Synthetic Study of 2-[(6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)-sulfinyl]-1*H*-benzimidazole Analogs and Their Biological Properties as Novel Proton Pump Inhibitors

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A series of 2-[(cycloalka[*b*]pyridinyl)sulfinyl]-1*H*-benzimidazoles (11) was synthesized and tested for antisecretory activity against pentagastrin-induced gastric acid secretion in rats. A novel benzimidazole derivative containing a cyclohepta[*b*]pyridine moiety was found to be the most potent among the congeners, which included five- to eight-membered cycloalka[*b*]pyridine ring systems. Some 2-[(6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole analogs (14) with various substituents on the aromatic rings showed superior properties to omeprazole (1) in biological examinations *in vivo*. A diastereoisomer, TY-11345 (28Ba), was selected as a promising agent for further evaluation.

Key words $(H^+ + K^+)$-ATPase inhibitor; antiulcer activity; 2-[(cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole; antisecretory activity; cytoprotective activity; TY-11345

Proton pump inhibitors, represented by omeprazole (**1**),[1] have potential for both curing peptic disease and controlling severe hyper-secretion. The promising clinical results obtained so far can be ascribed to the effective inhibition of gastric acid secretion and highly specific inhibitory action on the gastric proton pump, $(H^+ + K^+)$-ATPase, which is located in the apical membranes of parietal cells, and plays a major role in acid secretion.

Since substituted benzimidazoles were found to cause specific and long-lasting inhibition of the proton pump in the gastric mucosa, numerous synthetic studies have been carried out for the purpose of finding novel agents to treat peptic ulcer. Several analogs (**2**—**6**)[2] of 2-[(2-pyridylmethyl)sulfinyl]benzimidazole (PSBs, **7**) and 2-[(2-benzimidazolylsulfinyl)methyl]aniline were reported to have favorable properties for clinical use. The enzyme-blocking and antisecretory activities of the PSBs are believed to be exerted by covalent modification of one or more thiol groups on the acidic lumenal side of the enzyme. Recently, the chemical transformations of the PSBs under conditions resembling those of the extracytosolic part of the parietal cell were established (Chart 2).[3,4] The PSBs act as prodrugs, being chemically transformed to a biologically active intermediate, sulfenamide (**10**), in an acidic environment such as that of the apical membrane of the parietal cell. As shown in Chart 2, the acid-induced transformation of PSBs involves intramolecular nucleophilic attack to generate a spiro-intermediate (**8**), followed by C–S bond cleavage leading to highly active sulfenic acid (**9**) and N–S bond formation to afford the cyclic sulfenamide (**10**).

Accordingly, it is expected that 2-[(cycloalka[*b*]pyridinyl)sulfinyl]-1*H*-benzimidazoles (**11**) which are structurally modified by introduction of a bicyclo-ring system may have significant biological activities through forming a rigid ring system in the process of chemical transformation to the sulfenamide (**10**). Uchida *et al.* reported that a series of variously substituted benzimidazole derivatives (**12**) with a cyclohexa[*b*]pyridine moiety inhibited gastric $(H^+ + K^+)$-ATPase both *in vitro* and *in vivo*.[5]

Our synthetic study on the PSBs derivative was directed towards introducing cycloalka[*b*]pyridine rings instead of the pyridylmethyl moiety. We have found that the benzimidazole derivative with the seven-membered cyclohepta[*b*]pyridine ring moiety was the most potent compound among those derivatives (**11**), which included

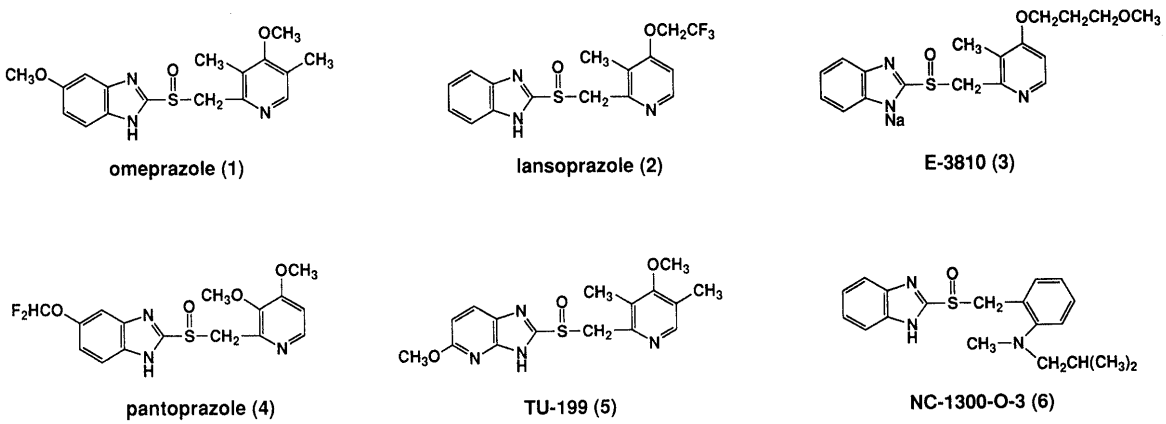

Chart 1

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five- to eight-membered cycloalka[*b*]pyridine ring systems and the α-methyl compound (**13**), as reported in our preceding paper[6] (Chart 3).

In this paper, we wish to describe in detail not only the relationship between the ring size of the cycloalka[*b*]-pyridine moiety in these compounds and the biological potency, but also further chemical modifications of the optimum compound selected among the 2-[(cycloalka[*b*]-pyridinyl)sulfinyl]-1*H*-benzimidazoles (**11**).

Synthesis As shown in Chart 4, 2-[(6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole (**11c**) and 2-[(5,6,7,8,9,10-hexahydroocta[*b*]pyridin-10-yl)sulfinyl]-1*H*-benzimidazole (**11d**) were synthesized by the reaction of 2-mercaptobenzimidazole with chloro compounds derived from alcohols (**17c, d**), followed by low-temperature oxidation of the sulfides (**18c, d**) with *m*-chloroperbenzoic acid (*m*-CPBA). The secondary alcohols (**17c, d**) were prepared as follows. Cycloalka[*b*]-pyridines (**15c, d**) were converted to *N*-oxides (**16c, d**) by 30% H_2O_2 in glacial acetic acid. The *N*-oxides (**16c, d**) underwent rearrangement with acetic anhydride to give 9- and 10-acetoxy derivatives, which were hydrolyzed with aqueous sodium hydroxide (NaOH).

Two cycloalka[*b*]pyridine derivatives (**11a, b**) and the α-methyl compound (**13**) were prepared according to previously reported methods.[5,7]

Further chemical modification of **11c** was carried out by introduction of an appropriate substituent into R^1, R^2 or R^3 in compound (**14**) in attempts to enhance the $(H^+ + K^+)$-ATPase inhibitory activity and antiulcer potency. As shown in Chart 5, 9-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridines (**24**) were synthesized from 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridines (**19**) by two methods, A and B. Nitration of *N*-oxides (**20**) with fuming HNO_3 efficiently gave 4-nitro derivatives (**21**), while nitration of **20** under standard conditions (HNO_3–H_2SO_4) gave **21** in only poor yield. The 4-nitro derivatives (**21**) were then converted to alkoxy (**22a—d, 22h, i**) and propylthio (**22j**) compounds by treatment with the corresponding alcohols or propylmercaptan in the presence of aqueous NaOH (method A, Table I).

The alkoxy compounds (**22e—g**) were synthesized *via* the 4-chloro compound (**23**) obtained by the reaction of **21** with acetyl chloride, followed by treatment with the corresponding alcohols in the presence of NaH (method B, Table I).

Treatment of **22** with acetic anhydride allowed smooth rearrangement to give secondary alcohols (**24**) after hydrolysis with aqueous NaOH (Chart 5, Table II).

The 9-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]-pyridines (**24**) were chlorinated with $SOCl_2$ and then condensed with 2-mercaptobenzimidazoles (**25**) to give sulfides (**26**). Oxidation of the sulfides (**26**) with *m*-CPBA gave a diastereoisomeric mixture of sulfoxides (**14A**) and (**14B**). The main diastereoisomers (**14A**) were easily separated by recrystallization of the crude products, whereas the minor diastereoisomers (**14B**) could not be isolated in a pure form by crystallization or chromatographic purification of the residue because of inherent instability (Chart 6, Tables III and IV).

Subsequently, we examined isomerization of the diastereoisomeric sulfoxides under basic conditions.

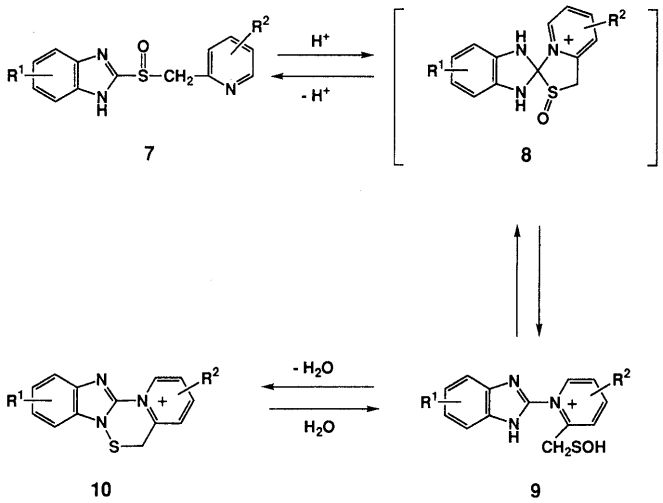


Chart 2

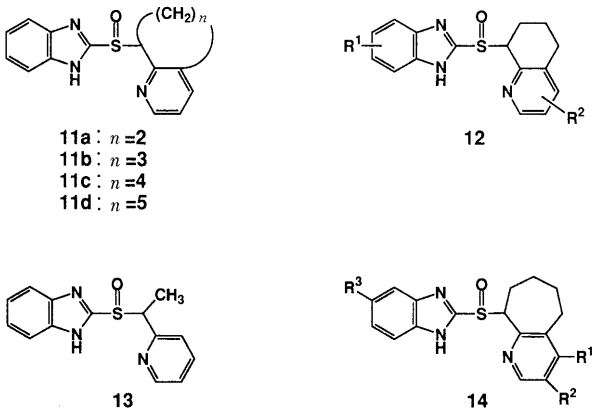


Chart 3

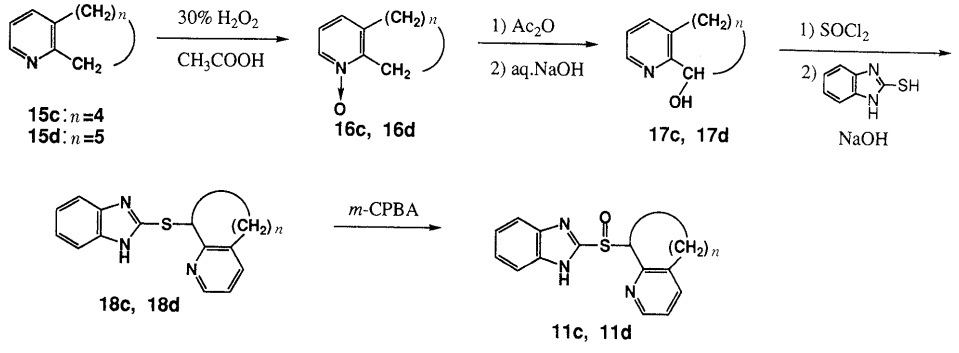


Chart 4

Oxidation of the sulfides (**26**) with *m*-CPBA gave an 8 : 2—7 : 3 diastereoisomeric mixture of **14A** and **14B**, of which **14A** was obtained by recrystallization of the crude reaction product, but **14B** could not be isolated. Treatment of diastereoisomeric mixtures of **14Aa, d, j, k** and **14Ba, d, j, k** with $NaOCH_3$ in CH_2Cl_2 followed by addition of H_2O gave *ca.* 1 : 1 mixtures (Chart 7). The sodium salt (**28Ba**) was found to be selectively precipitated by gradual addition of Et_2O to a CH_2Cl_2 solution of the diastereoisomeric salts. The stereochemistry of **28Ba** was determined by an X-ray analysis.[8] As a consequence, the sulfoxide (**28Ba**) could be obtained from **26a** in 87% overall yield by successive *m*-CPBA oxidation, isomerization and precipitation. However, application of the same procedure to the other sulfoxides (**28Bd, j, k**) failed to give diastereomerically pure products (Chart 7).

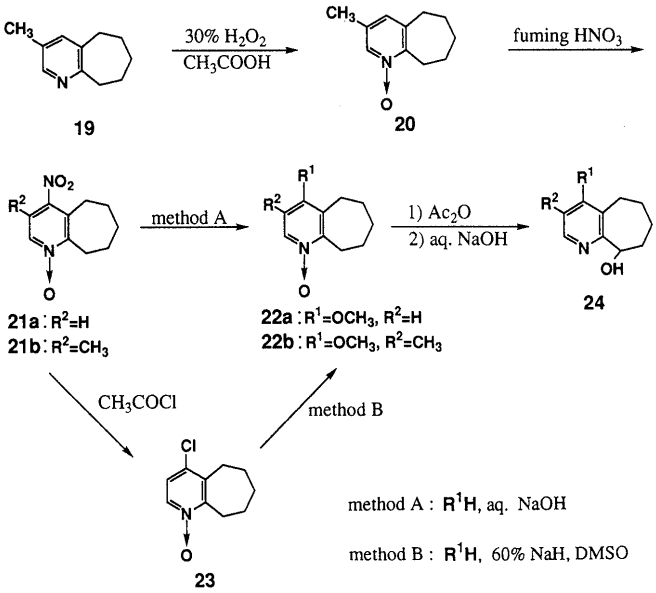


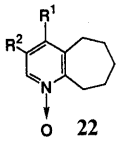
Chart 5

Biological Results and Discussion

A variety of 2-[(cycloalka[*b*]pyridinyl)sulfinyl]-1*H*-benzimidazoles (**11**) synthesized in this study were obtained as diastereoisomeric mixtures due to the presence of two chiral centers (asymmetric carbon atom and sulfinyl group). In most cases the main diastereoisomer prepared by oxidation at the final step was easily separated through repeated recrystallization of the crude reaction mixture, whereas attempts to isolate the minor diastereoisomers by usual procedures were unsuccessful.[9]

The benzimidazole derivatives obtained here were preliminarily examined in terms of inhibitory effect *in vivo* against pentagastrin-stimulated gastric acid secretion in rats after intravenous or intraduodenal administration. This assay system is thought to be suitable to predict the potency of a compound in the body, because it reflects both the inherent activity and the metabolic stability in the body. In this assay omeprazole (**1**) inhibited gastric

TABLE I. 6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridine *N*-Oxides (**22**)



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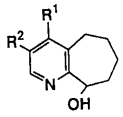
Compd. No.	R^1	R^2	Yield (%)	Appearance	mp (°C) (Recryst. solvent)	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ, ppm
22a	OCH_3	H	95	Colorless prisms	148—149 (AcOEt)	3075, 2916, 1615, 1570, 1344, 1284, 1242, 1188	1.43—2.04 (6H, m), 2.65—2.97 (2H, m), 3.20—3.54 (2H, m), 3.83 (3H, s), 6.57 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz)
22b	OCH_3	CH_3	100	Pale brown crystals	108—109 (AcOEt–hexane)	2932, 1479, 1344, 1296, 1250, 1198	1.42—2.06 (6H, m), 2.16 (3H, s), 2.65—2.95 (2H, m), 3.20—3.46 (2H, m), 3.68 (3H, s), 7.95 (1H, s)
22c	OC_2H_5	H	74	Pale brown crystals	148—149.5 (AcOEt–hexane)	2924, 1448, 1290, 1236, 1190	1.30—1.96 (6H, m), 1.43 (3H, t, J=7.5 Hz), 2.69—2.96 (2H, m), 3.26—3.53 (2H, m), 4.02 (2H, q, J=7.5 Hz), 6.53 (1H, d, J=9 Hz), 8.04 (1H, d, J=9 Hz)
22d	$OCH_2CH_2OCH_3$	H	56	Pale brown crystals	71—73 (Et_2O–hexane)	3016, 2980, 1454, 1292, 1240, 1204, 1190	1.41—2.00 (6H, m), 2.66—3.03 (2H, m), 3.41 (5H, br s), 3.58—3.86 (2H, m), 3.96—4.30 (2H, m), 6.57 (1H, d, J=8 Hz), 8.03 (1H, d, J=8 Hz)
22e	OCH_2— 	H	93	Colorless needles	129—131 (AcOEt–Et_2O)	3068, 2976, 1612, 1450, 1342, 1292, 1138	0.19—0.82 (4H, m), 1.03—1.36 (1H, m), 1.40—2.06 (6H, m), 2.71—3.03 (2H, m), 3.24—3.58 (2H, m), 3.80 (2H, d, J=7.5 Hz), 6.57 (1H, d, J=9 Hz), 8.04 (1H, d, J=9 Hz)
22f	OCH_2Ph	H	33	Colorless crystals	134—137 (AcOEt)	3036, 2924, 1446, 1240, 1136	1.30—2.06 (6H, m), 2.71—3.02 (2H, m), 3.21—3.53 (2H, m), 5.06 (2H, s), 6.67 (1H, d, J=6 Hz), 7.36 (5H, s), 8.04 (1H, d, J=6 Hz)
22g	OCH_2CF_3	H	49	Colorless needles	166—169 (AcOEt)	2944, 1454, 1296, 1274, 1240, 1202, 1174	1.40—2.17 (6H, m), 2.60—3.04 (2H, m), 3.16—3.56 (2H, m), 4.35 (2H, q, J=8 Hz), 6.55 (1H, d, J=8 Hz), 8.07 (1H, d, J=8 Hz)
22h	$OCH_2CF_2CHF_2$	H	60	Colorless crystals	106.5—108 (Et_2O–hexane)	2936, 1478, 1346, 1296, 1240, 1200	1.45—2.05 (6H, m), 2.68—2.95 (2H, m), 3.25—3.50 (2H, m), 4.35 (2H, t, J=12 Hz), 5.97 (1H, tt, J=60, 3 Hz), 6.57 (1H, d, J=6 Hz), 8.07 (1H, t, J=6 Hz)
22i	$OCH_2CF_2CF_3$	H	73	Colorless prisms	136—138 (AcOEt–hexane)	2936, 1478, 1346, 1296, 1270, 1240, 1200	1.45—2.97 (2H, m), 3.25—3.50 (2H, m), 4.40 (2H, t, J=12 Hz), 6.55 (1H, d, J=5 Hz), 8.08 (1H, t, J=5 Hz)
22j	$SCH_2CH_2CH_3$	H	80	Pale yellow needles	83—85 (AcOEt–hexane)	3068, 2960, 1426, 1336, 1268, 1214, 1194	1.06 (3H, t, J=6 Hz), 1.46—2.03 (8H, m), 2.52—3.14 (4H, m), 3.20—3.52 (2H, m), 6.87 (1H, d, J=6 Hz), 8.02 (1H, d, J=6 Hz)

TABLE II. 9-Hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (**24**)



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Compd. No.	R^1	R^2	Yield (%)	Appearance	mp (°C) (Recryst. solvent)	IR[a] cm^{-1}	^{1}H-NMR ($CDCl_3$) δ, ppm
24a	OCH_3	H	74	Pale yellow prisms	119—120 (Et_2O–hexane)	(KBr) 3312, 2984, 1590, 1478, 1398, 1284, 1260	0.80—2.34 (7H, m), 3.22—3.56 (1H, m), 3.84 (3H, s), 4.72 (1H, d, J=11 Hz), 6.69 (1H, d, J=6 Hz), 8.23 (1H, d, J=6 Hz)
24b	OCH_3	CH_3	100	Pale yellow oil	—	(neat) 3370, 2928, 1592, 1468, 1414, 1280, 1050	0.92—3.48 (8H, m), 2.25 (3H, s), 3.72 (3H, s), 4.59—4.80 (1H, d, J=10 Hz), 5.76 (1H, br s), 8.12 (1H, s)
24c	OC_2H_5	H	60	Pale yellow oil	—	(neat) 3352, 2980, 1588, 1469, 1282, 1052	0.90—2.33 (7H, m), 1.43 (3H, t, J=7 Hz), 3.23—3.63 (1H, m), 4.06 (2H, q, J=7 Hz), 4.70 (1H, d, J=10 Hz), 4.91—5.64 (1H, br), 6.64 (1H, d, J=6 Hz), 8.16 (1H, d, J=6 Hz)
24d	$OCH_2CH_2OCH_3$	H	90	Pale yellow oil	—	(neat) 3350, 2928, 1586, 1450, 1282, 1060	1.02—2.33 (7H, m), 2.56—3.06 (2H, m), 3.43 (3H, s), 3.76 (2H, t, J=3 Hz), 4.16 (2H, t, J=3 Hz), 4.72 (1H, d, J=10 Hz), 6.70 (1H, d, J=6 Hz), 8.21 (1H, d, J=6 Hz)
24e	OCH_2—	H	77	Pale yellow oil	—	(neat) 3348, 2924, 1588, 1462, 1282, 1042	0.13—2.40 (13H, m), 3.25—3.62 (1H, m), 3.83 (2H, d, J=6 Hz), 4.73 (1H, d, J=10 Hz), 6.62 (1H, d, J=6 Hz), 8.15 (1H, d, J=6 Hz)
24f	OCH_2Ph	H	53	Colorless needles	85—86 (AcOEt–hexane)	(KBr) 3388, 2928, 1582, 1476, 1392, 1052	0.86—2.36 (7H, m), 3.26—3.69 (1H, m), 4.43—5.16 (1H, br), 4.74 (1H, d, J=10 Hz), 5.11 (2H, s), 6.75 (1H, d, J=5 Hz), 7.36 (5H, s), 8.20 (1H, d, J=5 Hz)
24g	OCH_2CF_3	H	78	Colorless needles	69.5—71 (AcOEt–hexane)	(KBr) 3356, 2920, 1584, 1460, 1302, 1170, 1056	0.80—2.43 (7H, m), 3.06—3.62 (1H, m), 4.39 (2H, q, J=8 Hz), 4.75 (1H, d, J=10 Hz), 5.68 (1H, br s), 6.66 (1H, d, J=5 Hz), 8.30 (1H, d, J=5 Hz)
24h	$OCH_2CF_2CHF_2$	H	94	Pale yellow oil	—	(neat) 3352, 2932, 1586, 1454, 1284, 1106, 1078	0.86—2.42 (7H, m), 3.16—3.52 (1H, m), 4.40 (2H, t, J=10 Hz), 4.75 (1H, d, J=10 Hz), 5.40 (1H, br s), 6.00 (1H, tt, J=60, 3 Hz), 6.70 (1H, d, J=5 Hz), 8.30 (1H, d, J=5 Hz)
24i	$OCH_2CF_2CF_3$	H	84	Colorless prisms	47—48 (AcOEt–hexane)	(neat) 3364, 2932, 1584, 1476, 1286, 1198, 1080	0.95—2.55 (7H, m), 3.21—3.46 (1H, m), 4.43 (2H, t, J=10 Hz), 4.75 (1H, d, J=9 Hz), 5.78 (1H, br s), 6.65 (1H, d, J=5 Hz), 8.27 (1H, d, J=5 Hz)
24j	$SCH_2CH_2CH_3$	H	79	Pale yellow oil	—	(neat) 3360, 2960, 1574, 1450, 1392, 1066	1.07 (3H, t, J=7 Hz), 1.00—3.55 (12H, m), 4.74 (1H, d, J=9 Hz), 5.80 (1H, br s), 6.96 (1H, d, J=5 Hz), 8.14 (1H, d, J=5 Hz)
24k	Cl	H	98	Pale yellow amorphous solid	—	(KBr) 3400, 2924, 2852, 1564, 1422, 1380, 1064	0.80—2.70 (7H, m), 3.47 (1H, dd, J=11, 6 Hz), 4.80 (1H, d, J=11 Hz), 5.75 (1H, br s), 7.18 (1H, d, J=5 Hz), 8.17 (1H, d, J=5 Hz)

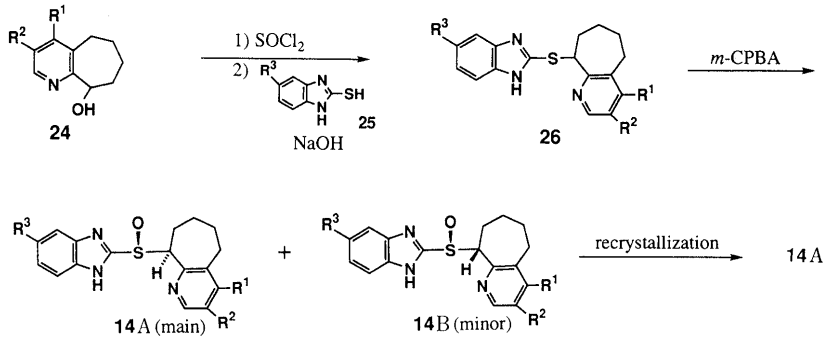


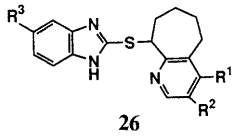
Chart 6

acid secretion with an ED_{50} value of 10.2 mg/kg (i.d.), in agreement with reported data.[10]

We investigated the structure–activity relationship in regard to the ring size of the cycloalka[*b*]pyridine moiety in the series of 2-[(cycloalka[*b*]pyridinyl)sulfinyl]-1*H*-benzimidazoles (**11**), compared with compounds not substituted in their aromatic rings. The results are presented in Table V. The five-membered ring derivative (**11a**) exhibited weaker activity than that of compound **13** without the bicyclo-ring system. Compound **11a** was physicochemically rather stable so that transformation to the biologically active sulfenamide (**10**) was suppressed, since the transformation is initiated exclusively *via* the activated form represented by the spiro-intermediate (**8**) and decomposition also proceeds in the same way (Chart 2).[3,4]

The six-membered ring derivatives (**11b**) tended to be less stable than the derivatives of the other ring systems, although they exhibited modest inhibition of acid secretion.[11] Both seven-membered (**11c**) and eight-membered

TABLE III. 2-[(6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)thio]-1*H*-benzimidazoles (**26**)



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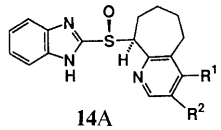
1. Compd. No.	R^1	R^2	R^3	Yield (%)	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ, ppm
26a	OCH_3	H	H	72	3044, 2920, 1578, 1436, 1156	1.16—2.42 (6H, m), 2.45—3.47 (2H, m), 3.82 (3H, s), 5.10 (1H, t, J=4 Hz), 6.68 (1H, d, J=6 Hz), 6.97—7.30 (2H, m), 7.30—7.63 (2H, m), 8.24 (1H, d, J=6 Hz)
26b	OCH_3	H	F	75	3045, 2976, 1628, 1580, 1438, 1290, 1134	1.15—2.43 (6H, m), 2.53—3.50 (2H, m), 3.83 (3H, s), 5.08 (1H, br s), 6.54—7.52 (3H, m), 6.72 (1H, d, J=6 Hz), 8.25 (1H, d, J=6 Hz)
26c	OCH_3	H	OCH_3	73	2924, 1578, 1432, 1288, 1152	1.22—2.39 (6H, m), 2.74—3.36 (2H, m), 3.79, 3.82 (each 3H, s), 5.06 (1H, t, J=4 Hz), 6.62—7.60 (3H, m), 6.70 (1H, d, J=6 Hz), 8.25 (1H, d, J=6 Hz)
26d	OCH_3	CH_3	H	57	3432, 2928, 1468, 1440, 1398, 1270	1.30—2.42 (7H, m), 2.23 (3H, s), 2.73—3.15 (1H, m), 3.70 (3H, s), 5.01—5.16 (1H, m), 6.96—7.71 (4H, m), 8.15 (1H, s)
26e	OCH_3	CH_3	OCH_3	37	2924, 1468, 1450, 1394, 1260	1.40—2.46 (6H, m), 2.23 (3H, s), 2.65—3.35 (2H, m), 3.69 (3H, s), 3.79 (3H, s), 4.93—5.13 (1H, m), 6.63—7.65 (2H, m), 8.14 (1H, s)
26f	OC_2H_5	H	H	74	3432, 2976, 1464, 1290, 1232	1.43 (3H, t, J=7 Hz), 1.66—3.32 (8H, m), 4.03 (2H, q, J=7 Hz), 5.19 (1H, t, J=6 Hz), 6.65 (1H, d, J=9 Hz), 6.96—7.66 (4H, m), 8.22 (1H, d, J=9 Hz)
26g	$OCH_2CH_2OCH_3$	H	H	56	2976, 1578, 1470, 1402, 1288, 1234	1.33—2.35 (6H, m), 2.65—3.23 (2H, m), 3.39 (3H, s), 3.56—3.83 (2H, m), 3.94—4.25 (2H, m), 5.02—5.26 (1H, m), 6.68 (1H, d, J=6 Hz), 6.93—7.28 (2H, m), 7.28—7.62 (2H, m), 8.21 (1H, d, J=6 Hz)
26h	OCH_2—◁	H	H	46	3080, 2960, 1468, 1350, 1272	0.13—0.76 (4H, m), 1.10—1.64 (1H, m), 1.66—3.46 (8H, m), 3.83 (1H, d, J=7 Hz), 5.10 (1H, t, J=6 Hz), 6.65 (1H, d, J=7 Hz), 6.97—7.64 (4H, m), 8.22 (1H, d, J=7 Hz)
26i	OCH_2Ph	H	H	65	3144, 2972, 1576, 1498, 1452, 1402, 1288, 1268	1.15—2.45 (6H, m), 2.63—3.40 (2H, m), 5.05 (2H, s), 5.20 (1H, t, J=4 Hz), 6.70 (1H, d, J=5 Hz), 7.10—7.95 (4H, m), 7.31 (5H, s), 8.21 (1H, d, J=5 Hz)
26j	OCH_2CF_3	H	H	58	3072, 2932, 1580, 1446, 1270, 1232	1.30—2.43 (6H, m), 2.73—3.33 (2H, m), 4.36 (2H, d, J=7 Hz), 4.96—5.26 (1H, m), 6.67 (1H, d, J=5 Hz), 6.98—7.82 (4H, m), 8.33 (1H, d, J=5 Hz)
26k	$OCH_2CF_2CHF_3$	H	H	52	3064, 2929, 1578, 1470, 1404, 1348, 1290	1.10—2.42 (6H, m), 2.73—3.35 (2H, m), 4.38 (2H, t, J=10 Hz), 5.06—5.26 (1H, m), 5.96 (1H, tt, J=60, 3 Hz), 6.70 (1H, d, J=5 Hz), 7.00—7.75 (4H, m), 8.32 (1H, d, J=5 Hz)
26l	$OCH_2CF_2CF_3$	H	H	58	2928, 1578, 1440, 1404, 1350, 1294	1.13—2.40 (6H, m), 2.70—3.38 (2H, m), 4.46 (2H, t, J=12 Hz), 5.20 (1H, t, J=4 Hz), 6.69 (1H, d, J=5 Hz), 7.00—7.78 (4H, m), 8.33 (1H, d, J=5 Hz)
26m	$SCH_2CH_2CH_3$	H	H	68	2960, 2928, 1564, 1434, 1398, 1270	1.08 (3H, t, J=7 Hz), 1.20—3.68 (12H, m), 5.20 (1H, br s), 6.97 (1H, d, J=5 Hz), 7.00—7.95 (4H, m), 8.21 (1H, d, J=5 Hz)
26n	Cl	H	OCH_3	64	2928, 1625, 1560, 1490, 1456, 1432, 1346, 1200	1.40—2.52 (6H, m), 3.07—3.38 (2H, m), 3.80 (3H, s), 5.06—5.33 (1H, m), 6.63—7.60 (4H, m), 8.20 (1H, d, J=5 Hz)

2. Compd. No.	Appearance (Recryst. solvent)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
26a	Colorless crystals ($CHCl_3$–Et_2O–hexane)	176—179	$C_{18}H_{19}N_3OS$	66.43	5.88	12.91	66.51	5.91	12.93
26b	Pale yellow crystals (EtOH)	178—180	$C_{18}H_{18}FN_3OS$	62.95	5.28	12.24	62.79	5.30	12.01
26c	Colorless amorphous solid	—	$C_{19}H_{21}N_3O_2S \cdot 1/5H_2O$	63.56	6.01	11.70	63.73	5.95	11.49
26d	Colorless crystals ($CHCl_3$–Et_2O)	196—196.5	$C_{18}H_{19}N_3OS$	66.44	5.88	12.91	66.52	5.79	12.83
26e	Pale yellow amorphous solid	—	$C_{20}H_{23}N_3O_2S$	65.02	6.27	11.37	65.23	6.19	11.26
26f	Colorless amorphous solid	—	$C_{19}H_{21}N_3OS$	67.23	6.24	12.38	67.16	6.31	12.11
26g	Colorless crystals (Et_2O)	124—125	$C_{20}H_{23}N_3O_2S$	65.01	6.27	11.37	64.78	6.32	11.30
26h	Colorless crystals ($CHCl_3$–Et_2O)	159—160	$C_{21}H_{23}N_3OS$	69.01	6.34	11.50	68.68	6.44	11.29
26i	Colorless amorphous solid	—	$C_{24}H_{23}N_3OS \cdot 1/4H_2O$[a]	62.50	5.68	12.15	62.62	5.71	11.90
26j	Colorless prisms (AcOEt–hexane)	193—195	$C_{19}H_{18}F_3N_3OS$	58.00	4.61	10.68	58.05	4.64	10.63
26k	Colorless amorphous solid	—	$C_{20}H_{19}F_4N_3OS$	56.46	4.50	9.88	56.34	4.59	9.64
26l	Colorless amorphous solid	—	$C_{20}H_{18}F_5N_3OS$	54.17	4.09	9.48	53.94	3.97	9.48
26m	Colorless needles (CH_3OH)	156—157.5	$C_{20}H_{23}N_3S_2$	65.00	6.27	11.37	64.90	6.21	11.18
26n	Colorless crystals (AcOEt–Et_2O)	113—116	$C_{18}H_{18}ClN_3OS$	60.08	5.04	11.68	60.11	5.03	11.62

a) HR FAB-MS ($M^+ + 1$) Calcd for $C_{24}H_{24}N_3OS$: 402.1640. Found: 402.1634.

TABLE IV. 2-[(6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazoles (**14A**)[a]



14A

Compd. No.	R^1	R^2	R^3	Yield (%)	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ, ppm
14Aa	OCH_3	H	H	68	3068, 2972, 1580, 1476, 1286, 1086, 1054	1.07—2.74 (6H, m), 2.95—3.40 (2H, m), 3.82 (3H, s), 4.73—4.98 (1H, m), 6.69 (1H, d, J=6 Hz), 7.06—7.92 (4H, m), 8.30 (1H, d, J=6 Hz)
14Ab	OCH_3	H	F	46	3068, 2972, 1580, 1476, 1284, 1088, 1058	1.00—2.55 (6H, m), 2.92—3.30 (2H, m), 3.79 (3H, s), 4.73—5.05 (1H, m), 6.68 (1H, d, J=5 Hz), 6.77—7.76 (3H, m), 8.28 (1H, d, J=5 Hz)
14Ac	OCH_3	H	OCH_3	57	2936, 1580, 1476, 1286, 1008	0.98—2.43 (7H, m), 2.83—3.33 (1H, m), 3.78 (6H, s), 4.79—5.05 (1H, m), 6.68 (1H, d, J=6 Hz), 6.84 (1H, d, J=8 Hz), 7.00—7.87 (2H, m), 8.30 (1H, d, J=6 Hz)
14Ad	OCH_3	CH_3	H	64	3448, 3070, 2932, 1470, 1398, 1266, 1056, 1011	1.38—2.70 (7H, m), 2.23 (3H, s), 2.87—3.26 (1H, m), 3.55 (3H, s), 4.86 (1H, d, J=9 Hz), 7.03—7.84 (4H, m), 8.20 (1H, s)
14Ae	OCH_3	CH_3	OCH_3	60	3064, 2924, 1454, 1396, 1184, 1054	1.10—3.20 (8H, m), 2.17 (3H, s), 3.41 (3H, s), 3.80 (3H, s), 4.86—5.26 (1H, m), 6.51 (1H, br s), 6.70—7.30 (2H, m), 7.52 (1H, d, J=10 Hz), 8.18 (1H, s)
14Af	OC_2H_5	H	H	52	3068, 2976, 1580, 1466, 1312, 1286, 1054	1.43 (3H, t, J=7 Hz), 1.60—2.65 (7H, m), 3.03—3.36 (1H, m), 4.03 (2H, q, J=7 Hz),4.93 (1H, d, J=6 Hz), 6.65 (1H, d, J=6 Hz), 7.09—7.70 (4H, m), 8.26 (1H, d, J=6 Hz)
14Ag	$OCH_2CH_2OCH_3$	H	H	42	2924, 1580, 1472, 1270, 1082, 1052	1.00—2.70 (8H, m), 3.39 (3H, s), 3.60—3.82 (2H, m), 3.95—4.21 (2H, m), 4.78—5.03 (1H, m), 6.66 (1H, d, J=6 Hz), 7.07—7.34 (2H, m), 7.36—7.67 (2H, m), 8.24 (1H, d, J=6 Hz)
14Ah	OCH_2—◁	H	H	60	3456, 2944, 1580, 1472, 1298, 1038, 1008	0.20—0.76 (4H, m), 1.05—2.66 (8H, m), 3.10—3.52 (1H, m), 3.12 (2H, d, J=6 Hz), 4.75 (1H, d, J=10 Hz), 6.65 (1H, d, J=6 Hz), 7.06—7.95 (4H, m), 8.25 (1H, d, J=6 Hz)
14Ai	OCH_2Ph	H	H	63	3064, 2932, 1578, 1462, 1284, 1044, 1024	1.00—2.66 (7H, m), 3.08—3.43 (1H, m), 4.84 (1H, d, J=7 Hz), 5.04 (2H, s), 6.73 (1H, d, J=5 Hz), 7.10—7.93 (4H, m), 7.33 (5H, s), 8.27 (1H, d, J=5 Hz)
14Aj	OCH_2CF_3	H	H	56	3308, 2932, 1580, 1454, 1266, 1164, 1044	1.26—3.39 (8H, m), 4.43 (2H, q, J=7 Hz), 4.76 (1H, d, J=5 Hz), 6.75 (1H, d, J=5 Hz), 7.08—7.94 (4H, m), 8.33 (1H, d, J=5 Hz)[b]
14Ak	$OCH_2CF_2CHF_2$	H	H	65	3320, 2932, 1580, 1472, 1270, 1068, 1046	1.15—3.52 (8H, m), 4.33 (2H, t, J=12 Hz), 4.92 (1H, d, J=6 Hz), 5.93 (1H, tt, J=60, 3 Hz), 6.65 (1H, d, J=6 Hz), 7.10—7.90 (4H, m), 8.32 (1H, d, J=6 Hz)
14Al	$OCH_2CF_2CF_3$	H	H	61	3320, 2940, 1578, 1470, 1266, 1102, 1046	1.04—2.66 (7H, m), 2.95—3.40 (1H, m), 4.38 (2H, t, J=12 Hz), 4.90 (1H, d, J=6 Hz), 6.63 (1H, d, J=5 Hz), 7.10—7.92 (4H, m), 8.32 (1H, d, J=5 Hz)
14Am	$SCH_2CH_2CH_3$	H	H	45	3068, 2960, 1564, 1432, 1266, 1024	1.06 (3H, t, J=7 Hz), 1.25—3.67 (10H, m), 2.87 (2H, t, J=7 Hz), 4.92 (1H, d, J=6 Hz), 6.96 (1H, d, J=5 Hz), 7.05—7.97 (4H, m), 8.24 (1H, d, J=5 Hz)
14An	Cl	H	OCH_3	44	3224, 3080, 2936, 1626, 1560, 1454, 1304, 1176, 1030	1.02—2.78 (7H, m), 2.93—3.41 (1H, m), 3.79 (3H, s), 5.05 (1H, br s), 6.56—7.75 (4H, m), 8.24 (1H, br s)

Compd. No.	Appearance (Recryst. solvent)	mp[c] (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
14Aa	Colorless crystals (AcOEt–hexane)	147—150	$C_{18}H_{19}N_3O_2S$	63.32	5.61	12.31	63.32	5.52	12.19
14Ab	Colorless crystals ($CHCl_3$–Et_2O)	161—163	$C_{18}H_{18}FN_3O_2S \cdot 1/4H_2O$	59.41	5.12	11.55	59.26	4.90	11.66
14Ac	Pale yellow crystals ($CHCl_3$–Et_2O)	145—148	$C_{19}H_{21}N_3O_3S \cdot 1/2H_2O$	60.30	5.33	11.10	60.46	5.62	10.97
14Ad	Colorless crystals (CH_2Cl_2–Et_2O)	166—168	$C_{19}H_{21}N_3O_2S \cdot 1/5H_2O$	63.56	6.01	11.70	63.73	5.96	11.68
14Ae	Colorless crystals (CH_2Cl_2–Et_2O)	163—165	$C_{20}H_{23}N_3O_3S$	62.31	6.01	10.90	62.25	5.94	10.81
14Af	Pale brown crystals (CH_2Cl_2–Et_2O–hexane)	112—118	$C_{19}H_{21}N_3O_2S$	64.20	5.95	11.82	64.44	6.32	11.46
14Ag	Colorless crystals ($CHCl_3$–Et_2O)	142—145	$C_{20}H_{23}N_3O_3S \cdot 1/4H_2O$[d]	61.60	6.07	10.78	61.75	5.98	10.56
14Ah	Colorless prisms ($CHCl_3$–Et_2O)	138—140	$C_{21}H_{23}N_3O_2S \cdot 1/4H_2O$[e]	65.34	6.14	10.89	65.35	6.15	10.72
14Ai	Colorless crystals (CH_2Cl_2–Et_2O)	155—158.5	$C_{24}H_{23}N_3O_2S$	69.04	5.55	10.06	68.79	5.49	9.85
14Aj	Colorless crystals ($CHCl_3$–Et_2O)	173—174	$C_{19}H_{18}F_3N_3O_2S \cdot 1/4H_2O$[f]	55.13	4.50	10.15	55.20	4.43	9.86
14Ak	Colorless crystals (Et_2O)	150—154	$C_{20}H_{19}F_4N_3O_2S$	54.41	4.34	9.52	54.25	4.25	9.59
14Al	Colorless crystals (Et_2O)	161—162	$C_{20}H_{18}F_5N_3O_2S$	52.28	3.95	9.15	52.19	3.88	9.19
14Am	Colorless crystals (CH_2Cl_2–Et_2O)	133—134	$C_{20}H_{23}N_3OS_2$	62.30	6.01	10.90	62.20	5.95	10.61
14An	Colorless crystals ($CHCl_3$–Et_2O)	153—155	$C_{18}H_{18}ClN_3O_2S$	57.52	4.83	11.18	57.70	4.81	11.12

a) All compounds were isolated in a diastereomerically pure form by repeated recrystallization of the crude reaction products. *b*) As the ^{1}H-NMR solvent, $CDCl_3/CD_3OD$ was employed. *c*) All compounds decomposed. *d*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{20}H_{24}N_3O_3S$: 386.1538. Found: 386.1521. *e*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{21}H_{24}N_3O_2S$: 382.1589. Found: 382.1602. *f*) HR FAB-MS ($M^+ + 1$) Calcd for $C_{19}H_{19}F_3N_3O_2S$: 410.1150. Found: 410.1179.

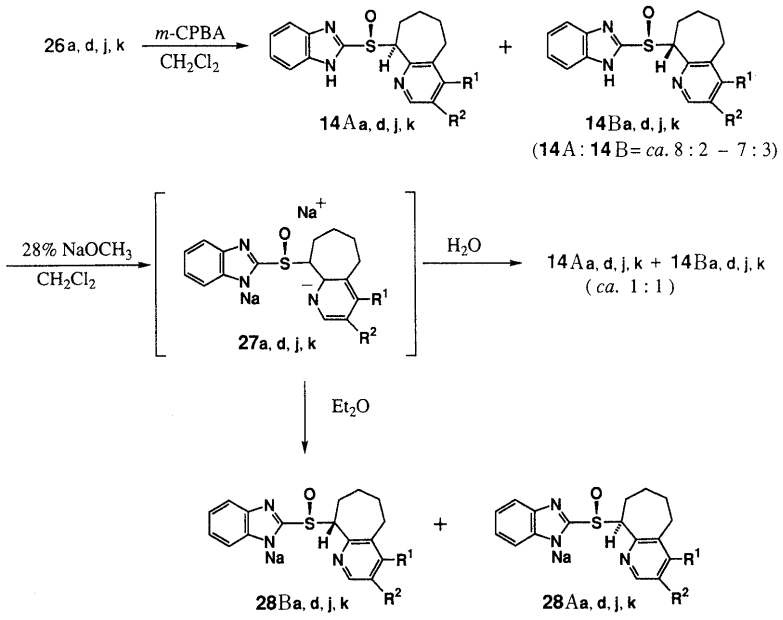


Chart 7

TABLE V. Inhibitory Effect of **11** and **13** on Pentagastrin-Stimulated Gastric Acid Secretion in Rats ($n=3$)

Compound	% inhibition (at i.v. 3 mg/kg)	
	Maximum	3 h after dosing
11a	NE	NE
11b	NE	NE
11c	63.5	29.5
11d	44.7	34.7
13	47.9	43.9

NE: not effective.

ring derivatives (**11d**) showed potent activities. The activity of **11c** is superior to that of **13**, while **11d** is approximately equipotent with **13**. It is, therefore, considered that the potency of the PSBs is enhanced by the replacement of the pyridylmethyl moiety with a bicyclo-ring system. Compound **11c**, with a seven-membered ring, appeared to possess the optimum structure in the series of 2-[(cycloalka[*b*]pyridinyl)sulfinyl]-1*H*-benzimidazoles (**11**) containing five- to eight-membered rings (Table V).

We carried out further chemical modification of **11c** by introduction of various substituents in the aromatic rings. The influence of substituents in the aromatic rings of PSBs, in particular the dominating electronic effect in the pyridine ring, has been discussed.[12,13] We examined the influence of substituents in the pyridine and the benzimidazole moieties in a new series of 2-[(6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole (**14**). As shown in Table VI, introduction of an electron-withdrawing substituent such as a chlorine atom at the 4-position in the pyridine ring resulted in remarkable attenuation of potency. On the other hand, electron-donating substituents such as alkoxy or alkylthio groups enhanced the potency, similar to the pattern previously found in PSBs. Substituents in the benzimidazole ring had little effect. It is, however, notewothy that the analog (**14Ab**) with a fluorine atom at the 5-position exhibited

TABLE VI. Inhibitory Effect of 2-[(6,7,8,9-Tetrahydro-5*H*-cyclohepta-[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazoles on Pentagastrin-Stimulated Gastric Acid Secretion in Rats ($n=3$—5)

Compd. No.	% inhibition	
	Maximum	3 h after dosing
14Aa	86.2 (1)[a]	44.7 (1)
14Ab	65.8 (1)	65.4 (1)
14Ac	67.8 (1)	45.7 (1)
14Ad	4.25[b]	
14Ae	NE[c]	
14Af	89.9 (3)	55.3 (3)
14Ag	77.1 (1)	38.6 (1)
14Ah	57.2 (3)	20.8 (3)
14Ai	NE[c]	
14Aj	NE[c]	
14Ak	63.6 (3)	60.0 (3)
14Al	NE[c]	
14Am	75.1 (3)	51.3 (3)
14An	NE[c]	
28Ba	83.4 (1)	72.8 (1)
28Bd[d]	79.0 (3)	77.6 (3)
28Bj[d]	66.9 (3)	66.9 (3)
28Bk[d]	52.8 (3)	52.0 (3)
Omeprazole (**1**)	86.3 (1)	36.9 (1)

a) The value in parentheses represents dose (mg/kg, i.v.). *b*) The value is ED_{50}, which represents inhibitory activity after intraduodenal administration in pylorus-ligated rats. *c*) NE: not effective (30 mg/kg, i.d. pylorus-ligated rats). *d*) The compound contains another diastereomer, in the following ratio (determined by HPLC analysis): **28Bd** (68.0 : 32.0), **28Bj** (69.8 : 30.2), **28Bk** (64.7 : 35.3).

extremely long-lasting inhibition, for more than 30 h after intravenous administration (data not shown).

Among substituted analogs synthesized in this study, those substituted by an alkoxy group in the pyridine ring were generally highly potent, especially analog **14Aa**, of which the antisecretory activity was almost the same as that of omeprazole (**1**) at the maximal suppression. Moreover, the duration of this activity was superior to that of omeprazole (**1**) (Table VI).

In an attempt to improve the biological activity, we selected the analog (**14Aa**) as a promising candidate and

TABLE VII. Inhibitory Effects of 2-[(6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazoles on ($H^+ + K^+$)-ATPase of Rabbit Gastric Mucosa

Compd. No.	H^+/K^+-ATPase IC_{50} (μM)[a]	
	pH 6.0	pH 7.4
14Aa	3.5	5.7
14Ab	3.9	5.4
28Ba	3.3	9.7
Omeprazole (**1**)	11.0	200.0

a) The IC_{50} value represents the mean of three experiments.

TABLE VIII. Biological Activities of 2-[(6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazoles

Compd. No.	Antisecretory activity	Antiulcer activity	Cytoprotective activity
	ED_{50} (mg/kg i.d.)	ED_{50} (mg/kg *p.o.*)	ED_{50} (mg/kg *p.o.*)
14Aa	5.9	9.4	13.0
14Ab	2.9	3.5	9.9
28Ba	1.3	0.9	10.3
Omeprazole (**1**)	10.2	7.6	11.8

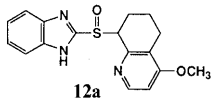
The ED_{50} values were calculated from the dose-inhibition relationships for 5 to 15 animals by the probit method.

TABLE IX. Stability of Cyclohepta[*b*]pyridine Derivatives and Cyclohexa[*b*]pyridine Derivatives

Compd. No.	Storage conditions	
	40 °C, 75% RH	60 °C
11b	0[a]	0[a]
11c	102.8	99.4
12a[b]	32.2	0
14Aa	101.3	98.1
12b[c]	55.0	12.7
14Ab	98.7	103.3
28Ba	99.6	89.7

a) Residual percent: a week after the start of storage. Determinations of each compound were performed by HPLC.

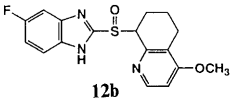
b)



12a

Pale yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.62—2.10 (2H, m), 2.15—2.49 (2H, m), 2.53—3.05 (2H, m), 3.89 (3H, s), 4.75 (1H, t, J=5 Hz), 6.73 (1H, d, J=6 Hz), 6.95—7.30 (2H, m), 7.38—7.70 (2H, m), 8.40 (1H, d, J=6 Hz). IR (KBr): 2940, 1580, 1438, 1436, 1290, 1266, 1051 cm^{-1}.

c)



12b

Pale yellow crystals, mp 138—139 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.78—2.80 (6H, m), 3.71 (3H, s), 4.83 (1H, br s), 6.56 (1H, d, J=6 Hz), 6.89—7.34 (2H, m), 7.40—7.78 (1H, m), 8.27 (1H, d, J=6 Hz). IR (KBr): 3196, 2924, 1578, 1476, 1436, 1290, 1110, 1038 cm^{-1}.

attempted to obtain others of the four possible stereoisomers. We found an efficient method to obtain predominantly diastereoisomer **14Ba** as the sodium salt in a solution of the diastereoisomeric mixture. Presumably there is equilibration between **14Aa** and **14Ba** *via* the anionic intermediate (**27a**) (Chart 7), suggesting that the stereochemical configuration of **14Ba** is thermodynamically more stable than that of **14Aa**. The absolute configurations of these diastereoisomers have been confirmed by X-ray crystallographic analysis.[8]

The sodium salt (**28Ba**) of **14Ba** thus obtained possessed excellent antisecretory activity and stability. Therefore, **14Aa**, **14Ab** and **28Ba** were selected for further biological evaluation compared to omeprazole (**1**).

In the *in vitro* examination, these analogs (**14Aa**, **14Ab**, **28Ba**) potently inhibited ($H^+ + K^+$)-ATPase obtained from the gastric mucosa of rabbits, in a concentration-dependent manner, with IC_{50} values of 3.5, 3.9 and 3.3 μM at pH 6.0 and 5.7, 5.4 and 9.7 μM at pH 7.4, respectively (Table VII), being more potent than omeprazole. We carried out three examinations in rats, *i.e.*, antisecretory activity after intraduodenal administration, antiulcer effect in stress-induced gastric lesions and cytoprotective effect in EtOH-induced gastric lesions, as *in vivo* pharmacological evaluations. Every analog showed potent activity, and the duration of activities was superior to that of omeprazole (**1**). The analog **28Ba** was several times more potent than omeprazole (**1**) (Table VIII).

As a result of these studies, 2-[(4-methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole sodium salt (**28Ba**, TY-11345) was selected as a promising agent, and is currently undergoing phase II clinical studies. Its biological characteristics and *in vivo* activity profile have been published in detail elsewhere.[14]

Experimental

Melting points were determined with a Yanagimoto apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrometer. Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-90H NMR spectrometer or a JEOL JNM-GX 270 NMR spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as an internal standard, and coupling constants (J) are given in Hz. The high-resolution fast atom bombardment mass spectra (HR FAB-MS) was obtained with a JXL-LX1000 mas spectrometer by using glycerol as the matrix. Elemental analysis (C, H, N) was performed on a Perkin–Elmer 240 or 2400 C, H, N instrument. Column chromatography was performed on silica gel (Wakogel C-300) or alumina, (about 300 mesh) manufactured by Wako Pure Chemical Industries, Ldt. HPLC was carried out on a Waters HPLC system (LC Module I).

6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridine *N*-Oxide (16c) A solution of 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (**15c**)[15] (14.7 g, 100 mmol) in acetic acid (100 ml) was treated with 30% hydrogen peroxide (13.3 ml, 115 mmol) at room temperature. The mixture was stirred at 80—90 °C for 16 h. After evaporation of most of the acetic acid *in vacuo*, the residue was poured into ice-water and extracted with $CHCl_3$. The extract was washed with 10% NaOH solution, water and brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was recrystallized from Et_2O–hexane to give **16c** (14.2 g, 87%) as colorless crystals, mp 107—109°C. ^{1}H-NMR ($CDCl_3$) δ: 1.09—2.03 (6H, m), 2.57—2.91 (2H, m), 3.18—3.50 (2H, m), 6.68—7.03 (2H, m), 7.92—8.23 (1H, m). IR (KBr): 3080, 2924, 1610, 1432, 1268, 1246 cm^{-1}. *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.38; H, 8.14; N, 8.45.

5,6,7,8,9,10-Hexahydrocycloocta[*b*]pyridine *N*-Oxide (16d) A solution of 5,6,7,8,9-hexahydrocycloocta[*b*]pyridine (**15d**)[16] (2.06 g, 12.8 mmol) in acetic acid (15 ml) was treated with 30% hydrogen peroxide (2.9 ml, 25.6 mmol) at room temperature. The mixture was refluxed for 7 h. After removal of the acetic acid *in vacuo*, the residue was poured into ice-water and extracted with $CHCl_3$. The extract was washed with 10% NaOH solution, water and brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was recrystallized from AcOEt to

give **16d** (1.60 g, 71%) as colorless crystals, mp 119—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.03—2.21 (8H, m), 2.63—2.92 (2H, m), 2.96—3.35 (2H, m), 6.72—7.14 (2H, m), 7.94—8.24 (1H, m). IR (KBr): 2920, 1482, 1432, 1258, 1098 cm^{-1}. *Anal.* Calcd for $C_{11}H_{15}NO$: C,74.54; H, 8.53; N, 7.90. Found: C, 74.37; H, 8.44; N, 7.91.

9-Hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (17c) A mixture of **16c** (816 mg, 5 mmol) and Ac_2O (4.8 ml) was refluxed for 1 h. The reaction mixture was poured into ice-water. The solution was neutralized with 20% NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in a solution of MeOH (20 ml) and 10% NaOH (10 ml), and the mixture was stirred at room temperature for 1 h, then extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$: MeOH = 200 : 1) to give **17c** (530 mg, 65%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.85—3.02 (8H, m), 4.48—4.95 (1H, m), 5.88 (1H, br s), 6.93—7.57 (2H, m), 8.32 (1H, d, J = 5 Hz). IR (neat): 3372, 2928, 1584, 1454, 1440, 1062 cm^{-1}. *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.22; H, 8.16; N, 8.43.

10-Hydroxy-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine (17d) A mixture of **16d** (1.32 g, 7.46 mmol) and Ac_2O (13 ml) was refluxed for 1.5 h, then poured into ice-water. The solution was neutralized with 20% NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in a solution of MeOH (5 ml) and 10% NaOH (2.5 ml), and the mixture was stirred at room temperature for 1 h, then extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by recrystallization from AcOEt to give **17d** (881 mg, 90%) as colorless crystals, mp 73—74 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.60—2.42 (8H, m), 2.50—2.98 (2H, m), 4.73—5.14 (2H, m), 6.97—7.55 (2H, m), 8.42 (1H, d, J = 5 Hz). IR (KBr): 3328, 2932, 2848, 1466, 1416, 1228, 1050 cm^{-1}. *Anal.* Calcd for $C_{11}H_{15}NO$; C, 74.54; H, 8.53; N, 7.90. Found: C, 74.31; H, 8.51; N, 7.92.

2-[(6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)thio]-1*H*-benzimidazole (18c) Thionyl chloride (8.6 ml, 119 mmol) was added to a solution of **17c** (4.0 g, 25 mmol) in $CHCl_3$ (37 ml) at 0 °C. The reaction mixture was stirred at room temperature for 48 h, poured into ice-water, neutralized with 1 N NaOH and extracted with $CHCl_3$. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in EtOH (9 ml) and this solution was added to a solution of 2-mercaptobenzimidazole (3.3 g, 22.2 mmol) in EtOH (10 ml) and an aqueous NaOH solution [wherein NaOH (977 mg) was dissolved in 39 ml of water]. The mixture was refluxed for 5 h and then concentrated *in vacuo*. The residue was extracted with CH_2Cl_2 and the extract was washed with an aqueous NaOH solution and brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was recrystallized from *N*,*N*-dimethylformamide (DMF) to give **18c** (4.13 g, 63%) as colorless needles, mp 281—282 °C. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.53—2.46 (6H, m), 3.35—3.67 (2H, m), 5.29—5.65 (1H, br s), 6.98—7.77 (6H, m), 8.30 (1H, d, J = 5 Hz), 11.56 (1H, br s). IR (KBr) : 2924, 1454, 1438, 1398, 1270 cm^{-1}. *Anal.* Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.23. Found: C, 68.88; H, 5.74; N, 14.19.

2-[(5,6,7,8,9,10-Hexahydrocycloocta[*b*]pyridin-10-yl)thio]-1*H*-benzimidazole (18d) Thionyl chloride (1.36 ml, 18.9 mmol) was added to a solution of **17d** (670 mg, 3.78 mmol) in $CHCl_3$ (20 ml) at 0 °C. The reaction mixture was stirred at room temperature for 72 h, poured into ice-water, neutralized with 1 N NaOH and extracted with $CHCl_3$. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in EtOH (5 ml) and added to a solution of 2-mercaptobenzimidazole (567 mg, 3.78 mmol) in EtOH (10 ml) and an aqueous NaOH solution [wherein NaOH (166 mg) was dissolved in 10 ml of water]. The mixture was refluxed for 5 h and then concentrated *in vacuo*. The residue was extracted with CH_2Cl_2 and the extract was washed with an aqueous NaOH solution and brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was purified by alumina column chromatography (AcOEt : hexane = 1 : 2) and recrystallized from MeOH to give **18d** (350 mg, 30%) as colorless crystals, mp 211—213 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.60—2.58 (8H, m), 2.50—3.26 (2H, m), 5.10 (1H, dd, J = 5, 13 Hz), 6.70—7.83 (6H, m), 8.53 (1H, d, J = 4 Hz), 12.32 (1H, br s). IR (KBr): 2928, 2848, 1438, 1398, 1350, 1272 cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.58. Found: C, 66.51; H, 5.91; N, 12.93.

2-[(6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole (11c) *m*-CPBA (500 mg, 2.0 mmol) was added to an ice-cooled solution of **18c** (740 mg, 2.5 mmol) in DMF (100 ml). The mixture was stirred at 0 °C for 20 min, then extracted with $CHCl_3$. The extract was quickly washed with a saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was purified by alumina column chromatography ($CHCl_3$: MeOH = 100 : 2) and crystallized from MeOH–Et_2O. The crystalline material was further recrystallized from MeOH–Et_2O to give **11c** (306 mg, 39%) as colorless needles, mp 153—156 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.02—2.26 (6H, m), 2.62—2.97 (2H, m), 4.95 (1H, d, J = 9 Hz), 6.90—7.82 (6H, m), 8.42 (1H, d, J = 6 Hz). IR (KBr): 3048, 2924, 1580, 1434, 1284, 1132, 1078 cm^{-1}. *Anal.* Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.45; H, 5.54; N, 13.56.

2-[(5,6,7,8,9,10-Hexahydrocycloocta[*b*]pyridin-10-yl)sulfinyl]-1*H*-benzimidazole (11d) A solution of *m*-CPBA (246 mg, 1 mmol) in CH_2Cl_2 (20 ml) was added to an ice-cooled solution of **18d** (309 mg, 1 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred at 0 °C for 10 min, quickly washed with a saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was crystallized from CH_2Cl_2–Et_2O. The crystals obtained were further recrystallized from CH_2Cl_2–Et_2O to give **11d** (176 mg, 54%) as colorless prisms, mp 197—200 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.61—2.89 (10H, m), 5.24 (1H, dd, J = 5, 13 Hz), 6.72 (1H, d, J = 7 Hz), 6.90—7.40 (4H, m), 6.71 (1H, d, J = 7 Hz), 8.67 (1H, br s). IR (KBr) : 3052, 2936, 2892, 1578, 1436, 1408, 1270, 1010 cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}N_3OS \cdot 2/5H_2O$: C, 64.99; H, 6.00; N, 12.63. Found: C, 65.12; H, 5.92; N, 12.82.

3-Methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine *N*-Oxide (20) Compound **20** was obtained from **19** in 89% yield as a pale yellow oil by a procedure similar to that described for **16c**. ^{1}H-NMR ($CDCl_3$) δ: 1.14—1.98 (6H, m), 2.20 (3H, s), 2.60—2.86 (2H, m), 3.20—3.48 (2H, m), 6.80 (1H, s), 7.97 (1H, s). IR (neat) : 3400, 2911, 1483, 1340, 1291, 1203, 1041 cm^{-1}.

4-Nitro-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine *N*-Oxide (21a) Fuming HNO_3 (15 ml) was added dropwise to **16c** (1.13 g, 6.93 mmol). The mixture was stirred at 80—85 °C for 1 h and poured into ice-water. After having been neutralized with 2% NaOH solution, the solution was extracted with CH_2Cl_2 and washed with brine. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from AcOEt to give **21a** (1.23 g, 85%) as pale yellow crystals, mp 118—120 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.54—2.08 (6H, m), 2.85—3.17 (2H, m), 3.27—3.63 (2H, m), 7.46 (1H, d, J = 8 Hz), 8.11 (1H, d, J = 8 Hz). IR (KBr): 3110, 2928, 1529, 1422, 1340, 1272, 1144 cm^{-1}.

3-Methyl-4-nitro-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine *N*-oxide (**21b**) was obtained in 74% as a pale yellow powder, mp 111—112 °C by a procedure similar to that described for **21a**. ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.98 (6H, m), 2.20 (3H, s), 2.56—2.77 (2H, m), 3.25—3.48 (2H, m), 8.01 (1H, s). IR (KBr): 3020, 2955, 1537, 1442, 1299, 1200 cm^{-1}.

4-Chloro-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine *N*-Oxide (23) Acetyl chloride (7.85 g, 100 mmol) was added dropwise to **21a** (2.23 g, 10.7 mmol) at 0 °C. The mixture was stirred at 0 °C temperature for 1 h, then poured into ice-water, and the whole was stirred at room temperature for 0.5 h. The mixture was extracted with AcOEt, washed with water and brine, and then dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was purified by silica gel column chromatography ($CHCl_3$: MeOH = 95 : 5) and recrystallized from Et_2O–hexane to give **23** (1.77 g, 84%) as pale yellow prisms, mp 117—118 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.50—2.05 (6H, m), 2.80—3.15 (2H, m), 3.22—3.55 (2H, m), 7.03 (1H, d, J = 5 Hz), 7.99 (1H, d, J = 5 Hz). IR (KBr): 3112, 2924, 2848, 1438, 1418, 1336, 1256, 1170, 1110 cm^{-1}.

4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine *N*-Oxide (22a) A solution of **21a** (810 mg, 3.89 mmol) in MeOH (10 ml) was treated with NaOH (250 mg, 3.89 mmol) at room temperature and the mixture was refluxed for 45 min. After removal of the MeOH *in vacuo*, the residue was extracted with $CHCl_3$. The extract was washed with brine and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was purified by silica gel column chromatography ($CHCl_3$: MeOH = 95 : 5) and recrystallized from AcOEt to give **22a** (710 mg, 95%) as colorless prisms. Melting point, IR and ^{1}H-NMR data are given in Table I.

Compounds **22b—d**, **22h—j** were obtained by a procedure similar to that described for **22a**; the yield, melting points, IR and ^{1}H-NMR data are given in Table I.

4-Cyclopropylmethoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine *N*-Oxide (22e) Cyclopropylmethanol (1.1 g, 15.0 mmol) was added to a suspension of NaH (60% in oil, 600 mg, 15 mmol) in dimethyl sulfoxide (DMSO) (7 ml) at 0 °C, and the mixture was stirred at 60 °C for 1 h. Then, a solution of **23** (1.5 g, 7.5 mmol) in DMSO (5 ml) was added dropwise with stirring at room temperature. The mixture was stirred at 40 °C for 1 h, poured into ice-water and extracted with $CHCl_3$. The extract was washed with water and brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was purified by recrystallization from AcOEt–Et_2O to give **22e** (1.7 g, 93%) as colorless needles. Melting point, IR and ^{1}H-NMR data are given in Table I.

Compounds **22f**, **22g** were obtained by a procedure similar to that described for **22e**; the yields, melting points, IR and ^{1}H-NMR data are given in Table I.

9-Hydroxy-4-methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (24a) A Typical Procedure: A mixture of **22a** (750 mg, 3.86 mmol) and Ac_2O (5 ml) was stirred at 80—90 °C for 1 h, then poured into ice-water, neutralized with 20% NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in a solution of MeOH (13 ml) and 10% NaOH (6.5 ml) and the mixture was stirred at room temperature for 1 h. After removal of the MeOH, the residue was extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by recrystallization from Et_2O–hexane to give **24a** (550 mg, 74%) as pale yellow prisms. Melting point, IR and ^{1}H-NMR data are given in Table II.

Compounds **24b**—**k** were obtained by a procedure similar to that described for **24a**; the yields, melting points and, IR and ^{1}H-NMR data are given in Table II.

2-[(4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)thio]-1*H*-benzimidazole (26a) A Typical Procedure: Thionyl chloride (1.3 ml, 17.9 mmol) was added to a solution of **24a** (700 mg, 3.62 mmol) in $CHCl_3$ (6 ml) at −12 °C. The reaction mixture was stirred at room temperature for 24 h, poured into ice-water, neutralized with 1 N NaOH and extracted with $CHCl_3$. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in EtOH (5 ml) and added to a solution of 2-mercaptobenzimidazole (651 mg, 4.34 mmol) in EtOH (10 ml) and an aqueous NaOH solution [wherein NaOH (130 mg) was dissolved in 2 ml of water]. The mixture was refluxed for 1.5 h and then concentrated *in vacuo*. The residue was extracted with CH_2Cl_2 and the extract was washed with an aqueous NaOH solution and brine, and dried ($MgSO_4$). After removal of solvent *in vacuo*, the residue was purified by alumina column chromatography (AcOEt : hexane = 1 : 3) and recrystallized from $CHCl_3$–Et_2O–hexane to give **26a** (847 mg, 72%) as a colorless powder. Melting point, IR, ^{1}H-NMR and elemental analysis data are given in Table III-1, 2.

Compounds **26b**—**n** were obtained by a procedure similar to that described for **26a**; the yields, melting points, IR, ^{1}H-NMR and elemental analysis data are given in Table III-1, 2.

2-[(4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole (14Aa) A Typical Procedure: A solution of *m*-CPBA (568 mg, 2.31 mmol) in CH_2Cl_2 (18 ml) was added to an ice-cooled solution of **26a** (750 mg, 2.31 mmol) in CH_2Cl_2 (50 ml). The mixture was stirred at 0 °C for 15 min, quickly washed with a saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). After removal of the solvent at 25—30 °C *in vacuo*, the residue was crystallized from AcOEt–hexane and further recrystallized from AcOEt–hexane to give **14Aa** (536 mg, 68%) as colorless crystals. Melting point, IR, ^{1}H-NMR and the data for elemental analysis is given in Table IV-1, 2.

Compounds **14Ab**—**n** were obtained by a procedure similar to that described for **14Aa**; the yields, melting points, IR, ^{1}H-NMR and elemental analysis data are given in Table IV-1, 2.

Determination of the Diastereoisomeric Purity of Sulfoxides The diastereoisomeric purity of sulfoxides was measured by HPLC under the following conditions: YMC-pak ODS-A (4.6 mm i.d. × 150 mm); mobile phase, 1% (v/v) Et_3N–phosphate buffer (pH 5.5); flow rate, 1 ml/min; detection, ultraviolet (UV) at 280 nm.

Isomerization of 2-[(6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)-sulfinyl]-^{1}*H*-benzimidazole (14Aa, d, j, k) with $NaOCH_3$ The sulfoxide (**14Aa**) (102 mg, 0.3 mmol) was treated with a 28% methanol solution of $NaOCH_3$ (139 mg, 0.72 mmol) in CH_2Cl_2 (10 ml) at room temperature for 15 min. Then water (3 ml) was added to the solution, and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the diastereoisomer ratio (purity) of the obtained residue was measured by HPLC. The ratio of **14Aa** and **14Ba** was determined to be 42 : 58. The ratios of **14Ad, j, k** and **14Bd, j, k** were similarly determined to be *ca.* 1 : 1.

2-[(4-Methoxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)sulfinyl]-1*H*-benzimidazole Sodium Salt (28Ba) *m*-CPBA (86 g, 352 mmol) was added to an ice-cooled solution of **26a** (114.2 g, 352 mol) in CH_2Cl_2 (7.6 l) in portions. After having been stirred at 0 °C for 20 min, the mixture was washed with a saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in a 28% methanol solution of $NaOCH_3$ (100 g, 527 mmol) in CH_2Cl_2 (530 ml) at room temperature. After 2 h, Et_2O (about 3 l) was gradually added to the solution, and the mixture was stirred at room temperature for 0.5 h and then at −30 °C for 2 h. The precipitated powder was collected by filtration and recrystallized from CH_2Cl_2–Et_2O to give **28Ba** (111 g, 87%) as colorless crystals, mp 167—175 °C (dec.). **28Ba** could also be obtained from isolated **14Aa** under the same conditions as mentioned above. The diastereoisomeric purity of **28Ba** was determined to be >99%. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.00—2.67 (7H, m), 2.95—3.34 (1H, m), 3.82 (3H, s), 4.75 (1H, d, J = 6 Hz), 6.65 (1H, d, J = 5 Hz), 6.85—7.10 (2H, m), 7.40—7.65 (2H, m), 8.23 (1H, d, J = 5 Hz). IR (KBr) : 3372, 3048, 2972, 2928, 2856, 1580, 1474, 1298, 1270, 1090, 1052, 820, 800, 744 cm^{-1}. *Anal.* Calcd for $C_{18}H_{18}N_3NaO_2S \cdot H_2O$: C, 56.68; H, 5.29; N, 11.02. Found: C, 56.56; H, 5.03; N, 10.86. MS (FAB) *m/z*: 386 (M^+ + Na), 364 (M^+ + 1).

Sodium salts of diastereomeric mixtures (**28Bd, j, k** + **28Ad, j, k**) were obtained by a procedure similar to that described for **28Ba**.

They were separated into two peaks at t_R (min) = 20.72, 39.51, 37.93 (**28B** type) and t_R (min) = 22.33, 43.40, 42.13 (**28A** type) in a ratio of 68.0 : 32.0, 69.8 : 30.2, 64.7 : 35.3, respectively. **28Bd** + **28Ad** (68.0 : 32.0): Colorless crystals (CH_2Cl_2–Et_2O), mp 189—195 °C (dec.). yield 68%, ^{1}H-NMR [$CDCl_3$ + $(CD_3)_2CO$] δ: 1.33—2.26 (6H, m), 2.10 (3H, s), 2.84—3.25 (2H, m), 3.63 (3H, s), 4.60—4.85 (1H, m), 6.76—7.10 (2H, m), 7.30—7.63 (2H, m), 8.02 (1H, s). IR(KBr): 3432, 2932, 1562, 1470, 1450, 1380, 1290, 1270, 1056 cm^{-1}. MS (FAB) *m/z*: 378 (M^+ + 1). **28Bj** + **28Aj** (69.8 : 30.2): Colorless amorphous solid, yield 78%. ^{1}H-NMR [$(CD_3)_2CO$] δ: 1.23—3.52 (8H, m), 4.31—4.96 (3H, m), 6.64—7.08 (3H, m), 7.31—7.67 (2H, m), 8.26 (1H, d, J = 5 Hz). IR (KBr): 3420, 2931, 1580, 1472, 1454, 1376, 1290, 1264, 1090, 1068 cm^{-1}. MS (FAB) *m/z*: 432 (M^+ + 1). **28Bk** + **28Ak** (64.7 : 35.3): Colorless crystals (CH_2Cl_2–Et_2O), mp 169—171.5 °C (dec.), yield 73%. ^{1}H-NMR [$CDCl_3$ + $(CD_3)_2CO$] δ: 1.15—3.43 (8H, m), 4.16—4.97 (3H, m), 6.13—6.36 (1H, m), 6.62—7.11(3H, m), 7.33—7.67 (2H, m), 8.23 (1H, d, J = 6 Hz). IR (KBr): 3388, 3052, 2932, 1580, 1472, 1454, 1378, 1292, 1270, 1020 cm^{-1}. MS (FAB) *m/z*: 442 (M^+ + 1).

Measurement of Gastric Acid Secretion Pentagastrin-Stimulated Secretion (Ghosh and Schild Rats): A modified method based on the technique of Ghosh and Schild was utilized.[17] Male Sprague–Dawley rats (213—364 g) were deprived of food but allowed free access to water for 24 h prior to the experiments. Rats were anesthetized with urethane (1.25 g/kg, i.p.). Polyethylene tubing was inserted into the trachea to facilitate spontaneous breathing. A midline laparotomy was then performed, and the stomach was exteriorized. Through an incision in the forestomach, the gastric contents were gently washed out with saline. A double-lumen cannula (outer: Tygon with a diameter of 7 mm, inner: polyethylene with diameter of 2 mm) was inserted into the forestomach and secured by a ligature at the forestomach. The pylorus was ligated, and saline at room temperature was infused through the inner cannula at a rate of 1.0 ml/min and drained from the outer tube. The gastric secretion was stimulated by a constant infusion of pentagastrin (ICI Pharma, Tokyo; 10 μg/kg/h, i.v.). The gastric effluent was collected at 10 min intervals. The acid output (in microequivalents per min) was determined by titration of the perfusate with 0.01 N NaOH to pH 7.0 with an automatic titrator (AUT-201, Toa Denpa, Tokyo). Compounds were administered intravenously or intraduodenally after the gastric acid secretion reached a plateau. The total acid output was calculated as the volume times the acid concentration.

Inhibition of ($H^+ + K^+$)-ATPase Activity Gastric ($H^+ + K^+$)-ATPase was purified from the parietal cell-rich fraction of the rabbit stomach in accordance with the method of Saccomani *et al.*[18] The stomach of Japanese white rabbits (2.5 to 3.5 kg) was dissected out and washed quickly with ice-cold 3 M NaCl. The fundic mucosa was removed from the underlying muscular layer and homogenized in 10 volumes of ice-cold Tris–HCl/sucrose buffer (20 mM/250 mM, pH 7.4) by a Teflon-glass homogenizer. The resulting homogenates were centrifuged at 9,000 × *g*

for 10 min. The pellets were suspended in a twofold volume of homogenate buffer and centrifuged again under the same conditions. The resulting supernatants of the two centrifugations were combined and recentrifuged at 105000 × *g* for 60 min. The microsomal pellets were resuspended in 250 mM sucrose and layered over 7.5% Ficol (w/w) in 250 mM sucrose. Centrifugation was carried out in an SRP 28A swinging rotor (Hitachi, Tokyo) at 25000 rpm for 4 h. The light microsomal bands at the interface between the 250 mM sucrose and Ficol were collected. $(H^+ + K^+)$-ATPase was measured as described by Saccomani *et al.*[18] Briefly, membrane protein (80 μg protein) was preincubated for 3 to 30 min at 37 °C in an assay medium consisting of 10 mM imidazole buffer (pH 6.0 or 7.4) and various concentrations of compounds (final volume of 0.5 ml). The enzyme reaction was started by adding 0.5 ml of a solution containing 4 mM $MgCl_2$, 4 mM ATP, 2×10^{-5} M valinomycin and 80 mM imidazole buffer (pH 7.4), with or without 20 mM KCl. The reaction was stopped after a 15 min incubation at 37 °C by placing the tubes in ice-slush and adding 1 mM ice-cold 12% trichloroacetic acid. Inorganic phosphate produced from ATP hydrolysis was measured by a commercially available assay reagent for inorganic phosphate (Iatron-Ma701 Pi, Iatron, Tokyo).

Antiulcer Activity Water-Immersion Stress-Induced Gastric Lesions: Male Sprague–Dawley rats (190—273 g) were deprived of food but allowed free access to water for 24 h prior to the experiments. The rats were placed in a restraint cage, and then immersed vertically to the level of the xiphoid process in a water bath (23 °C) for 6 h and killed.[19] The stomach of each rat was removed and inflated by injecting 8 ml of 1% formalin to fix the inner and outer layers of the gastric wall. This formalin treatment was performed in all of the following experiments. Subsequently, the stomach was incised along the greater curvature and examined for lesions in the glandular portion. Test compounds were administered orally at 30 min before the stress load.

Cytoprotective Activity Male Sprague–Dawley rats (215—315 g) were deprived of food but allowed free access to water for 24 h prior to the experiments. The rats were each orally given 1 ml of absolute ethanol.[20] The rats were killed at 1 h after receiving the ethanol, and then the stomach was examined for lesions in the glandular portion. Test compounds were administered orally at 30 min before the ethanol treatment.

References and Notes

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