Studies on Proton Pump Inhibitors. II. Synthesis and Antiulcer Activity of 8-[(2-Benzimidazolyl)-sulfinylmethyl]-1,2,3,4-tetrahydroquinolines and Related Compounds

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Many 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinoline derivatives were synthesized and tested for their ($H^+ + K^+$)adenosine triphosphatase (ATPase)-inhibitory and antisecretory activities against histamine-induced gastric acid secretion in rats. These sulfinyl compounds were synthesized by the oxidation of the corresponding sulfides, which were obtained from the reaction of 8-chloromethyl-1,2,3,4-tetrahydroquinolines and 2-mercaptobenzimidazoles in the presence of potassium carbonate. All compounds tested were potent inhibitors of ($H^+ + K^+$)ATPase. Most of the compounds showed antisecretory activity. Among them, 8-[(2-benzimidazolyl)sulfinylmethyl]-1-ethyl-1,2,3,4-tetrahydroquinoline (IXa) was found to have the most potent activity. The structure–activity relationships are discussed.

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

In the previous paper,[1] we reported that a proton pump[2] inhibitor, 8-[(5-fluoro-2-benzimidazolyl)sulfinyl]-3-methyl-5,6,7,8-tetrahydroquinoline (OPC-22321, Chart 1), showed potent antisecretory and antiulcer activities. This compound, however, has little practical utility because it is readily decomposed under various conditions. It appears that the change from a primary to a secondary sulfinyl group is detrimental to the stability. Therefore, we undertook further studies to prepare a series of novel compounds which have a methylene group in between the 2-sulfinylbenzimidazole moiety and the 1,2,3,4-tetrahydroquinoline ring. Some of the compounds were found to have potent ($H^+ + K^+$) adenosine triphosphatase (ATPase)-inhibitory and antisecretory activities, and were stable. Herein, we report the synthesis, biological activity and structure–activity relationships of 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinolines. The synthesis of a similar series of these compounds was disclosed in a patent.[3] Only one of the present compounds, 8-[(2-benzimidazolyl)sulfinylmethyl]-1,6-dimethyl-1,2,3,4-tetrahydroquinoline, was synthesized, by a different route from ours, and the biological activity of this compound was not described.

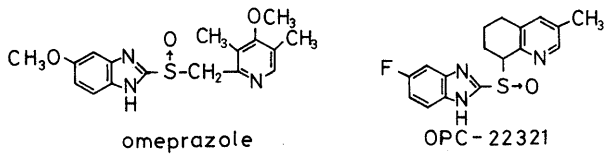
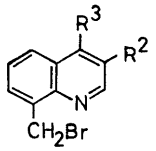


Chart 1

Synthesis Our chemical approach was to examine the effects of varying the following three structural parameters on the activity of 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinolines (IX): (1) the effect of the *N*-substituents on the tetrahydroquinoline ring, (2) the effect of the position and nature of substituents on the tetrahydroquinoline ring, and (3) the effect of substituents on the benzimidazole ring.

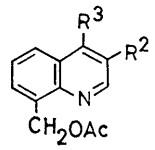
The 1-substituted 8-hydroxymethyl-1,2,3,4-tetrahydroquinolines (VIa—j), which are key intermediates in the synthesis of the corresponding sulfides (IXa—fl), were synthesized by the pathway shown in Chart 2. Bromination of 8-methylquinolines (Ia—d)[4] with *N*-bromosuccinimide (NBS) in carbon tetrachloride gave 8-bromomethylquinolines (IIa—d), which were converted to the acetates (IIIa—d) by treatment with sodium acetate in *N*,*N*-dimethylformamide (DMF), followed by hydrolysis with sodium hydroxide to give the alcohols (IVa—d). Hydrogenation of IVa—d with platinum oxide readily gave 8-hydroxymethyl-1,2,3,4-tetrahydroquinolines (Va—d). 1-Substituted 8-hydroxymethyl-1,2,3,4-tetrahydroquinolines (VIa—j) were prepared by the following method. Treatment of Va—d with sodium hydride in tetrahydrofuran (THF) afforded the corresponding sodium salts, which were alkylated with

TABLE I. 8-Bromomethylquinolines



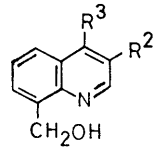
Compd. No.	R^2	R^3	Yield (%)	Appearance	Recrystn. solv.	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
IIa	H	H	58	Colorless needles	Ligroin	83—84.5	$C_{10}H_8BrN$	54.08	3.63	6.31	54.02	3.75	6.28
IIb	CH_3	H	97	Colorless needles	AcOEt	121—122	$C_{11}H_{10}BrN$	55.96	4.27	5.93	55.94	4.06	5.78
IIc	H	CH_3	89	Colorless prisms	AcOEt–hexane	78—79	$C_{11}H_{10}BrN$	55.96	4.27	5.93	55.87	4.21	5.83
IId	H	C_6H_5	98	Brown powder	EtOH	250—251 (dec.)	$C_{16}H_{12}BrN \cdot HBr$	50.69	3.46	3.69	50.98	3.51	3.50

TABLE II. 8-Acetoxymethylquinolines



Compd. No.	R^2	R^3	Yield (%)	Appearance	Recrystn. solv.	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
IIIa	H	H	85	Colorless prisms	AcOEt–hexane	40—41	$C_{12}H_{11}NO_2$	71.63	5.51	6.96	71.42	5.57	6.96
IIIb	CH_3	H	91	Colorless prisms	AcOEt–hexane	46—48	$C_{13}H_{13}NO_2$	72.54	6.09	6.51	72.45	5.91	6.50
IIIc	H	CH_3	87	Colorless plates	AcOEt–hexane	50—51.5	$C_{13}H_{13}NO_2$	72.54	6.09	6.51	72.52	6.04	6.29
IIId	H	C_6H_5	98	Colorless prisms	AcOEt–hexane	86—88	$C_{18}H_{15}NO_2$	77.96	5.45	5.05	77.69	5.43	5.01

TABLE III. 8-Hydroxymethylquinolines



Compd. No.	R^2	R^3	Yield (%)	Appearance	Recrystn. solv.	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
IVa	H	H	96	Colorless needles	EtOH–hexane	73.5—74.5	$C_{10}H_9NO$	75.45	5.70	8.80	75.45	5.65	8.74
IVb	CH_3	H	53	Colorless needles	AcOEt–hexane	54—55	$C_{11}H_{11}NO \cdot 1/2\,H_2O$	72.51	6.64	7.69	72.03	6.24	7.62
IVc	H	CH_3	50	Brown needles	EtOH–AcOEt	111—113	$C_{11}H_{11}NO \cdot 1/4\,H_2O$	74.34	6.52	7.88	74.81	6.41	7.68
IVd	H	C_6H_5	70	Colorless needles	AcOEt	67—68.5	$C_{16}H_{13}NO \cdot 1/4\,H_2O$	80.14	5.67	5.84	80.03	5.51	5.81

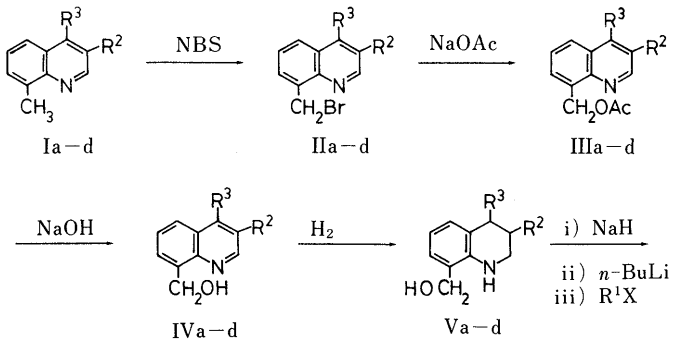
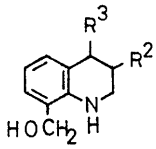


TABLE IV. 8-Hydroxymethyl-1,2,3,4-tetrahydroquinolines



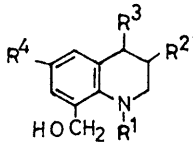
Compd. No.	R^1	R^2	R^3	Yield (%)	^{1}H-NMR δ ($CDCl_3$, J=Hz)
Va	H	H	H	98[a]	1.67—2.10 (2H, m), 2.77 (2H, t, 7), 3.34 (2H, t, 7), 4.57 (2H, s), 6.50 (1H, t, 8), 6.70—7.00 (2H, m)
Vb	H	CH_3	H	90[b]	1.04 (3H, d, 7), 1.40—2.20 (2H, m), 2.72—2.86 (1H, m), 3.28—3.40 (1H, m), 4.58 (2H, s), 6.55 (1H, t, 8), 6.80—7.00 (2H, m)
Vc	H	H	CH_3	27[b]	1.27 (3H, d, 7), 1.43—2.20 (2H, m), 2.77—3.07 (1H, m), 3.17—3.50 (2H, m), 4.57 (2H, s), 6.53 (1H, t, 8), 6.85 (1H, d, 8), 7.02 (1H, d, 8)
Vd	H	H	C_6H_5	22[a]	1.90—2.30 (2H, m), 3.20—3.50 (2H, m), 4.17 (1H, t, 6), 4.64 (2H, s), 6.53 (1H, t, 8), 6.77 (1H, d, 8), 6.94 (1H, d, 8), 7.10—7.40 (5H, m)

a) Va; Yellow needles (AcOEt–hexane), mp 67—68 °C, *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.49; H, 7.98; N, 8.56. Vd; White powder (AcOEt–hexane), mp 104—106 °C, *Anal.* Calcd for $C_{16}H_{17}NO \cdot 1/4\,H_2O$: C, 78.82; H, 7.23; N, 5.74. Found: C, 79.23; H, 7.05; N, 5.44. *b*) Oily compounds were purified by column chromatography.

alkyl halides in the presence of *n*-butyllithium to give VIa—j (Tables I—V).

Bromination of VIb with 2,4,4,6-tetrabromocyclohexa-2,5-dienone[5] gave the 6-bromo compound (VIk), which was converted to the 6-methoxy derivative (VII) by treatment with sodium methoxide–cupric iodide in methanol

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



Compd. No.	R^1	R^2	R^3	R^4	Yield (%)	^{1}H-NMR ($CDCl_3$, J=Hz)
VIa	CH_3	H	H	H	57[a]	1.70—2.10 (2H, m), 2.77 (3H, s), 2.80 (2H, t, 6), 3.00—3.20 (2H, m), 4.80 (2H, s), 5.20 (1H, br s), 6.97 (3H, s)
VIb	C_2H_5	H	H	H	37[a]	1.27 (3H, t, 7.5), 1.66—2.00 (2H, m), 2.85 (2H, q, 7.5), 3.00—3.20 (2H, m), 4.00 (1H, br s), 4.75 (2H, s), 6.93 (3H, s)
VIc	C_4H_9	H	H	H	39[a]	0.97 (3H, t, 7), 1.13—2.00 (6H, m), 2.67—3.00 (4H, m), 3.00—3.23 (2H, m), 4.77 (2H, s), 6.97 (3H, br s)
VId	$CH_2CH=CH_2$	H	H	H	55[a]	1.57—2.00 (2H, m), 2.73 (2H, t, 7), 2.90—3.13 (2H, m), 3.42 (2H, d, 6), 4.63 (2H, s), 5.03—5.40 (2H, m), 5.67—6.17 (1H, m), 6.70—7.20 (3H, m)
VIe[b]	$CH_2C\equiv CSi(CH_3)_3$	H	H	H	61	0.17 (9H, s), 1.67—2.07 (2H, m), 2.80 (2H, t, 7), 3.13—3.37 (2H, m), 3.72 (2H, s), 4.73 (2H, s), 6.77—7.13 (3H, m)
VIf	$CH_2C_6H_5$	H	H	H	42[a]	1.63—2.07 (2H, m), 2.73—3.07 (4H, m), 4.07 (2H, s), 4.82 (2H, s), 6.90—7.60 (8H, m)
VIg	C_2H_5	CH_3	H	H	25[a]	1.01 (3H, d, 6.5), 1.24 (3H, t, 7), 1.95—2.25 (1H, m), 2.25—2.60 (2H, m), 2.80—3.20 (4H, m), 4.49 (1H, d, 13), 5.02 (1H, d, 7), 5.05 (1H, d, 6), 6.80—7.10 (3H, m)
VIh	$CH_2CH=CH_2$	CH_3	H	H	66[a]	0.96 (3H, d, 7), 2.00—2.67 (3H, m), 2.70—3.30 (2H, m), 3.40—3.60 (2H, m), 4.27 (1H, br s), 4.50 (1H, d, 13), 4.97 (1H, d, 13), 5.10—5.47 (2H, m), 5.70—6.23 (1H, m), 6.70—7.20 (3H, m)
VIi	C_2H_5	H	CH_3	H	35[a]	1.29 (3H, t, 7), 1.33 (3H, t, 7), 1.40—1.70 (1H, m), 1.90—2.20 (1H, m), 2.80—3.00 (1H, m), 3.00—3.20 (2H, m), 2.94 (2H, q, 7), 4.79 (2H, d, 2), 5.10—5.60 (1H, br s), 6.90—7.20 (3H, m)
VIj	C_2H_5	H	C_6H_5	H	45[a]	1.29 (3H, t, 7), 1.70—2.20 (2H, m), 2.80—3.20 (4H, m), 4.14 (1H, t, 7), 4.73 (1H, d, 13), 4.89 (1H, d, 13), 5.10 (1H, br s), 6.70—7.30 (8H, m)
VIk	C_2H_5	H	H	Br	59	1.22 (3H, t, 7.5), 1.63—2.00 (2H, m), 2.63—2.93 (4H, m), 2.93—3.17 (2H, m), 4.67 (2H, s), 6.93—7.30 (2H, m)
VIl	C_2H_5	H	H	OCH_3	73	1.23 (3H, t, 8), 1.63—2.00 (2H, m), 2.60—3.17 (6H, m), 3.73 (3H, s), 4.73 (2H, s), 6.47 (1H, d, 2), 6.57 (1H, d, 2)

a) Oily compounds were purified by column chromatography. *b*) The starting material (3-bromo-1-trimethylsilyl-1-propyne) was prepared from propargyl alcohol by the method described in reference 8.

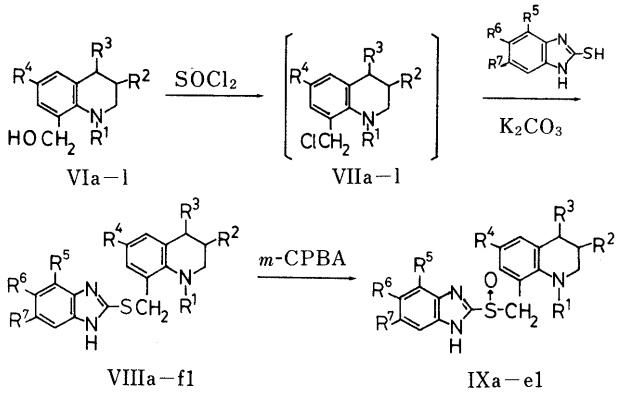


Chart 4

(MeOH)–DMF at 140 °C (Chart 3).

On the other hand, 2-mercaptobenzimidazoles were prepared according to the reported methods.[6] Condensation of 2-mercaptobenzimidazoles with 8-chloromethyl-1,2,3,4-tetrahydroquinolines (VII), which were synthesized by treatment of the 8-hydroxymethyl derivatives (VIa—l) with thionyl chloride, in the presence of potassium carbonate afforded the corresponding sulfides (VIIIa—fl) in good yield. Oxidation of the sulfides (VIIIa—u, w—fl) with *m*-chloroperbenzoic acid (*m*-CPBA) in chloroform or methylene chloride was conveniently carried out at 0 °C to give the corresponding sulfoxides (IXa—el) (Chart 4) (Tables VI and VII).

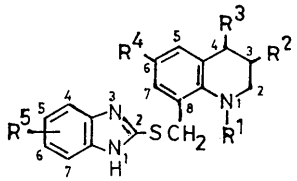
Structure–Activity Relationships The $(H^+ + K^+)$ATPase-inhibitory and antisecretory activities of the synthesized compounds are summarized in Table VII. All compounds tested showed potent activity *in vitro*. Most of the compounds inhibited *in vivo* histamine-induced gastric acid secretion in rats.

First, the effect of substitution on the nitrogen of tetrahydroquinoline was examined. It was found that the alkyl derivatives (IXa, n, s) and an allyl derivative (IXt) showed potent enzyme-inhibitory activity. The propargyl (IXv) and benzyl (IXw) derivatives were less active than the alkyl derivatives *in vitro*. These alkyl, allyl and propargyl derivatives possessed *in vivo* antisecretory activity and the order of activity was methyl (IXn) ≥ ethyl (IXa) > allyl (IXt) > propargyl (IXt). The butyl (IXs) and benzyl (IXw) derivatives had no antisecretory activity even at 30 mg/kg.

Next, the effect of substituents on the tetrahydroquinoline moiety was examined. It was found that the 3-methyl (IXx), 4-methyl (IXz) and 6-methoxy (IXel) compounds were slightly less active than the 1-ethyl compound (IXa) in *in vitro* assay. Methyl substitution at the 3- or 4-position of the tetrahydroquinoline ring decreased the *in vivo* antisecretory activity. The 4-phenyl (IXc) and 6-bromo (IXdl) compounds exhibited decreased *in vitro* and *in vivo* activities.

Finally, the enzyme-inhibitory activity of compounds substituted in the benzimidazole ring was similar to that of the non-substituted compound (IXa). The acetyl (IXg, q) and fluoro substituted compounds (IXd, k, l) were less

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



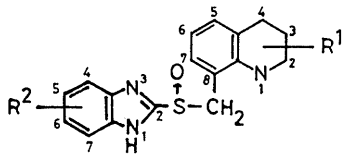
Compd. No.	R^1	R^2	R^3	R^4	R^5	Yield (%)	^{1}H-NMR δ ($CDCl_3$, J=Hz)
VIIIa	C_2H_5	H	H	H	H	53	1.43 (3H, t, 7.5), 1.73—2.17 (2H, m), 2.83 (2H, t, 7), 3.09 (2H, q, 7.5), 3.23—3.50 (2H, m), 4.25 (2H, s), 6.80—7.70 (7H, m)
VIIIb	C_2H_5	H	H	H	5-CH_3O	35	1.42 (3H, t, 7.5), 2.83 (2H, t, 7), 3.08 (2H, q, 7.5), 3.23—3.50 (2H, m), 3.83 (3H, s), 4.27 (2H, s), 6.66—7.50 (6H, m)
VIIIc	C_2H_5	H	H	H	5-CH_3	42	1.30 (3H, t, 7.5), 1.66—2.10 (2H, m), 2.08 (3H, s), 2.73 (2H, t, 7), 2.97 (2H, q, 7.5), 3.10—3.34 (2H, m), 4.25 (2H, s), 6.80—7.50 (6H, m)
VIIId	C_2H_5	H	H	H	5-F	30	1.40 (3H, t, 7.5), 1.70—2.20 (2H, m), 2.83 (2H, t, 7), 3.07 (2H, q, 7.5), 3.23—3.50 (2H, m), 4.23 (2H, s), 6.70—7.60 (6H, m)
VIIIe	C_2H_5	H	H	H	5-Cl	57	1.38 (3H, t, 7.5), 1.66—2.10 (2H, m), 2.50—3.00 (2H, m), 3.05 (2H, q, 7.5), 3.10—3.40 (2H, m), 4.25 (2H, s), 6.67—7.63 (6H, m), 12.17 (1H, br s)
VIIIf	C_2H_5	H	H	H	5-CF_3	45	1.42 (3H, t, 7), 1.66—2.20 (2H, m), 2.80 (2H, t, 6), 3.03 (2H, q, 7), 3.20—3.50 (2H, m), 4.28 (2H, s), 6.70—7.50 (6H, m)
VIIIg	C_2H_5	H	H	H	5-CH_3CO	20	1.40 (3H, t, 7.5), 1.70—2.20 (2H, m), 2.63 (3H, s), 2.83 (2H, t, 7), 3.07 (2H, q, 7.5), 3.10—3.20 (2H, m), 4.30 (2H, s), 6.80—7.20 (6H, m)
VIIIh	C_2H_5	H	H	H	4-CH_3	78	1.35 (3H, t, 7.5), 1.66—2.10 (2H, m), 2.55 (3H, s), 2.77 (2H, t, 7), 3.00 (2H, q, 7.5), 3.00—3.20 (2H, m), 4.25 (2H, s), 6.67—7.50 (6H, m), 12.80 (1H, br s)
VIIIi	C_2H_5	H	H	H	5,6-diCH_3	38	1.40 (3H, t, 7.5), 1.83—2.20 (2H, m), 2.33 (6H, s), 2.83 (2H, t, 7), 3.07 (2H, q, 7.5), 3.23—3.47 (2H, m), 4.23 (2H, s), 6.90—7.50 (5H, m), 12.37 (1H, br s)
VIIIj	C_2H_5	H	H	H	5-F 6-CH_3O	46	1.33 (3H, t, 7.5), 1.66—2.10 (2H, m), 2.77 (2H, t, 7), 3.00 (2H, q, 7.5), 3.00—3.33 (2H, m), 3.83 (3H, s), 4.30 (2H, s), 6.66—7.40 (5H, m), 13.00 (1H, br s)
VIIIk	C_2H_5	H	H	H	5-C_2H_5O 6-F	16	1.40 (3H, t, 7.5), 1.43 (3H, t, 7), 1.66—2.13 (2H, m), 2.85 (2H, t, 7), 3.07 (2H, q, 7.5), 3.20—3.50 (2H, m), 3.50 (2H, q, 7), 4.26 (2H, s), 6.50—7.50 (5H, m)
VIIIl	C_2H_5	H	H	H	5-F 6-CH_3	64	1.33 (3H, t, 7), 1.66—2.10 (2H, m), 2.30 (3H, d, 2), 2.77 (2H, t, 7), 2.98 (2H, q, 7), 3.10—3.40 (2H, m), 4.27 (2H, s), 6.73—7.50 (5H, m), 12.97 (1H, br s)
VIIIm	C_2H_5	H	H	H	5,6-diF	39	1.42 (3H, t, 7.5), 1.83—2.30 (2H, m), 2.50—3.00 (2H, m), 3.10 (2H, q, 7.5), 3.23—3.43 (2H, m), 4.25 (2H, s), 6.67—7.60 (5H, m), 13.17 (1H, br s)
VIIIn	CH_3	H	H	H	H	30	2.00—2.16 (2H, m), 2.85 (2H, t, 7), 2.95 (3H, s), 3.35—3.45 (2H, m), 4.32 (2H, s), 6.90—7.50 (7H, m)
VIIIo	CH_3	H	H	H	5-CH_3O	47	1.60—2.00 (2H, m), 2.70 (2H, t, 7), 2.73 (3H, s), 2.83—3.23 (2H, m), 3.73 (3H, s), 4.30 (2H, s), 6.67—7.40 (6H, m), 12.50 (1H, br s)
VIIIp	CH_3	H	H	H	5-CH_3	24	1.83—2.23 (2H, m), 2.43 (3H, s), 2.87 (2H, t, 7), 2.93 (3H, s), 3.23—3.47 (2H, m), 4.30 (2H, s), 6.83—7.50 (6H, m)
VIIIq	CH_3	H	H	H	5-CH_3CO	9	1.70—2.30 (2H, m), 2.63 (3H, s), 2.87 (2H, t, 7), 2.95 (3H, s), 3.20—3.47 (2H, m), 4.35 (2H, s), 6.80—7.90 (5H, m), 8.07 (1H, s)
VIIIr	CH_3	H	H	H	5-F 6-CH_3O	73	1.73—2.13 (2H, m), 2.80 (2H, t, 6), 2.83 (3H, s), 3.10—3.33 (2H, m), 3.83 (3H, s), 4.33 (2H, s), 6.80—7.33 (5H, m), 11.50 (1H, br s)
VIIIs	C_4H_9	H	H	H	H	55	0.95 (3H, t, 6), 1.13—1.63 (2H, m), 1.63—2.17 (4H, m), 2.67—3.18 (4H, m), 3.18—3.50 (2H, m), 4.30 (2H, s), 6.80—7.83 (7H, m)
VIIIt	$CH_2CH=CH_2$	H	H	H	H	36	1.67—2.07 (2H, m), 2.60—2.93 (2H, m), 3.07—3.37 (2H, m), 3.57 (2H, d, 6), 4.33 (2H, s), 5.07—5.63 (2H, m), 5.77—6.33 (1H, m), 6.73—7.63 (7H, m)
VIIIu	$CH_2CH=CH_2$	H	H	H	5-CH_3	73	1.60—2.05 (2H, m), 2.38 (3H, s), 2.73 (2H, t, 7), 3.06—3.33 (2H, m), 3.50 (2H, d, 6), 4.30 (2H, s), 5.06—5.47 (2H, m), 5.73—6.30 (1H, m), 6.70—7.50 (6H, m)
VIIIv	$CH_2C\equiv CSi(CH_3)_3$	H	H	H	H	28	1.80—2.17 (2H, m), 2.83 (2H, t, 7), 3.37—3.60 (2H, m), 3.80 (2H, s), 4.35 (2H, s), 6.77—7.57 (7H, m)
VIIIw	$CH_2C\equiv CH$	H	H	H	H	95	1.80—2.16 (2H, m), 2.35 (1H, t, 3), 2.83 (2H, t, 6), 3.37—3.60 (2H, m), 3.78 (2H, d, 3), 4.36 (2H, s), 6.83—7.70 (7H, m)
VIIIx	$CH_2C_6H_5$	H	H	H	5-CH_3	38	1.80—2.20 (2H, m), 2.40 (3H, s), 2.83 (2H, d, 7), 3.07—3.30 (2H, m), 4.25 (2H, s), 4.43 (2H, s), 6.67—7.80 (6H, m)
VIIIy	C_2H_5	CH_3	H	H	H	76	1.13 (3H, d, 6), 1.44 (3H, t, 7), 2.10—2.50 (2H, m), 2.60—2.80 (1H, m), 2.80—3.10 (2H, m), 3.10—3.35 (1H, m), 3.35—3.60 (1H, m), 4.02 (1H, d, 15), 4.49 (1H, d, 15), 6.80—7.45 (6H, m), 7.56 (1H, br s), 12.73 (1H, br s)
VIIIz	$CH_2CH=CH_2$	CH_3	H	H	H	69	1.09 (3H, d, 6), 2.05—2.60 (2H, m), 2.60—3.10 (2H, m), 3.40—3.60 (1H, m), 3.60—3.80 (2H, m), 4.04 (1H, d, 15), 4.57 (1H, d, 15), 5.30—5.56 (2H, m), 6.00—6.30 (1H, m), 6.90—7.80 (7H, m), 12.42 (1H, br s)
VIIIa1	C_2H_5	H	CH_3	H	H	62	1.22 (3H, d, 7.5), 1.35 (3H, t, 7.5), 1.40—2.20 (2H, m), 2.60—3.30 (5H, m), 4.25 (2H, s), 6.80—7.40 (7H, m)
VIIIb1	C_2H_5	H	CH_3	H	5-F 6-CH_3O	58	1.27 (3H, d, 7.5), 1.37 (3H, t, 7), 1.50—2.20 (2H, m), 2.80—3.40 (5H, m), 3.87 (3H, s), 4.27 (2H, s), 6.60—7.40 (5H, m)
VIIIc1	C_2H_5	H	CH_3	H	5-CH_3CO	61	1.23 (3H, d, 7), 1.37 (3H, t, 7), 1.50—2.50 (2H, m), 2.60 (3H, s), 2.70—3.50 (5H, m), 4.30 (2H, s), 6.80—7.60 (4H, m), 7.79 (1H, dd, 3, 9), 8.07 (1H, br s)

TABLE VI. (continued)

Compd. No.	R^1	R^2	R^3	R^4	R^5	Yield (%)	^{1}H-NMR δ ($CDCl_3$, J=Hz)
VIIId1	C_2H_5	H	C_6H_5	H	H	85	1.46 (3H, t, 7), 2.00—2.40 (2H, m), 3.10—3.40 (3H, m), 3.40—3.70 (1H, m), 4.10—4.20 (1H, m), 4.24 (1H, d, 15), 4.40 (1H, d, 15), 6.70—6.80 (12H, m)
VIIIe1	C_2H_5	H	H	Br	H	83	1.33 (3H, t, 8), 1.67—2.07 (2H, m), 2.77 (2H, t, 7), 3.00 (2H, q, 8), 3.13—3.37 (2H, m), 4.22 (2H, s), 6.93—7.60 (6H, m)
VIIIf1	C_2H_5	H	H	CH_3O	H	56	1.40 (3H, t, 8), 1.80—2.13 (2H, m), 2.80 (2H, t, 7), 3.03 (2H, q, 8), 3.23—3.47 (2H, m), 3.73 (3H, s), 4.23 (2H, s), 6.50 (1H, d, 3), 6.85 (1H, d, 3), 7.00—7.67 (4H, m)

Compd. No.	Appearance	Recrystn. solv.	mp (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
VIIIa	Colorless needles	AcOEt–hexane	153—153.5	$C_{19}H_{21}N_3S$	70.55	6.54	12.99	70.45	6.55	12.86
VIIId	Yellow powder	Et_2O–hexane	125—126	$C_{19}H_{20}FN_3S$	66.84	5.90	12.31	67.08	5.90	12.25
VIIIi	Pale yellow powder	Et_2O–hexane	153—156	$C_{21}H_{25}N_3S$	71.76	7.17	11.95	72.16	7.00	11.58
VIIIn	White powder	AcOEt–hexane	140—142	$C_{18}H_{19}N_3S$	69.87	6.19	13.58	69.83	6.24	13.21
VIIIp	Colorless needles	AcOEt–hexane	150—152.5	$C_{19}H_{21}N_3S$	70.55	6.54	12.99	70.50	6.50	12.78
VIIIt	White powder	CH_2Cl_2–Et_2O	137.5—138.5	$C_{20}H_{21}N_3S$	71.61	6.31	12.53	71.34	6.26	12.31
VIIIu	Colorless needles	Et_2O	143—145	$C_{21}H_{23}N_3S$	72.17	6.63	12.02	72.15	6.67	11.97
VIIIv	White powder	CH_2Cl_2–Et_2O	140.5—141.5	$C_{23}H_{27}N_3SSi$	68.10	6.71	10.36	68.07	6.69	10.24
VIIIw	White powder	CH_2Cl_2–Et_2O	122—122.5	$C_{20}H_{19}N_3S$	72.04	5.74	12.60	72.07	5.81	12.48
VIIIx	White powder	EtOAc	169.5—170	$C_{25}H_{25}N_3S$	75.15	6.31	10.52	75.06	6.40	10.30
VIIIy	Colorless needles	AcOEt–hexane	134—135	$C_{20}H_{23}N_3S$	71.18	6.87	12.45	71.12	6.95	12.45
VIIIz	Colorless needles	Et_2O	151.5—152	$C_{21}H_{23}N_3S \cdot 1/4\,H_2O$	71.25	6.69	11.87	71.34	6.59	11.53
VIIIa1	White powder	Et_2O	135.5—136.5	$C_{20}H_{23}N_3S$	71.18	6.87	12.45	70.88	6.91	12.12
VIIId1	White powder	Et_2O	162—163	$C_{25}H_{25}N_3S$	75.15	6.31	10.52	75.21	6.31	10.34
VIIIf1	Pale brown powder	AcOEt–hexane	142—143	$C_{20}H_{23}N_3OS$	67.96	6.56	11.89	67.82	6.43	11.65

TABLE VII. 8-[(2-Benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinoline derivatives



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
IXa	1-C_2H_5	H	1.9×10^{-7}	70.5 (3)	59	White powder (Et_2O–hexane)	125—125.5	$C_{19}H_{21}N_3OS$	67.23 (67.51)	6.24 (6.30)	12.38 (12.16)
IXb	1-C_2H_5	5-CH_3O	4.5×10^{-7}	88.7 (10)	50	White powder (Et_2O–hexane)	115—117	$C_{20}H_{23}N_3O_2S$	65.02 (64.56)	6.27 (6.22)	11.37 (11.23)
IXc	1-C_2H_5	5-CH_3	1.8×10^{-7}	47.4 (3) 85.8 (10)	46	Colorless needles (CH_2Cl_2–Et_2O)	140—141	$C_{20}H_{23}N_3OS$	67.96 (68.01)	6.56 (6.44)	11.89 (11.94)
IXd	1-C_2H_5	5-F	1.0×10^{-6}	87.3 (10)	63	White powder (Et_2O)	139—139.5	$C_{19}H_{20}FN_3OS$	63.84 (63.54)	5.64 (5.52)	11.76 (12.03)
IXe	1-C_2H_5	5-Cl	1.7×10^{-7}	NE[c]	33	White powder (Et_2O)	117—119	$C_{19}H_{20}ClN_3OS$	61.03 (60.66)	5.39 (5.45)	11.24 (10.82)
IXf	1-C_2H_5	5-CF_3	4.3×10^{-7}	NE[c]	43	White powder (Et_2O)	120—121.5	$C_{20}H_{20}F_3N_3OS$	58.96 (58.78)	4.95 (5.18)	10.31 (9.89)
IXg	1-C_2H_5	5-CH_3CO	2.3×10^{-6}	76.4 (10)	37	Brown powder (Et_2O)	119—122	$C_{21}H_{23}N_3O_2S \cdot 1/4\,H_2O$	65.35 (65.66)	6.14 (6.26)	10.89 (10.46)
IXh	1-C_2H_5	4-CH_3	5.0×10^{-7}	52.0 (10)	12	White powder (AcOEt–hexane)	139.5—140.5	$C_{21}H_{25}N_3OS$	68.63 (68.60)	6.86 (6.92)	11.43 (11.05)
IXi	1-C_2H_5	5,6-diCH_3	1.9×10^{-7}	NE[c]	79	Pale yellow powder (CH_2Cl_2–Et_2O)	137—138.5	$C_{21}H_{25}N_3OS \cdot 1/2\,H_2O$	66.99 (66.76)	6.96 (6.47)	11.16 (10.68)
IXj	1-C_2H_5	5-F 6-CH_3O	6.2×10^{-7}	94.7 (10)	48	White powder (Et_2O)	129—130.5	$C_{20}H_{22}FN_3O_2S \cdot 1/4\,H_2O$	61.28 (61.36)	5.79 (5.62)	10.72 (10.80)
IXk	1-C_2H_5	5-C_2H_5O 6-F	1.6×10^{-6}	57.0 (30)	80	White powder (Et_2O–hexane)	117—118.5	$C_{21}H_{24}FN_3O_2S$	62.82 (63.12)	6.02 (6.27)	10.47 (10.27)

TABLE VII. (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
IXl	1-C_2H_5	5-F 6-CH_3	2.3×10^{-6}	NE[c]	44	White powder (AcOEt)	151—153	$C_{20}H_{22}FN_3OS$	64.67 (64.31)	5.97 (6.05)	11.31 (11.12)
IXm	1-C_2H_5	5,6-diF	5.4×10^{-7}	NE[c]	80	White powder (Et_2O)	129—130.5	$C_{20}H_{22}FN_3O_2S\cdot 1/4H_2O$	61.28 (61.36)	5.79 (5.62)	10.72 (10.80)
IXn	1-CH_3	H	1.7×10^{-7}	81.5 (3)	92	White powder (Et_2O–hexane)	112—113	$C_{18}H_{19}N_3OS\cdot 1/2H_2O$	64.65 (64.40)	6.03 (5.80)	12.56 (12.24)
IXo	1-CH_3	5-CH_3O	6.9×10^{-7}	19.2 (3) 83.7 (10)	45	Colorless needles (AcOEt)	137—137.5	$C_{19}H_{21}N_3O_2S$	64.20 (64.04)	5.95 (5.86)	11.82 (11.72)
IXp	1-CH_3	5-CH_3	5.3×10^{-7}	41.2 (3) 101.2 (10)	18	Colorless needles (AcOEt–hexane)	126—127	$C_{19}H_{21}N_3OS$	67.23 (67.32)	6.24 (6.23)	12.38 (12.49)
IXq	1-CH_3	5-CH_3CO	5.1×10^{-6}	15.4 (3) 89.2 (10)	20	Yellow powder (Et_2O–hexane)	123—124	$C_{20}H_{21}N_3O_2S$	65.37 (65.20)	5.76 (5.60)	11.44 (11.34)
IXr	1-CH_3	5-F 6-CH_3O	3.3×10^{-7}	56.9 (3) 80.4 (10)	47	White powder (AcOEt)	159.5—160	$C_{19}H_{20}FN_3O_2S$	61.11 (60.99)	5.40 (5.40)	11.25 (11.10)
IXs	1-C_4H_9	H	1.2×10^{-7}	NE[c]	30	White needles (CH_2Cl_2–Et_2O)	118—119	$C_{21}H_{25}N_3OS$	68.63 (68.24)	6.86 (6.87)	11.43 (11.10)
IXt	1-$CH_2CH=CH_2$	H	1.7×10^{-7}	86.6 (10)	53	White needles (CH_2Cl_2–Et_2O)	127.5—128	$C_{20}H_{21}N_3OS$	68.35 (66.29)	6.02 (5.93)	11.96 (12.04)
IXu	1-$CH_2CH=CH_2$	5-CH_3	5.8×10^{-7}	66.7 (10)	55	Colorless needles (AcOEt)	136.5—138.5	$C_{21}H_{23}N_3OS$	69.01 (68.95)	6.34 (6.32)	11.50 (11.47)
IXv	1-$CH_2C\equiv CH$	H	1.6×10^{-6}	62.6 (10)	49	White powder (CH_2Cl_2–Et_2O)	145—146.5	$C_{20}H_{19}N_3OS$	68.74 (68.58)	5.48 (5.50)	12.03 (12.07)
IXw	1-$CH_2C_6H_5$	5-CH_3	8.3×10^{-7}	NE[c]	83	White powder (CH_2Cl_2–Et_2O)	145—146.5	$C_{25}H_{25}N_3OS$	72.26 (72.32)	6.06 (6.07)	10.11 (9.95)
IXx[d]	1-C_2H_5 3-CH_3	H	7.2×10^{-7}	57.4 (10)	18	Colorless needles (EtOH–AcOEt)	136—137	$C_{20}H_{23}N_3OS\cdot 1/2H_2O$	62.27 (66.01)	6.67 (6.43)	11.59 (11.37)
IXy[d]	1-$CH_2CH=CH_2$ 3-CH_3	H	8.3×10^{-7}	21.7 (3) 89.1 (10)	16	Colorless needles (Et_2O)	124.5—125.5	$C_{21}H_{23}N_3OS\cdot 1/4H_2O$	68.17 (68.47)	6.40 (6.35)	11.36 (11.29)
IXz[d]	1-C_2H_5 4-CH_3	H	4.5×10^{-7}	8.7 (3) 105.2 (10)	43	Colorless needles (AcOEt)	125—126	$C_{20}H_{23}N_3OS$	67.97 (67.93)	6.56 (6.54)	11.89 (11.66)
IXa1[d]	1-C_2H_5 4-CH_3	5-F 6-CH_3O	8.9×10^{-7}	34.0 (10) 80.6 (30)	27	Colorless needles (AcOEt)	135—137	$C_{21}H_{24}FN_3O_2S$	62.82 (62.76)	6.02 (5.81)	10.47 (10.54)
IXb1[d]	1-C_2H_5 4-CH_3	5-CH_3CO	1.1×10^{-6}	25.0 (10) 102.3 (30)	25	Colorless needles (AcOEt)	140—141.5	$C_{22}H_{25}N_3O_2S$	66.81 (66.81)	6.38 (6.33)	10.62 (10.42)
IXc1[d]	1-C_2H_5 4-C_6H_5	H	2.1×10^{-6}	NE[c]	38	Colorless needles (Petroleum ether)	87—89	$C_{25}H_{25}N_3OS$	72.26 (72.04)	6.06 (6.20)	10.11 (9.85)
IXd1	1-C_2H_5 6-Br	H	6.4×10^{-7}	NE[c]	59	Colorless powder (CH_2Cl_2)	140—140.5	$C_{19}H_{20}BrN_3OS\cdot 1/3H_2O$	53.78 (53.90)	4.91 (4.93)	9.90 (9.71)
IXe1	1-C_2H_5 6-OCH_3	H	9.2×10^{-7}	84.6 (10)	43	Colorless powder (CH_2Cl_2–Et_2O)	135—136	$C_{20}H_{23}N_3O_2S\cdot 1/2H_2O$	63.47 (63.74)	6.39 (6.15)	11.10 (11.05)

a) Omeprazole, 2.0×10^{-6} M. *b*) Omeprazole, 78.6% (1 mg/kg). *c*) NE = no effect. *d*) NMR δ ($CDCl_3$, J = Hz): IXx; 0.89 (3H, d, 5.5), 1.25 (3H, t, 7), 1.40—2.30 (3H, m), 2.70—3.10 (4H, m), 4.51 (1H, d, 13), 4.59 (1H, d, 13), 6.70—8.00 (7H, m), 11.51 (1H, br s). IXy; 0.82 (3H, d, 5.5), 1.80—2.20 (3H, m), 2.60—3.00 (2H, m), 3.45 (2H, d, 5), 4.49 (1H, d, 13), 4.61 (1H, d, 13), 5.10—5.50 (2H, m), 4.70—6.10 (1H, m), 6.70—7.90 (7H, m), 12.02 (1H, br s). IXz; 1.13 (0.5H, d, 7), 1.19 (0.5H, d, 7), 1.24 (3H, t, 7), 1.10—1.90 (2H, m), 2.60—3.00 (5H, m), 4.38 (1H, dd, 6, 12), 4.69 (1H, dd, 6, 12), 6.80—8.00 (7H, m), 11.80 and 11.95 (1H, br s). IXa1; 1.18 (0.5H, d, 7), 1.22 (0.5H, d, 7), 1.27 (3H, t, 7), 1.30—2.00 (2H, m), 2.70—3.10 (5H, m), 3.91 (3H, d, 10.5), 4.44 (1H, dd, 5.5, 14), 4.72 (1H, dd, 8.5, 14), 6.70—7.70 (5H, m), 12.63 and 12.74 (1H, br s). IXb1; 1.09 (0.5H, d, 7), 1.15 (0.5H, d, 7), 1.21 (3H, t, 7), 1.20—2.00 (2H, m), 2.60 (3H, s), 2.50—3.00 (5H, m), 4.37 (1H, dd, 5, 14), 4.70 (1H, dd, 11, 14), 6.70—8.40 (6H, m), 12.49 (1H, br s). IXc1; 1.30 (3H, t, 7.5), 1.50—2.20 (2H, m), 2.60—3.20 (4H, m), 3.80—4.20 (1H, m), 4.49 (1H, dd, 13, 14), 4.80 (1H, dd, 10.5, 14), 6.60—8.00 (12H, m), 11.85 (1H, br s).

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

Compd. No.	Antiulcer activity ED_{50} (mg/kg) *p.o.*	Cytoprotective activity ED_{50} (mg/kg) *p.o.*
IXa	3.1	15.0
IXc	>30	ND[a]
IXn	>30	ND[a]
IXr	>30	ND[a]
IXt	14.7	6.4
IXy	13.7	20.1
IXz	14.4	3.2
Omeprazole	8.3	30.2

a) ND = not determined.

active than IXa in *in vitro* assay, but the acetyl compounds (IXg, q) showed some antisecretory activity.

Although the ($H^+ + K^+$) ATPase-inhibitory activities of the tetrahydroquinoline derivatives are more potent than that of omeprazole,[7] their antisecretory activity was less than that of omeprazole. This suggests that these compounds may be unable to permeate through the membrane.

Seven compounds (IXa, c, n, r, t, y, z) were selected for further study. The antiulcer activity against aspirin-induced gastric ulcer and the gastric cytoprotective activity against necrosis induced by 0.6 N hydrochloric acid were tested in the rat (Table VIII). Compounds IXc n, r showed no antiulcer activity in spite of their potent antisecretory activities. The other compounds showed potent antiulcer

and cytoprotective activities.

Among the compounds synthesized, 8-[(2-benzimidazolyl)sulfinylmethyl]-1-ethyl-1,2,3,4-tetrahydroquinoline (IXa, OPC-22381) was found to have the most potent activity. This compound is more stable than OPC-22321 having a 5,6,7,8-tetrahydroquinoline ring.

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 Varian EM-390 NMR and Brucker AC-200 spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Varian MAT-312 instrument.

Compounds Ia—c were prepared according to the reported methods.[4]

8-Methyl-4-phenylquinoline (Id) 8-Methyl-4-phenyl-2(1*H*)-quinolinone[9] (38.4 g, 0.16 mol) was added to stirred and ice-cooled phosphorus oxychloride (50 ml). The reaction mixture was heated at 100—110 °C for 2 h with stirring, then allowed to cool. The mixture was poured into ice-water. The precipitates were collected by filtration and dissolved in AcOH (300 ml). To this solution, AcONa (14.5 g) and 10% Pd–C (3.5 g) were added. The mixture was heated at 70 °C under atmospheric pressure of hydrogen with stirring until the theoretical amount of hydrogen was absorbed. The mixture was cooled to room temperature, the catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with 30% NaOH aqueous solution. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2) to give Id (28 g, 78%) as a pale yellow oil. NMR δ: 2.87 (3H, s), 7.33 (1H, d, J=4.5 Hz), 7.38—7.78 (3H, m), 7.50 (5H, s), 8.97 (1H, d, J=4.5 Hz). IR ν (neat): 3050, 3020, 2900, 1580, 1505, 1485, 1400, 850, 810, 760, 695 cm^{-1}. MS *m/z*: 108 (13%), 204 (18), 217 (18), 218 (36), 219 (M^+, 100), 220 (22).

8-Bromomethylquinolines (IIa—d): A Typical Procedure A mixture of 8-methylquinoline (4.0 g, 28 mol), NBS (6.0 g, 34 mmol) and benzoyl peroxide (0.15 g) in CCl_4 (40 ml) was refluxed for 3 h. After removal of the precipitates by filtration, the filtrate was concentrated *in vacuo*. The residue was recrystallized from ligroin to give IIa (3.6 g, 58%) as pale brown needles, mp 76—78 °C. NMR δ: 5.24 (2H, s), 7.40—7.60 (2H, m), 7.79 (1H, d, J=7 Hz), 7.83 (1H, d, J=6 Hz), 8.16 (1H, dd, J=8, 2 Hz), 9.01 (1H, dd, J=4, 2 Hz). IR ν (KBr): 3425, 1500, 1220, 795 cm^{-1}. The elemental analysis data are given in Table I.

Compounds IIb—d were obtained by a similar procedure to that described for IIa; the yields, melting points and elemental analysis data are listed in Table I.

8-Acetoxymethylquinolines (IIIa—d): A Typical Procedure A suspension of IIa (1.1 g, 5.5 mmol) and NaOAc (0.8 g, 10 mmol) in DMF (20 ml) was heated at 80—90 °C for 2 h with stirring and then concentrated *in vacuo*. The residue was poured into water. The precipitates were collected by filtration. Recrystallization from AcOEt–hexane gave IIIa (0.9 g, 85%) as colorless prisms, mp 40—41 °C. NMR δ: 2.15 (3H, s), 5.86 (2H, s), 7.42 (1H, dd, J=8, 4 Hz), 7.55 (1H, d, J=8 Hz), 7.70—7.90 (2H, m), 8.15 (1H, dd, J=8, 2 Hz), 8.95 (1H, dd, J=4, 2 Hz). IR ν (KBr): 3450, 1740, 1240, 830 cm^{-1}. The elemental analysis data are given in Table II.

Compounds IIIb—d were obtained by a similar procedure to that described for IIIa; the yields, melting points and elemental analysis data are given in Table II.

8-Hydroxymethylquinolines (IVa—d): A Typical Procedure A mixture of IIIa (12 g, 60 mmol) and 30% NaOH (45 ml) in MeOH (80 ml) was refluxed for 1.5 h. After removal of MeOH, the residue was extracted with $CHCl_3$, and the extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give IVa (9.2 g, 96%) as pale yellow needles, mp 73.5—74.5 °C. NMR δ: 5.08 (1H, br s), 5.21 (2H, s), 7.40—7.70 (3H, m), 7.76 (1H, dd, J=8, 2 Hz), 8.20 (1H, dd, J=8, 2 Hz), 8.87 (1H, dd, J=4, 2 Hz). IR ν (KBr): 3290, 1500, 1085, 820 cm^{-1}. The elemental analysis data are given in Table III.

Compounds IVb—d were obtained by a similar procedure to that described for IVa; the yields, melting points and elemental analysis data are listed in Table III.

8-Hydroxymethyl-1,2,3,4-tetrahydroquinolines (Va—d): A Typical Procedure A mixture of IVa (1.0 g, 6 mmol) and PtO_2 (0.25 g) in MeOH (30 ml) was hydrogenated at 40 °C and 3.5 kg/cm^2. The mixture was cooled to room temperature and the catalyst was removed by filtration. The filtrate was concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give Va (1.0 g, 98%) as yellow needles, mp 67—68 °C. NMR δ: 1.60 (1H, br s), 1.70—2.10 (2H, m), 2.78 (2H, t, J=7 Hz), 3.37 (2H, t, J=7 Hz), 4.57 (2H, s), 4.70 (1H, br s), 6.52 (1H, t, J=8 Hz), 6.70—7.00 (2H, m). IR ν (KBr): 3295, 1500, 1085, 820 cm^{-1}. *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; H, 8.58. Found: C, 73.49; H, 7.98; N, 8.56.

Compounds Vb-d were obtained by a similar procedure to that described for Va; the yields and NMR data are given in Table IV.

1-Substituted 8-hydroxymethyl-1,2,3,4-tetrahydroquinolines (VIa—j): A Typical Procedure NaH (60%, 1.0 g, 25 mmol) was added to a stirred solution of Va (4.0 g, 25 mmol) in THF (60 ml) under argon, and the reaction mixture was stirred at 70—75 °C for 2 h. *n*-Butyllithium (16% solution in hexane, 10 ml) was added dropwise with stirring at −70 °C. The mixture was stirred at the same temperature for 30 min, then a solution of ethyl bromide (2.7 g, 25 mmol) in THF (10 ml) was added dropwise and the reaction mixture was stirred at 5—10 °C overnight. 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 = 4 : 1) to give VIb (1.6 g, 34%) as a yellow oil. IR ν (neat): 3400, 2925, 1450, 760 cm^{-1}. MS *m/z*: 134 (46%), 162 (100), 176 (74), 191 (M^+, 68). NMR data are given in Table V.

Compounds VIa and VIc—j were obtained by a similar procedure to that described for VIb; the yields and NMR data are listed in Table V.

6-Bromo-1-ethyl-8-hydroxymethyl-1,2,3,4-tetrahydroquinoline (VIk) A solution of 2,4,4,6-tetrabromocyclohexa-2,5-dienone (1.1 g, 2.7 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred and cooled (−20 °C) solution of VIb (0.52 g, 2.7 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred at the same temperature for 30 min, and washed successively with Na_2CO_3 solution and a saturated NaCl solution. The CH_2Cl_2 layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give VIk (0.43 g, 59%) as a yellow powder, mp 105—106 °C. IR ν (KBr): 3280, 2970, 2960, 1440, 1230, 1070, 1060, 890 cm^{-1}. *Anal.* Calcd for $C_{12}H_{16}BrNO$: C, 53.35; H, 5.97; N, 5.18. Found: C, 53.08; H, 5.80; N, 5.11. NMR data are given in Table V.

1-Ethyl-8-hydroxymethyl-6-methoxy-1,2,3,4-tetrahydroquinoline (VII) A solution of sodium metal (111 mg, 4.8 mmol) in MeOH (5 ml) was added to a solution of VIk (0.25 g, 0.9 mmol) and CuI (89 mg) in DMF (5 ml). The reaction mixture was heated at 140 °C for 6 h with stirring, and then concentrated *in vacuo*. The residue was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give VII (0.15 g, 73%) as a white powder, mp 69—70 °C. IR ν (KBr): 3250, 2930, 1470, 1290, 1160, 1060 cm^{-1}. *Anal.* Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.80; H, 8.66; N, 6.28. NMR data are listed in Table V.

8-[(2-Benzimidazolyl)thiomethyl]-1,2,3,4-tetrahydroquinolines (VIIIa—v, x—f1): A Typical Procedure Thionyl chloride (1.1 ml, 14.7 mmol) was added dropwise to a stirred and ice-cooled solution of VId (1.0 g, 4.9 mmol) in CH_2Cl_2 (15 ml). The reaction mixture was stirred at 0—10 °C for 1.5 h and then concentrated *in vacuo*. The residue was dissolved in DMF (10 ml) containing 2-mercaptobenzimidazole (0.74 g, 4.9 mmol) and K_2CO_3 (1.35 g, 9.8 mmol). The reaction mixture was stirred at room temperature for 18 h, then poured into water and extracted with toluene–AcOEt (1 : 3). 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, hexane : AcOEt = 5 : 1) and recrystallized from CH_2Cl_2–Et_2O to give VIIIt (1.42 g, 87%) as a white powder, mp 137—138.5 °C. IR ν (KBr): 2940, 1435, 1395, 740 cm^{-1}.

Compounds VIIIa—s, u, v, x-f1 were obtained by a similar procedure to that described for VIIIt; the yields, NMR, melting points and elemental analysis data are given in Table VI.

8-[(2-Benzimidazolyl)thiomethyl]-1-propargyl-1,2,3,4-tetrahydroquinoline (VIIIw) Tetrabutylammonium fluoride (1 M solution in THF, 1.1 ml) was added to a stirred and ice-cooled solution of VIIIv (0.4 g, 1 mmol), 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 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 = 5.5 : 1) to give VIIIw (0.3 g, 91%), which was recrystallized from CH_2Cl_2–Et_2O to give VIIIw as a white powder, mp 122—122.5 °C. IR ν (KBr): 3300, 2950, 2820, 1440, 1400, 1350, 740 cm^{-1}. NMR and elemental analysis data are listed in Table VI.

8-[(2-Benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinolines (IXa): A Typical Procedure A solution of 80% *m*-CPBA (0.56 g,

2.6 mmol) in CH_2Cl_2 (30 ml) was added dropwise to a stirred and ice-cooled solution of VIIIa (0.84 g, 2.6 mmol) in CH_2Cl_2 (10 ml) and the reaction mixture was stirred at the same temperature for 30 min. The CH_2Cl_2 layer was separated, 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 = 3 : 1) and the product was recrystallized from Et_2O–hexane to give IXa (0.53 g, 60%) as a white powder, mp 125—125.5 °C. NMR δ: 1.26 (3H, t, J=7 Hz), 1.40—2.00 (2H, m), 2.50—3.20 (6H, m), 4.40 (1H, d, J=14 Hz), 4.73 (1H, d, J=14 Hz), 6.70—8.00 (7H, m). IR ν (KBr): 3220, 1400, 1050, 735 cm^{-1}. The elemental analysis data are given in Table VII.

Compounds IXb—el were obtained by a similar procedure to that described for IXa; the yields, melting points and elemental analysis data are listed in Table VII.

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

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