

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 pump²⁾ 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.

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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–f1), 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

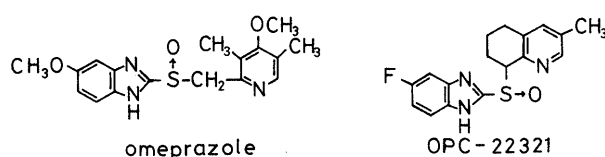
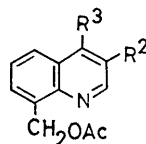


Chart 1

TABLE I. 8-Bromomethylquinolines

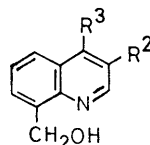
Compd. No.	R ²	R ³	Yield (%)	Appearance	Recrystn. solv.	mp (°C)	Formula	Analysis (%)					
								Calcd			Found		
								C	H	N	C	H	N
IIa	H	H	58	Colorless needles	Ligroin	83–84.5	C ₁₀ H ₈ BrN	54.08	3.63	6.31	54.02	3.75	6.28
IIb	CH ₃	H	97	Colorless needles	AcOEt	121–122	C ₁₁ H ₁₀ BrN	55.96	4.27	5.93	55.94	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 ₆ H ₅	98	Brown powder	EtOH	250–251 (dec.)	C ₁₆ H ₁₂ BrN·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			Found		
								C	H	N	C	H	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 ₆ H 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			Found		
								C	H	N	C	H	N
IVa	H	H	96	Colorless needles	EtOH-hexane	73.5—74.5	C ₁₀ H ₉ NO	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 · 1/2 H ₂ O	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 · 1/4 H ₂ O	74.34	6.52	7.88	74.81	6.41	7.68
IVd	H	C ₆ H ₅	70	Colorless needles	AcOEt	67—68.5	C ₁₆ H ₁₃ NO · 1/4 H ₂ O	80.14	5.67	5.84	80.03	5.51	5.81

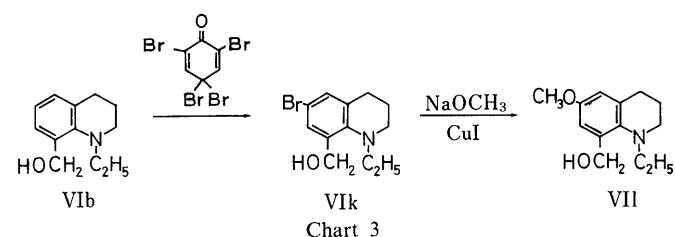
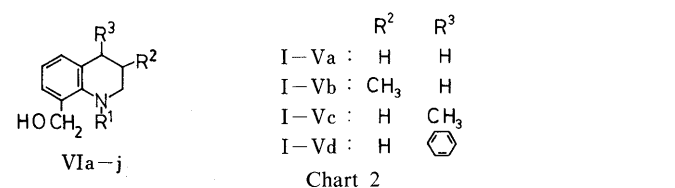
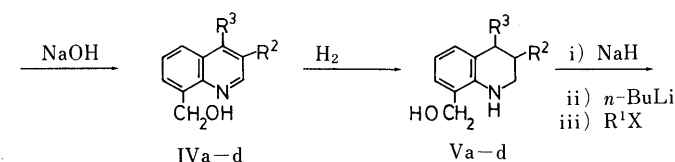
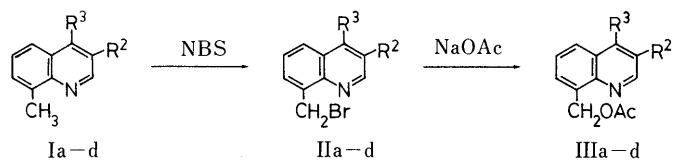
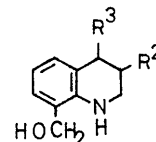


TABLE IV. 8-Hydroxymethyl-1,2,3,4-tetrahydroquinolines



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 ₆ H 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)

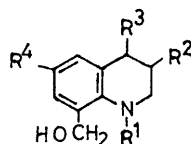
a) Va; Yellow needles (AcOEt-hexane), mp 67—68°C, *Anal.* Calcd for C₁₀H₁₃NO: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.49; H, 7.98; N, 8.56. Vd; White powder (AcOEt-hexane), mp 104—106°C, *Anal.* Calcd for C₁₆H₁₇NO · 1/4 H₂O: C, 78.82; H, 7.23; N, 5.74. Found: C, 79.23; H, 7.05; N, 5.44. b) Oily compounds 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-dienone⁵⁾ 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 ₂ H 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 ₄ H 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)
VI d	CH ₂ CH=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)
VI e ^{b)}	CH ₂ C≡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)
VI f	CH ₂ C ₆ H 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)
VI g	C ₂ H 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)
VI h	CH ₂ CH=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)
VI i	C ₂ H 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)
VI j	C ₂ H ₅	H	C ₆ H 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)
VI k	C ₂ H 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)
VII	C ₂ H 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.

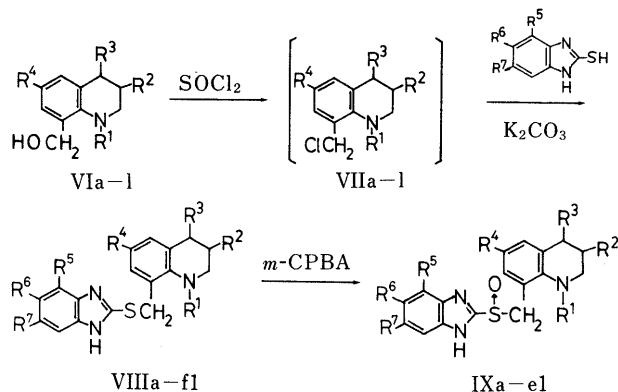


Chart 4

(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—f1) in good yield. Oxidation of the sulfides (VIIIa—u, w—f1) with *m*-chloroperbenzoic acid (*m*-CPBA) in chloroform or methylene chloride was conveniently carried out at 0 °C to give the corresponding sulfoxides (IXa—e1) (Chart 4) (Tables VI and VII).

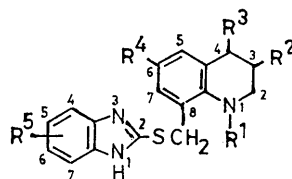
Structure–Activity Relationships The (H⁺ + K⁺)ATPase-inhibitory and antisecretory activities of the synthesized compounds are summarized in Table VII. All compounds tested showed potent activity *in vitro*. Most of the compounds inhibited *in vivo* histamine-induced gastric acid secretion in rats.

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 (IXv). 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 (IXe1) 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 (IXd1) 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



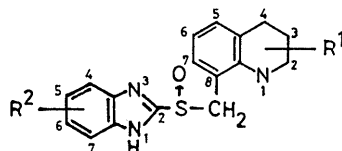
Compd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%)	¹ H-NMR δ (CDCl ₃ , J = Hz)
VIIIa	C ₂ H ₅	H	H	H	H	53	1.43 (3H, t, 7.5), 1.73—2.17 (2H, m), 2.83 (2H, t, 7), 3.09 (2H, q, 7.5), 3.23—3.50 (2H, m), 4.25 (2H, s), 6.80—7.70 (7H, m)
VIIIb	C ₂ H ₅	H	H	H	5-CH ₃ O	35	1.42 (3H, t, 7.5), 2.83 (2H, t, 7), 3.08 (2H, q, 7.5), 3.23—3.50 (2H, m), 3.83 (3H, s), 4.27 (2H, s), 6.66—7.50 (6H, m)
VIIIc	C ₂ H 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 ₂ H 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 ₂ H 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, brs)
VIIIf	C ₂ H 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 ₂ H ₅	H	H	H	5-CH ₃ CO	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 ₂ H 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, brs)
VIIIi	C ₂ H 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, brs)
VIIIj	C ₂ H ₅	H	H	H	5-F 6-CH ₃ O	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, brs)
VIIIk	C ₂ H ₅	H	H	H	5-C ₂ H ₅ O 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 ₂ H ₅	H	H	H	5-F 6-CH ₃	64	1.33 (3H, t, 7.5), 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, brs)
VIIIIm	C ₂ H 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, brs)
VIIIIn	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 ₃ O	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, brs)
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 ₃ CO	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 ₃ O	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, brs)
VIIIs	C ₄ H 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)
VIIIIt	CH ₂ CH=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 ₂ CH=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 ₂ C $\equiv$ 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 ₂ C $\equiv$ 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 ₂ C ₆ H 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 ₂ H 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, brs), 12.73 (1H, brs)
VIIIz	CH ₂ CH=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, brs)
VIIIa1	C ₂ H 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 ₂ H ₅	H	CH ₃	H	5-F 6-CH ₃ O	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 ₂ H ₅	H	CH ₃	H	5-CH ₃ CO	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, brs)

TABLE VI. (continued)

Compd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%)	¹ H-NMR δ (CDCl ₃ , J = Hz)
VIIIId1	C ₂ H ₅	H	C ₆ H 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 ₂ H 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)
VIIIfl	C ₂ H ₅	H	H	CH ₃ O	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			Found		
					C	H	N	C	H	N
VIIIa	Colorless needles	AcOEt-hexane	153—153.5	C ₁₉ H ₂₁ N ₃ S	70.55	6.54	12.99	70.45	6.55	12.86
VIIIId	Yellow powder	Et ₂ O-hexane	125—126	C ₁₉ H ₂₀ FN ₃ S	66.84	5.90	12.31	67.08	5.90	12.25
VIIIi	Pale yellow powder	Et ₂ O-hexane	153—156	C ₂₁ H ₂₅ N ₃ S	71.76	7.17	11.95	72.16	7.00	11.58
VIIIIn	White powder	AcOEt-hexane	140—142	C ₁₈ H ₁₉ N ₃ S	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 ₃ S	70.55	6.54	12.99	70.50	6.50	12.78
VIIIr	White powder	CH ₂ Cl ₂ -Et ₂ O	137.5—138.5	C ₂₀ H ₂₁ N ₃ S	71.61	6.31	12.53	71.34	6.26	12.31
VIIIu	Colorless needles	Et ₂ O	143—145	C ₂₁ H ₂₃ N ₃ S	72.17	6.63	12.02	72.15	6.67	11.97
VIIIv	White powder	CH ₂ Cl ₂ -Et ₂ O	140.5—141.5	C ₂₃ H ₂₇ N ₃ Si	68.10	6.71	10.36	68.07	6.69	10.24
VIIIw	White powder	CH ₂ Cl ₂ -Et ₂ O	122—122.5	C ₂₀ H ₁₉ N ₃ S	72.04	5.74	12.60	72.07	5.81	12.48
VIIIx	White powder	EtOAc	169.5—170	C ₂₅ H ₂₅ N ₃ S	75.15	6.31	10.52	75.06	6.40	10.30
VIIIy	Colorless needles	AcOEt-hexane	134—135	C ₂₀ H ₂₃ N ₃ S	71.18	6.87	12.45	71.12	6.95	12.45
VIIIz	Colorless needles	Et ₂ O	151.5—152	C ₂₁ H ₂₃ N ₃ S · 1/4 H ₂ O	71.25	6.69	11.87	71.34	6.59	11.53
VIIIa1	White powder	Et ₂ O	135.5—136.5	C ₂₀ H ₂₃ N ₃ S	71.18	6.87	12.45	70.88	6.91	12.12
VIIIId1	White powder	Et ₂ O	162—163	C ₂₅ H ₂₅ N ₃ S	75.15	6.31	10.52	75.21	6.31	10.34
VIIIfl	Pale brown powder	AcOEt-hexane	142—143	C ₂₀ H ₂₃ N ₃ OS	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 ₂ H ₅	H	1.9 × 10 ⁻⁷	70.5 (3)	59	White powder (Et ₂ O-hexane)	125—125.5	C ₁₉ H ₂₁ N ₃ OS	67.23	6.24	12.38 (67.51 6.30 12.16)
IXb	1-C ₂ H ₅	5-CH ₃ O	4.5 × 10 ⁻⁷	88.7 (10)	50	White powder (Et ₂ O-hexane)	115—117	C ₂₀ H ₂₃ N ₃ O ₂ S	65.02	6.27	11.37 (64.56 6.22 11.23)
IXc	1-C ₂ H ₅	5-CH ₃	1.8 × 10 ⁻⁷	47.4 (3)	46	Colorless needles (CH ₂ Cl ₂ -Et ₂ O)	140—141	C ₂₀ H ₂₃ N ₃ OS	67.96	6.56	11.89 (68.01 6.44 11.94)
IXd	1-C ₂ H ₅	5-F	1.0 × 10 ⁻⁶	87.3 (10)	63	White powder (Et ₂ O)	139—139.5	C ₁₉ H ₂₀ FN ₃ OS	63.84	5.64	11.76 (63.54 5.52 12.03)
IXe	1-C ₂ H ₅	5-Cl	1.7 × 10 ⁻⁷	NE ^{c)}	33	White powder (Et ₂ O)	117—119	C ₁₉ H ₂₀ ClN ₃ OS	61.03	5.39	11.24 (60.66 5.45 10.82)
IXf	1-C ₂ H ₅	5-CF ₃	4.3 × 10 ⁻⁷	NE ^{c)}	43	White powder (Et ₂ O)	120—121.5	C ₂₀ H ₂₀ F ₃ N ₃ OS	58.96	4.95	10.31 (58.78 5.18 9.89)
IXg	1-C ₂ H ₅	5-CH ₃ CO	2.3 × 10 ⁻⁶	76.4 (10)	37	Brown powder (Et ₂ O)	119—122	C ₂₁ H ₂₃ N ₃ O ₂ S · 1/4 H ₂ O	65.35	6.14	10.89 (65.66 6.26 10.46)
IXh	1-C ₂ H 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 ₃ OS	68.63	6.86	11.43 (68.60 6.92 11.05)
IXi	1-C ₂ H ₅	5,6-diCH ₃	1.9 × 10 ⁻⁷	NE ^{c)}	79	Pale yellow powder (CH ₂ Cl ₂ -Et ₂ O)	137—138.5	C ₂₁ H ₂₅ N ₃ OS · 1/2 H ₂ O	66.99	6.96	11.16 (66.76 6.47 10.68)
IXj	1-C ₂ H ₅	5-F	6.2 × 10 ⁻⁷	94.7 (10)	48	White powder (Et ₂ O)	129—130.5	C ₂₀ H ₂₂ FN ₃ O ₂ S · 1/4 H ₂ O	61.28	5.79	10.72 (61.36 5.62 10.80)
IXk	1-C ₂ H ₅	5-C ₂ H ₅ O	1.6 × 10 ⁻⁶	57.0 (30)	80	White powder (Et ₂ O-hexane)	117—118.5	C ₂₁ H ₂₄ FN ₃ O ₂ S	62.82	6.02	10.47 (63.12 6.27 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 ₂ H ₅	5-F	2.3 × 10 ⁻⁶	NE ^{c)}	44	White powder (AcOEt)	151—153	C ₂₀ H ₂₂ FN ₃ OS	64.67	5.97	11.31
		6-CH ₃							(64.31	6.05	11.12)
IXm	1-C ₂ H ₅	5,6-diF	5.4 × 10 ⁻⁷	NE ^{c)}	80	White powder (Et ₂ O)	129—130.5	C ₂₀ H ₂₂ FN ₃ O ₂ S · 1/4 H ₂ O	61.28	5.79	10.72
									(61.36	5.62	10.80)
IXn	1-CH ₃	H	1.7 × 10 ⁻⁷	81.5 (3)	92	White powder (Et ₂ O—hexane)	112—113	C ₁₈ H ₁₉ N ₃ OS · 1/2 H ₂ O	64.65	6.03	12.56
									(64.40	5.80	12.24)
IXo	1-CH ₃	5-CH ₃ O	6.9 × 10 ⁻⁷	19.2 (3)	45	Colorless needles (AcOEt)	137—137.5	C ₁₉ H ₂₁ N ₃ O ₂ S	64.20	5.95	11.82
				83.7 (10)					(64.04	5.86	11.72)
IXp	1-CH ₃	5-CH ₃	5.3 × 10 ⁻⁷	41.2 (3)	18	Colorless needles (AcOEt—hexane)	126—127	C ₁₉ H ₂₁ N ₃ OS	67.23	6.24	12.38
				101.2 (10)					(67.32	6.23	12.49)
IXq	1-CH ₃	5-CH ₃ CO	5.1 × 10 ⁻⁶	15.4 (3)	20	Yellow powder (Et ₂ O—hexane)	123—124	C ₂₀ H ₂₁ N ₃ O ₂ S	65.37	5.76	11.44
				89.2 (10)					(65.20	5.60	11.34)
IXr	1-CH ₃	5-F	3.3 × 10 ⁻⁷	56.9 (3)	47	White powder (AcOEt)	159.5—160	C ₁₉ H ₂₀ FN ₃ O ₂ S	61.11	5.40	11.25
		6-CH ₃ O		80.4 (10)					(60.99	5.40	11.10)
IXs	1-C ₄ H ₉	H	1.2 × 10 ⁻⁷	NE ^{c)}	30	White needles (CH ₂ Cl ₂ —Et ₂ O)	118—119	C ₂₁ H ₂₅ N ₃ OS	68.63	6.86	11.43
									(68.24	6.87	11.10)
IXt	1-CH ₂ CH=CH ₂	H	1.7 × 10 ⁻⁷	86.6 (10)	53	White needles (CH ₂ Cl ₂ —Et ₂ O)	127.5—128	C ₂₀ H ₂₁ N ₃ OS	68.35	6.02	11.96
									(66.29	5.93	12.04)
IXu	1-CH ₂ CH=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 ₃ OS	69.01	6.34	11.50
									(68.95	6.32	11.47)
IXv	1-CH ₂ C≡CH	H	1.6 × 10 ⁻⁶	62.6 (10)	49	White powder (CH ₂ Cl ₂ —Et ₂ O)	145—146.5	C ₂₀ H ₁₉ N ₃ OS	68.74	5.48	12.03
									(68.58	5.50	12.07)
IXw	1-CH ₂ C ₆ H ₅	5-CH ₃	8.3 × 10 ⁻⁷	NE ^{c)}	83	White powder (CH ₂ Cl ₂ —Et ₂ O)	145—146.5	C ₂₅ H ₂₅ N ₃ OS	72.26	6.06	10.11
									(72.32	6.07	9.95)
IXx ^{d)}	1-C ₂ H ₅	H	7.2 × 10 ⁻⁷	57.4 (10)	18	Colorless needles (EtOH—AcOEt)	136—137	C ₂₀ H ₂₃ N ₃ OS · 1/2 H ₂ O	62.27	6.67	11.59
	3-CH ₃								(66.01	6.43	11.37)
IXy ^{d)}	1-CH ₂ CH=CH ₂	H	8.3 × 10 ⁻⁷	21.7 (3)	16	Colorless needles (Et ₂ O)	124.5—125.5	C ₂₁ H ₂₃ N ₃ OS · 1/4 H ₂ O	68.17	6.40	11.36
	3-CH ₃			89.1 (10)					(68.47	6.35	11.29)
IXz ^{d)}	1-C ₂ H ₅	H	4.5 × 10 ⁻⁷	8.7 (3)	43	Colorless needles (AcOEt)	125—126	C ₂₀ H ₂₃ N ₃ OS	67.97	6.56	11.89
	4-CH ₃			105.2 (10)					(67.93	6.54	11.66)
IXa1 ^{d)}	1-C ₂ H ₅	5-F	8.9 × 10 ⁻⁷	34.0 (10)	27	Colorless needles (AcOEt)	135—137	C ₂₁ H ₂₄ FN ₃ O ₂ S	62.82	6.02	10.47
	4-CH ₃	6-CH ₃ O		80.6 (30)					(62.76	5.81	10.54)
IXb1 ^{d)}	1-C ₂ H ₅	5-CH ₃ CO	1.1 × 10 ⁻⁶	25.0 (10)	25	Colorless needles (AcOEt)	140—141.5	C ₂₂ H ₂₅ N ₃ O ₂ S	66.81	6.38	10.62
	4-CH ₃			102.3 (30)					(66.81	6.33	10.42)
IXc1 ^{d)}	1-C ₂ H ₅	H	2.1 × 10 ⁻⁶	NE ^{c)}	38	Colorless needles (Petroleum ether)	87—89	C ₂₅ H ₂₅ N ₃ OS	72.26	6.06	10.11
	4-C ₆ H ₅								(72.04	6.20	9.85)
IXd1	1-C ₂ H ₅	H	6.4 × 10 ⁻⁶	NE ^{c)}	59	Colorless powder (CH ₂ Cl ₂)	140—140.5	C ₁₉ H ₂₀ BrN ₃ OS · 1/3 H ₂ O	53.78	4.91	9.90
	6-Br								(53.90	4.93	9.71)
IXe1	1-C ₂ H ₅	H	9.2 × 10 ⁻⁷	84.6 (10)	43	Colorless powder (CH ₂ Cl ₂ —Et ₂ O)	135—136	C ₂₀ H ₂₃ N ₃ O ₂ S · 1/2 H ₂ O	63.47	6.39	11.10
	6-OCH ₃								(63.74	6.15	11.05)

a) Omeprazole, 2.0 × 10⁻⁶ M. b) Omeprazole, 78.6% (1 mg/kg). c) NE=no effect. d) NMR δ (CDCl₃, 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, brs). 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, brs). 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, brs). 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, brs). 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, brs). 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, brs).

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 CDCl₃ on Varian EM-390 NMR and Bruker 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(1H)-quinolinone⁹⁾ (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 CH₂Cl₂ and washed with 30% NaOH aqueous solution. The CH₂Cl₂ solution was dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH₂Cl₂) 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 mmol), NBS (6.0 g, 34 mmol) and benzoyl peroxide (0.15 g) in CCl₄ (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 CHCl₃, and the extract was dried over MgSO₄ 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 PtO₂ (0.25 g) in MeOH (30 ml) was hydrogenated at 40 °C and 3.5 kg/cm². 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 C₁₀H₁₃NO: C, 73.59; H, 8.03; N, 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 CHCl₃. The extract was dried over MgSO₄ 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 CH₂Cl₂ (10 ml) was added dropwise to a stirred and cooled (–20 °C) solution of VIb (0.52 g, 2.7 mmol) in CH₂Cl₂ (10 ml). The reaction mixture was stirred at the same temperature for 30 min, and washed successively with Na₂CO₃ solution and a saturated NaCl solution. The CH₂Cl₂ layer was separated, dried over MgSO₄ 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 C₁₂H₁₆BrNO: 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 CHCl₃. The extract was washed with water, dried over MgSO₄ 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 C₁₃H₁₉NO₂: 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 CH₂Cl₂ (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 K₂CO₃ (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 MgSO₄. After removal of the solvent, the residue was purified by column chromatography (silica gel; eluent, hexane:AcOEt = 5:1) and recrystallized from CH₂Cl₂–Et₂O to give VIIIa (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 VIIIa; 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 CH₂Cl₂. The extract was dried over MgSO₄ 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 CH₂Cl₂–Et₂O 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–e1 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 ($\text{H}^+ + \text{K}^+$) ATPase-inhibitory, gastric anti-secretory, antiulcer and cytoprotective activities were tested by the reported methods.¹⁾

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