Synthesis and Antiulcer Activity of 4-Substituted 8-[(2-Benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinolines and Related Compounds

Minoru UCHIDA,* Masatoshi CHIHIRO, Seiji MORITA, Hiroshi YAMASHITA, Katsuya YAMASAKI, Toshimi KANBE, Youichi YABUUCHI and Kazuyuki NAKAGAWA

Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., Kagasuno 463-10, Kawauchi-cho, Tokushima 771-01, Japan. *Received October 23, 1989*

A series of 4-substituted 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinolines was synthesized and examined for their ($H^+ + K^+$)adenosine triphosphatase (ATPase)-inhibitory and antisecretory activities against histamine-induced gastric acid secretion in rats. Many compounds tested were potent inhibitors of ($H^+ + K^+$)ATPase. Most compounds showed antisecretory activity. The antiulcer activity against water-immersion stress-induced gastric ulcer, aspirin-induced gastric ulcer and gastric necrosis induced by hydrochloric acid also were tested in the rat. Some of these compounds, in particular, 4-(*N*-allyl-*N*-methylamino)-1-ethyl-8-[(5-fluoro-6-methoxy-2-benzimidazolyl) sulfinylmethyl]-1-ethyl-1,2,3,4-tetrahydroquinoline (XVIIx) were found to have potent activity. The structure–activity relationships are discussed.

Keywords proton pump inhibitor; ($H^+ + K^+$) ATPase-inhibitory activity; 4-substituted 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinoline; antisecretory activity; antiulcer activity; cytoprotective activity; structure–activity relationship

In two earlier papers,[1,2] we reported that proton pump inhibitors, 8-[(5-fluoro-2-benzimidazolyl)sulfinyl]-3-methyl-5,6,7,8-tetrahydroquinoline (OPC-22321) and 8-[(2-benzimidazolyl)sulfinylmethyl]-1-ethyl-1,2,3,4-tetrahydroquinoline (OPC-22381) showed potent antisecretory and antiulcer activities (Chart 1). We also found that the methyl substitution at the 4-position of the 1,2,3,4-tetrahydroquinoline ring maintained potent antisecretory activity. As a continuation of our search for much more active compounds, we were interested in the synthesizing of 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinoline derivatives having various substituents at the 4-position of 1,2,3,4-tetrahydroquinoline ring. We describe here the synthesis, biological activity and structure–activity relationships of 4-substituted 8-[(2-benzimidazolyl) sulfinylmethyl]-1,2,3,4-tetrahydroquinolines.

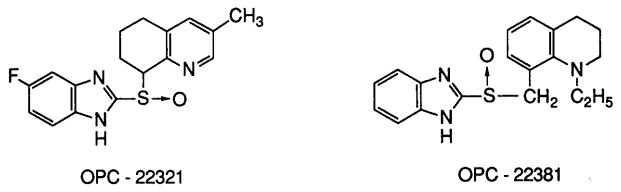


Chart 1

Synthesis Pyrido[3,2,1-*ij*]benzoxazine (V), key intermediate in the synthesis of 1,4-disubstituted 8-hydroxymethyl-1,2,3,4-tetrahydroquinolines (IXa—q), was synthesized by the pathway shown in Chart 2. Treatment of *o*-aminobenzyl alcohol (I) with trichloromethyl chloroformate gave the benzoxazine (II), which was converted to the ester (III) by Michael addition with methyl acrylate in the presence of potassium carbonate, followed by hydrolysis with sodium carbonate to give the carboxylic acid (IV). Cyclization of IV was achieved using polyphosphoric acid (PPA) at 120 °C to give the key intermediate pyrido[3,2,1-*ij*]benzoxazine (V) in 60% yield (Chart 2).

The structure–activity relationships in the preceding paper[2] indicated that ethyl and allyl groups at the 1-position of tetrahydroquinoline were most promising, and hence our synthetic work on various derivatives of tetrahydroquinoline was concentrated on 1-ethyl and 1-allyl compounds.

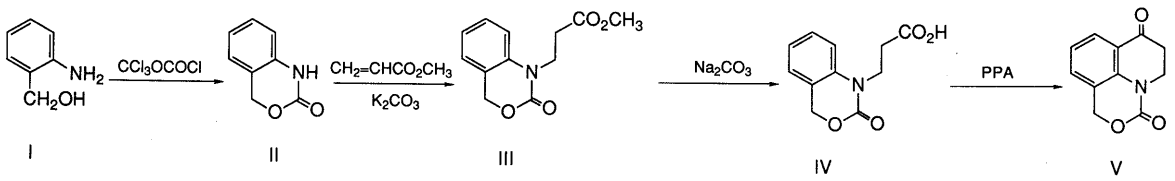


Chart 2

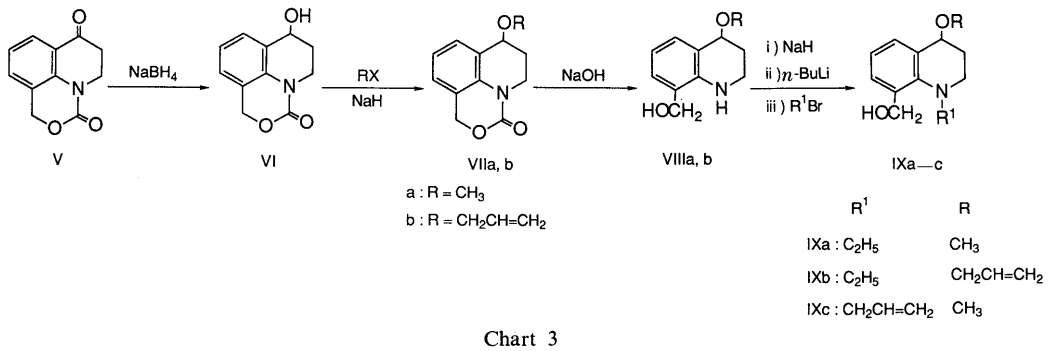
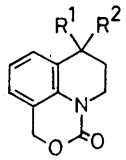


Chart 3

TABLE I. 1*H*,3*H*,5*H*,6*H*,7*H*-3-Oxopyrido[3,2,1-*ij*][3,1]bezoxazine Derivatives



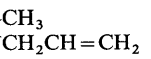
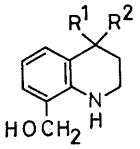
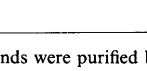
Compd. No.	R^1	R^2	Yield (%)	^{1}H-NMR ($CDCl_3$, J=Hz)
VI	OH	H	79	2.00—2.20 (2H, m), 2.70—2.80 (1H, br s), 3.70—3.90 (1H, m), 3.90—4.10 (1H, m), 4.70—4.90 (1H, m), 5.17 (2H, s), 7.00—7.10 (2H, m), 7.30—7.40 (1H, m)
VIIa	OCH_3	H	94	1.87—2.08 (1H, m), 2.15—2.31 (1H, m), 3.42 (3H, s), 3.70—3.87 (1H, m), 4.02—4.18 (1H, m), 4.29 (1H, t, 4), 5.20 (2H, s), 6.96—7.12 (2H, m), 7.22—7.32 (1H, m)
VIIb	$OCH_2CH=CH_2$	H	64	1.90—2.10 (1H, m), 2.10—2.30 (1H, m), 3.70—3.90 (1H, m), 4.00—4.20 (3H, m), 4.40—4.50 (1H, m), 5.19 (2H, s), 5.10—5.40 (2H, m), 5.80–6.10 (1H, m), 6.90—7.10 (2H, m), 7.20—7.30 (1H, m)
X			72	2.05—2.15 (2H, m), 4.00—4.08 (2H, m), 4.09—4.26 (4H, m), 5.20 (2H, s), 7.04—7.10 (2H, m), 7.40—7.45 (1H, m)
XII	$NHCH_2CH=CH_2$	H	80	1.90—2.15 (2H, m), 3.25—3.50 (2H, m), 3.70—3.95 (2H, m), 3.95—4.10 (1H, m), 5.10—5.30 (2H, m), 5.19 (2H, s), 5.85—6.10 (1H, m), 6.95—7.10 (2H, m), 7.25—7.40 (1H, m)
XIII		H	95	1.80—2.00 (1H, m), 2.00—2.20 (1H, m), 2.24 (3H, s), 3.00 (1H, dd, 11, 5.5), 3.18 (1H, dd, 11, 4.5), 3.50—3.65 (1H, m), 3.84 (1H, dd, 8, 3.5), 4.25—4.35 (1H, m), 5.10—5.30 (2H, m), 5.19 (2H, s), 5.75—5.95 (1H, m), 6.90—7.10 (2H, m), 7.56 (1H, d, 5.5)

TABLE II. 4-Substituted 8-Hydroxymethyl-1,2,3,4-tetrahydroquinolines



Compd. No.	R^1	R^2	Yield (%)	^{1}H-NMR ($CDCl_3$, J=Hz)
VIIa[a]	OCH_3	H	64	1.65—1.88 (1H, m), 2.01—2.18 (1H, m), 2.92 (1H, br s), 3.16—3.50 (2H, m), 3.33 (3H, s), 4.20 (1H, t, 3), 4.40 (2H, s), 4.95 (1H, br s), 6.55 (1H, t, 7.5), 6.91 (1H, dd, 1.5, 7.5), 7.06 (1H, dd, 1.5, 7.5)
VIII[a]	$OCH_2CH=CH_2$	H	97	1.27 (3H, t, 7), 1.98 (2H, q, 4.5), 3.10—3.35 (2H, m), 3.95—4.25 (2H, m), 4.43 (1H, t, 4.5), 4.30—4.80 (1H, m), 4.60—4.90 (2H, m), 5.10—5.40 (2H, m), 5.70—6.10 (1H, m), 6.90—7.30 (3H, m)
XI			61	1.60—1.90 (1H, m), 1.90—2.10 (2H, m), 3.40—3.50 (2H, m), 4.00—4.30 (4H, m), 4.56 (2H, s), 5.00 (1H, br s), 6.62 (1H, t, 7.5), 6.98 (1H, dd, 1.5, 7.5), 7.34 (1H, dd, 1.5, 7.5)
XIV[a]		H	91	1.70 (1H, br s), 1.93 (2H, q, 6.5), 2.24 (3H, s), 3.01 (1H, dd, 7, 14), 3.20 (1H, dd, 7, 14), 3.30—3.55 (2H, m), 3.89 (1H, t, 7), 4.55 (1H, d, 12), 4.63 (1H, d, 12), 4.80 (1H, br s), 5.05—5.30 (2H, m), 5.75—6.00 (1H, m), 6.60 (1H, t, 7.5), 6.92 (1H, dd, 1.5, 7.5), 7.42 (1H, t, 7.5)

a) Oily compounds were purified by column chromatography.

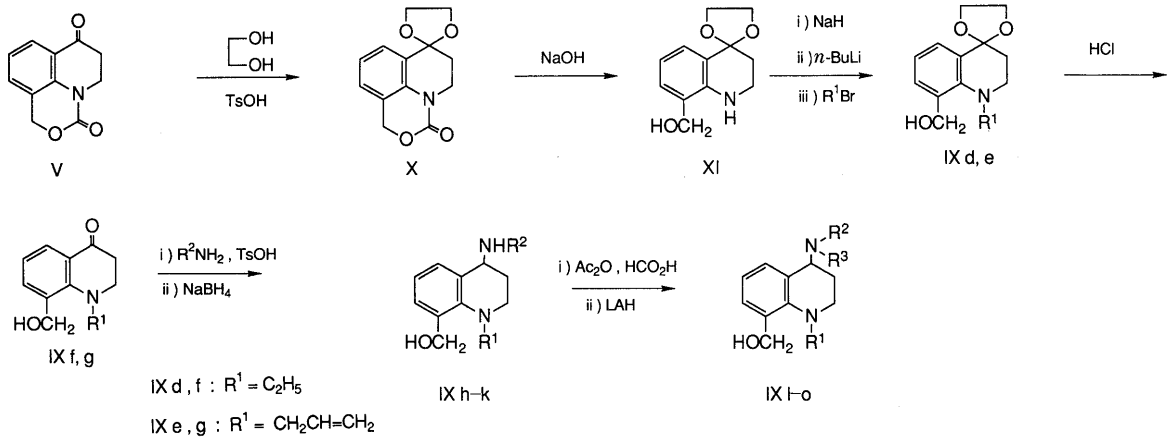
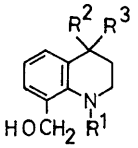


Chart 4

TABLE III. 4-Substituted 8-Hydroxymethyl-1,2,3,4-tetrahydroquinolines



Compd. No.	R^1	R^2	R^3	Yield (%)	^{1}H-NMR ($CDCl_3$, J=Hz)
IXa	C_2H_5	OCH_3	H	50	1.25 (3H, t, 7), 1.95—2.10 (2H, m), 2.96 (2H, q, 7), 3.15—3.25 (2H, m), 3.41 (3H, s), 4.28 (1H, t, 4.5), 4.46 (1H, br s), 4.70 (1H, d, 13.5), 4.80 (1H, d, 13.5), 6.98 (1H, t, 7.5), 7.10—7.35 (2H, m)
IXb	C_2H_5	$OCH_2CH=CH_2$	H	95	1.35 (3H, t, 7), 1.90—2.05 (2H, m), 2.85—3.05 (2H, m), 3.10—3.30 (2H, m), 4.00—4.20 (2H, m), 4.43 (1H, t, 4.5), 4.60—4.85 (2H, m), 5.10—5.40 (2H, m), 5.80—6.10 (1H, m), 6.90—7.10 (1H, m), 7.10—7.30 (2H, m)
IXc	$CH_2CH=CH_2$	OCH_3	H	28	1.90—2.10 (2H, m), 3.00—3.20 (2H, m), 3.42 (3H, s), 3.53 (2H, d, 6), 3.90 (1H, s), 4.27 (1H, t, 4.5), 4.64 (1H, d, 13), 4.74 (1H, d, 13), 5.20—5.40 (2H, m), 5.80—6.10 (1H, m), 6.97 (1H, t, 7.5), 7.21 (2H, d, 7)
IXd	C_2H_5			40	1.19 (3H, t, 7), 1.90—2.00 (2H, m), 2.90 (2H, q, 7), 3.20—3.30 (2H, m), 3.90—4.20 (4H, m), 4.40 (1H, br s), 4.61 (2H, s), 6.95 (1H, t, 7.5), 7.22 (1H, d, 7.5), 7.32 (1H, dd, 1.5, 7.5)
IXe	$CH_2CH=CH_2$			42	1.90—2.10 (2H, m), 3.20—3.30 (2H, m), 3.59 (2H, d, 6), 3.70 (1H, br s), 4.00—4.30 (4H, m), 4.72 (2H, s), 5.23 (1H, dd, 1.5, 10), 5.32 (1H, dd, 1.5, 17), 5.80—6.10 (1H, m), 7.03 (1H, t, 7.5), 7.26 (1H, dd, 1.5, 7.5), 7.39 (1H, dd, 1.5, 7.5)
IXf	C_2H_5	=O		98	1.32 (3H, t, 7), 2.73 (2H, t, 6.5), 3.16 (2H, q, 7), 3.57 (2H, t, 6.5), 3.75 (1H, br s), 4.76 (2H, s), 7.10 (1H, t, 7.5), 7.50 (1H, dd, 1.5, 7.5), 7.92 (1H, dd, 1.5, 7.5)
IXg	$CH_2CH=CH_2$	=O		95	2.60—2.70 (2H, m), 3.40—3.60 (2H, m), 3.60 (1H, br s), 3.74 (2H, d, 5.5), 4.80 (2H, br s), 5.20—5.50 (2H, m), 5.80—6.10 (1H, m), 7.05 (1H, t, 7.5), 7.55 (1H, dd, 1.5, 7.5), 7.89 (1H, dd, 1.5, 7.5)
IXh	C_2H_5		H	81	0.30—0.60 (3H, m), 1.27 (3H, t, 7), 1.80—2.15 (2H, m), 2.15—2.30 (1H, m), 2.93 (2H, q, 7), 3.00—3.30 (2H, m), 3.85 (1H, t, 5), 4.68 (1H, d, 13), 4.73 (1H, d, 13), 6.95 (1H, t, 7.5), 7.00—7.35 (2H, m)
IXi	C_2H_5		H	98	1.00—1.50 (8H, m), 1.50—2.20 (7H, m), 2.55—2.75 (1H, m), 2.80—3.05 (3H, m), 3.05—3.35 (2H, m), 3.86 (1H, t, 4.5), 4.60—4.95 (3H, m), 6.90—7.40 (3H, m)
IXj	C_2H_5	$NHCH_2CH=CH_2$	H	98	1.25 (3H, t, 7), 1.70—2.20 (3H, m), 2.91 (2H, q, 7), 3.00—3.50 (5H, m), 3.75 (1H, t, 5), 4.50—4.90 (3H, m), 5.00—5.30 (2H, m), 5.80—6.05 (1H, m), 6.90—7.30 (3H, m)
IXk	$CH_2CH=CH_2$	$NHCH_3$	H	89	1.70—2.00 (2H, m), 2.46 (3H, s), 3.00—3.20 (2H, m), 3.50 (2H, d, 6), 3.62 (1H, t, 4.5), 4.61 (1H, d, 13), 4.73 (1H, d, 13), 5.10—5.40 (2H, m), 5.80—6.10 (1H, m), 6.95 (1H, t, 7.5), 7.17 (2H, d, 8)
IXl	C_2H_5		H	80	0.35—0.60 (4H, m), 1.26 (3H, t, 7), 1.65—1.90 (1H, m), 2.00—2.30 (2H, m), 2.16 (3H, s), 2.70—3.40 (4H, m), 4.02 (1H, t, 8), 4.61 (1H, d, 13), 4.92 (1H, d, 13), 5.31 (1H, br s), 6.90—7.10 (2H, m), 7.37 (1H, dd, 1.5, 7)
IXm	C_2H_5		H	43	1.25 (3H, t, 7), 1.20—2.30 (12H, m), 2.13 (3H, s), 2.40—2.60 (1H, m), 2.80—3.30 (4H, m), 4.04 (1H, t, 8), 4.59 (1H, d, 13), 4.94 (1H, d, 13), 5.30 (1H, br s), 6.90—7.10 (2H, m), 7.55 (1H, dd, 2.5, 7)
IXn	C_2H_5		H	68	1.04 (3H, t, 7), 1.25 (3H, t, 7), 1.60—1.80 (1H, m), 1.80—2.10 (1H, m), 2.30—2.70 (2H, m), 2.75—3.15 (4H, m), 3.15—3.35 (2H, m), 3.90—4.10 (1H, m), 4.55 (1H, d, 13), 4.95 (1H, d, 13), 5.00—5.35 (2H, m), 5.25 (1H, br s), 5.70—6.00 (1H, m), 6.90—7.10 (2H, m), 7.66 (1H, dd, 2.5, 6.5)
IXo	$CH_2CH=CH_2$		H	51	1.59—1.78 (1H, m), 1.92—2.18 (1H, m), 2.28 (6H, s), 3.00—3.28 (2H, m), 3.48—3.60 (2H, m), 3.80 (1H, t, 7.5), 4.62 (1H, d, 13), 4.90 (1H, d, 13), 5.17—5.42 (2H, m), 5.85—6.11 (1H, m), 7.00 (1H, t, 7.5), 7.10 (1H, dd, 1.5, 7.5), 7.51 (1H, dd, 1.5, 7.5)
IXp	C_2H_5		H	59	1.25 (3H, t, 7), 1.55—1.75 (1H, m), 1.85—2.15 (1H, m), 2.20 (3H, s), 2.75—3.40 (5H, m), 3.93 (1H, t, 7), 4.59 (1H, d, 13), 4.93 (1H, d, 13), 5.00—5.35 (2H, m), 5.70—6.00 (1H, m), 6.90—7.10 (2H, m), 7.55—7.65 (1H, m)
IXq	$CH_2CH=CH_2$		H	72	1.60—1.80 (1H, m), 1.90—2.20 (1H, m), 2.21 (3H, s), 2.90—3.30 (4H, m), 3.40—3.60 (2H, m), 3.93 (1H, t, 8), 4.60 (1H, d, 13), 4.92 (1H, d, 13), 5.00—5.40 (4H, m), 5.70—6.10 (2H, m), 6.90—7.15 (2H, m), 7.61 (1H, d, 6.5)

1,4-Disubstituted 8-hydroxymethyl-1,2,3,4-tetrahydroquinolines (IXa—q) were prepared from V by four different methods.

First, reduction of V with sodium borohydride easily gave the hydroxy derivative (VI), which was alkylated with alkyl halides in the presence of sodium hydride to the alkoxy derivatives (VIIa, b), followed by hydrolysis with sodium hydroxide to give the tetrahydroquinolines (VIIIa, b). Treatment of VIIIa, b with sodium hydride in tetrahydrofuran (THF) afforded the corresponding sodium salts, which were alkylated with alkyl halides in the presence of *n*-butyllithium to give 1-substituted 4-alkoxy-tetrahydro-

quinolines (IXa—c) (Chart 3, Tables I and II).

Secondly, pyrido[3,2,1-*ij*]benzoxazine (V) was protected as the acetal (X) in the usual manner and X was hydrolyzed with sodium hydroxide to give tetrahydroquinoline (XI); these were alkylated in the same manner as described for the synthesis of IXa to give the 1-substituted tetrahydroquinolines (IXd, e), followed by removal of the acetal group with hydrochloric acid to give the 4-oxo-1,2,3,4-tetrahydroquinolines (IXf, g) (Chart 4).

Thirdly, 4-(*N*-alkyl-*N*-methylamino)-1,2,3,4-tetrahydroquinolines (IXl—o) were synthesized through reduction of the imide group with sodium borohydride. Treatment of the 4-oxo derivatives (IXf, g) with alkylamine in the presence of *p*-toluenesulfonic acid (TsOH) gave the imide compounds, followed by reduction with sodium borohydride to give the 4-alkylamino derivatives (IXh—k). Formylation of IXh—k with formic acid–acetic anhydride gave the formyl products, followed by reduction with lithium aluminum hydride (LAH) to give the *N*-alkyl-*N*-methylamino derivatives (IXl—o) (Chart 4). *N*-Allyl-*N*-methylamino derivatives (IXp, q) were also synthesized by this method, but did not give a satisfactory yield.

Finally, 4-(*N*-allyl-*N*-methylamino)-1,2,3,4-tetrahydroquinolines (IXp, q) were synthesized from V according to the procedure shown in Chart 5. Treatment of V with allylamine in the presence of TsOH gave the imide products, followed by reduction with sodium borohydride to give 7-(*N*-allylamino)-3-oxopyrido[3,2,1-*ij*]benzoxazine (XII). Methylation of XII with formic acid–formaldehyde gave the *N*-allyl-*N*-methylamino compound (XIII). Hydrolysis of XIII with sodium hydroxide gave the tetrahydroquinoline (XIV), which was alkylated in the same manner as described for the synthesis of IXa to give the *N*-allyl-*N*-methylamino derivatives (IXp, q) (Chart 5 and Table III).

Condensation of 2-mercaptobenzimidazoles[3] with 8-chloromethyl-1,2,3,4-tetrahydroquinolines, which were synthesized by treatment of 8-hydroxymethyl derivatives (IXa—q) with thionyl chloride, in the presence of potassium carbonate afforded the corresponding sulfides (XVIa—i, k, l, o—e1, i1) in good yields (Chart 6). The following sulfides (XVIf1, g1, i1) were synthesized as shown in Charts 7 and 8. *N*-Methylamino derivative (XVIe1) was acylated with cyclopropanecarboxylic anhydride to give the cyclopropylcarbonyl derivative, followed by reduction with LAH to give the *N*-cyclopropylmethyl-*N*-methylamino derivative (XVIf1). *N*-(2-Hydroxyethyl)-*N*-methylamino derivative

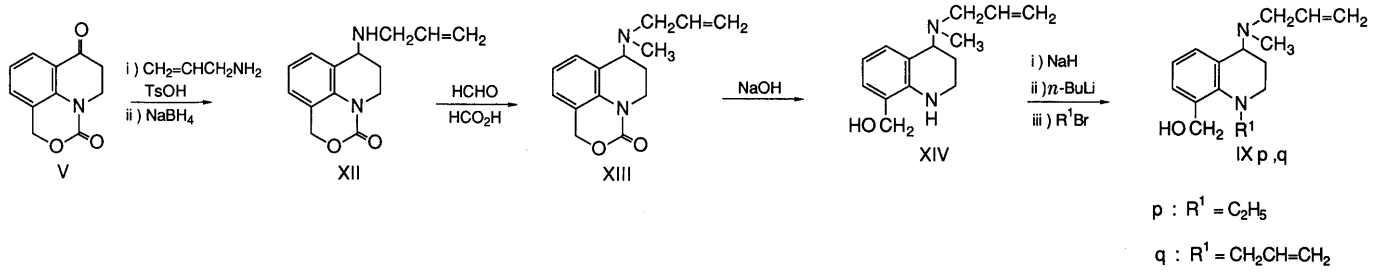


Chart 5

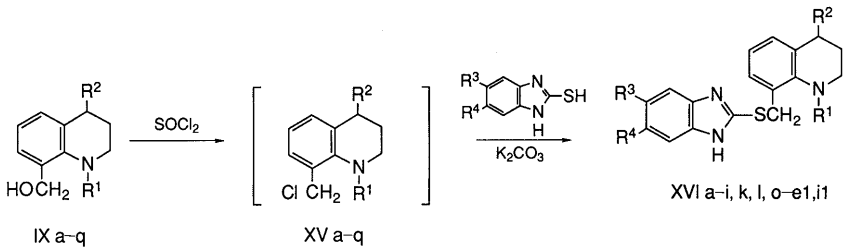


Chart 6

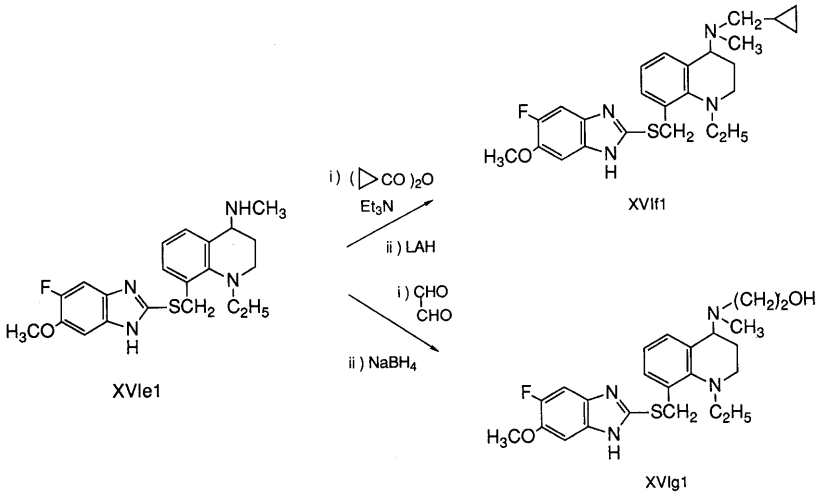
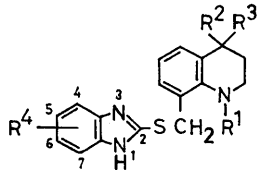


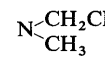
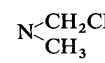
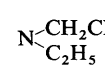
Chart 7

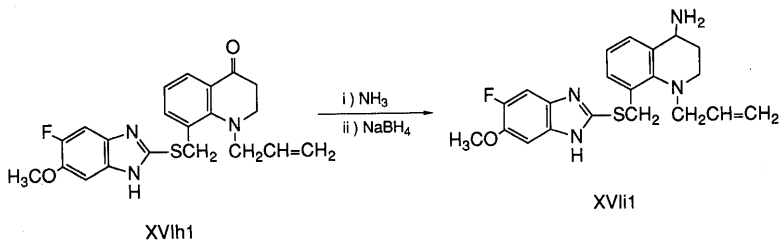
TABLE IV-1. 4-Substituted 8-[(2-Benzimidazolyl)thiomethyl]-1,2,3,4-tetrahydroquinolines



Compd. No.	R^1	R^2 R^3	R^4	Yield (%)	^{1}H-NMR ($CDCl_3$, J=Hz)
XVIa	C_2H_5	CH_3O H	H	43	1.25 (3H, t, 7), 1.80—2.10 (2H, m), 2.80—3.30 (4H, m), 3.35 (3H, s), 3.74 (3H, s), 4.10—4.30 (1H, m), 4.45 (2H, s), 6.70—7.40 (6H, m), 12.00—12.60 (1H, br s)
XVIb	C_2H_5	CH_3O H	5-CH_3	58	1.29 (3H, t, 7), 1.90—2.20 (2H, m), 2.43 (3H, s), 2.90—3.20 (2H, m), 3.25 (2H, br s), 3.41 (3H, s), 4.24 (1H, br s), 4.47 (2H, s), 6.90—7.60 (6H, m)
XVIc	C_2H_5	CH_3O H	5-CH_3O	63	1.25 (3H, t, 7), 1.95 (2H, br s), 2.80—3.20 (2H, m), 3.16 (2H, br s), 3.36 (3H, d, 6), 3.75 (3H, d, 5.5), 4.17 (1H, br s), 4.45 (2H, s), 6.70—7.50 (6H, m), 12.23 (1H, br s)
XVId	C_2H_5	CH_3O H	5-F 6-CH_3O	61	1.41 (3H, t, 7), 2.05—2.20 (2H, m), 2.98—3.27 (2H, m), 3.33—3.48 (2H, m), 3.44 (3H, s), 3.89 (3H, br s), 4.23—4.34 (3H, m), 6.79—7.33 (4H, m), 7.42 (1H, dd, 2, 8)
XVIe	C_2H_5	CH_3O H	5-CH_3CO	36	1.33 (3H, t, 7), 2.00—2.10 (2H, m), 2.60 (3H, s), 2.90—3.20 (2H, m), 3.30—3.40 (2H, m), 3.39 (3H, s), 4.23 (1H, t, 4), 4.39 (2H, d, 5.5), 6.90—7.70 (6H, m)
XVIf	C_2H_5	CH_2=$CHCH_2O$ H	H	95	1.38 (3H, t, 7.5), 2.04—2.12 (2H, m), 3.04 (2H, q, 7.5), 3.40—3.45 (2H, m), 4.00—4.20 (2H, m), 4.29 (2H, s), 4.43 (1H, t, 0.5), 5.15—5.35 (2H, m), 5.85—6.00 (1H, m), 7.00—7.60 (7H, m), 12.54 (1H, br s)
XVIg	C_2H_5	CH_2=$CHCH_2O$ H	5-CH_3CO	96	1.45 (3H, t, 7.5), 2.05—2.20 (2H, m), 2.65 (3H, s), 3.13 (2H, q, 7.5), 3.49 (2H, br s), 4.00—4.30 (2H, m), 4.30 (2H, s), 4.46 (1H, t, 0.5), 5.10—5.35 (2H, m), 5.85—6.05 (1H, m), 7.13 (1H, t, 8), 7.35 (2H, dd, 0.3, 8), 7.50—8.20 (3H, m), 13.00 (1H, br s)
XVIh	C_2H_5		H	58	1.22 (3H, t, 7), 1.90—2.05 (2H, m), 3.04 (2H, q, 7), 3.16—3.29 (2H, m), 3.98—4.23 (4H, m), 4.57 (2H, s), 6.94 (1H, t, 7.5), 7.10—7.22 (2H, m), 7.27—7.56 (4H, m)
XVIi	C_2H_5	=O	H	57	1.40 (3H, t, 7), 2.70—2.90 (2H, m), 3.23 (2H, q, 7), 3.60—3.80 (2H, m), 4.44 (2H, s), 7.00—7.30 (4H, m), 7.30—7.60 (2H, m), 7.66 (1H, dd, 1.5, 8), 7.90 (1H, dd, 1.5, 8)
XVIj	C_2H_5	OH H	H	88	1.40 (3H, t, 7), 1.90—2.30 (2H, m), 2.90—3.20 (2H, m), 3.30—3.50 (2H, m), 4.12 (1H, d, 15), 4.33 (1H, d, 15), 7.00—7.50 (7H, m), 12.10—12.80 (1H, br s)
XVIk	CH_2CH=CH_2	CH_3O H	5-CH_3CO	61	1.90—2.10 (2H, m), 2.59 (3H, s), 3.20—3.30 (2H, m), 3.40 (3H, s), 3.59 (2H, d, 5.5), 4.23 (1H, t, 4.5), 4.40 (1H, d, 14), 4.49 (1H, d, 14), 5.22 (1H, d, 10.5), 5.36 (1H, d, 17), 5.60—6.10 (1H, m), 6.98 (1H, t, 7.5), 7.21 (1H, d, 7), 7.36 (1H, d, 7), 7.30—7.50 (1H, m), 7.81 (1H, d, 8.5), 8.00—8.20 (1H, m)
XVIl	CH_2CH=CH_2	CH_3O H	5-F 6-CH_3O	64	1.90—2.10 (2H, m), 3.10—3.30 (2H, m), 3.40 (3H, s), 3.50—3.60 (2H, m), 3.82 (3H, s), 4.23 (1H, t, 4.5), 4.30—4.50 (2H, m), 5.10—5.50 (2H, m), 5.80—6.00 (1H, m), 6.70—7.50 (5H, m)
XVIm	C_2H_5	=N–OH	H	61	1.44 (3H, t, 7), 2.93—3.19 (4H, m), 3.49 (2H, t, 6.5), 4.32 (2H, s), 7.05—7.96 (8H, m), 12.00 (1H, br s)
XVIn	C_2H_5	$NHCH_3$ H	H	92	1.43 (3H, t, 7), 1.88—2.17 (2H, m), 2.48 (3H, s), 2.95—3.25 (2H, m), 3.30—3.58 (2H, m), 3.67 (1H, t, 5), 4.21 (1H, d, 15), 4.32 (1H, d, 15), 7.00—7.45 (6H, m), 7.56 (1H, br s)
XVIo	C_2H_5	$NHCH_2CH$=CH_2 H	5-CH_3	85	1.33 (3H, t, 7), 1.75—2.10 (2H, m), 2.41 (3H, s), 2.90—3.20 (2H, m), 3.20—3.50 (4H, m), 3.76 (1H, t, 5), 4.23 (1H, d, 14.5), 4.31 (1H, d, 14.5), 5.00—5.30 (2H, m), 5.80—6.10 (1H, m), 6.90—7.50 (6H, m), 12.67 (1H, br s)
XVIp	C_2H_5	 H	5-CH_3	81	0.95—2.20 (10H, m), 1.28 (3H, t, 7), 2.39 (3H, s), 2.55—2.80 (1H, m), 2.80—3.20 (2H, m), 3.20—3.50 (2H, m), 3.82 (1H, t, 4.5), 4.20 (1H, d, 14.5), 4.31 (1H, d, 14.5), 6.80—7.50 (6H, m)
XVIq	C_2H_5	$N(CH_3)_2$ H	H	31	1.42 (3H, t, 7), 1.70—1.90 (1H, m), 2.09—2.36 (1H, m), 2.26 (6H, s), 2.90—3.42 (3H, m), 3.42—3.65 (1H, m), 4.81 (1H, t, 7.5), 4.09 (1H, d, 15), 4.42 (1H, d, 15), 7.00—7.70 (7H, m)
XVIr	C_2H_5	$N(CH_3)_2$ H	5-F 6-CH_3O	40	1.41 (3H, t, 7), 1.65—1.93 (1H, m), 2.06—2.38 (1H, m), 2.26 (6H, s), 2.88—3.12 (1H, m), 3.12—3.37 (2H, m), 3.40—3.61 (1H, m), 3.80 (1H, t, 7), 3.89 (3H, br s), 4.09 (1H, d, 15), 4.39 (1H, d, 15), 6.80—7.23 (3H, m), 7.36 (1H, d, 7), 7.52 (1H, d, 8)
XVIs	CH_2CH=CH_2	$N(CH_3)_2$ H	H	95	1.70—1.90 (1H, m), 2.10—2.30 (1H, m), 2.27 (6H, s), 3.20—3.40 (1H, m), 3.40—3.90 (4H, m), 4.14 (1H, d, 15), 4.48 (1H, d, 15), 5.38 (1H, d, 11), 5.44 (1H, d, 18), 6.00—6.20 (1H, m), 7.00—7.70 (7H, m), 12.30 (1H, br s)
XVIt	CH_2CH=CH_2	$N(CH_3)_2$ H	5-F 6-CH_3O	92	1.55—1.80 (1H, m), 1.90—2.10 (1H, m), 2.18 (6H, s), 2.95—3.15 (1H, m), 3.20—3.35 (1H, m), 3.50—3.60 (2H, m), 3.65—3.85 (1H, m), 3.78 (3H, s), 3.88 (1H, br s), 4.19 (1H, d, 14), 4.39 (1H, d, 14), 5.10—5.40 (2H, m), 5.80—6.10 (1H, m), 6.75—7.30 (4H, m), 7.39 (1H, d, 7.5)

TABLE IV-1. (continued)

Compd. No.	R^1	R^2 R^3	R^4	Yield (%)	^{1}H-NMR ($CDCl_3$, J=Hz)
XVIu	$CH_2CH=CH_2$	$N(CH_3)_2$ H	5-CH_3CO	22	1.72—1.93 (1H, m), 2.09—2.40 (1H, m), 2.28 (6H, s), 2.64 (3H, s), 3.20—3.41 (1H, m), 3.44—3.77 (3H, m), 3.82 (1H, t, 8), 4.15 and 4.19 (1H, d, 15), 4.50 (1H, d, 15), 5.30—5.55 (2H, m), 5.98—6.24 (1H, m), 7.11 (1H, t, 8), 7.29 (0.5H, d, 3.5), 7.38 (1H, d, 7.5), 7.50—7.66 (1.5H, m), 7.73—7.90 (1H, m), 7.94 and 8.21 (1H, br s)
XVIv	C_2H_5	 H	5-CH_3	73	1.41 (3H, t, 7), 1.70—1.90 (1H, m), 2.15—2.30 (1H, m), 2.19 (3H, s), 2.43 (3H, s), 2.60—3.30 (6H, m), 3.45—3.60 (1H, m), 3.95 (1H, t, 8), 4.06 (1H, d, 15), 4.41 (1H, d, 15), 5.05—5.25 (2H, m), 5.70—6.00 (1H, m), 6.90—7.65 (6H, m), 12.48 (1H, br s)
XVIw	C_2H_5	 H	5-CH_3CO	60	1.40 (3H, t, 7), 1.70—1.95 (1H, m), 2.05—2.30 (1H, m), 2.20 (3H, s), 2.67 (3H, s), 2.80—3.35 (5H, m), 3.45—3.70 (1H, m), 3.97 (1H, t, 8.5), 4.27 (1H, d, 14.5), 4.50 (1H, d, 14.5), 5.05—5.35 (2H, m), 5.70—6.00 (1H, m), 7.00—8.30 (6H, m)
XVIx	C_2H_5	 H	5-F 6-CH_3O	66	1.40 (3H, t, 7), 1.70—1.95 (1H, m), 2.05—2.30 (1H, m), 2.20 (3H, s), 2.67 (3H, s), 2.80—3.35 (5H, m), 3.45—3.70 (1H, m), 3.97 (1H, t, 8.5), 4.27 (1H, d, 14.5), 4.50 (1H, d, 14.5), 5.05—5.35 (2H, m), 5.70—6.00 (1H, m), 7.00—8.30 (6H, m)
XVIy	C_2H_5	 H	5-F 6-CH_3O	75	0.30—0.60 (4H, m), 1.38 (3H, t, 7), 1.80—2.00 (1H, m), 2.00—2.40 (2H, m), 2.14 (3H, s), 2.80—3.15 (1H, m), 3.15—3.35 (2H, m), 3.35—3.60 (1H, m), 3.87 (3H, s), 3.97 (1H, t, 6.5), 4.15 (1H, d, 14.5), 4.40 (1H, d, 14.5), 6.80—7.60 (5H, m), 12.90 (1H, br s)
XVIz	C_2H_5	 H	5-CH_3CO	56	0.30—0.65 (4H, m), 1.44 (3H, t, 7), 1.80—2.45 (4H, m), 2.15 (3H, s), 2.65 (3H, s), 2.90—3.10 (1H, m), 3.10—3.40 (2H, m), 3.50—3.75 (1H, m), 4.02 (1H, t, 8), 4.13 (1H, d, 15), 4.43 (1H, d, 15), 7.06 (1H, t, 7.5), 7.25—8.30 (5H, m), 13.33 (1H, br s)
XVIa1	C_2H_5	 H	5-F 6-CH_3O	89	1.00—1.50 (5H, m), 1.36 (3H, t, 7), 1.50—2.00 (6H, m), 2.11 (3H, s), 2.10—2.35 (1H, m), 2.40—2.60 (1H, m), 2.85—3.10 (1H, m), 3.10—3.35 (2H, m), 3.35—3.60 (1H, m), 3.88 (3H, s), 4.05 (1H, t, 7), 4.19 (1H, d, 14.5), 4.44 (1H, d, 14.5), 6.90—7.60 (5H, m)
XVIb1	C_2H_5	 H	5-F 6-CH_3O	83	1.03 (3H, t, 7), 1.41 (3H, t, 7), 1.60—1.95 (1H, m), 2.00—2.20 (1H, m), 2.30—2.70 (2H, m), 2.80—3.05 (2H, m), 3.05—3.35 (3H, m), 3.45—3.65 (1H, m), 3.88 (3H, s), 3.95—4.20 (2H, m), 4.40 (1H, d, 15), 5.00—5.30 (2H, m), 5.70—5.90 (1H, m), 6.80—7.40 (4H, m), 7.69 (1H, d, 7.5), 12.70 (1H, br s)
XVIc1	$CH_2CH=CH_2$	H	5-F 6-CH_3O	93	1.60—1.90 (1H, m), 1.90—2.30 (1H, m), 2.20 (3H, s), 2.90—4.00 (7H, m), 3.88 (3H, s), 4.00—4.20 (1H, m), 4.45 (1H, d, 15), 5.00—5.50 (4H, m), 5.70—6.20 (2H, m), 6.80—7.40 (4H, m), 7.62 (1H, d, 7.5), 12.00—12.50 (1H, br s)
XVId1	C_2H_5	=O	5-F 6-CH_3O	95	1.42 (3H, t, 7), 2.80 (2H, t, 6), 3.25 (2H, q, 7), 3.68 (2H, t, 6), 3.90 (3H, s), 4.41 (2H, s), 6.87—7.47 (2H, br s), 7.12 (1H, t, 7.5), 7.65 (1H, d, 7.5), 7.00 (1H, d, 7.5)
XVIe1	C_2H_5	$NHCH_3$ H	5-F 6-CH_3O	87	1.42 (3H, t, 7.5), 1.98 (2H, br s), 2.49 (3H, s), 2.95—3.26 (2H, m), 3.30—3.58 (2H, m), 3.88 (3H, br s), 4.10—4.40 (2H, m), 6.75—7.45 (5H, m)
XVIf1	C_2H_5	 H	5-F 6-CH_3O	48	0—0.20 (2H, m), 0.35—0.62 (2H, m), 0.76—0.99 (1H, m), 1.41 (3H, t, 7), 1.66—1.90 (1H, m), 2.02—2.47 (3H, m), 2.29 (3H, s), 2.83—3.09 (1H, m), 3.09—3.34 (2H, m), 3.34—3.62 (1H, m), 3.88 (3H, s), 4.02 (1H, t, 6.5), 4.08 (1H, d, 15), 4.38 (1H, d, 15), 6.78—7.22 (3H, m), 7.34 (1H, d, 7.5), 7.64 (1H, d, 8), 12.55 and 12.83 (1H, br s)
XVIg1	C_2H_5	 H	5-F 6-CH_3O	45	1.42 (3H, t, 7), 1.51—1.98 (2H, m), 2.24 (3H, s), 2.58—2.74 (2H, m), 2.87—4.10 (7H, m), 3.88 (3H, s), 4.10 (1H, d, 15), 4.39 (1H, d, 15), 6.74—7.61 (5H, m), 12.20—12.70 (1H, br s)
XVIh1	$CH_2CH=CH_2$	=O	5-F 6-CH_3O	66	2.78 (2H, t, 6.5), 3.63 (2H, t, 6.5), 3.83 (2H, d, 6), 3.90 (3H, s), 4.45 (2H, s), 5.30—5.51 (2H, m), 6.00—6.20 (1H, m), 6.80—8.00 (5H, m), 10.28 and 10.68 (1H, br s)
XVIi1	$CH_2CH=CH_2$	NH_2 H	5-F 6-CH_3O	38	1.70—1.90 (1H, m), 2.09—2.32 (1H, m), 3.23—3.51 (2H, m), 3.66 (2H, d, 6), 3.89 (3H, s), 4.05 (1H, t, 5.5), 4.26 (1H, d, 14.5), 4.36 (1H, d, 14.5), 5.30—5.52 (2H, m), 5.97—6.23 (1H, m), 6.77—7.43 (5H, m)



XVIh1 XVIi1

Chart 8

TABLE IV-2. 4-Substituted 8-[(2-Benzimidazolyl)thiomethyl]-1,2,3,4-tetrahydroquinolines

Compd. No.	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
XVIa	Pale yellow powder(AcOEt–hexane)	136—137	$C_{20}H_{23}N_3OS$	67.96	6.59	11.89	67.83	6.42	11.80
XVIh	White powder (MeOH)	193—194	$C_{22}H_{21}N_3O_2S$	67.50	5.41	10.73	67.55	5.35	10.80
XVIi	Yellow powder (CH_2Cl_2–Et_2O)	165—167	$C_{19}H_{19}N_3OS$	67.63	5.68	12.45	67.69	5.71	12.08
XVIl	White powder (AcOEt–hexane)	154—155	$C_{22}H_{24}FN_3O_2S$	63.90	5.85	10.16	63.72	5.89	10.04
XVIm	Colorless prisms (MeOH)	201—202	$C_{19}H_{20}N_4OS$	64.75	5.72	15.90	64.34	5.69	15.67
XVIn	Yellow powder (AcOEt)	144—145	$C_{20}H_{24}N_4S \cdot 1/4H_2O$	67.29	6.92	15.69	67.51	6.80	15.37
XVIq	Pale yellow powder (CH_2Cl_2–Et_2O)	150—151.5	$C_{21}H_{26}N_4S$	68.82	7.15	15.29	68.63	6.95	15.04
XVIs	Yellow powder (Et_2O–hexane)	145—146	$C_{22}H_{26}N_4S \cdot 1/4H_2O$	68.98	6.97	14.63	69.12	6.85	14.60
XVIt	Pale yellow powder (Et_2O–hexane)	131—132	$C_{23}H_{27}FN_4OS$	64.76	6.38	13.13	64.58	6.28	13.15
XVIu	Yellow powder (Et_2O–hexane)	143—145	$C_{24}H_{28}N_4OS \cdot 1/4H_2O$	67.81	6.76	13.18	67.79	6.51	13.31
XVIv	White powder (Et_2O)	132—133	$C_{24}H_{30}N_4S \cdot 1/4H_2O$	70.12	7.48	13.63	70.08	7.35	13.80
XVIz	Yellow powder (AcOEt–hexane)	167.5—168.5	$C_{25}H_{30}N_4OS \cdot 1/4H_2O$	68.38	7.00	12.76	68.75	6.69	12.28
XVIb1	Colorless needles (AcOEt–hexane)	146—147	$C_{25}H_{31}FN_4OS \cdot 1/4H_2O$	65.40	6.92	12.20	65.57	6.90	12.04

(XVIg1) was synthesized by reduction of the formyl derivative which was prepared from XVIe1 by reaction with glyoxal. Treatment of 4-oxo derivative (XVIh1) with ammonia gave the imide product, followed by reduction with sodium borohydride to give 4-amino derivative (XVIi1) (Tables IV-1 and IV-2).

Various sulfinyl compounds (XVIIa—f1) were prepared from XVIa—c1, f1—h1 by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA). These compounds (XVIIa—h, j—l, n—f1) are the mixture of the diastereomer; however, we were not able to separate these isomers (Chart 9 and Table V).

Biological Activity and Discussion The *in vitro* $(H^+ + K^+)$ adenosine triphosphatase (ATPase) assay and *in vivo* rat gastric acid secretory study described in Table V suggested the following structure–activity relationships. Most of the compounds inhibited both $(H^+ + K^+)$ATPase activity and gastric acid secretion stimulated by histamine.

As regards the substituents in the benzimidazole ring, non-substituted compounds (XVIIq, s) inhibited $(H^+ + K^+)$ATPase in gastric microsomes more potently than substituted compounds (XVIIr, u), while these substituted compounds still showed a significant inhibition of gastric acid secretion.

The inhibitory effect of a number of substituted tetrahydroquinolines including different functional groups at the 4-position on $(H^+ + K^+)$ATPase in gastric microsomes and on gastric acid secretion stimulated by histamine were investigated. It was found that $(H^+ + K^+)$-ATPase was inhibited potently by methoxy and hydroxy derivatives (XVIIa, j) and the order of potency was CH_3O (XVIIa) $\geq$ OH (XVIIj) $>=$ N–OH (XVIIm) $>$ $NHCH_3$ (XVIIn) $\geq$  (XVIIh) $\geq =$O (XVIIi). These substituted derivatives also possessed inhibiting effect on histamine-induced gastric acid secretion except for the compound containing oxime group.

The primary (XVIIf1) and secondary (XVIIn) amine substituted compounds were more potent than tertiary amine substituted compounds (XVIIr, x) in inhibiting the $(H^+ + K^+)$ATPase. Since the secondary and tertiary amine compounds, however, showed potent antisecretory activity, the inhibitory effects of *N*-substitutents were further investigated. The potency of antisecretory activities of *N*-substituents was in the following order.

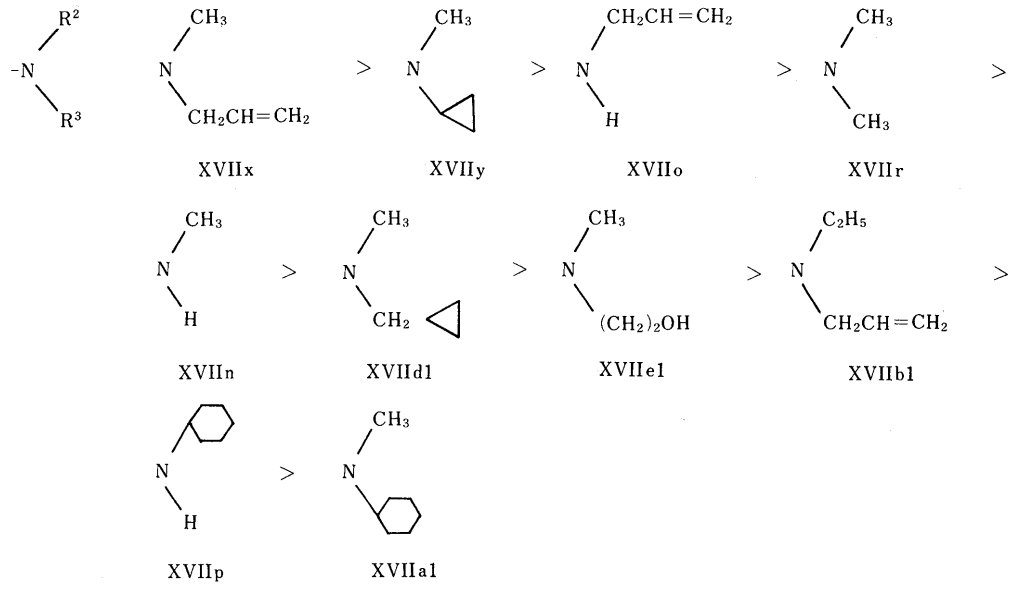
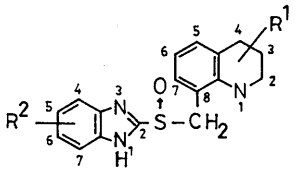


TABLE V. 4-Substituted 8-[(2-Benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinolines

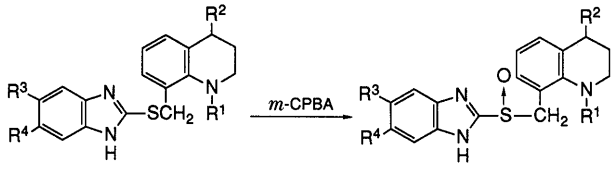


Compd. No.	R^1	R^2	H^+/K^+ ATPase IC_{50} (M)[a]	Histamine-stimulated rat % inhibn. (at i.v. dose, mg/kg)[b]	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
XVIIa	1-C_2H_5 4-CH_3O	H	1.1×10^{-6}	88.9 (10)	28	Yellow powder (CH_2Cl_2–Et_2O)	118—118.5 (dec.)	$C_{20}H_{23}N_3O_2S\cdot1/4H_2O$	64.23 (64.27)	6.33 6.33	11.24 11.24)
XVIIb	1-C_2H_5 4-CH_3O	5-CH_3	1.3×10^{-6}	35.7 (3) 87.7 (10)	17	White powder (CH_2Cl_2–Et_2O)	148.5—149.5	$C_{21}H_{25}O_2N_3S$	65.77 (65.55)	6.57 6.53	10.96 10.74)
XVIIc	1-C_2H_5 4-CH_3O	5-CH_3O	3.1×10^{-6}	54.9 (10)	21	White powder (CH_2Cl_2–Et_2O)	149—150	$C_{21}H_{25}O_3N_3S$	63.14 (63.16)	6.31 6.36	10.52 10.42)
XVIId	1-C_2H_5 4-CH_3O	5-F 6-CH_3O	4.5×10^{-6}	31.5 (10) 101.9 (30)	42	Yellow powder (CH_2Cl_2–Et_2O)	131—132	$C_{21}H_{24}FN_3O_3S\cdot1/4H_2O$	59.77 (59.79)	5.85 5.76	9.96 9.64)
XVIIe	1-C_2H_5 4-CH_3O	5-CH_3CO	7.2×10^{-6}	60.4 (10)	42	White powder (CH_2Cl_2–Et_2O)	149—150.5	$C_{22}H_{25}N_3O_3S$	64.21 (63.99)	6.12 6.06	10.21 10.08)
XVIIf	1-C_2H_5 4-CH_2=$CHCH_2O$	H	2.9×10^{-6}	31.2 (3) 73.7 (10)	26	Colorless needles (AcOEt–hexane)	128.5—129	$C_{22}H_{25}N_3O_2S$	66.81 (66.52)	6.37 6.38	10.62 10.49)
XVIIg	1-C_2H_5 4-CH_2CH=CH_2O	5-CH_3CO	8.2×10^{-6}	10.4 (10) 85.4 (30)	36	Colorless needles (CH_2Cl_2–Et_2O)	131—133	$C_{24}H_{27}N_3O_3S$	65.88 (65.80)	6.22 6.23	9.60 9.29)
XVIIh	1-C_2H_5 4-	H	1.4×10^{-5}	83.1 (10)	67	White powder (CH_2Cl_2–Et_2O)	141—142	$C_{21}H_{23}N_3O_3S$	63.46 (63.53)	5.83 5.80	10.57 10.44)
XVIIi	1-C_2H_5 4,4-=O	H	2.2×10^{-5}	57.7 (10)	32	Yellow powder ($CHCl_3$–Et_2O)	168—169	$C_{19}H_{19}N_3O_2S$	64.57 (64.20)	5.42 5.33	11.89 11.50)
XVIIj	1-C_2H_5 4-OH	H	1.7×10^{-6}	13.6 (3) 81.8 (10)	39	White powder (CH_2Cl_2–Et_2O)	117—118	$C_{19}H_{21}N_3O_2S\cdot1/2H_2O$	62.61 (62.52)	6.08 6.06	11.53 11.12)
XVIIk	1-CH_2CH=CH_2 4-CH_3O	5-CH_3CO	1.1×10^{-5}	37.8 (10) 84.4 (30)	36	White needles (CH_2Cl_2–Et_2O)	129—130	$C_{23}H_{25}N_3O_3S$	65.23 (64.87)	5.95 6.16	9.92 9.68)
XVIIl	1-CH_2CH=CH_2 4-CH_3O	5-F 6-CH_3O	8.7×10^{-6}	22.2 (10) 100.0 (30)	30	White powder (CH_2Cl_2–Et_2O)	143—144	$C_{22}H_{24}FN_3O_3S$	61.52 (61.50)	5.63 5.62	9.78 9.73)
XVIIm	1-C_2H_5 4,4-=NOH	H	4.7×10^{-6}	38.6 (30)	77	White powder (CH_2Cl_2–Et_2O)	168—169	$C_{19}H_{20}N_4O_2S\cdot H_2O$	59.05 (58.72)	5.74 5.36	14.50 14.49)
XVIIn	1-C_2H_5 4-$NHCH_3$	H	1.2×10^{-5}	86.8 (10)	30	White powder (pet. ether)	118—120	$C_{20}H_{24}N_4OS$	65.19 (65.08)	6.56 6.54	15.20 15.18)
XVIIo	1-C_2H_5 4-$NHCH_2CH$=CH_2	5-CH_3	3.3×10^{-6}	37.5 (3) 108.3 (10)	30	White powder (CH_2Cl_2–Et_2O)	162—164	$C_{23}H_{28}N_4OS$	67.62 (67.48)	6.91 6.68	13.71 13.48)
XVIIp	1-C_2H_5 4-NH– 	5-CH_3	1.4×10^{-6}	46.9 (30[c])	53	White powder (pet. ether)	135—138	$C_{26}H_{34}N_4OS\cdot1/4H_2O$	68.61 (68.80)	7.64 7.43	12.31 11.95)
XVIIq	1-C_2H_5 4-$N(CH_3)_2$	H	2.6×10^{-5}	58.8 (10)	31	Yellow needles (CH_2Cl_2–pet. ether)	141—142	$C_{21}H_{26}N_4OS$	65.94 (65.45)	6.85 6.86	14.65 14.33)
XVIIr	1-C_2H_5 4-$N(CH_3)_2$	5-F 6-CH_3O	7.0×10^{-5}	89.4 (10)	47	White powder (CH_2Cl_2–Et_2O)	162—163	$C_{22}H_{27}FN_4O_2S$	61.37 (61.11)	6.32 6.39	13.01 12.83)
XVIIs	1-CH_2CH=CH_2 4-$N(CH_3)_2$	H	5.5×10^{-6}	35.4 (10) 70.8 (30)	52	Pale yellow powder (CH_2Cl_2–pet. ether)	124—125	$C_{22}H_{26}N_4OS$	66.97 (66.58)	6.64 6.52	14.20 13.82)
XVIIt	1-CH_2CH=CH_2 4-$N(CH_3)_2$	5-F 6-CH_3O	5.2×10^{-6}	106.8 (30)	47	Pale yellow powder (CH_2Cl_2–Et_2O)	152—153	$C_{23}H_{27}FN_4O_2S$	62.42 (62.47)	6.15 6.18	12.66 12.54)
XVIIu	1-CH_2CH=CH_2 4-$N(CH_3)_2$	5-CH_3CO	$>10^{-4}$	38.1 (10) 95.2 (30)	36	White powder (Et_2O–hexane)	114—116	$C_{24}H_{28}N_4O_2S$	66.03 (65.70)	6.47 6.44	12.83 12.79)
XVIIv	1-C_2H_5 4-N()CH_3	5-CH_3	1.3×10^{-5}	NE	21	White powder (pet. ether)	109—111	$C_{24}H_{30}N_4OS$	68.21 (68.38)	7.16 7.24	13.26 13.14)
XVIIw	1-C_2H_5 4-N()CH_3	5-CH_3CO	6.1×10^{-5}	49.0 (10)	28	Pale yellow powder (pet. ether)	115—118	$C_{24}H_{30}N_4O_2S$	66.64 (66.58)	6.71 6.61	12.43 12.27)
XVIIx	1-C_2H_5 4-N()CH_3	5-F 6-CH_3O	3.8×10^{-5}	64.9 (3)	54	White powder (pet. ether)	111—115	$C_{24}H_{29}FN_4O_2S$	63.14 (63.20)	6.40 6.34	12.27 11.96)
XVIIy	1-C_2H_5 4-N()CH_3	5-F 6-CH_3O	4.0×10^{-6}	28.8 (3) 88.8 (10)	41	White powder (Et_2O–hexane)	141—143	$C_{24}H_{29}FN_4O_2S$	63.14 (63.08)	6.40 6.10	12.27 11.72)

TABLE V. (continued)

Compd. No.	R^1	R^2	H^+/K^+ ATPase IC_{50} (M)[a]	Histamine-stimulated rat % inhibn. (at i.v. dose, mg/kg)[b]	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
XVIIz	1-C_2H_5, 4-N(CH$_3$)(cyclopropylmethyl)	5-CH_3CO	5.2×10^{-6}	58.1 (10)	46	White powder (pet. ether)	125—128	$C_{25}H_{30}N_4O_2S$	66.64 (66.43)	6.71 (6.19)	12.43 (11.87)
XVIIa1	1-C_2H_5, 4-N(CH$_3$)(cyclohexyl)	5-F, 6-CH_3O	6.5×10^{-6}	17.4 (30[c])	46	Colorless needles (AcOEt–hexane)	164—168 (dec.)	$C_{27}H_{35}FN_4O_2S\cdot1/4H_2O$	64.45 (64.41)	7.11 (6.84)	11.13 (11.06)
XVIIb1	1-C_2H_5, 4-N(C_2H_5)($CH_2CH=CH_2$)	5-F, 6-CH_3O	1.0×10^{-4}	60.5 (30[c])	54	Colorless prisms (Et_2O–hexane)	110—114	$C_{25}H_{31}FN_4O_2S$	63.81 (63.80)	6.64 (6.93)	11.91 (11.45)
XVIIc1	1-$CH_2CH=CH_2$, 4-N(CH$_3$)($CH_2CH=CH_2$)	5-F, 6-CH_3O	4.4×10^{-6}	15.1 (30[c])	37	Colorless needles (Et_2O)	135—137.5	$C_{25}H_{31}FN_4O_2S$	64.08 (63.97)	6.24 (6.26)	11.96 (11.70)
XVIId1	1-C_2H_5, 4-N(CH$_3$)(CH_2-cyclopropyl)	5-F, 6-CH_3O	5.2×10^{-5}	43.6 (10) 101.5 (30)	22	Yellow powder (CH_2Cl_2–pet. ether)	116—118	$C_{25}H_{31}FN_4O_2S$	63.81 (63.56)	6.64 (6.65)	11.91 (11.84)
XVIIe1	1-C_2H_5, 4-N(CH$_3$)($(CH_2)_2OH$)	5-F, 6-CH_3O	1.8×10^{-5}	26.3 (10) 90.4 (30)	72	White powder (CH_2Cl_2–pet. ether)	149—150	$C_{25}H_{29}FN_4O_2S$	59.98 (59.71)	6.35 (6.41)	12.17 (11.88)
XVIIf1	1-$CH_2CH=CH_2$, 4-NH_2	5-F, 6-CH_3O	1.6×10^{-5}	42.2 (30)	61	Yellow powder (CH_2Cl_2–Et_2O)	101—103	$C_{21}H_{23}FN_4O_2S\cdot1/3H_2O$	59.98 (59.75)	5.67 (5.61)	13.32 (13.09)

a) Omeprazole, 2.0×10^{-6} (M). *b*) Omeprazole, 78.6% (1 mg/kg). *c*) Compound administered intraperitoneally. NE = no effect.



XVIa–c1, f1–h1 XVIIa–f1

Chart 9

The best compound (XVIIx) has a methyl group as R^2 and an allyl group as R^3. The compounds (XVIIq, r) in which both R^2 and R^3 were methyl showed high potency, whereas in the compounds (XVIIa1, b1), in which both R^2 and R^3 were methyl and cyclohexyl, ethyl and allyl showed less antisecretory activity. The secondary amine compounds (XVIIo, n) also showed potent antisecretory activity.

On the other hand, 8-[(5-acetyl-2-benzimidazolyl)sulfinylmethyl]-1-allyl-4-(*N*,*N*-dimethylamino)-1,2,3,4-tetrahydroquinoline (XVIIu) having very weak inhibitory effect on $(H^+ + K^+)$ATPase decreased gastric acid secretion. Therefore, it is possible that XVIIu has a different mechanism from omeprazole and it seems worthy of further pharmacological evaluation.

Some compounds were selected for further study. The antiulcer activity against water-immersion stress-induced gastric ulcer,[4] aspirin-induced gastric ulcer and gastric necrosis induced by 0.6 N hydrochloric acid was investigated in the rat (Table VI). Most compounds possessing the potent antisecretory activity inhibited the production of gastric mucosal lesions induced by aspirin. Only the 4-amino substituted analogues showed inhibitory effect on stress-induced gastric ulcer. Many compounds showed cytoprotective activity. It appears from these results that the presence of an amino group necessary for activity and the basicity are probably important contributing factors.

TABLE VI. Antiulcer and Cytoprotective Activities 4-Substituted 8-[(2-Benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinolines

Compd. No.	Aspirin-induced ulcer ED_{50} (mg/kg) *p.o.*	Stress ulcer ED_{50} (mg/kg) *p.o.*	Cytoprotective activity ED_{50} (mg/kg) *p.o.*
XVIIa	7.7	NE	5.4
XVIIb	16.0	NE	ND
XVIIc	13.6	>30	8.3
XVIIe	7.1	15.1	9.2
XVIIf	16.8	NE	ND
XVIIj	>30	NE	12.0
XVIIh	>30	NE	16.5
XVIIr	3.5	9.3	20.1
XVIIo	15.5	>30	17.0
XVIIu	11.9	17.6	14.6
XVIIx	5.5	7.6	13.3
XVIIy	7.2	9.3	17.5
Omeprazole	8.3	9.8	30.2

NE = no effect. ND = not determined.

Among these compounds, 4-(*N*-allyl-*N*-methylamino)-1-ethyl-8-[(5-fluoro-6-methoxy-2-benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinoline (XVIIx, OPC-22575) showed the most potent activity. It was confirmed that the amino substitution at the 4-position of the 1,2,3,4-tetrahydroquinoline ring leads to interesting products.

Experimental

Melting points were determined with a Yamato MP-21 apparatus and

are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a Bruker AC-200 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Varian MAT-312 instrument.

4*H*-1,2-Dihydro-2-oxo-3,1-benzoxazine (II) To a solution of 2-aminobenzyl alcohol (5.0 g, 41 mmol) and Et_3N (32 ml) in THF (250 ml) was added trichloromethyl chloroformate (2.7 ml, 22 mmol) at 0—10 °C. The mixture was stirred at room temperature for 2 h. After removal of the insoluble meterial by filtration, the filtrate was concentrated *in vacuo*. The residue was recrystallized from Et_2O–hexane to give II (4.5 g, 74%) as white needles, mp 120—121 °C. NMR δ: 5.33 (2H, s), 6.86 (1H, d, J=6.5 Hz), 7.00—7.16 (2H, m), 7.20—7.30 (1H, m), 8.59 (1H, br s). IR ν (KBr): 3160, 3104, 1716, 1606 cm^{-1}. *Anal.* Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.65; H, 4.79; N, 9.26.

Methyl 3-(4*H*-1,2-Dihydro-2-oxo-3,1-benzoxazin-1-yl)propionate (III) A mixture of II (792 g, 4.06 mol), methyl acrylate (440 ml, 4.87 mol) and K_2CO_3 (840 g) in *N*,*N*-dimethylformamide (DMF) (6 l) was stirred at 50 °C for 5 h. The reaction mixture was poured into water and extracted with AcOEt–benzene (3 : 1). The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give III (870 g, 90%) as colorless needles, mp 66—67 °C. NMR δ: 2.81 (2H, t, J=6.2 Hz), 3.70 (3H, s), 4.20 (2H, t, J=6.2 Hz), 5.19 (2H, s), 6.99 (1H, d, J=6.5 Hz), 7.05—7.20 (2H, m), 7.30—7.40 (1H, m). IR ν (KBr): 2965, 1730, 1700, 1180 cm^{-1}. *Anal.* Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.35; H, 5.63; N, 5.88.

3-(4*H*-1,2-Dihydro-2-oxo-3,1-benzoxazin-1-yl)propionic Acid (IV) A mixture of III (870 g, 37 mol) and saturated Na_2CO_3 solution (1.5 l) in MeOH (5.5 l) was refluxed for 8 h. After removal of the solvent, the residue was dissolved in water, neutralized with citric acid and extracted with Et_2O. Then, the aqueous layer was acidified with citric acid and extracted with AcOEt. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give IV (770 g, 92%) as colorless needles, mp 147—148.5 °C. NMR δ: 2.87 (2H, t, J=7.5 Hz), 4.22 (2H, t, J=7.5 Hz), 5.20 (2H, s), 6.90—7.50 (4H, m). IR ν (KBr): 2970, 1720, 1660, 1185 cm^{-1}. *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.69; H, 5.03; N, 6.23.

1*H*,3*H*,5*H*,6*H*,7*H*-3,7-Dioxopyrido[3,2,1-*ij*][3,1]benzoxazine (V) IV (200 g, 0.97 mol) was added to PPA prepared from phosphorus pentoxide (1.5 kg) and phosphoric acid (1.5 l) and the mixture was heated at 120 °C for 1 h. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with saturated Na_2CO_3 solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give V (110 g, 60%) as colorless needles, mp 130—130.5 °C. NMR δ: 2.85 (2H, t, J=6.8 Hz), 4.30 (2H, t, J=7.8 Hz), 5.32 (2H, s), 7.16 (1H, t, J=7.5 Hz), 7.25—7.45 (1H, m), 7.92 (1H, d, J=7.8 Hz). IR ν (KBr): 1715, 1685, 1605, 1490 cm^{-1}. *Anal.* Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.11; H, 4.29; N, 6.79.

1*H*,3*H*,5*H*,6*H*,7*H*-7-Hydroxy-3-oxopyrido[3,2,1-*ij*][3,1]benzoxazine (VI) To a solution of V (1.0 g, 5 mmol) in MeOH (20 ml) was added $NaBH_4$ (186 mg, 5 mmol) in small portions at room temperature and the mixture was stirred at the same temperature for 30 min. After removal of the solvent, the residue was poured into water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt to give VI (0.9 g, 79%) as colorless needles, mp 133—135 °C. NMR δ: 2.00—2.20 (2H, m), 2.70—2.80 (1H, br s), 3.70—3.90 (1H, m), 3.90—4.10 (1H, m), 4.70—4.90 (1H, m), 5.17 (2H, s), 7.00—7.10 (2H, m), 7.30—7.40 (1H, m). IR ν (KBr): 3450, 1690, 1600, 1480, 1400, 1290, 1110, 1090, 810 cm^{-1}. *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.51; H, 5.43; N, 6.68.

1*H*,3*H*,5*H*,6*H*,7*H*-7-Alkoxy-3-oxopyrido[3,2,1-*ij*][3,1]benzoxazines (VIIa, b). A Typical Procedure To a solution of VI (4.3 g, 21 mmol) in DMF (50 ml) was added 60% NaH (0.94 g, 24 mmol) at room temperature. The mixture was stirred at the same temperature for 30 min, then CH_3I (3.35 g, 24 mmol) was added dropwise with stirring at room temperature. After being stirred for 1 h, the reaction mixture was poured into water and extracted with benzene–AcOEt (1 : 3). The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2: MeOH = 300 : 1) and gave VIIa (4.3 g, 94%) as a yellow oil. IR ν (neat): 2930, 1720, 1610, 1490, 1410, 1270, 1100, 770 cm^{-1}. MS *m*/*z* (%): 219 (M^+, 24), 144 (40), 143 (100), 142 (25). NMR data are given in Table I.

Compound VIIb was obtained by a similar procedure to that described for VIIa; the yields and NMR data are listed in Table I.

1*H*,3*H*,5*H*,6*H*,7*H*-7,7-Ethylenedioxy-3-oxopyrido[3,2,1-*ij*][3,1]benzoxazine (X) A mixture of V (2.0 g, 9.8 mmol), ethylene glycol (2.2 ml) and *p*-TsOH (0.1 g) in toluene (60 ml) was refluxed on Dean-Stark for 3 h. The reaction mixture was washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give an oily X (1.9 g, 72%). IR ν (neat): 2900, 1720, 1610, 1490, 1460, 1410, 1220, 1130, 1040, 750 cm^{-1}. MS *m*/*z* (%): 247 (M^+, 15), 203 (28), 159 (33), 131 (53), 130 (100), 77 (26), 51 (33). NMR data are given in Table I.

8-Hydroxymethyl-1,2,3,4-tetrahydroquinolines (VIIIa, b, XI, XIV). A Typical Procedure A mixture of X (2.2 g, 8.9 mmol) and NaOH (0.43 g) in MeOH (10 ml) was refluxed for 5 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 4 : 1) to give XI (1.2 g, 61%). Recrystallization from AcOEt–hexane gave XI as pale yellow prisms, mp 125—128 °C. IR ν (KBr): 3450, 3350, 1610, 1505, 1120, 1020 cm^{-1}. *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.08; H, 6.82; N, 6.35. NMR data are given in Table II.

Compounds VIIIa, b and XIV were obtained by a similar procedure to that described for XI; the yields and NMR data are listed in Table II.

1-Substituted 8-Hydroxymethyl-1,2,3,4-tetrahydroquinolines (IXa—e, p, q). A Typical Procedure To a stirred solution of XI (11.0 g, 50 mmol), in THF (120 ml) was added NaH (60%, 2.0 g, 50 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 1 h and cooled at −60 °C. Then, *n*-butyllithium (16% solution in hexane, 21.2 ml) was added dropwise with stirring. After being stirred at the same temperature for 30 min, allyl bromide (6.0 g, 50 mmol) was added dropwise and the reaction mixture was stirred at −65—−40 °C for 4 h. After removal of the solvent, the residue was poured into water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 3 : 1) to give IXe (6.6 g, 51%). Recrystallization from AcOEt–hexane gave IXe as pale yellow prisms, mp 76—78 °C. IR ν (KBr): 3320, 1440, 1350, 1145, 1105, 1080, 1020, 950, 930, 790 cm^{-1}. *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.07; H, 7.33; N, 5.28. NMR data are given in Table III.

Compounds IXa—d, p and IXq were obtained by a similar procedure to that described for IXa, the yields and NMR data are shown in Table III.

1-Substituted 8-Hydroxymethyl-4-oxo-1,2,3,4-tetrahydroquinolines (IXf, g). A Typical Procedure A mixture of IXe (6.6 g, 25 mmol) and 10% HCl (20 ml) in THF (100 ml) was stirred at room temperature for 2 h. The reaction mixture was adjusted to pH 9 (aqueous Na_2CO_3 solution) and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 4 : 1) to give IXg (6.0 g, 92%) as a yellow oil. IR ν (neat): 3420, 1680, 1595, 1480, 1440, 1370, 1280, 1100 cm^{-1}. MS *m*/*z* (%): 218 (79), 217 (M^+, 100), 200 (30), 199 (50), 198 (46), 176 (35), 148 (64), 130 (69), 77 (37), 41 (70). NMR data are given in Table III.

Compound IXg was obtained by a similar procedure to that described for IXf; the yields and NMR data are listed in Table III.

***N*-Substituted 4-Amino-8-hydroxymethyl-1,2,3,4-tetrahydroquinolines (IXh—k). A Typical Procedure** A mixture of IXg (34 g, 0.16 mol), methylamine (40% MeOH solution, 243 ml, 1.6 mol), molecular sieves 3A (40 g) and *p*-TsOH (0.5 g) in MeOH (100 ml) was stirred at 65 °C for 5 h. The mixture was cooled and the molecular sieves were removed by filtration. To the stirred and ice-cooled filtrate was added $NaBH_4$ (8.9 g, 0.24 mol) in small portions. The mixture was stirred at room temperature for 1 h, then water was added and the mixture was concentrated *in vacuo*. The residue was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 2 : 1) to give IXk (32 g, 89%) as a yellow oil. IR ν (neat): 3320, 2950, 2870, 1450, 1420, 1060, 760 cm^{-1}. MS *m*/*z* (%): 232 (M^+, 3), 201 (100), 200 (47), 172 (41), 160 (62), 158 (44), 142 (62), 130 (42), 86 (81), 84 (76), 47 (42). NMR data are given in Table III.

Compounds IXh—j were obtained by a similar procedure to that described for IXk; the yields, elemental analysis and NMR data are listed in Table III.

***N*,*N*-Disubstituted 4-Amino-8-hydroxymethyl-1,2,3,4-tetrahydroquinolines (IXl—o). A Typical Procedure** A mixture of acetic anhydride (42 ml) and formic acid (21 ml) was stirred at 60 °C for 2 h. Then, IXk (32 g, 0.14 mol) was added dropwise with stirring at 0—10 °C and stirred at room temperature for 16 h. The reaction mixture was made alkaline with 30% NaOH and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. This residue was added to a suspension of $LiAlH_4$ (11.3 g, 0.3 mol) in THF (800 ml) dropwise at 0—10 °C. The mixture was then refluxed for 2 h. Saturated Rochelle solution was carefully added

to destroy the excess $LiAlH_4$. After removal of the insoluble material by filtration, the filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt : MeOH = 2 : 5 : 0.5) to give IXo (43.6 g, 57%) as a yellow oil. IR ν (neat): 3400, 2940, 2870, 2820, 1450, 1360, 1080, 1040, 930, 780, 760 cm^{-1}. MS *m/z* (%): 246 (M^+, 2.4), 201 (100), 200 (43), 160 (42), 158 (33), 142 (32), 130 (29), 86 (39), 84 (64). NMR data are given in Table III.

Compounds IXl—n were obtained by a similar procedure to that described for IXo; the yields and NMR data are listed in Table III.

7-(*N*-Allylamino)-1*H*,3*H*,5*H*,6*H*,7*H*-3-oxopyrido[3,2,1-*ij*][3,1]benzoxazine (XII) A mixture of V (6.1 g, 30 mmol), allylamine (50 ml), moleular sieves 3A (12 g) and *p*-TsOH (0.1 g) in MeOH (100 ml) was refluxed overnight. The mixture was cooled and the molecular sieves removed by filtration. To the stirred and ice-cooled filtrate was added $NaBH_4$ (1.7 g, 45 mmol) in small portions. The reaction mixture was stirred at room temperature for 1 h, then water (50 ml) was added, and the mixture was concentrated *in vacuo*. The residue was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 3 : 1) to give XII (5.9 g, 80%) as a yellow oil. IR ν (neat): 1720, 1610, 1490, 1460, 1410, 1300, 1290, 770 cm^{-1}. MS *m/z* (%): 244 (M^+, 4), 227 (5), 187 (7), 144 (37), 143 (100), 142 (22), 117 (10), 115 (12), 58 (13), 41 (18). NMR data are given in Table I.

7-(*N*-Allyl-*N*-methylamino)-1*H*,3*H*,5*H*,6*H*,7*H*-3-oxopyrido[3,2,1-*ij*][3,1]benzoxazine (XIII) A solution of XII (5.9 g, 24 mmol) in formic acid (7 ml) and formalin (7 ml) was stirred at 90 °C for 2 h. After removal of the formic acid and formalin, the residue was poured into water, made alkaline with Na_2CO_3 and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 100 : 1) to give XIII (5.9 g, 95%) as an orange oil. IR ν (neat): 1720, 1610, 1480, 1460, 1400, 1300, 1290, 1090, 770 cm^{-1}. MS *m/z* (%): 258 (M^+, 20), 227 (6), 188 (18), 144 (82), 143 (100), 142 (26), 117 (10), 72 (36), 70 (16). NMR data are given in Table I.

4-Substituted 8-[(2-Benzimidazolyl)thiomethyl]-1,2,3,4-tetrahydroquinolines (XVIa—i, k, l, o—e1, i1). A Typical Procedure Thionyl chloride (17 ml, 0.23 mol) was added dropwise to a stirred and ice-cooled solution of IXo (19.2 g, 78 mmol) in CH_2Cl_2 (460 ml). The reaction mixture was stirred at 0—10 °C for 1 h and concentrated *in vacuo*. The residue was dissolved in DMF (380 ml), then to this solution was added 5-acetyl-2-mercaptobenzimidazole (15.0 g, 78 mmol) and K_2CO_3 (21.6 g, 0.16 mol). The mixture was stirred at room temperature for 24 h, poured into water and extracted with toluene–AcOEt (1 : 4). The extract was washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 100 : 1) to give XVIu (28.0 g, 85%). Recrystallization from Et_2O–hexane gave XVIu as yellow powder, mp 143—145 °C. IR ν (KBr): 2930, 2820, 1670, 1450, 1420, 1360, 1280 cm^{-1}. The elemental analysis and NMR data are given in Tables IV-1 and IV-2.

Compounds XVIa—i, k, l, o—t, v—e1 and XVIi1 were obtained by a similar procedure to that described for XVIu; the yields, mp, elemental analyses and NMR data are listed in Tables IV-1 and IV-2.

8-[(2-Benzimidazolyl)thiomethyl]-1-ethyl-4-hydroxy-1,2,3,4-tetrahydroquinoline (XVIj) Sodium borohydride (0.1 g, 2.6 mmol) was added to a stirred and ice-cooled solution of XVIi (0.84 g, 2.5 mmol) in MeOH (40 ml). The mixture was stirred at room temperature for 1 h, then water was added, and the mixture was concentrated *in vacuo*. The residue was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 1 : 1) to give XVIj (0.74 g, 88%) as a white amorphous powder. IR ν (KBr): 2970, 1450, 1410, 1350, 1270, 770, 750 cm^{-1}. MS *m/z* (%): 339 (M^+, 1.5), 191 (36), 190 (63), 174 (40), 173 (67), 150 (100), 146 (42), 144 (43), 130 (32). NMR data are given in Table IV-1.

8-[(2-Benzimidazolyl)thiomethyl]-1-ethyl-4-oxo-1,2,3,4-tetrahydroquinoline Oxime (XVIm) A mixture of XVIi (1.5 g, 4.4 mmol), hydroxylamine hydrochloride (0.49 g, 6.6 mmol) and sodium acetate (1.7 g) in EtOH (20 ml) and H_2O (3 ml) was refluxed for 3 h. After removal of the solvent, the residue was poured into water. The precipitated crystals were collected by filtration. Recrystallization from MeOH gave XVIm (0.94 g, 61%) as colorless columns, mp 201—202 °C. IR ν (KBr): 3050, 2970, 2820, 1450, 1410, 1270, 1000, 770, 750 cm^{-1}. The elemental analysis and NMR data are listed in Tables IV-1 and IV-2.

8-[(2-Benzimidazolyl)thiomethyl]-1-ethyl-4-(*N*-methylamino)-1,2,3,4-tetrahydroquinolines (XVIn) Compound XVIn was obtained by the same procedure as described for IXk. Yield 92%, as yellow powder from AcOEt, mp 144—145 °C. IR ν (KBr): 2970, 2850, 1440, 1400, 1350, 1270, 750 cm^{-1}. The elemental analysis and NMR data are given in Tables IV-1 and IV-2.

4-(*N*-Cyclopropylmethyl-*N*-methylamino)-1-ethyl-8-[(5-fluoro-6-methoxy-2-benzimidazolyl)thiomethyl]-1,2,3,4-tetrahydroquinoline (XVIf1) Cyclopropanecarbonyl chloride (0.35 g, 3.3 mmol) was added to a stirred solution of cyclopropanecarboxylic acid (0.29 g, 3.4 mmol) and Et_3N (0.33 g, 3.3 mmol) in CH_2Cl_2 (10 ml) at 0—10 °C. The mixture was stirred at the same temperature for 30 min, then XVIe1 (0.7 g, 1.8 mmol) was added, and stirring continued at room temperature for 2 h. The reaction mixture was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. To the stirred and ice-cooled solution of residue (0.9 g) in THF (20 ml) was added $LiAlH_4$ (0.2 g, 5.3 mmol) in small portions. The mixture was stirred at room temperature for 1 h. Saturated Rochelle solution was carefully added to destroy the excess $LiAlH_4$. After removal of the insoluble material by filtration, the filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : hexane = 99 : 1) to give XVIf1 (0.6 g, 48%) as a yellow oil. IR ν (neat): 3080, 2970, 2940, 2870, 1490, 1470, 1450, 1430, 1350, 1200, 1160, 1130, 1030, 890, 760 cm^{-1}. MS *m/z* (%): 455 ($M^+ + 1$, 31), 370 (17), 307 (9), 257 (52), 172 (100), 136 (71), 107 (23), 89 (22), 79 (38). NMR data are given in Table IV-1.

1-Ethyl-8-[(5-fluoro-6-methoxy-2-benzimidazolyl)thiomethyl]-4-[*N*-(2-hydroxyethyl)-*N*-methylamino]-1,2,3,4-tetrahydroquinoline (XVIg1) Glyoxal (5 ml) was added to a solution of XVIe1 (1.3 g, 3 mmol) in MeOH (20 ml). The mixture was stirred at room temperature for 3 h. After removal of the solvent, the residue was dissolved in MeOH (20 ml) and $NaBH_4$ (0.7 g) was added to this solution in small portions. The reaction mixture was stirred at room temperature for 1 h, then water was added and the mixture was concentrated *in vacuo*. The residue was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 99 : 1) to give XVIg1 (0.6 g, 45%) as a white amorphous powder. IR ν (KBr): 3400, 3070, 2950, 1490, 1450, 1430, 1350, 1200, 1160, 1130, 890, 760 cm^{-1}. MS *m/z* (%): 445 ($M^+ + 1$, 1.1), 370 (1.5), 307 (7), 289 (7), 247 (7), 172 (48), 154 (100), 136 (86), 107 (32), 89 (38), 77 (38). NMR data are given in Table IV-1.

1-Allyl-4-amino-8-[(5-fluoro-6-methoxy-2-benzimidazolyl)thiomethyl]-1,2,3,4-tetrahydroquinoline (XVIi) Compound XVIi was obtained by the same procedure as described for IXk. Yield 38%, a pale yellow amorphous powder. IR ν (KBr): 3070, 2940, 1490, 1450, 1430, 1350, 1200, 1170, 1130, 890, 760 cm^{-1}. MS *m/z* (%): 398 (M^+, 3.4), 365 (10), 338 (23), 201 (53), 198 (58), 185 (31), 184 (74), 183 (100), 182 (67), 172 (40), 168 (30), 158 (38), 155 (33). NMR data are given in Table IV-1.

4-Substituted 8-[(2-Benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinolines (XVIIa-f1). A Typical Procedure A solution of 80% *m*-CPBA (8.6 g, 40 mmol) in CH_2Cl_2 (60 ml) was added dropwise to a stirred and dry ice acetone-cooled solution of XVIx (17.5 g, 40 mmol) in CH_2Cl_2 (170 ml) and the reaction mixture was stirred at the same temperature for 1 h. The CH_2Cl_2 solution was washed with Na_2CO_3 aqueous solution and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 2.5 : 1) and recrystallized from petroleum ether to give XVIIx (15.0 g, 83%) as a white powder, mp 111—115 °C. NMR δ: 1.10—1.40 (3H, m), 1.40—1.75 (1H, m), 1.75—2.00 (1H, m), 2.14 (3H, s), 2.50—3.20 (6H, m), 3.68 (1H, t, J = 7.5 Hz), 3.91 (3H, s), 4.30—4.90 (2H, m), 5.00—5.30 (2H, m), 5.80—6.00 (1H, m), 6.75—7.70 (5H, m), 12.47 (1H, br s). IR ν (KBr): 2945, 1450, 1200, 1045 cm^{-1}. The elemental analysis data are given in Table V.

Compounds XVIIa—w and XVIIy—f1 were obtained by a similar procedure to that described for XVIIx; the yields, mp, and elemental analyses data are listed in Table V.

Biological Methods The $(H^+ + K^+)$ATPase-inhibitory, gastric antisecretory, antiulcer and cytoprotective activities were tested by the reported method.[1)]

Water-Immersion Stress Ulcer[4)] Male Wistar rats weighing 160—200 g were fasted but allowed free access to water for 24 h before the experiment. The test compounds and the vehicle were given orally 30 min before the water immersion suspended in 0.5% carboxymethyl cellulose (CMC). Each rat was placed in a stress cage and immersed to the level of the xiphoid process for 7 h in a water bath maintained at 23 °C. The animals were sacrificed and the stomachs were removed. The stomach was fixed by instilling it with 10 ml of 1% formalin solution and then immersing it in the formalin solution for 30 min, after which it was incised along the greater curvature. The length of each lesion in the glandular portion was measured under a dissecting microscope. The sum of the length (mm) of

all lesions for each rat was used as an ulcer index. Percent inhibition was calculated as follows: [(ulcer index of control − ulcer index of test compound/ulcer index of control] × 100. The doses inhibiting water-immersion stress ulcer by 50% (ED_{50}) were calculated by linear regression analysis.

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