Synthesis and SAR of Benzimidazole Derivatives Containing Oxycyclic Pyridine as a Gastric H^+/K^+-ATPase Inhibitors

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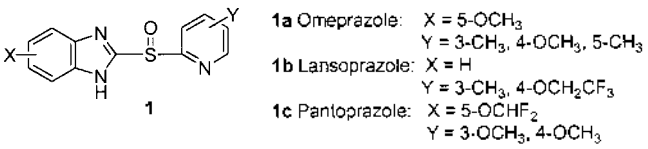
A series of benzimidazole derivatives containing oxycyclic pyridine was prepared and evaluated for their gastric H^+/K^+-ATPase inhibitory activity. Several of the synthesized compound exhibited potent antisecretion in pylorus-ligated rats when administered intradoudenally. Their inhibitory activities were equivalent or comparable to omeprazole.

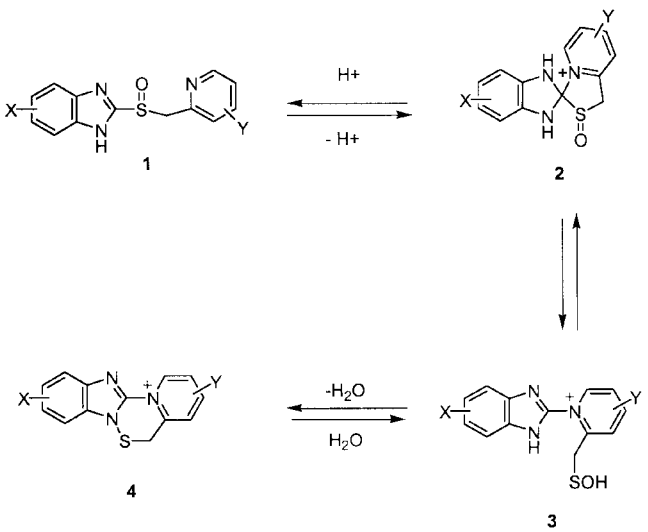
Keywords : Benzimidazole, Oxycyclic pyridine, Gastric H^+/K^+-ATPase inhibitor.

Introduction

Inhibition of gastric acid secretion has been proven to be a powerful therapeutic principle in the treatment of gastric and doudenal ulcer disease.[1] Recently, 2-[(2-pyridylmethyl)sulfinyl]benzimidazoles (PSBs) such as omeprazole, lansoprazole, and pantoprazole (Scheme 1) have been found to have superior properties for complete suppression of gastric acid secretion.[2] Their antisecretory activity has been ascribed to a highly specific inhibitory action on the gastric proton pump, the H^+/K^+-ATPase, which is responsible for the transport of gastric acid into lumen of the stomach.[3] Acid secretion is therefore blocked at the final step of its production, independent of the different kinds of its stimulation.[4]



Scheme 1



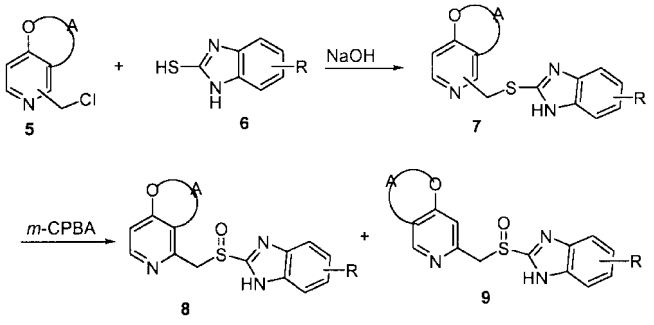
Scheme 2

The PSB analogs act as prodrugs, being chemically transformed to a biologically active intermediate in an acidic environment such as that of the apical membrane of the parietal cell. As shown in Scheme 2,[5,6] the acid induced transformation of PSBs involves intramolecular nucleophilic attack to generate a spiro-intermediate (**2**), followed by C-S bond cleavage leading to highly active sulfenic acid (**3**) and N-S bond formation to afford the cyclic sulfenamide (**4**). All known irreversible H^+/K^+-ATPase inhibitors do not exhibit activity by the mechanism described above, but they are structurally similar to the PSBs and their analogs. On the basis of the mechanism of pH-dependent inhibition as observed in the PSBs, Brandstorm *et al.*[7] claimed the three structural elements of omeprazole analogs, the substituted pyridine ring, the substituted benzimidazole moiety, and the methylsulfinyl chain connecting these two, as being essential for the biological effects. Omeprazole's superiority to the H_2-receptor antagonists in the treatment of duodenal ulcer and reflux oesophagitis is evident,[8] but its safety is still controversial in view of the side effects of long-lasting inhibition of acid secretion, hypergastrinemia and enterochromaffin-like cell hyperplasia.[9] Numerous modifications of pyridine substituents have been carried out for the purpose of finding novel agents to overcome controversial side effects.[10] Due to omeprazole's highly specific mode of action,[11] structural modifications are very restricted to substituents of pyridine and benzimidazole.[12]

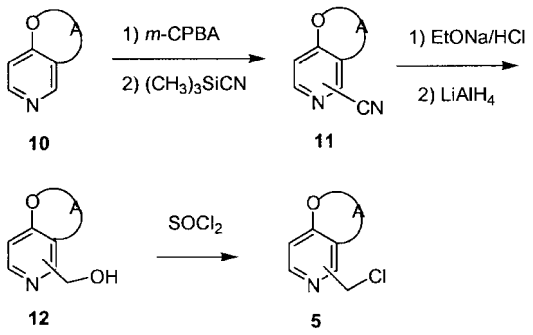
We were interested in pyrano- and furopyridines instead of substituted pyridines to find potent and more selective inhibitiors of H^+/K^+-ATPase *in vitro* and *in vivo*. The pyrano- and furopyridines are chemically interesting molecules because of their structural similarity to quinoline, isoquinoline, and benzofuran which are important nuclei in many biologically active compounds.[13] In this paper, we wish to describe in detail substituent effects of oxycyclic pyridines and their biological activities.

Chemistry

The benzimidazole derivatives containing oxycyclic pyridine



Scheme 3



Scheme 4

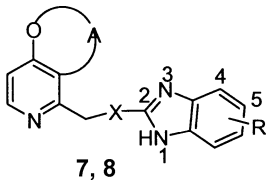
derivatives (**8**, **9**) were synthesized by the reaction of 2-mercaptobenzimidazole (**6**) with chloromethyl oxycyclic pyridine compounds (**5**), followed by low-temperature oxidation of the sulfides with *m*-chloroperbenzoic acid as shown in Scheme 3.

The synthesized benzimidazole derivatives containing oxycyclic pyridine as a gastric H^+/K^+-ATPase inhibitors are summarized in Table 1-2. The chloromethyl oxycyclic pyridines (**5**) were prepared as outlined in Scheme 4. Oxycyclic pyridines (**10**) were converted to the corresponding *N*-oxides by *m*-chloroperbenzoic acid. The regioselectively cyanated oxycyclic pyridines (**11**) were obtained from the *N*-oxide under trimethylsilyl cyanide/Et_3N conditions.[14] The reaction usually provided an isomer with the cyano group at α-carbon on more substituted side of the pyridine as a main product. The cyanated oxycyclic pyridines (**11**) were converted to carboethoxy oxycyclic pyridines with sodium ethoxide in ethanol, followed by HCl treatment. Reduction of carboethoxy oxycyclic pyridines with $LiAlH_4$ afforded hydroxymethyl oxycyclic pyridines (**12**) which were converted to the corresponding 2-chloromethyl-oxycyclic pyridines by treatment with thionyl chloride in dichloromethane.

The oxycyclic pyrano- and furopyridines (**10**) were prepared by our previously reported palladium-catalyzed cyclization of iodopyridine allyl ethers (method A)[15,16,17] or thermal [3,3]-sigmatropic rearrangement of 4-pyridine propargyl ether (method B)[18] as shown in Scheme 5.

The iodopyridine allyl ether (**13**) was prepared from 4-

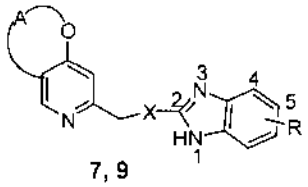
Table 1. Structure of synthesized benzimidazoles containing oxycyclic pyridine (**7**, **8**)



7, 8

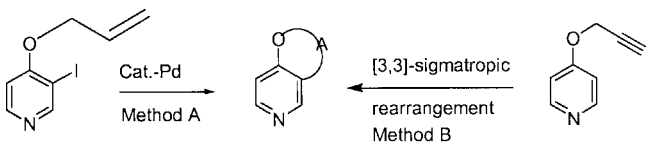
Entry	OA	X	R	Yield (%)	^{1}H NMR ($CDCl_3$) δ ppm
7a	$OC(CH_3)_2CH=CH-$	S	H	61	1.50 (s, 6H), 4.23 (s, 2H), 5.67 (d, 1H), 6.32 (d, 1H), 7.42 (m, 4H), 8.14 (s, 1H), 8.21 (d, 1H).
8a	"	SO	H	68	1.46 (s, 6H), 4.92 (d, 2H), 5.60 (d, 1H), 6.60 (d, 1H), 6.76-7.69 (m, 5H), 7.90 (m, 1H).
8b	"	SO	4-OCH_3	83	1.42 (s, 6H), 3.87 (s, 3H), 4.95 (d, 2H), 5.58 (d, 1H), 6.58 (d, 1H), 6.92-7.92 (m, 4H), 7.95 (m, 1H).
8c	"	SO	5-OCH_3	79	1.46 (s, 6H), 3.81 (s, 3H), 4.92 (d, 2H), 5.60 (d, 1H), 6.60 (d, 1H), 6.69-7.69 (m, 4H), 7.95 (m, 1H).
8d		SO	5-Cl	26	1.19 (s, 6H), 4.72 (d, 2H), 5.42 (d, 1H), 6.28 (d, 1H), 6.69-7.69 (m, 4H), 7.95 (m, 1H).
7b	$OC(CH_3)_2CH_2CH_2-$	S	H	59	1.39 (m, 8H), 2.01 (t, 2H), 4.45 (s, 2H), 7.09 (d, 1H), 7.72 (m, 4H), 8.45 (d, 1H)
8e	"	SO	H	72	1.23 (s, 6H), 1.69 (t, 2H), 4.89 (d, 2H), 6.64 (d, 1H), 6.85 (d, 1H), 6.93 (m, 2H), 7.25 (m, 1H), 8.23 (m, 1H).
8f	"	SO	5-OCH_3	70	1.23 (s, 6H), 1.69 (t, 2H), 2.62 (t, 2H), 3.82 (s, 3H), 4.89 (d, 2H), 6.93 (m, 1H), 7.23 (m, 1H), 8.25 (m, 1H).
8g	"	SO	4-OCH_3	69	1.69 (t, 2H), 2.62 (t, 2H), 3.82 (s, 3H), 4.89 (s, 3H), 6.64 (d, 1H), 7.23 (m, 1H), 8.24 (m, 1H).
7c	$OCH=C(CH_3)-$	S	5-OCH_3	68	2.38 (s, 3H), 4.69 (s, 2H), 7.16 (m, 1H), 7.35 (m, 2H), 7.50 (m, 2H), 8.39 (m, 1H).
8h	"	SO	5-OCH_3	71	2.31 (s, 3H), 3.76 (s, 3H), 5.02 (s, 2H), 6.90 (m, 2H), 7.32 (m, 2H), 7.48 (m, 1H), 8.36 (d, 1H).
8i	"	SO	H	89	2.31 (s, 3H), 4.49 (s, 2H), 7.50 (m, 6H), 8.19 (d, 1H).

Table 2. Structure of synthesized benzimidazoles containing oxycyclic pyridine (**7**, **9**)



7, 9

Entry	-O-A-	X	R	Yield (%)	^{1}H NMR ($CDCl_3$) δ ppm
7d	$OC(CH_3)_2CH=CH-$	S	H	51	1.49 (s, 6H), 4.29 (s, 2H), 6.72 (d, 1H), 6.45 (d, 1H), 6.81 (s, 1H), 7.54 (m, 4H), 8.29 (s, 1H).
9a	"	SO	H	87	1.43 (s, 6H), 4.51 (d, 2H), 5.70 (d, 1H), 6.51 (d, 1H), 6.75 (s, 1H), 7.42 (m, 3H), 8.21 (s, 1H).
9b	"	SO	4-OCH_3	82	1.37 (s, 6H), 3.84 (s, 3H), 4.59 (d, 2H), 5.60 (d, 1H), 6.35 (d, 1H), 6.71 (s, 1H), 7.09 (m, 1H), 7.45 (d, 1H), 8.19 (s, 1H).
9c	"	SO	5-OCH_3	84	2.35 (s, 6H), 3.79 (s, 3H), 4.59 (d, 2H), 6.35 (d, 1H), 6.55 (d, 1H), 6.70 (s, 1H), 6.90 (m, 3H), 7.32 (d, 1H), 8.10 (s, 1H).
9d	$OCH_2CH_2C(CH_3)_2$-	SO	H	38	1.31 (s, 6H), 1.75 (t, 2H), 4.16 (t, 2H), 4.56 (d, 2H), 7.28 (s, 1H), 7.31 (m, 2H), 7.65 (m, 2H), 8.35 (s, 1H).
9e	"	SO	4-OCH_3	60	1.30 (s, 6H), 1.74 (t, 2H), 3.84 (s, 1H), 4.11(t, 2H), 4.61 (d, 2H), 6.62 (s, 1H), 6.96 (m, 2H), 8.32 (s, 1H).
9f	"	SO	H	79	1.54 (m, 8H), 2.65 (t, 2H), 4.65 (s, 2H), 7.67 (s, 1H), 7.80 (m, 4H), 8.21 (s, 1H).
9g	"	SO	4-OCH_3	64	1.74 (t, 2H), 2.67 (t, 2H), 3.82 (s, 3H), 4.56 (d, 2H), 6.58 (s, 1H), 6.95 (m, 2H), 5.53 (m, 1H), 8.17 (s, 1H).
9h	$OC(CH_3)_2CH_2CH_2$-	SO	5-OCH_3	87	1.35 (m, 8H), 2.15 (t, 2H), 3.85 (s, 3H), 4.65 (s, 2H), 6.68 (s, 1H), 7.35 (m, 4H), 8.18 (s, 1H).
7e	$OCH_2CH=C(CH_3)$-	S	H	75	2.21 (s, 3H), 3.78 (s, 3H), 4.49 (s, 2H), 6.79 (d, 1H), 7.03 (s, 1H), 7.40 (m, 3H), 8.77 (m, 1H)
9j	"	SO	H	34	2.21 (s, 3H), 3.89 (s, 3H), 4.79 (s, 2H), 6.91 (d, 1H), 7.28 (m, 2H), 7.49 (m, 3H), 8.77 (m, 1H).
9k	"	SO	4-OCH_3	78	2.20 (s, 3H), 3.77 (s, 3H), 4.78 (m, 2H), 6.87 (m, 1H), 7.29 (m, 1H), 7.48 (m, 1H), 8.09 (s, 1H).
7f	$OCH_2C(CH_3)_2$-	S	H	33	1.42 (s, 6H), 4.27 (s, 3H), 4.36 (s, 2H), 6.79 (s, 1H), 7.20 (s, 2H), 7.56 (m, 2H), 8.23 (s, 1H).
9l	"	SO	H	41	1.33 (s, 6H), 4.26 (s, 2H), 4.64 (s, 2H), 6.67 (s, 1H), 7.30 (m, 2H), 7.66 (m, 2H), 8.16 (s, 1H).
9m	"	SO	4-OCH_3	53	1.28 (s, 6H), 3.80 (s, 3H), 4.22 (s, 3H), 4.61(s, 2H), 6.62 (s, 1H), 6.92 (m, 2H), 7.79 (m, 1H), 8.07 (s, 1H).
9n	"	SO	5-OCH_3	53	1.43 (s, 6H), 4.24 (s, 3H), 4.38 (s, 2H), 6.78 (s, 1H), 6.84 (d, 1H), 7.07 (d, 1H), 7.44 (d, 1H), 8.31 (s, 1H).
9i	"	SO	5-Cl	34	1.22 (s, 6H), 1.72 (t, 2H), 2.66 (t, 2H), 4.56 (d, 2H), 6.55 (s, 1H), 7.25 (m, 1H), 7.59 (m, 2H), 8.14 (s, 1H).



13 **10** **14**

Scheme 5

chloro-3-iodopyridine which was prepared by regioselective lithiation of 4-chloropyridines with LDA followed by treatment with I_2 as an electrophile.[19] and the resulting 4-chloro-3-iodopyridine with sodium allyl alkoxide afforded (**13**) in 70-85% isolated yield. On the other hand. 4-pyridine propargyl ethers (**14**) were prepared by 4-hydroxypyridine and propargyl halides under phase transfer catalysis with $(Bn)_4NOH$ at room temperature.[18]

Biological Results and Discussion

The gastric H^+/K^--ATPase inhibitory and antisecretory activities of benzimidazole derivatives containing oxycyclic pyridine are summarized in Table 3. The compounds containing pyranopyridines (**8a-8g**) showed significant biological activities. The hydrogenation of 2.2-dimethyl-2*H*-pyrano[3.2-c] pyridine (**8e-8g**) did not show any significant activity difference compared with that of unsaturated compounds. We carried out further chemical modification with the size of oxycyclic pyridine. The compounds containing furo[3.2-c]pyri-

Table 3. Biological activities of synthesized benzimidazoles (**7**, **8**, **9**)

Compounds	Inhibition of H^+/K^+-ATPase IC_{50} (μM) or % inhibtion (100 μM)	Antisecretory activty (*in vivo*) Compound/Omeprazole
7a	NA	ND
8a	34	0.39
8b	20	0.48
8c	50	0.36
8d	15	1.04
7b	NA	ND
8e	103%	-0.08
8f	50	-0.03
8g	10	1.05
7c	NA	ND
8h	60	0.48
8i	20	1.04
7d	NA	ND
9a	107%	0.79
9b	124%	0.29
9c	118	0.48
9d	5.8	0.78
9e	15	0.17
9f	140%	0.33
9g	10	0.49
9h	NA	ND
9i	10	0.49
7e	NA	ND
9j	43	ND
9k	48	ND
7f	NA	ND
9l	6	0.96
9m	8	0.74
9n	15	0.64
Omeprazole	15	1.00

NA = not active; ND = not determined.

dine (**8h-8j**) showed almost same ATPase inhibitory and antisecretory effect with that of 6-membered oxycyclic pyridines. We examined the influence of substituents on the benzimidazole moieties and found they had little effect. In addition, replacing sulfoxide connecting two ring systems with sulfide diminished the biological activity completely (**7a-c**). Then, we examined positional effect of pyrano and furopyridine derivatives. The benzimidazole derivatives containing oxycyclic pyridine (**9**) showed similar biological activities with that of compounds (**8**). The compounds were given to rats to determine *in vivo* biological activity and their effects on the gastric acid secretion were determined. The degree of acid output blockade was similar to that of omeprazole. The volume as well as the concentration of gastric juice was decreased, which resulted in the reduction of total acid output. The newly synthesized benzimidazole derivatives containing oxycyclic pyridine have potential gastric H^+/K^+-ATPase activity to be developed as antiulcer agents.

Conclusions. The present results show that the introduction of 5-membered or 6-membered oxycycles to pyridine potentiated the inhibitory activity of the compounds. while no significant change of biological activities was observed by the size and position of oxycycles to pyridine. The biological activities and pharmaceutical profiles of selected benzimidazole derivatives containing oxycyclic pyridines have shown as potential gastric K^+/H^+-ATPase inhibitors.[20]

Experimental Section

The ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz NMR Spectrometer. The GC-MS spectra were obtained on a Shimazu QP 1000 GC/MS and on a JEOL JMS-DX-305 high resolution mass spectrometer. The substituted 2-mercaptobenzimidazoles were either purchased or synthesized by known methods. The H^+/K^+-ATPase-inhibitory and gastric antisecretory activity were tested by the reported methods.[20]

Synthesis of Pyrano- and Furopyridines *via* Palladium-catalyzed Cyclization (Method A)[16,17]

4-Allyloxy-3-iodopyridine (13). In a round-bottom flask was placed Na (0.23 g. 10 mmol), allyl alcohol (20 mmol) and THF (20 mL). The mixture was stirred until sodium disappeared. 4-Chloro-3-iodopyridine (10 mmol) was dissolved to the reaction mixture, and refluxed for 3-4 hours under a nitrogen atmosphere. After cooling, the reaction mixture was poured into water and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography using hexane-ethyl acetate as an eluent. The 4-allyloxy-3-iodopyridine was obtained in a 75% yield as yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.65 (d, 2H, J = 6.4 Hz, OCH_2). 5.40 (m. 2H, vinyl), 6.00 (m. 1H, vinyl). 6.72 (d. 1H. J = 5.6 Hz, ArH), 8.35 (d. 1H, J = 5.4 Hz, ArH), 8.76 (d, 1H. J = 5.6 Hz. ArH): Mass z/e (%): 41 (100). 134 (23). 261 (M^-, 43): HRMS C_8H_8NOI: 260.9651, Found: 260.9639.

3-Methylfuro[2,3-*b*]pyridine (10). To a 50 mL pressure bottle containing a magnetic stirring bar was added the following reagents: $Pd(OAc)_2$ (70 mg. 0.25 mmol), K_2CO_3 (1.3 g. 1.0 mmol), HCO_2Na (0.67 g. 10 mmol). *n*-Bu_4NCl (2.7 g, 10 mmol). 4-allyloxy-3-iodopyridine (2.61 g. 10 mmol), and 30 mL of DMF. The reaction mixture was stirred at 100 °C for 4 hours. The resulting mixture was diluted with ether (30 mL) and washed with saturated NH_4Cl (2 × 200 mL) solution. The combined organic extract was concentrated under reduced pressure and purified by flash column chromatography with hexane-ethyl acetate as an eluent. 3-Methylfuro[3,2-*c*]pyridine was obtained in 40% yield as yellow oil: IR (neat) 3080. 1796. 1620. 1580. 1460. 1300. 1160, 1080, 870. 820, 620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 7.37 (d, 1H. J = 5.6 Hz. ArH). 7.39 (s. 1H, ArH), 8.47 (d. 1H, J = 5.6 Hz. ArH). 8.85 (s, 1H, ArH): Mass z/e (%): 41 (22), 57 (18). 73 (25). 94 (15). 104 (21), 121 (19). 133 (M^+. 100): HRMS Calculated C_8H_7ON: 133.0528. Found: 133.0526.

Preparation of Pyranopyridines by [3,3]-Sigmatropic Rearrangement (Method B)[19]

1,1-Dimethyl-2-propynyl-4-pyridyl ether (14). To a solution of 4-hydroxypyridine (23 g, 0.24 mol) and 40% $(Bn)_4NOH$

in 50 mL of methanol was added 3-chloro-3,3-dimethyl-1-butyne (37 g, 0.36 mol) in 50 mL of dichloromethane. Sodium hydroxide (14 g, 0.36 mol) dissolved in 150 mL of water was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for 48 hours. After separating the organic layer, the aqueous layer was extracted with chloroform. The combined organic extract was washed with 10% aqueous sodium hydroxide solution and dried to remove the organic solvent under reduced pressure. The 4-pyridyl propargyl ether was obtained in 62% yield as oil: ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 6H, CH_3), 2.61 (s, 1H, CH), 7.09 (m, 2H, ArH), 8.30 (m, 2H, ArH).

2,2-Dimethyl-2*H*-pyrano[3,2-*c*]pyridine (6). 1,1-Dimethyl-2-propynyl-4-pyridyl ether (1.8 g, 10 mmol) was refluxed in *o*-dichlorobenzene for an hour. Then, the solvent was completely removed by vacuum distillation. The residue was purified by column chromatography with hexane-ethyl acetate (4 : 1) as an eluent. 2,2-Dimethyl-2*H*-pyrano[3,2-*c*]pyridine was obtained in 50% yield as an oil: ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 6H, CH_3), 5.95 (d, 1H, J = 6.2 Hz, vinyl), 7.47 (d, 1H, J = 6.2 Hz, vinyl), 7.65 (d, 1H, J = 7.5 Hz, ArH), 8.26 (s, 1H, ArH), 8.41 (d, 1H, J = 7.5 Hz, ArH).

The other oxycyclic pyridines were obtained using the above general procedures.

4,4-Dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]pyridine. 4-Methlyene-3,4-dihydro-2*H*-pyrano[3,2-*c*]pyridine (5.4 g, 37 mmol) was dissolved in 50 mL ethanol. After addition of 5% Pd/C (2.5 g) to the reaction mixture, the solution was hydrogenated under 70 psi at 25 °C for an hour. The mixture was filtered and concentrated under reduced pressure. 4,4-Dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]pyridine was obtained in 94% yield as yellow oil: ^{1}H NMR($CDCl_3$) δ 1.34 (s, 6H, J = 5.5 Hz, CH_3), 4.36 (t, 2H, J = 5.5 Hz, CH_2), 6.87 (d, 1H, J = 7.5 Hz, ArH), 7.60 (d, 1H, J = 7.5 Hz, ArH), 8.06 (d, 1H, J = 7.5 Hz, ArH).

4-Cyano-3-methylfuro[3,2-*c*]pyridine *N*-oxide. 3-Methylfuro[3,2-*c*]pyridine (4.2 g, 31 mmol) and *m*-chloroperbenzoic acid (42 mmol) were dissolved in 200 mL of CH_2Cl_2, and stirred at room temperature for 5 hours. The resulting mixture was filtered, dried over anhydrous $MgSO_4$, and concentrated. The 4-cyano-3-methylfuro[3,2-*c*]pyridine *N*-oxide was obtained in 90% yield after column chromatography (hexane : ethyl acetate : methanol = 4 : 4 : 1): ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H, CH_3), 7.46 (d, 1H, J = 5.6 Hz, ArH), 7.53 (s, 1H, ArH), 8.42 (d, 1H, J = 5.6 Hz, ArH), 8.83 (s, 1H, ArH); Mass (z/e): 41 (20), 57 (13), 73 (25), 94 (15), 104 (21), 121 (19), 133 (35), 158 (100, M^-)

4-Cyano-3-methylfuro[3,2-*c*]pyridine (11). 3-Methylfuro-[3,2-*c*]pyridine *N*-oxide (4.4 g, 27 mmol), trimethylsilyl cyanide (8.0 g, 81 mmol) were dissolved in 60 mL of Et_3N. The reaction mixture was refluxed for 3-4 hours. The reaction mixture was poured into water. The desired product was extracted with two portions of ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The 4-cyano-3-methylfuro[3,2-*c*]pyridine was obtained after column chromatography in a 62% yield as an oil: mp = 120-122 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H, CH_3), 7.55 (s, 1H, ArH), 7.60 (d, 1H, J = 5.6 Hz, ArH), 8.60 (d, 1H, J = 5.6 Hz, ArH); MS (z/e): 130 (24), 158 (100, M^+).

4-Hydroxymethyl-3-methyfuro[3,2-*c*]pyridine (12). 4-Cyano-3-methylfuro[3,2-*c*]pyridine (1.0 g, 6.3 mmol) was dissolved 50 mL of ethanol. Sodium ethoxide (0.65 g, 9.5 mmol) was slowly added to the ethanol solution of 4-cyano-3-methylfuro[3,2-*c*]pyridine. The resulting mixture was stirred at room temperature overnight and treated with 6 *N* HCl solution (20 mL) at 0 °C for an hour. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane, dried over anhydrous magnesium sulfate, and concentrated. The 4-carboethoxy-3-methylfuro [3,2-*c*]pyridine (0.5 g, 38% yield) was obtained by column chromatography with ethyl acetate-hexane as an eluent: ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, J = 7.2 Hz, CH_3), 2.27 (s, 3H, CH_3), 4.42 (q, 2H, J = 7.2 Hz, OCH_2), 7.41 (m, 2H, vinyl and ArH), 8.45 (d, 1H, J = 7.5 Hz, ArH). The resulting 4-carboethoxy-3-methylfuro[3,2-*c*]pyridine (0.50 g, 2.50 mmol) was dissolved in 50 mL of THF and $LiAlH_4$ (0.247 g, 6.60 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for an hour and quenched with 2 mL of 10% sodium hydroxide solution. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated. The residue was separated by column chromatography with dichloromethane-methanol (10 : 1) as an eluent. 4-Hydroxymethyl-3-methylfuro[3,2-*c*]pyridine was obtained in 54% yield as an oil: ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 4.60 (s, 2H, CH_2OH), 7.42 (m, 2H, ArH), 8.43 (d, 1H, ArH); MS (z/e): 41 (18), 44 (73), 51 (76), 77 (69), 104 (66), 131 (100), 159 (25), 163 (5).

4-Chloromethyl-3-methylfuro[3,2-*c*]pyridine (5). $SOCl_2$ (0.39 mL, 5.3 mmol) was slowly added to a solution of 4-hydroxymethyl-3-methy-furo[3,2-*c*]pyridine (0.23 g, 1.4 mmol) in 20 mL of dichloromethane at 0 °C. The reaction mixture was stirred at room temperature for 4 hours. The resulting mixture was poured into ice-water, neutralized with saturated $NaHCO_3$, and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography with hexane-ethyl acetate to give 52% of 4-chloromethyl-3-methylfuro[3,2-*c*]pyridine as oil. ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 4.75 (s, 2H, CH_2Cl), 7.42 (m, 2H, ArH), 8.43 (d, 1H, ArH); MS (z/e): 41 (18), 44 (73), 51 (76), 77 (69), 104 (66), 131 (100), 146 (20), 181 (M^+, 5).

4-(1*H*-Benzimidazol-2-thiomethyl)-furo[3,2-c]pyridine (7). Sodium hydroxide (0.13 g, 3.3 mmol) was slowly added over 5 min to a stirred solution of 2-mercaptobenzimidazole (0.29 g, 1.4 mmol) in ethanol (20 mL). 4-Chloromethyl-3-methylfuro[3,2-*c*]pyridine (0.29 g, 1.6 mmol) (**5**) was slowly added to the 2-mercaptobenzimdazole (**6**) solution at 0 °C, and stirred for 12 hours at room temperature. After the solvent was removed under reduced pressure, the residue was poured into 10% $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and concentrated. The desired coupling product (0.35 g, 74%) was obtained as a semi-solid: ^{1}H NMR ($CDCl_3$) δ 2.38 (s,

3H, CH_3). 4.69 (s, 2H, SCH_2), 7.16 (m, 2H. ArH and vinyl). 7.35 (m, 3H, ArH), 8.39 (m, 1H. ArH); Ms (z/e): 51 (27). 65 (28), 91 (39), 118 (42), 146 (72), 163 (19). 262 (100), 295 (74).

4-(1*H*-Benzimidazol-2-sulfinylmethyl)-furo[3,2-*c*]pyridine (8). A solution of *m*-chloroperbenzoic acid (0.30 g. 1.75 mmol) was added dropwise to solution of 4-(1*H*-benzimidazole-2-thiomethyl)-furo[3,2-*c*]pyridine (0.43 g. 1.7 mmol) in 35 mL of CH_2Cl_2 at -78 °C. The reaction mixture was stirred at the same temperature for an hour. The solution was washed with 10% Na_2CO_3 solution and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography. 4-(1*H*-benzimidazol-2-sulfinylmethyl)-furo[3.2-*c*]pyridine was obtained in 89% yield: ^{1}H NMR ($CDCl_3$) δ 2.18 (s. 3H, CH_3), 4.49 (s, 2H. CH_2SO). 7.50 (m. 6H, ArH and vinyl). 8.19 (d. 1H. ArH); Ms (z/e): 51 (25), 65 (23). 91 (35). 118 (40). 146 (63). 163 (15), 262 (100). 295 (53). 331 (6. M^-).

Biological Methods

Enzyme preparation. H^+/K^--ATPase was prepared from the fundic mucosae of New Zealand white rabbits (2-3 Kg, male) as described previously.[20] The mucosal layer of the gastric fundus was scraped, and homogenized in 40 mM Tris/HCl. pH 7.4 containing 0.25 M sucrose. 2 mM HEPEs. 2 mM $MgCl_2$. 2 mM EDTA. The homogenate was centrifuged at 10.000 × g for 30 min at 4 °C. The resulting supernatant was recentrifuged at 100.000 × g for 60 min at 4 °C. The pellets were resuspended in 40 mM Tris/HCl Buffer (pH 7.4). and stored at -70 °C. The protein concentration of the preparation was determined by the method of Bradford.[21]

***In vitro* screening of benzimidazole derivatives**[20]. Prepared enzyme (25 μg) was incubated at 37 °C in 250 μL of a medium consisting of 4 mM Tris/HCl, pH 7.4. 4 mM $MgCl_2$. 5 μg/mL nigercin in methanol. 6.7 mM NH_4Cl. Specific H^+/K^+-ATPase activity was determined after subtracting the basal enzyme activity which was measured without KCl and NH_4Cl. After incubation for 30 min. the reaction was terminated by the addition of 30% cold TCA. and centrifuged. The inorganic phosphate released in the supernatant was determined by the method of Yoda and Hokin.[22] Assay medium for the H^+/K^--ATPase activity contained 2% methanol. which did not affect the enzyme activity.

***In vivo* antisecretory effect of benzimidazole derivatives**.[20] *In vivo* antisecretory effects of benzimidazoles were determined using pyrorus-ligated rat according to Shay *et al.*[23] Sprague-Dawley rats (150-250 g. male) were obtained from KRICT, and food was withdrawn for 24 hours before experiment. The pylorus of the rats was ligated under ethyl ether anesthesia. The benzimidazole derivatives in PEG 400 suspension (20 mg/Kg) was administered intraduodenally. Control groups were given PEG 400 solution alone. 5 Hours after the surgery, the stomach was isolated and the accumulated gastric juice was collected. After centrifugation of gastric juice at 5000 rpm for 10 min, the supernatant was analyzed for gastric acid volume. pH. and acid output by using Orion 960 autochemistry analyzer.

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References

1. Prous, J. R. *Drug News Perspect* **1988**, *1*, 38.
2. Sach, G. *Scad. J. Gastroenterol. Suppl.* **1986**, *21*, 1.
3. Pharmd, J. H. *Clinical Therapeutic* **2000**, *22*, 266.
4. Lindberg, P.; Nordberg, P.; Alminger, T.; Brandstrom, A.; Wallmark, B. *J. Med. Chem.* **1986**, *29*, 1327.
5. Cederberg, C.; Ekenved, G.; Lind, T.: Olbe, L. *Scand. J. Gastroentrol. Suppl.* **1985**, *20*, 105.
6. Bransrom, A.; Linberg, P.; Bergman, A.: Aliminer, T.: Ankner, K.; Junggren, U.; Lamm, B.; Nordberg, P.; Erickson, M.; Grundevik, I.; Haign, I.; Hoffmann, K. J.; Johansson, S.; Larsson, S.: Lofberg, I.; Ohlson, K.: Presson, B.: Skanberg, I.: Tekenbergs, H. *Acta Chem. Scand.* **1989**, *43*, 536.
7. (a) Figala, V.; Klemm, K.; Kohl, B.; Kruger, U.; Rainer, H.; Schaefer, H.; Senn-Bilfinger, J.; Sturm, E. *J. Chem. Soc., Chem. Commun.* **1986**, 125. (b) Strum, E.; Kruger, U.; Senn-Bilfinger, J.; Figala, V.; Klemm, K.; Kohl, B.; Rainer, G.; Schaefer, H.; Blake, T. J.; Darkin, D. W.; Ife, R. J.; Leach, C. A.: Mitchell, R. C.: Pepper, E. S.: Salter, C. J.; Viney, N. J.: Huttner, G.: Zsolnai, L. *J. Org. Chem.* **1987**, *52*, 4573. (c) Senn-Bilfinger, J.; Kruger, U.: Strum, E.: Figala, V.: Klemm, K.: Kohl, B.: Rainer, G.: Schaefer, H.: Blake, T. J.: Darkin, D. W.: Ife, R. J.: Leach, C. A.; Mitchell, R. C.; Pepper, E. S.; Salter, C. J.: Viney, N. J.; Huttner, G.; Zsolnai, L. *J. Org. Chem.* **1987**, *52*, 4582.
8. Brandstrom, A.; Lindberg, P.; Junggren, U.; *Scand. J. Gastroenterol. Suppl.* **1985**, *20*, 15.
9. Clissold, S. P.; Campoli-Richards, D. M. *Drugs* **1986**, *32*, 12.
10. (a) Penston, J.; Wormsley, K. G. *Gut* **1987**, *28*, 488. (b) Hakanson, R.; Sundler, F. *Eur. J. Clin. Invest.* **1990**, *20*, 65.
11. (a) Creutzfeldt, W.: Stockmann, F.; Conion, J. M.: Folsch, U. R.; Bonatz, G.: Wulfrath, M. *Digestion* **1986**, *35*, 84. (b) Larsson, H.: Carlsson, E.: Mattsson, H. *Gastroenterology* **1986**, *90*, 391.
12. (a) Lindberg, P.; Brandstorm, A.; Wallmark, B. *Trends Pharmscol. Sci.* **1987**, *8*, 399. (b) Lindberg, P.; Nordberg, P.; Alminger, T.; Brandstrom, A.; Wallmark, B. *J. Med. Chem.* **1986**, *29*, 1327. (c) Figala, V.; Kelmn, K.; Kohl, B.; Kruger, U.; Rainer, G.; Schaefer, H.; Stenn-Ilfinger, J.; Sturm, E. *J. Chem. Soc., Chem. Commun.* **1986**, 125. (d) Rackur, G.; Bickel, M.; Eehlhaber, H.-W.: Herling, A.; Hitzel, V.; Lang, H.-J.; Rosner, M.; Weyer, R. *Biochem. Biophys. Res. Commun.* **1985**, *128*, 477.
13. (a) Kuhler, T. C.; Swanson, M.; Scherbuchin, V.: Lasson, H.: Mellgard, B.; Sjostrom, J.-E. *J. Med. Chem.* **1998**, *41*, 1777. (b) Masaki, Y.: Takeshi, Y.: Masamichi, M.; Tsunehiro, H.; Koichiro, Y.; Yasushi, H.; Mine, K.; Masaki, S. *J. Med. Chem.* **1996**, *39*, 596. (c) Yamada, S.; Goto, T.; Yamaguchi, T.; Aihara, K.; Kogi, K.; Narita, S. *Chem. Pharm. Bull.* **1995**, *43*, 421. (d) Weidmann, K.; Herling, A. W.; Lang, H.-J.; Scheunemann, K.-H.; Rippel, R.; Nimmesgern, H.; Scholl, T.; Bickel, M.; Metzger, H. *J. Med. Chem.* **1992**, *35*, 438.
14. Sammes, P. G.: Taylor, J. B. *Comprehensive Medicinal Chemistry*; Drayton, C. J., Ed.; Pregman Press Ltd: 1990; Vol. 6.
15. Cho, S. Y.; Kang, S. K.: Park, K.-H.: Kim, S. S.: Cheon, H.-G.: Hwang, K.-J.; Yum, E. K. *Bull. Korean Chem. Soc.*

1998, *19*, 1014.
16. Cho, S. Y.; Kim, S. S.; Park, K.-H.; Kang, S. K.; Choi, J.-K.; Hwang, K.-J.; Yum, E. K. *Heterocycles* **1996**, *43*, 1641.
17. Kang, S. K.; Yum, E. K. *Bull. Korean Chem. Soc.* **1999**, *20*, 503.
18. Evans, J. M.; Stemp, G. *Synthetic Commun.* **1988**, *18*, 1111.
19. Gribble, G.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151.
20. (a) Cheon, H.-G.; Yum, E. K.; Kim, S. S. *Arch. Pharm. Res.* **1996**, *19*, 126. (b) Cheon, H.-G.; Kim, H. J.; Yum, E. K.; Cho, S. Y.; Kim, D. Y.; Yang, S. I. *The Journal of Applied Pharmacoloy* **1995**, *3*, 205.
21. Bradford, M. M. *Anal. Biochem.* **1976**, *72*, 248.
22. Yoda, A.; Hokin, L. E. *Biochem. Biophys. Res. Commun.* **1970**, *40*, 880.
23. Shay, M.; Sun, O. C. H.; Gruenstein, M. *Gastroentorology* **1954**, *26*, 906.