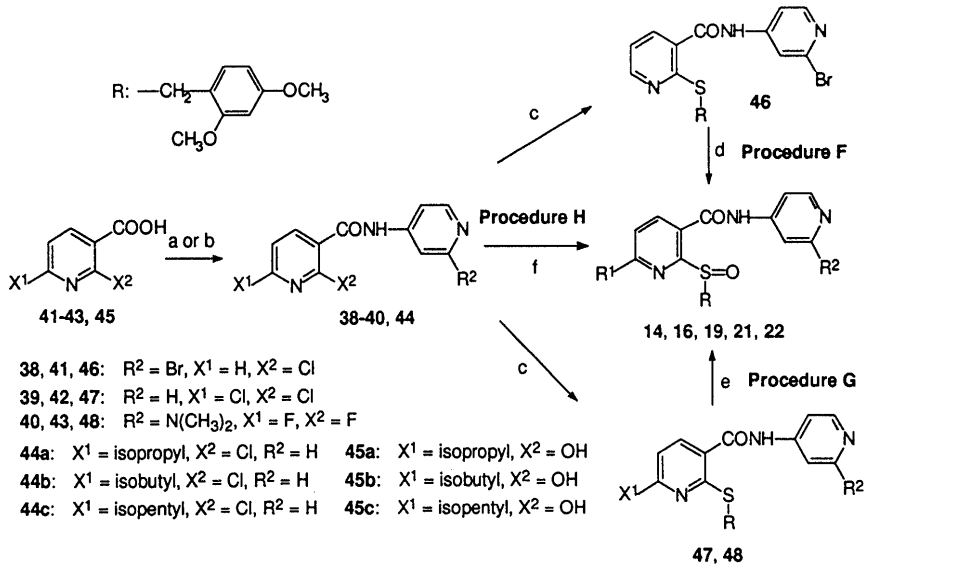
The desired carboxamides **3**—**22** (Table 1) were synthesized *via* the routes shown in Charts 2 and 3. The requisite carboxylic acid **23** (Table 2) was prepared from 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acid according to the method reported previously,[1,18] whereas the carboxylic acids **24**—**27** (Table 2) were synthesized from the corresponding 2-chloro-, 2,6-dichloro- or 2,6-difluoro-pyridine-3-carboxylic acid by treatment with 2,4-dimethoxybenzenemethanethiol in the presence of NaH or K_2CO_3. The carboxamides **5**, **15**, **18**, and **20** were prepared by condensation of the corresponding carboxylic acids **23**—**25** with the corresponding 4-aminopyridines by the use of oxalyl chloride, followed by oxidation with *m*-chloroperbenzoic acid (*m*CPBA), as reported previously[1,18] (procedure A). The carboxamide **17** was prepared *via* the 2-(4-oxo-1-piperidinyl)pyridinyl derivative obtained by condensation as described above, followed by reduction with $NaBH_4$ and subsequent oxidation. Pyridine 1-oxides **28**—**31** (Table 3), key intermediates for the carboxamides **3**, **4**, and **6**—**13**, were prepared by condensation of the carboxylic acid **23** with corresponding 4-aminopyridine 1-oxides, whereas **29e** and **31** were prepared *via* the 2-fluoro- (**32**) or 2-chloro (**33**) derivative obtained from the carboxylic acids **26** and **27**, followed by treatment with dimethylamine. The carboxamides **3**, **4**, and **6** were prepared from the corresponding pyridine 1-oxides **28**—**30** by reduction with PCl_3, followed by oxidation (procedure B). The carboxamides **8**, **9**, and **11** were prepared by rearrangement of the pyridine 1-oxides **29a**—**d** and **31** with acetic anhydride or propionic anhydride, followed by oxidation of the resulting esters **34**—**36** (procedure C). The carboxamides **7a**—**d** were prepared *via* the corresponding esters **34a**—**d**, followed by hydrolysis and subsequent oxidation (procedure D). The carboxamides **10**, **12**, and **13** were prepared from hydroxymethyl derivative **37** by condensation with the corresponding acid chlorides and subsequent oxidation (procedure E).

Compounds **38**—**40**, key intermediates for the carboxamides **14**, **16**, **21**, and **22** were prepared by condensation of the corresponding carboxylic acids **41**—**43** with 4-aminopyridine or 4-amino-2-dimethylaminopyridine by the use of oxalyl chloride, whereas compounds **44a**—**c**



a) (1) corresponding 4-aminopyridine, $(COCl)_2$ (2) *m*CPBA b) corresponding 4-aminopyridine 1-oxide, $(COCl)_2$; c) $(CH_3)_2NH$; d) (1)PCl_3 (2) *m*CPBA; e) $(CH_3CO)_2O$ or $(C_2H_5CO)_2O$; f) *m*CPBA; g) (1) aq. K_2CO_3 (2) *m*CPBA; h) aq. K_2CO_3 i) (1) R^4COCl, pyridine; (2) *m*CPBA.

Chart 2



a) corresponding 4-aminopyridine, $(COCl)_2$; b) (1) $POCl_3$ (2) 4-aminopyridine; c) 2,4-dimethoxybenzenemethanethiol, NaH; d) (1) corresponding amine, CuBr (2) *m*CPBA; e) (1) corresponding amine (2) *m*CPBA or $NaIO_4$; f) (1) 2,4-dimethoxybenzenemethanethiol, K_2CO_3 (2) *m*CPBA

Chart 3

were prepared from the corresponding 2-hydroxypyridine-3-carboxylic acids **45a—c**, which were chlorinated with $POCl_3$, followed by condensation. The carboxamides **14**, **16**, **21**, and **22** were prepared *via* the sulfides **46—48** obtained from **38—40** according to the method used for the preparation of the carboxylic acids **24—27**, followed by treatment with the corresponding amines and subsequent oxidation (procedures F and G). In the case of procedure F, the treatment with the amines was performed in the presence of CuBr. The carboxamides **19a—c** were prepared from the corresponding 2-chloropyridine-3-carboxamides **44a—c**, which were converted to the

corresponding sulfides, similarly to **38**—**40**, followed by direct oxidation (procedure H).

In the cases of **16c** and **21d**, oxidation of the respective sulfides with *m*CPBA was performed in the presence of borane–tetrahydrofuran complex to avoid formation of the 1-oxide derivatives.

Pharmacological Results and Discussion

Compounds **3**—**22** were first evaluated for their ability to inhibit histamine-induced gastric acid secretion in pylorus-ligated rats after i.d. administration and AP accumulation stimulated by dbcAMP in isolated rabbit parietal cells. The results are summarized in Table 4 in comparison with the those for parent compound **1** and omeprazole.

The effect of substituents R^1, R^2, and R^3 of the pyridine-3-carboxamides on the *in vitro* and *in vivo* activities was examined from the viewpoint of reduction of the 7-EC deethylase-inhibitory activity.

Introduction of a methyl group(s) into the 2-position (**4a**), 2- and 5-positions (**4c**), and 2- and 6-positions (**4d**) of the pyridine ring on the nitrogen atom of the carbamoyl moiety tended to enhance the inhibitory activities against both AP accumulation and histamine-induced acid secretion, whereas introduction of the methyl group(s) into the 3-position (**3**), and 2- and 3-positions (**4b**) seemed to reduce the *in vivo* activity. Introduction of bulkier alkyl groups such as ethyl (**5**) and *n*-propyl (**6**) groups as R^2 resulted in a decrease in the *in vivo* activity. On the other hand, introduction of methyl (**18**), isopropyl (**19a**), isobutyl (**19b**), and phenyl (**20**) groups as R^1 caused a slight increase in the inhibitory activity against AP accumulation, but resulted in a considerable decrease in the *in vivo* activity. Compounds bearing alkanoyloxymethyl groups such as acetyloxymethyl (**8a**), propanoyloxymethyl (**10**), butanoyloxymethyl (**12**), and valeryloxymethyl (**13**) groups as R^2 were not as potent as **1** and omeprazole in terms of inhibitory activity against AP accumulation; nevertheless, they exhibited *in vivo* activity equivalent to or superior to those of **1** and omeprazole independently of their alkyl chain length. These compounds (**8a**, **10**, **12**, and **13**) might exhibit potent *in vivo* activity after having been metabolized to the hydroxymethyl derivative (**7a**), because **7a** ($ED_{50}=0.9$ mg/kg) inhibited histamine-induced gastric acid secretion as potently as omeprazole ($ED_{50}=0.6$ mg/kg) when administered intravenously although it showed weak *in vivo* activity when administered intraduodenally. Introduction of a methyl group into the 3-position (**8b**), 5-position (**8c**) or 6-position (**8d** and **11**) of the pyridine ring on the nitrogen atom of the carbamoyl moiety of **8a** and **10** did not cause a considerable increase in the *in vivo* activity. Interestingly, introduction of a methyl group (**7b**) into the 3-position of the pyridine ring of **7a**, which showed weak *in vivo* activity, resulted in potent activity after i.d. administration, but introduction into the 5- or 6-position (**7c** and **7d**) decreased the activity. The lack of correlation between the *in vitro* and *in vivo* assays may be due to a disparity in the ability of the compounds to reach the parietal cells.

Introduction of a dimethylamino group as R^2 (**15a**) and R^1 (**21b**) tended to enhance both the *in vitro* and *in vivo* activities. The compounds bearing other amino groups as R^2 (**14a, b**, **15e**, **16a**—**c**, and **17**) and R^1 (**21a** and **21c**—**e**) showed lower *in vivo* activity than **15a** and **21b**. Substitution of amino groups as R^2 seemed to influence the *in vivo* activity more significantly than substitution as R^1. Introduction of a methyl group into the 3-position (**15b**) of the

Table 4. Antisecretory Activities of 2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamides **3**—**22**

Compd.	[^{14}C]AP accumulation[a,b] IC_{50}[c] or % inhibition (μM)	*In vivo* inhibition of gastric acid secretion pylorus-ligated rats[b] ED_{50}[d] or % inhibition (i.d. dose mg/kg)[e]
1	0.59	4.2 [1.4—12.2]
3		54.3% (10)[f]
4a	0.19	1.9 [0.5—7.6]
4b		55.9% (10)[g]
4c	0.24	2.8 [1.0—8.0]
4d	0.24	2.7 [1.0—6.8]
4e	0.12	3.2 [1.0—9.9]
5		41.5% (10)[g]
6		12.0% (10)
7a	3.7	31.9% (10)[f]
7b	1.6	3.3 [1.3—8.8]
7c		NE[h]
7d	54.1% (5.0)	12.6% (10)
8a	6.0	2.3 [0.9—6.4]
8b	2.6	2.0 [0.4—11.0]
8c		30.3% (10)
8d	41.9% (5.0)	85.6% (10)[g]
		32.6% (3)
9	0.20	12.3% (10)
10	2.6	71.4% (10)[g]
		48.5% (3)[f]
11	60.2% (5.0)	4.1 [1.3—13.1]
12	2.4	2.3 [0.3—17.3]
13	>3.0 (27.1%)	3.8 [1.5—10.0]
14a		38.4% (10)
14b		NE[h]
15a	0.27	2.5 [0.8—8.6]
15b		78.8 (10)[g]
15c		1.1% (10)
15d		NE[h]
15e		27.4% (10)
16a		NE[h]
16b		NE[h]
16c		36.8% (10)
17		24.5% (10)
18	0.38	77.0% (100)[g]
		41.8% (10)[f]
19a	0.23	37.1% (100)
19b	0.21	12.3% (100)
19c	4.9	64.9% (100)[g]
		21.3% (10)
20	0.23	15.8% (100)
21a	0.15	71.0% (10)
		39.2% (3)
21b	0.14	2.6 [1.0—6.6]
21c	0.87	40.7% (10)[f]
21d	0.97	4.1 [0.5—33.7]
21e	1.0	84.8% (10)[g]
		16.7% (3)
22	0.10	57.5% (10)[g]
		29.2% (3)
Omeprazole	0.37	4.1 [1.5—10.9]

a) Inhibition of [^{14}C]AP accumulation determined in isolated rabbit parietal cells after dbcAMP stimulation. *b*) See Experimental. *c*) IC_{50} values were calculated from the regression lines. *d*) ED_{50} values were calculated from the regression lines (95% confidence limits in brackets). *e*) $n=4$—7 at each dose. *f*) $0.01<p<0.05$. *g*) $p<0.01$. *h*) NE: not effective.

Table 5. Inhibitory Activities of 2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamides against 7-Ethoxycoumarin (EC) Deethylase Activity in Rat Liver Microsomes

Compd.	EC Deethylase activity[a] IC_{50} or % inhibition (μM)	Compd.	EC Deethylase activity[a] IC_{50} or % inhibition (μM)
1	4.5	**11**	>100 (33.2%)
4a	85	**12**	>100 (25.4%)
4b	>100 (16.1%)	**15a**	>30 (36.2%)
4c	>100 (42.7%)	**18**	3.8
4d	>100 (28.9%)	**19a**	1.6
7a	>100 (23.0%)	**19b**	1.6
7b	>100 (20.8%)	**20**	3.2
7d	80	**21b**	3.7
8a	>100 (31.8%)	**21c**	5.6
8b	>100 (32.9%)	**21d**	5.5
8d	>100 (26.7%)	**22**	>30 (47.9%)
10	>100 (34.8%)	Omeprazole	69

a) See Experimental. The IC_{50} values were calculated from the regression lines.

pyridine ring on the nitrogen atom of the carbamoyl moiety of **15a** had little effect on the *in vivo* activity, whereas introduction into the 5-position (**15c**) or 6-position (**15d**) caused a considerable decrease in the activity. It was expected that introduction (**4e**, **9**, and **22**) of a dimethylamino group as R^1 into **4d**, **8a**, and **15a**, which potently inhibit histamine-induced gastric acid secretion, would cause an increase in their *in vitro* and *in vivo* activities, and indeed these compounds inhibited the AP accumulation more potently than **4d**, **8a**, and **15a**, respectively. Compounds **9** and **22**, but not **4e**, however, showed weaker *in vivo* activity as compared with **8a** and **15a**, respectively.

Finally, we selected **4a**, **4c**, **4d**, **15a**, and **21b** which have been found to have inhibitory activities equivalent to or superior to those of **1** and omeprazole against both histamine-induced gastric acid secretion and AP accumulation, because it was thought to be likely that high potency in both the *in vitro* and *in vivo* assays might imply good efficacy in other species besides rats.

Next, the parent compound **1** and many of the compounds synthesized were evaluated for the ability to inhibit cytochrome P450-dependent *O*-dealkylation of the 7-EC in rat liver microsomes. The results are summarized in Table 5.

The pyridine-3-carboxamides bearing substituent(s) other than a hydrogen atom at the α-positions at the pyridine ring on the nitrogen atom of the carbamoyl moiety exhibited considerably reduced inhibitory activity against 7-EC deethylase as compared with **1**. Although we expected that disubstitution at the 2- and 6-positions of the pyridine ring would result in lower inhibition than monosubstitution at the 2-position, additional substitution at the 6-position was not particularly effective. In order to confirm our hypothesis, the effect of substituents R^1 on the activity was also examined. Introduction of substituents R^1 had little effect on the activity. We deduced from these findings that the substituents at the α-position of the pyridine ring hindered the nitrogen atom of the pyridine ring from binding to the heme moiety of the cytochrome P450 molecule, as suggested by Kobayashi *et al.*[17] Accordingly, it is supposed that introduction of a substituent into this position leads to reduced inhibitory activity against other P450-dependent enzymes. Among the compounds which have a substituent R^2 and exhibit potent gastric antisecretory activity *in vitro* and *in vivo*, **4c** and **4d** exhibited weaker 7-EC deethylase-inhibitory activity as compared with not only **4a** and **15a**, but also omeprazole.

As a result of the present study, we have found that **4c** (AD-9161) and **4d** (AD-8717) possess not only inhibitory activities equivalent to or superior to those of omeprazole against [^{14}C]AP accumulation stimulated by dbcAMP in isolated rabbit parietal cells and histamine-induced gastric acid secretion in pylorus-ligated rats after i.d. administration, but also lower *in vitro* inhibitory activity against the 7-EC deethylase in rat liver microsomes as compared with omeprazole or **1**. It thus seems likely that these compounds would not interfere with the metabolism of other drugs *in vivo*. The compounds, therefore, seem to be more promising agents for treating acid-related gastrointestinal disorders than the parent compound **1** reported previously.

Experimental

All melting points were determined on a Yanagimoto micromelting 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). Organic extracts were dried over anhydrous $MgSO_4$.

The following known intermediates were prepared according to the literature: 4-amino-2-ethylpyridine[19]; 4-amino-2-dimethylaminopyridine[20]; 4-amino-2-diethylaminopyridine[20]; 4-amino-2-methylpyridine 1-oxide[21]; 4-amino-3-methylpyridine 1-oxide[22]; 4-amino-2,6-dimethylpyridine 1-oxide[23]; 2-chloro-6-phenylpyridine-3-carboxylic acid.[24]

4-Amino-2,5-dimethylpyridine 1-Oxide and 4-Amino-2-propylpyridine 1-Oxide These compounds were prepared from 2,5-dimethylpyridine and 2-propylpyridine, respectively, in a manner similar to that described in the literature.[21] The overall yields of the 4-aminopyridine 1-oxide derivatives were 55% and 48%, respectively.

4-Amino-2-dimethylamino-3-methylpyridine, 4-Amino-2-dimethylamino-5-methylpyridine, and 4-Amino-2-dimethylamino-6-methylpyridine These compounds were prepared from 2-chloro-3-methylpyridine, 2-chloro-5-methylpyridine, and 2-chloro-6-methylpyridine, respectively, in a manner similar to that described in the literature.[19] The overall yields of the 4-aminopyridine derivatives were 56%, 65%, and 87%, respectively.

4-Amino-2-(4-oxopiperidinyl)pyridine and 4-Amino-2-(4-methyl-1-piperazinyl)pyridine These compounds were prepared from 2-bromo-4-nitropyridine 1-oxide in a manner similar to that described in the literature.[19] The overall yields of the 4-aminopyridine derivatives were 36% and 47%, respectively.

2,4-Dimethoxybenzenemethanethiol A mixture of 2,4-dimethoxybenzyl alcohol (18.9 g, 0.112 mol), 2,4-bis(4-methoxyphenyl)-1,3-dithia 2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (25.0 g, 0.062 mol) and toluene (300 ml) was heated at reflux temperature for 30 min with stirring and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel and eluted with $CHCl_3$–hexane (1 : 2) to give 6.1 g (30%) of 2,4-dimethoxybenzenemethanethiol as an oily product: ^{1}H-NMR δ: 2.52 (1H, t, J=7.5 Hz), 3.61 (2H, d, J=7.5 Hz), 3.75 (3H, s), 3.80 (3H, s), 6.46 (1H, dd, J=2.6, 8.2 Hz), 6.53 (1H, d, J=2.6 Hz), 7.16 (1H, d, J=8.2 Hz).

2,4-Dimethoxybenzenemethanethiol, without further purification, was

used for the preparation of various pyridine-3-carboxylic acids and pyridine-3-carboxamides.

2,6-Difluoropyridine-3-carboxylic Acid (43) *n*-Butyllithium (1.56 M) in hexane (130 ml, 0.20 mol) was added dropwise to a stirred solution of 2,6-difluoropyridine (20 g, 0.17 mol) in tetrahydrofuran (THF) (200 ml) at −78 °C. After 30 min, dry ice (300 g) was added slowly and the resulting mixture was stirred for 1 h. The mixture was taken up in 10 ml of CH_3OH and 70 ml of water, washed with $(C_2H_5)_2O$, and neutralized with concentrated HCl. The aqueous mixture was extracted with two 200-ml portions of $(C_2H_5)_2O$. The combined extracts were washed with brine, dried, and concentrated to dryness *in vacuo*. The residue was recrystallized from toluene to give 26 g (95%) of **55b**: ^{1}H-NMR δ: 7.80 (1H, ddd, J=0.8, 2.7, 8.0 Hz), 9.09 (1H, dt, J=8.0, 9.6 Hz), 14.21 (1H, s). MS m/z: 160 (MH^+). IR (KBr) cm^{-1}: 1697 (C=O). *Anal.* Calcd for $C_6H_3F_2NO_2$: C, 45.30; H, 1.90; F, 23.88; N, 8.80. Found: C, 45.31; H, 1.77; F, 23.89; N, 8.86.

2-[(2,4-Dimethoxybenzyl)thio]-6-methylpyridine-3-carboxylic Acid (24) A mixture of 2-chloro-6-methylpyridine-3-carboxylic acid (5.1 g, 0.027 mol), 2,4-dimethoxybenzenemethanethiol (5.0 g, 0.027 mol), K_2CO_3 (4.5 g, 0.033 mol), and *N*,*N*-dimethylformamide (DMF) (200 ml) was heated at 110 °C for 24 h with stirring and concentrated to dryness *in vacuo*. The residue was dissolved in 100 ml of water and neutralized with concentrated HCl. The resulting precipitates were collected by filtration and dried to give 7.0 g (82%) of **24**. Compound **24** was recrystallized from CH_3OH and subjected to analysis: ^{1}H-NMR δ: 2.55 (3H, s), 3.73 (3H, s), 3.80 (3H, s), 4.23 (2H, s), 6.45 (1H, dd, J=2.4, 8.3 Hz), 6.55 (1H, d, J=2.4 Hz), 7.06 (1H, d, J=7.9 Hz), 7.30 (1H, d, J=8.3 Hz), 8.07 (1H, d, J=7.9 Hz), 13.23 (1H, s). SIMS m/z: 319 (M^+). IR (KBr) cm^{-1}: 1686 (C=O).

Compound **25** was prepared from 2-chloro-6-phenylpyridine-3-carboxylic acid in a manner similar to that described above.

6-Fluoro-2-[(2,4-dimethoxybenzyl)thio]pyridine-3-carboxylic Acid (27) 2,4-Dimethoxybenzenemethanethiol (6.0 g, 0.033 mol) was added slowly to a suspension of NaH (60% dispersion in mineral oil, 3.7 g, 0.093 mol) in anhydrous THF (50 ml) at 0 °C. The reaction mixture was stirred at room temperature for 20 min, and then a solution of 2,6-difluoropyridine-3-carboxylic acid (5.8 g, 0.036 mol) in THF (50 ml) was added. The resulting mixture was heated at reflux temperature with stirring for 1 h. The reaction mixture was taken up in 70 ml of water and neutralized with concentrated HCl. The aqueous mixture was extracted with two 200-ml portions of $CH_3CO_2C_2H_5$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was crystallized from CH_3CN to give 6.0 g (52%) of **27**: mp 200—203 °C. ^{1}H-NMR δ: 3.76 (3H, s), 3.82 (3H, s), 4.20 (2H, s), 6.48 (1H, dd, J=2.3, 8.7 Hz), 6.57 (1H, d, J=2.3 Hz), 6.96 (1H, dd, J=3.2, 8.4 Hz), 7.29 (1H, d, J=8.7 Hz), 8.70 (1H, dd, J=8.3, 8.4 Hz), 13.43 (1H, br). APCIMS m/z: 324 (MH^+). IR (KBr) cm^{-1}: 1693 (C=O).

Compound **26** was prepared from 2,6-dichloropyridine-3-carboxylic acid in a similar manner to that described above.

4-[2-[(2,4-Dimethoxybenzyl)thio]-3-pyridinecarbonylamino]-2,6-dimethylpyridine 1-Oxide (29d) This compound was prepared starting from 2-[(2,4-dimethoxybenzyl)thio]pyridine-3-carboxylic acid (**23**), which was chlorinated with oxalyl chloride, followed by condensation with 4-amino-2,6-dimethylpyridine 1-oxide in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 2.37 (6H, s), 3.72 (3H, s), 3.79 (3H, s), 4.33 (2H, s), 6.43 (1H, dd, J=2.2, 8.1 Hz), 6.55 (1H, d, J=2.2 Hz), 7.25 (1H, d, J=8.1 Hz), 7.66 (2H, s), 7.93 (1H, dd, J=2.1, 7.8 Hz), 8.63 (1H, dd, J=2.1, 4.8 Hz). APCIMS m/z: 426 (MH^+). IR (KBr) cm^{-1}: 1681 (C=O).

Compounds **28**, **29a—c**, and **30** were prepared in a manner similar to that described above.

4-[2-[(2,4-Dimethoxybenzyl)thio]-6-dimethylamino-3-pyridinecarbonylamino]-2-methylpyridine 1-Oxide (31) Compound **32** was prepared starting from **26**, which was chlorinated with oxalyl chloride, followed by condensation with 4-amino-2-methylpyridine 1-oxide in a manner similar to that described previously.[1,18] The overall yield was 51%. MS m/z: 446 (MH^+).

A mixture of **32** (2.0 g, 4.5 mmol), 50% $(CH_3)_2NH$ aqueous solution (60 ml), and C_2H_5OH (30 ml) was heated at reflux temperature for 3 h and concentrated to dryness *in vacuo*. The residue was taken up in 30 ml of water, and the aqueous mixture was extracted with two 100-ml portions of $CHCl_3$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was crystallized from CH_3CN to give 1.8 g (88%) of **31**: ^{1}H-NMR δ: 2.33 (3H, s), 3.14 (6H, s), 3.73 (3H, s), 3.80 (3H, s), 4.25 (2H, s), 6.55 (1H, d, J=2.3 Hz), 7.21 (1H, d, J=8.2 Hz), 7.54 (1H, dd, J=3.1, 7.2 Hz), 7.82 (1H, d, J=3.1 Hz), 7.88 (1H, d, J=8.5 Hz), 8.14 (1H, d, J=7.2 Hz), 10.27 (1H, s). SIMS m/z: 455 (MH^+). IR (KBr) cm^{-1}: 1663 (C=O).

Compound **29e** was derived from **27** in a manner similar to that described above.

2-Chloro-6-isopentyl-*N*-(4-pyridinyl)pyridine-3-carboxamide (44c) A mixture of **45c** (13.0 g, 0.062 mol) and $POCl_3$ (50 ml) was heated at reflux temperature for 3 h with stirring and concentrated to dryness *in vacuo*. The residue was dissolved in THF (200 ml), and then a solution of 4-aminopyridine (17.5 g, 0.186 mol) and $N(C_2H_5)_3$ (18.8 g, 0.186 mol) in THF (100 ml) was added slowly at 0 °C. The reaction mixture was stirred at room temperature for 3 h and concentrated to dryness *in vacuo*. The residue was taken up in 200 ml of water, and the aqueous mixture was extracted with two 400-ml portions of $CHCl_3$. The combined extracts were washed with saturated aqueous $NaHCO_3$, dried, and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel and eluted with $CHCl_3$–CH_3OH (50 : 1) to give **44c** (13.0 g, 69%) as an oily product: ^{1}H-NMR δ: 0.92 (6H, d, J=5 Hz), 2.79 (2H, t, J=7 Hz), 7.44 (1H, d, J=8 Hz), 7.66 (2H, m), 8.01 (1H, d, =8 Hz), 8.50 (2H, m). APCIMS m/z: 304 (MH^+). IR (KBr) cm^{-1}: 1693 (C=O).

Compounds **44a**, **b** were prepared in a manner similar to that described above.

2-Chloro-6-isopropyl-*N*-(4-pyridinyl)pyridine-3-carboxamide (44a) Yield 74%, mp 196—199 °C (from CH_3CN). *Anal.* Calcd for $C_{14}H_{14}ClN_3O$: C, 60.98; H, 5.12; Cl, 12.86; N, 15.24. Found: C, 61.04; H, 5.05; Cl, 12.74; N, 15.11.

2-Chloro-6-isobutyl-*N*-(4-pyridinyl)pyridine-3-carboxamide (44b) Yield 39%, mp 110—112 °C (from CH_3CN). *Anal.* Calcd for $C_{15}H_{16}ClN_3O$: C, 62.18; H, 5.57; Cl, 12.23; N, 14.50. Found: C, 61.82; H, 5.53; Cl, 12.39; N, 14.41.

***N*-(2-Bromo-4-pyridinyl)-2-[(2,4-dimethoxybenzyl)thio]pyridine-3-carboxamide (46)** Compound **38** was prepared starting from **41**, which was chlorinated with oxalyl chloride, followed by condensation with 4-amino-2-bromopyridine in a manner similar to that described previously,[1,18] yield 78%. APCIMS m/z: 313 (MH^+).

2,4-Dimethoxybenzenemethanethiol (19.7 g, 107 mmol) was added slowly to a suspension of NaH (60% dispersion in mineral oil, 4.3 g, 107 mmol) in anhydrous THF (50 ml) at 0 °C. The reaction mixture was stirred at room temperature, and then a solution of **38** (28.0 g, 89 mmol) in THF (50 ml) was added. The resulting mixture was heated at reflux temperature for 1 h with stirring. The reaction mixture was taken up in 200 ml of water, and the aqueous mixture was neutralized with concentrated HCl, and extracted with two 500-ml portions of $CH_3CO_2C_2H_5$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel, eluted with $CHCl_3$–CH_3OH (40 : 1), and recrystallized from CH_3CN to give 38.2 g (93%) of **46**: mp 128—131 °C. ^{1}H-NMR δ: 3.72 (3H, s), 3.79 (3H, s), 4.32 (2H, s), 6.43 (1H, dd, J=2.2, 8.2 Hz), 6.55 (1H, d, J=2.2 Hz), 7.62 (1H, dd, J=2.1, 5.7 Hz), 8.29 (1H, d, J=5.7 Hz), 8.66 (1H, dd, J=2.0, 5.1 Hz). APCIMS m/z: 461 (MH^+). IR (KBr) cm^{-1}: 1686 (C=O). *Anal.* Calcd for $C_{20}H_{18}BrN_3O_3S$: C, 52.18; H, 3.94; Br, 17.36; N, 9.13; S, 6.96. Found: C, 52.04; H, 3.89; Br, 17.17; N, 9.08; S, 6.93.

6-Chloro-2-[(2,4-dimethoxybenzyl)thio]-*N*-(4-pyridinyl)pyridine-3-carboxamide (47) This compound was prepared starting from **42** in 79% yield in a manner similar to that described above: mp 153—155 °C (from CH_3CN). *Anal.* Calcd for $C_{20}H_{18}ClN_3O_3S$: C, 57.76; H, 4.36; Cl, 8.52; N, 10.10; S, 7.71. Found: C, 57.68; H, 4.33; Br, 8.24; N, 10.09; S, 7.62.

6-Fluoro-2-[(2,4-dimethoxybenzyl)thio]-(2-dimethylamino-4-pyridinyl)-pyridine-3-carboxamide (48) This compound was prepared starting from **43** in 30% yield in a manner similar to that described above: mp 160—162 °C (from CH_3CN). *Anal.* Calcd for $C_{22}H_{23}FN_4O_3S$: C, 59.71; H, 5.24; F, 4.29; N, 12.66; S, 7.25. Found: C, 59.78; H, 5.17; F, 4.19; N, 12.72; S, 7.00.

2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(4-pyridinyl)pyridine-3-carboxamides 3-22 (Table 1). Procedure A. 2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(2-dimethylamino-4-pyridinyl)pyridine-3-carboxamide (15a) Crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-(2-dimethylamino-4-pyridinyl)pyridine-3-carboxamide was prepared starting from 2-[(2,4-dimethoxybenzyl)thio]pyridine-3-carboxylic acid (**23**), which was chlorinated with oxalyl chloride, followed by condensation with 4-amino-2-dimethylaminopyridine in a manner similar to that described previously.[1,18] This compound was obtained as an oily product. The overall yield was 79%:

^{1}H-NMR δ: 2.99 (6H, s), 3.73 (3H, s), 3.78 (3H, s), 4.32 (2H, s), 6.43 (1H, dd, J=2.0, 8.1 Hz), 6.54 (1H, d, J=2.0 Hz), 6.85 (1H, dd, J=1.8, 5.6 Hz), 7.03 (1H, d, J=1.8 Hz), 7.25 (1H, d, J=8.1 Hz), 7.26 (1H, dd, J=5.0, 7.7 Hz), 7.91 (1H, dd, J=1.9, 7.7 Hz), 7.97 (1H, d, J=5.6 Hz), 8.62 (1H, dd, J=1.9, 5.0 Hz), 10.49 (1H, s). APCIMS m/z: 425 (MH^+).

Compound **15a** was derived from the crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-(2-dimethylamino-4-pyridinyl)pyridine-3-carboxamide in 58% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 3.01 (6H, s), 3.62 (3H, s), 3.74 (3H, s), 6.45 (1H, dd, J=2.3, 8.1 Hz), 6.51 (1H, d, J=2.3 Hz), 6.87 (1H, dd, J=1.8, 5.9 Hz), 7.69 (1H, dd, J=4.9, 7.9 Hz), 8.01 (1H, d, J=5.9 Hz), 8.18 (1H, dd, J=1.9, 7.9 Hz), 8.84 (1H, dd, J=1.9, 4.9 Hz), 10.63 (1H, s). APCIMS m/z: 441 (MH^+). IR (KBr) cm^{-1}: 1041 (S=O), 1681 (C=O).

2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-[2-(4-hydroxy-1-piperidinyl)-4-pyridinyl]pyridine-3-carboxamide (17) Crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-[2-(4-oxo-1-piperidinyl)-4-pyridinyl]pyridine-3-carboxamide was prepared from 2-[(2,4-dimethoxybenzyl)thio]pyridine-3-carboxylic acid (**23**), which was chlorinated with oxalyl chloride, followed by condensation with 4-amino-2-(4-oxo-1-piperidinyl)pyridine in a manner similar to that described previously.[1,18] The overall yield was 56%: ^{1}H-NMR δ: 2.40 (4H, t, J=7.4 Hz), 3.73 (3H, s), 3.78 (3H, s), 3.82 (4H, t, J=7.4 Hz), 4.32 (2H, s), 6.44 (1H, dd, J=2.2, 8.3 Hz), 6.54 (1H, d, J=2.2 Hz), 6.77 (1H, dd, J=1.6, 5.6 Hz), 7.93 (1H, dd, J=1.8, 7.6 Hz), 8.06 (1H, d, J=5.6 Hz), 8.63 (1H, dd, J=1.8, 4.8 Hz), 10.57 (1H, s). APCIMS m/z: 479 (MH^+).

To a stirred solution of the crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-[2-(4-oxo-1-piperidinyl)-4-pyridinyl]pyridine-3-carboxamide (900 mg, 1.9 mmol) in CH_3OH (100 ml) was added slowly 71 mg (1.9 mmol) of $NaBH_4$ at 0 °C. The resulting mixture was stirred at room temperature for 1 h and concentrated to dryness *in vacuo*. The residue was taken up in 20 ml of water, and the aqueous mixture was extracted with two 50-ml portions of $CHCl_3$. The combined extracts were washed with brine, dried, and concentrated to dryness *in vacuo* to give 870 mg (96%) of crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-[2-(4-hydroxy-1-piperidinyl)-4-pyridinyl]pyridine-3-carboxamide. APCIMS m/z: 481 (MH^+).

Compound **17** was derived from the crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-[2-(4-hydroxy-1-piperidinyl)-4-pyridinyl]pyridine-3-carboxamide in 58% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 1.37 (2H, m), 1.80 (2H, m), 3.09 (2H, m), 3.62 (3H, s), 3.74 (3H, s), 3.95 (2H, m), 4.16 (1H, d, J=12.3 Hz), 4.37 (1H, d, J=12.3 Hz), 4.70 (1H, d, J=4.3 Hz), 6.44 (1H, dd, J=2.5, 8.4 Hz), 6.50 (1H, d, J=2.5 Hz), 6.89 (1H, dd, J=1.6, 5.5 Hz), 6.99 (1H, d, J=8.4 Hz), 7.18 (1H, d, J=1.6 Hz), 7.69 (1H, dd, J=4.7, 7.8 Hz), 8.03 (1H, d, J=5.5 Hz), 8.18 (1H, dd, J=1.8, 7.8 Hz), 8.84 (1H, dd, J=1.8, 4.7 Hz), 10.64 (1H, s). APCIMS m/z: 497 (MH^+). IR (KBr) cm^{-1}: 1037 (S=O), 1670 (C=O).

Procedure B. 2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(2,6-dimethyl-4-pyridinyl)pyridine-3-carboxamide (4d) PCl_3 (3.4 g, 0.025 mol) was added dropwise to a stirred suspension of **29d** (7.0 g, 0.016 mol) in CH_2Cl_2 (200 ml) at room temperature. The resulting mixture was heated at reflux temperature for 30 min with stirring. The resulting solution was cooled, washed with saturated aqueous $NaHCO_3$ and dried. The solvent was removed by distillation *in vacuo*. The residue was chromatographed on silica gel and eluted with $CHCl_3$–CH_3OH (20:1) to give crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-(2,6-dimethyl-4-pyridinyl)pyridine-3-carboxamide (4.8 g, 71%) as an oily product. ^{1}H-NMR δ: 2.40 (6H, s), 3.72 (3H, s), 3.79 (3H, s), 4.32 (2H, s), 6.43 (1H, dd, J=2.9, 8.0 Hz), 6.54 (1H, d, J=2.9 Hz), 7.34 (2H, s), 7.91 (1H, dd, J=2.0, 7.0 Hz), 8.63 (1H, dd, J=2.0, 5.0 Hz), 10.62 (1H, s). APCIMS m/z: 410 (MH^+).

Compound **4d** was derived from the crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-(2,6-dimethyl-4-pyridinyl)pyridine-3-carboxamide in 84% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 2.40 (6H, s), 3.60 (3H, s), 3.73 (3H, s), 4.16 (1H, d, J=12.1 Hz), 4.38 (1H, d, J=12.1 Hz), 6.44 (1H, dd, J=2.2, 8.7 Hz), 6.49 (1H, d, J=2.2 Hz), 6.98 (1H, d, J=8.7 Hz), 7.33 (2H, s), 7.70 (1H, dd, J=4.9, 8.6 Hz), 8.17 (1H, dd, J=1.8, 8.6 Hz), 8.83 (1H, dd, J=1.8, 4.9 Hz), 10.75 (1H, s). APCIMS m/z: 426 (MH^+). IR (KBr) cm^{-1}: 1039 (S=O), 1688 (C=O).

Procedure C. 2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(6-methyl-2-propinoyloxymethyl-4-pyridinyl)pyridine-3-carboxamide (11) A mixture of **29d** (2.0 g, 4.7 mmol) and propionic anhydride (15 ml) was heated at 100 °C for 2 h with stirring and concentrated to dryness *in vacuo*. The residue was taken up in 50 ml of water, and the aqueous mixture was extracted with two 200-ml portions of $CHCl_3$. The combined extracts were washed with saturated aqueous $NaHCO_3$ and dried. The solvent was removed by distillation *in vacuo*. The residue was chromatographed on silica gel and eluted with $CHCl_3$–CH_3OH (100:1) to give crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-(6-methyl-2-propinoyloxymethyl-4-pyridinyl)pyridine-3-carboxamide (1.9 g, 84%) as an oily product: ^{1}H-NMR δ: 1.10 (3H, t, J=6.9 Hz), 3.73 (3H, s), 3.79 (3H, s), 4.33 (2H, s), 5.08 (2H, s), 6.31 (1H, dd, J=2.4, 8.3 Hz), 6.54 (1H, d, J=2.4 Hz), 7.44 (1H, d, J=1.3 Hz), 7.52 (1H, d, J=1.3 Hz), 7.94 (1H, dd, J=2.1, 7.6 Hz), 8.64 (1H, dd, J=2.1, 5.0 Hz), 10.76 (1H, s). APCIMS m/z: 482 (MH^+).

Compound **11** was derived from the crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-(6-methyl-2-propinoyloxymethyl-4-pyridinyl)pyridine-3-carboxamide in 61% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 1.10 (3H, t, J=6.9 Hz), 3.61 (3H, s), 3.74 (3H, s), 4.17 (1H, d, J=12.2 Hz), 4.40 (1H, d, J=12.2 Hz), 5.10 (2H, s), 6.44 (1H, dd, J=2.2, 8.1 Hz), 6.50 (1H, d, J=2.2 Hz), 6.99 (1H, d, J=8.1 Hz), 7.46 (1H, d, J=1.3 Hz), 7.52 (1H, d, J=1.3 Hz), 7.71 (1H, dd, J=5.1, 8.0 Hz), 8.20 (1H, dd, J=2.1, 8.0 Hz), 8.84 (1H, dd, J=2.1, 5.1 Hz), 10.89 (1H, s). APCIMS m/z: 498 (MH^+). IR (KBr) cm^{-1}: 1034 (S=O), 1693 (CONH), 1740 (COO).

Procedure D. 2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(2-hydroxymethyl-4-pyridinyl)pyridine-3-carboxamide (7a) A mixture of **29a** (6.9 g, 0.017 mol) and acetic anhydride (300 ml) was heated at 90 °C for 2 h with stirring and concentrated to dryness *in vacuo*. The residue was taken up in 100 ml of water, and the aqueous mixture was extracted with two 200-ml portions of $CHCl_3$. The combined extracts were washed with saturated aqueous $NaHCO_3$ and dried. The solvent was removed by distillation *in vacuo*. The residue was chromatographed on silica gel and eluted with $CHCl_3$–CH_3OH (40:1) to give **34a** (4.3 g, 57%) as an oily product: ^{1}H-NMR δ: 2.10 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 4.31 (2H, s), 5.10 (2H, s), 6.43 (1H, dd, J=2.4, 8.2 Hz), 6.54 (1H, d, J=2.4 Hz), 7.25 (1H, d, J=8.2 Hz), 7.28 (1H, dd, J=3.8, 7.9 Hz), 7.62 (1H, dd, J=2.0, 7.8 Hz), 7.64 (1H, d, J=2.0 Hz), 7.96 (1H, dd, J=1.4, 7.9 Hz), 8.43 (1H, d, J=7.8 Hz), 8.64 (1H, dd, J=1.4, 3.8 Hz), 10.84 (1H, s). APCIMS m/z: 454 (MH^+).

A 0.1 N solution of K_2CO_3 (100 ml) was added to a stirred solution of **34a** (2.7 g, 0.006 mol) in CH_3OH (150 ml) at room temperature. The resulting mixture was stirred at the same temperature for 30 min, concentrated to about 100 ml, and neutralized with 1 N HCl at 0 °C. The aqueous mixture was extracted with two 100-ml portions of $CHCl_3$. The combined extracts were washed with two 30-ml portions of brine, dried, and concentrated to dryness *in vacuo* to **37** (2.4 g, 96%) as an oily product: ^{1}H-NMR δ: 3.72 (3H, s), 3.79 (3H, s), 4.33 (2H, s), 4.62 (2H, s), 5.74 (1H, br), 6.44 (1H, dd, J=2.4, 8.1 Hz), 6.55 (1H, d, J=2.4 Hz), 7.73 (1H, dd, J=2.1, 6.2 Hz), 8.45 (1H, d, J=6.2 Hz), 8.66 (1H, dd, J=1.9, 4.8 Hz). APCIMS m/z: 412 (MH^+). IR (KBr) cm^{-1}: 1678 (C=O).

Compound **7a** was derived from **37** in 29% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 3.62 (3H, s), 3.75 (3H, s), 4.18 (1H, d, J=12.2 Hz), 4.39 (1H, d, J=12.2 Hz), 4.55 (2H, d, J=5.8 Hz), 5.46 (1H, t, J=5.8 Hz), 6.44 (1H, dd, J=2.6, 8.1 Hz), 6.50 (1H, d, J=2.6 Hz), 7.00 (1H, d, J=8.1 Hz), 7.54 (1H, dd, J=2.2, 5.7 Hz), 7.71 (1H, dd, J=4.8, 7.9 Hz), 7.82 (1H, d, J=2.2 Hz), 8.22 (1H, dd, J=1.8, 7.9 Hz), 8.40 (1H, d, J=5.7 Hz), 8.84 (1H, dd, J=1.8, 4.8 Hz), 10.92 (1H, s). APCIMS m/z: 428 (MH^+). IR (KBr) cm^{-1}: 1042 (S=O), 1686 (C=O).

Procedure E. 2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(2-propionyloxymethyl-4-pyridinyl)pyridine-3-carboxamide (10) Propionyl chloride (0.74 g, 8.0 mmol) was added to a stirred solution of **37** (3.0 g, 7.3 mmol) in pyridine (50 ml) at room temperature. The resulting mixture was stirred at the same temperature for 2 h and concentrated to dryness *in vacuo*. The residue was taken up in 30 ml of water, and the aqueous mixture was extracted with two 50-ml portions of $CHCl_3$. The combined extracts were washed with two 10-ml portions of brine, dried, and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (50:1) as the eluent to give 2.53 g (74%) of crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-(2-propionyloxymethyl-4-pyridinyl)-pyridine-3-carboxamide: ^{1}H-NMR δ: 1.09 (3H, t, J=7.6 Hz), 2.44 (2H, q, J=7.6 Hz), 3.73 (3H, s), 3.78 (3H, s), 4.33 (2H, s), 5.13 (2H, s), 6.43 (1H, dd, J=2.3, 8.4 Hz), 6.54 (1H, d, J=2.3 Hz), 7.62 (1H, dd, J=2.1, 5.7 Hz), 7.68 (1H, d, J=2.1 Hz), 7.96 (1H, dd, J=1.8, 7.5 Hz), 8.44 (1H, d, J=5.7 Hz), 8.64 (1H, dd, J=1.8, 4.8 Hz), 10.84 (1H, s). APCIMS m/z: 468 (MH^+).

Compound **10** was derived from the crude 2-[(2,4-dimethoxy-

benzyl)thio]-*N*-(2-propionyloxymethyl-4-pyridinyl)pyridine-3-carboxamide in 39% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 1.10 (3H, t, J=7.7 Hz), 2.46 (2H, q, J=7.7 Hz), 3.62 (3H, s), 3.74 (3H, s), 4.17 (1H, d, J=12.5 Hz), 4.38 (1H, d, J=12.5 Hz), 5.16 (2H, s), 6.44 (1H, dd, J=2.3, 8.2 Hz), 6.50 (1H, d, J=2.3 Hz), 6.99 (1H, d, J=8.2 Hz), 7.62 (1H, dd, J=1.8, 5.8 Hz), 8.22 (1H, dd, J=1.7, 7.9 Hz), 8.47 (1H, d, J=5.8 Hz), 8.84 (1H, dd, J=1.7, 4.8 Hz), 10.97 (1H, s). APCIMS m/z: 484 (MH^+). IR (KBr) cm^{-1}: 1037 (S=O), 1670 (CONH), 1743 (COO).

Procedure F. *N*-(2-Amino-4-pyridinyl)-2-[(2,4-dimethoxybenzyl)sulfinyl]pyridine-3-carboxamide (14a) A mixture of **46** (6.0 g, 0.013 mol), CuBr (1.9 g, 0.013 mol), 28% aqueous NH_3 (120 ml), and CH_3OH (50 ml) was heated at 110 °C for 12 h in a sealed tube and concentrated to dryness *in vacuo*. The residue was taken up in 100 ml of water, and the aqueous mixture was extracted with two 200-ml portions of $CHCl_3$. The combined extracts were washed with 50 ml of brine, dried, and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (20:1) as the eluent to give 2.7 g (50%) of crude *N*-(2-amino-4-pyridinyl)-2-[(2,4-dimethoxybenzyl)thio]pyridine-3-carboxamide: ^{1}H-NMR δ: 3.72 (3H, s), 3.80 (3H, s), 4.31 (2H, s), 5.88 (2H, s), 6.43 (1H, dd, J=2.1, 8.1 Hz), 6.54 (1H, d, J=2.1 Hz), 6.66 (1H, dd, J=2.0, 5.9 Hz), 7.78 (1H, d, J=5.9 Hz), 7.88 (1H, dd, J =1.9, 7.8 Hz), 8.61 (1H, dd, J=1.9, 4.9 Hz), 10.42 (1H, s). APCIMS m/z: 397 (MH^+).

Compound **14a** was derived from the crude *N*-(2-amino-4-pyridinyl)-2-[(2,4-dimethoxybenzyl)thio]pyridine-3-carboxamide in 60% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 3.62 (3H, s), 3.75 (3H, s), 4.17 (1H, d, J=12.0 Hz), 4.37 (1H, d, J=12.0), 5.95 (2H, s), 6.46 (1H, dd, J=2.2, 7.9 Hz), 6.51 (1H, d, J=2.2 Hz), 6.69 (1H, dd, J=2.1, 5.9 Hz), 7.68 (1H, dd, J=4.9, 7.8 Hz), 7.83 (1H, d, J=5.9 Hz), 8.18 (1H, dd, J=1.9, 7.8 Hz), 8.82 (1H, dd, J=1.9, 5.9 Hz). SIMS m/z: 413 (MH^+). IR (KBr) cm^{-1}: 1041 (S=O), 1682 (C=O).

Compound **14b** was prepared in a manner similar to that described above.

2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-[2-(2-hydroxyethyl)amino-4-pyridinyl]pyridine-3-carboxamide (16a) A mixture of **46** (5.00 g, 0.011 mol), 2-aminoethanol (6.63 g, 0.109 mol), CuBr (1.56 g, 0.011 mol), and DMF (200 ml) was heated at 100 °C for 10 h with stirring and concentrated to dryness *in vacuo*. The residue was taken up in 100 ml of water, and the aqueous mixture was extracted with two 300-ml portions of $CHCl_3$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (15:1) as the eluent to give 0.42 g (9%) of crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-[2-(2-hydroxyethyl)amino-4-pyridinyl]pyridine-3-carboxamide: ^{1}H-NMR δ: 3.24—3.34 (2H, m), 3.50 (2H, t, J=2.5 Hz), 3.73 (3H, s), 3.80 (3H, s), 4.32 (2H, s), 4.79 (1H, br), 6.43 (1H, dd, J=2.1, 7.9 Hz), 6.68 (1H, dd, J=2.0, 5.8 Hz), 8.62 (1H, dd, J=1.9, 5.1 Hz). SIMS m/z: 441 (MH^+).

Compound **16a** was derived from the crude 2-[(2,4-dimethoxybenzyl)thio]-*N*-[2-(2-hydroxyethyl)amino-4-pyridinyl]pyridine-3-carboxamide in 61% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 3.27—3.35 (2H, m), 3.52 (2H, t, J=5.1 Hz), 3.62 (3H, s), 3.76 (3H, s), 4.17 (1H, d, J=12.1 Hz), 4.38 (1H, d, J=12.1 Hz), 5.48 (1H, br), 6.45 (1H, dd, J=2.2, 8.1 Hz), 6.51 (1H, d, J=2.2 Hz), 7.69 (1H, dd, J=4.6, 7.9 Hz), 7.87 (1H, d, J=5.9 Hz), 8.17 (1H, dd, J=1.9, 7.9 Hz), 8.83 (1H, dd, J=1.9, 4.6 Hz). SIMS m/z: 457 (MH^+). IR (KBr) cm^{-1}: 1042 (S=O), 1682 (C=O).

Compounds **16b, c** were obtained in a manner similar to that described above.

Procedure G. 2-[(2,4-Dimethoxybenzyl)sulfinyl]-6-methylamino-*N*-(4-pyridinyl)pyridine-3-carboxamide (21a) A mixture of **47** (1.5 g, 3.6 mmol), 30% CH_3NH_2 solution in ethanol (20 ml), and C_2H_5OH (20 ml) was heated at 160 °C for 24 h in a sealed tube and concentrated to dryness *in vacuo*. The residue was taken up in 50 ml of water, and the aqueous mixture was extracted with two 100-ml portions of $CHCl_3$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (15:1) as the eluent and recrystallized from CH_3OH to give 1.4 g (95%) of crude 2-[(2,4-dimethoxybenzyl)thio]-6-methylamino-*N*-(4-pyridinyl)pyridine-3-carboxamide: ^{1}H-NMR δ: 2.91 (3H, d, J=4.8 Hz), 3.74 (3H, s), 3.80 (3H, s), 4.28 (2H, s), 6.23 (1H, d, J=8.3 Hz), 6.44 (1H, dd, J=2.4, 8.2 Hz), 6.54 (1H, d, J=2.4 Hz), 7.64 (2H, m), 7.77 (1H, d, J=8.3 Hz), 8.40 (2H, m), 10.46 (1H, s). APCIMS m/z: 411 (MH^+).

Compound **21a** was derived from the crude 2-[(2,4-dimethoxybenzyl)thio]-6-methylamino-*N*-(4-pyridinyl)pyridine-3-carboxamide in 59% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 2.84 (3H, d, J=4.5 Hz), 3.61 (3H, s), 3.72 (3H, s), 4.13 (1H, d, J=12.0 Hz), 4.33 (1H, d, J=12.0 Hz), 6.59 (1H, d, J=8.9 Hz), 7.06 (1H, d, J=8.0 Hz), 7.55 (1H, q, J=4.5 Hz), 7.66 (2H, m), 7.89 (1H, d, J=8.0 Hz), 8.46 (2H, m), 10.46 (1H, s). APCIMS m/z: 427 (MH^+). IR (KBr) cm^{-1}: 1038 (S=O), 1666 (C=O).

Compound **21b** was obtained in a manner similar to that described above.

2-[(2,4-Dimethoxybenzyl)sulfinyl]-6-[(2-hydroxyethyl)methylamino]-*N*-(4-pyridinyl)pyridine-3-carboxamide (21c) A mixture of **33** (5.0 g, 0.012 mol), *N*-methylethanolamine (1.8 g, 0.024 mol), K_2CO_3 (3.3 g, 0.024 mol), and CH_3CN (150 ml) was heated at reflux temperature for 10 h with stirring and concentrated to dryness *in vacuo*. The residue was taken up in 70 ml of water, and the aqueous mixture was extracted with two 200-ml portions of $CHCl_3$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (50:1) as the eluent to give 4.3 g (79%) of crude 2-[(2,4-dimethoxybenzyl)thio]-6-[(2-hydroxyethyl)methylamino]-*N*-(4-pyridinyl)pyridine-3-carboxamide: ^{1}H-NMR δ: 3.18 (3H, s), 3.50—3.78 (4H, m), 3.74 (3H, s), 3.79 (3H, s), 4.23 (2H, s), 4.78 (1H, br), 6.55 (1H, d, J=2.2 Hz), 7.21 (1H, d, J=8.8 Hz), 7.75—7.91 (2H, m), 7.98 (1H, d, J=8.7 Hz), 8.35—8.61 (2H, m), 10.54 (1H, s). APCIMS m/z: 455 (MH^+).

2-[(2,4-Dimethoxybenzyl)thio]-6-[(2-hydroxyethyl)methylamino]-*N*-(4-pyridinyl)pyridine-3-carboxamide (1.00 g, 2.2 mmol) in CH_3OH (40 ml) was added slowly to a stirred solution of $NaIO_4$ (0.49 g, 2.3 mmol) in H_2O (10 ml) at 0 °C. The resulting mixture was stirred at the same temperature for 24 h and concentrated to about 10 ml. The aqueous mixture was extracted with two 50-ml portions of CH_2Cl_2. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (20:1) as the eluent and recrystallized from CH_3CN to give **21c** (0.42 g, 41%): ^{1}H-NMR δ: 3.13 (3H, s), 3.55 (3H, s), 3.55—3.70 (4H, m), 3.70 (3H, s), 4.14 (1H, d, J=12.0 Hz), 4.29 (1H, d, J=12.0 Hz), 4.78 (1H, br), 6.82 (1H, d, J=8.7 Hz), 7.18 (1H, d, J=8.8 Hz), 7.61—7.71 (2H, m), 7.99 (1H, d, J=8.7 Hz), 8.38—8.53 (2H, m), 10.60 (1H, s). APCIMS m/z: 471 (MH^+). IR (KBr) cm^{-1}: 1030 (S=O), 1666 (C=O).

Compounds **21d, e** and **22** were prepared in a manner similar to that described above. In the case of the carboxamides **21d, e** and **22**, oxidation of the respective 2-(benzylthio)pyridine-3-carboxamides was carried out by the use of *m*CPBA.

Procedure H. 2-[(2,4-Dimethoxybenzyl)sulfinyl]-6-isopentyl-*N*-(4-pyridinyl)pyridine-3-carboxamide (19c) A mixture of **44c** (10.0 g, 0.033 mol), 2,4-dimethoxybenzenemethanethiol (7.3 g, 0.040 mol), K_2CO_3 (9.1 g, 0.066 mol), and DMF (300 ml) was heated at 100 °C for 24 h with stirring and concentrated to dryness *in vacuo*. The residue was taken up in 200 ml of water, and the aqueous mixture was extracted with two 500-ml portions of $CHCl_3$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (70:1) as the eluent to give 10.8 g (73%) of crude 2-[(2,4-dimethoxybenzyl)thio]-6-isopentyl-*N*-(4-pyridinyl)pyridine-3-carboxamide: ^{1}H-NMR δ: 0.94 (6H, d, J=6.5 Hz), 2.83 (2H, t, J=7.3 Hz), 3.72 (3H, s), 3.79 (3H, s), 4.33 (2H, s), 6.41 (1H, dd, J=2.2, 8.2 Hz), 6.54 (1H, d, J=2.2 Hz), 7.12 (1H, J=7.9 Hz), 7.27 (1H, d, J=7.9 Hz), 7.65 (2H, m), 7.87 (1H, d, J=8.2 Hz), 8.46 (2H, m), 10.68 (1H, s). APCIMS m/z: 452 (MH^+).

Compound **19c** was derived from the crude 2-[(2,4-dimethoxybenzyl)thio]-6-isopentyl-*N*-(4-pyridinyl)pyridine-3-carboxamide in 72% yield by oxidation with *m*CPBA in a manner similar to that described previously:[1,18] ^{1}H-NMR δ: 0.93 (6H, d, J=6.1 Hz), 2.82 (2H, t, J=7.8 Hz), 3.60 (3H, s), 3.72 (3H, s), 4.20 (1H, d, J=12.2 Hz), 4.37 (1H, d, J=12.2 Hz), 6.42 (1H, dd, J=2.3, 8.2 Hz), 6.48 (1H, d, J=2.3 Hz), 6.95 (1H, d, J=8.2 Hz), 7.54 (1H, d, J=8.0 Hz), 7.69 (2H, m), 8.10 (1H, d, J=8.0 Hz), 8.18 (2H, m). IR (KBr) cm^{-1}: 1034 (S=O), 1674 (C=O).

Oxidation with *m*CPBA in the Presence of Borane–Tetrahydrofuran Complex. 2-[(2,4-Dimethoxybenzyl)sulfinyl]-6-(4-methyl-1-piperazinyl)-*N*-(4-pyridinyl)pyridine-3-carboxamide (21d) Boran tetrahydrofuran complex (1.0 M) in THF (15.0 ml, 15.0 mmol) was added dropwise to a stirred suspension of crude 2-[(2,4-dimethoxybenzyl)thio]-6-(4-methyl-1-piperazinyl)-*N*-(4-pyridinyl)pyridine-3-carboxamide (3.7 g, 7.7 mmol) in CH_2Cl_2 (200 ml) at 0 °C. After 30 min, the resulting solution was washed with water, dried, and concentrated to dryness *in vacuo*. The residue was dissolved in 100 ml of CH_2Cl_2, and then a solution of 70%

*m*CPBA (3.8 g, 15.4 mmol) in CH_2Cl_2 (50 ml) was added dropwise at 0 °C. The resulting mixture was stirred at the same temperature for 10 min, washed with saturated aqueous $NaHCO_3$, dried, and concentrated to dryness *in vacuo*. The residue was dissolved in 300 ml of CH_3OH and then Na_2CO_3 (3.2 g, 30.2 mmol) was added. The resulting mixture was heated at reflux temperature for 90 min with stirring and concentrated to dryness *in vacuo*. The residue was taken up in 70 ml of water, and the aqueous mixture was extracted with two 200-ml portions of $CHCl_3$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (7 : 1) as the eluent and recrystallized from CH_3CN to give 1.2 g (31%) of **21d**: ^{1}H-NMR δ: 2.22 (3H, s), 2.32—2.39 (4H, m), 3.50 (3H, s), 3.55—3.62 (4H, m), 3.72 (3H, s), 4.23 (2H, s), 6.96 (1H, d, J=9.0 Hz), 7.30 (1H, d, J=8.2 Hz), 7.70 (2H, m), 8.06 (1H, d, J=9.0 Hz), 8.47 (2H, m), 10.62 (1H, s). APCIMS *m/z*: 496 (MH^+). IR (KBr) cm^{-1}: 1026 (S=O), 1666 (C=O).

2-[(2,4-Dimethoxybenzyl)thio]-6-(4-methyl-1-piperazinyl)-*N*-(4-pyridinyl)pyridine-3-carboxamide was derived from **47** in 78% yield in a manner similar to that described in Procedure I:[1,18] ^{1}H-NMR δ: 2.22 (3H, s), 2.38—2.45 (4H, m), 3.62—3.69 (4H, m), 3.73 (3H, s), 3.79 (3H, s), 4.20 (2H, s), 6.45 (1H, dd, J=2.3, 8.2 Hz), 6.55 (1H, d, J=2.3 Hz), 6.63 (1H, d, J=8.7 Hz), 7.20 (1H, d, J=8.2 Hz), 7.65 (2H, m), 7.91 (1H, d, J=8.7 Hz), 8.41 (2H, m), 10.26 (1H, s). APCIMS *m/z*: 480 (MH^+).

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.*[25] Acid formation in the parietal cells was assessed in terms of accumulation of [^{14}C]AP.[26] 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 cyclic AMP (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[3] Male Std: 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 control vehicle or drug was administered intraduodenally immediately after ligating 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.

7-Ethoxycoumarin Dealkylase Activity in Rat Liver Microsomes Rat liver microsomes containing 7-ethoxycoumarin dealkylase were prepared as described by Reiners *et al.*[27] The microsomal protein (80 μg) was preincubated at 37 °C for 10 min in an assay medium containing 100 mM Tris–HCl buffer, pH 7.8, 5 mM $MgSO_4$, 6 mM glucose-6-phosphate (G-6-P), 0.2 mg/ml bovine serum albumin (BSA), 2 units/ml G-6-P dehydrogenase, 1 mM NADP, and a test compound. The enzyme reaction was initiated by adding 0.1 ml of 1 mM 7-ethoxycoumarin (total volume 1.0 ml). After incubation for 20 min at 37 °C, the reaction was terminated by adding 1 ml of 5% trichloroacetic acid. Precipitated protein was removed by centrifugation. 7-Hydroxycoumarin produced by *O*-deethylation of 7-ethoxycoumarin was measured by fluorescence detection (365-nm excitation, 455-nm emission) after mixing 0.9 ml of supernatant fluid with 1.8 ml of 1.6 M glycine, pH 10.3. 7-Ethoxycoumarin of predetermined concentrations was used as a standard.

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