Synthesis and Pharmacological Properties of *N*-[3-{3-(1-Piperidinylmethyl)phenoxy}propyl]-2-(2-hydroxyethylthio)acetamide and Related Compounds as Antiulcer Agents. I

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***N*-Phenoxypropylacetamide derivatives were prepared and tested for antiulcer activity. These compounds exhibited both gastric acid antisecretory and cytoprotective properties. Structure–activity studies led to the identification of *N*-[3-{3-(1-piperidinylmethyl)phenoxy}propyl]-2-(2-hydroxyethylthio)acetamide (8), which was selected for further development and clinical evaluation.**

Keywords antiulcer activity; cytoprotective activity; structure–activity relationship; histamine H_2-receptor antagonist; *N*-[3-{3-(1-piperidinylmethyl)phenoxy}propyl]acetamide

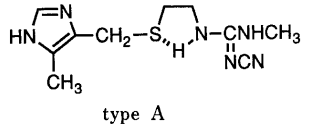
The introduction of cimetidine,[1] ranitidine,[2] famotidine[3] and roxatidine[4] as H_2-receptor antagonists for the control of peptic ulcer disease has been responsible for intense synthetic efforts by medicinal chemists in this therapeutic area to prepare highly efficacious drugs with greater potency and lower toxicity.

As part of our efforts to explore a new antiulcer agent, this work was initiated with the goal of preparing a new compound which possesses potent gastric acid antisecretory and gastrointestinal cytoprotective activities with lower toxicity. In the present paper, we describe the preparation and antiulcer activity of *N*-[3-{3-(1-piperidinylmethyl)phenoxy}propyl]-2-(2-hydroxyethylthio)acetamide (**8**) and related compounds. The structure–activity relationships of gastric acid antisecretory activity are also discussed.

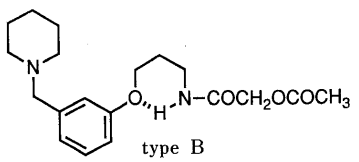
Target Design Known H_2-receptor antagonists can be broadly considered to fall into four principle structural categories on the basis of the pattern of intramolecular hydrogen bond formation between the NH of the amide group and the side chain ether atom (sulfur atom or oxygen atom),[5] that is, (1) compounds with a 5-membered intramolecular hydrogen bond, *e.g.*, cimetidine and ranitidine (type A), (2) compounds with a 6-membered intramolecular hydrogen bond, *e.g.*, roxatidine (type B) and famotidine (type C), (3) compounds which do not form an intramolecular hydrogen bond, *e.g.*, bicyclic heterocyclic derivatives[6] (type D). From our structure–activity relationship (SAR) studies of compounds which fall into type B we selected roxatidine as a target molecule for bioisosteric analysis.[7,8] This drug can be divided into two components, a 3-[3-(1-piperidinylmethyl)phenoxy]propanamine group and an acyl side chain. Focusing first on the acyl side chain, we searched for bioisosteres of acetoxy ($OCOCH_3$) on the basis of hydrophobic parameter π and Swain–Lupton's parameter F and prepared compounds **1**—**8**. As compound **8** was shown to have the desired gastric acid antisecretory and cytoprotective activities, we next prepared analogues (**9**—**22**) of **8** shown in Table I.

Chemistry Key intermediates for the preparation of *N*-[(3-phenoxy)propyl]acetamide derivatives were 3-[3-(1-piperidinylmethyl)phenoxy]- (**23**)[9] and 3-[3-(1-pyrrolidinylmethyl)phenoxy]propanamines (**24**).[10] *N*-[3-{3-(1-Piperidinylmethyl)phenoxy}propyl]-2-chloroacetamide (**25**) was prepared by the reaction of **23** with monochloroacetyl chloride in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA). *N*-[3-{3-(1-Piperidinylmethyl)phenoxy}propyl]-2-mercaptoacetamide (**26**) was prepared by the condensation of **23** with methyl thioglycolate in toluene. Compounds studied in this series were prepared by the procedures illustrated in Chart 2. Most of the compounds were prepared by the reaction of amines **23** and **24** with ester derivatives shown in Table IV (method A). Method B involves the reaction of amine **23** with such lactone derivatives as 1,4-dioxan-2-one, 1,4-oxathian-2-one and δ-valerolactone. *O*-Acetyl derivatives (**11**, **12** and **13**) were prepared from the corresponding alcohols (**8**, **9** and **10**) and acetic anhydride in dry pyridine (method D). Sulfonyl derivative (**10**) was prepared by oxidation of **8** with 30% H_2O_2 in acetic acid (method E). Compounds prepared by methods A—E are summarized in Table I.

Interest in developing alternative pathways to **8**, an early promising therapeutic agent, prompted us to explore several synthetic routes. As seen in Table I, **8** was prepared by treating **23** with methyl *S*-(2-hydroxyethyl)thioglycolate (**27**)



type A



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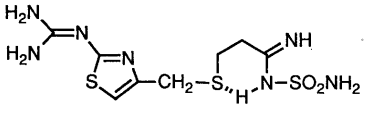

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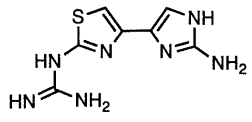
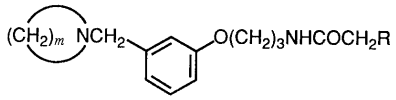


type D

Chart 1

TABLE I. *N*-Phenoxypropylacetamide Derivatives



Compd. No.	*m*	R	Method	Yield (%)	Appearance	Recrystn.[a] solvent	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
1	5	CN	C_1	31	Crystal	Acetone	122.0	$C_{18}H_{25}N_3O_2$[b]	56.50	5.85	10.54
						–MeOH	—125.0	$C_7H_6BrNO_2$	(56.20	5.78	10.33)
2[a]	5	$OCOCH_3$						$C_{19}H_{28}N_2O_3$			
3	5	$COCH_3$	A	71	Crystal	Acetone	168.0	$C_{19}H_{28}N_2O_3$[b]	56.94	6.25	7.66
						–MeOH	—169.5	$C_7H_6BrNO_2$	(56.66	6.38	7.39)
4	5	$CONH_2$	A	64	Colorless crystal	$CHCl_3$ –MeOH	85.3—88.3	$C_{18}H_{27}N_3O_3 \cdot 1/3H_2O$	63.69 (63.90	8.21 7.91	12.38 12.48)
5	4	$CONH_2$	A	75	Powder	$CHCl_3$ –MeOH	85.2—87.1	$C_{17}H_{25}N_3O_3 \cdot HCl \cdot 2/3H_2O$	55.50 (55.49	7.49 7.34	11.42 11.19)
6	5	CH_2CONH_2	A	37	Powder	AcOEt	126.9 —128.3	$C_{19}H_{29}N_3O_3$	65.68 (65.85	8.41 8.61	12.09 12.28)
7	5	CH_2OCH_3	A	77	Crystal	Acetone	189.9	$C_{19}H_{30}N_2O_3$[b]	56.12	6.64	7.55
						–MeOH	—190.6	$C_7H_6BrNO_2$	(56.30	6.34	7.41)
8	5	SCH_2CH_2OH	A	87	Powder	EtOH	146.5	$C_{19}H_{30}N_2O_3S$	65.11	6.62	4.60
			B, C_1, C_2				—147.0	$C_{14}H_{10}O_4$	(64.82	6.40	4.70)
9	4	SCH_2CH_2OH	A	74	Oil			$C_{18}H_{28}N_2O_3S$[c]	352.1820 (352.1823)		
10	5	$SO_2CH_2CH_2OH$	E	36	Crystal	Acetone –MeOH	93.1—95.4	$C_{19}H_{30}N_2O_5S$[b] $C_7H_6BrNO_2 \cdot 2H_2O$	48.00 (48.15	5.58 5.87	6.46 6.45)
11[d]	5	$SCH_2CH_2OCOCH_3$	D	55	Oil			$C_{21}H_{32}N_2O_4S$			
12[d]	4	$SCH_2CH_2OCOCH_3$	D	70	Oil			$C_{20}H_{30}N_2O_4S$			
13[d]	5	$SO_2CH_2CH_2OCOCH_3$	D	59	Oil			$C_{21}H_{32}N_2O_6S$			
14	5	$SCH_2CH_2CH_2OH$	A	81	Oil			$C_{20}H_{32}N_2O_3S$[c]	380.2132 (380.2164)		
15	5	$SCH_2CH(OH)CH_3$	A	85	Oil			$C_{20}H_{32}N_2O_3S$[c]	380.2132 (380.2161)		
16	5	$SCH_2CH(OH)CH_2OH$	A	57	Crystal	Acetone –MeOH	135.9 —139.2	$C_{20}H_{32}N_2O_4S$[b] $C_7H_6BrNO_2 \cdot 1/2H_2O$	52.17 (52.23	6.32 6.04	6.76 6.78)
17	5	$SCH_2CH_2SCH_2CH_2OH$	A	64	Oil			$C_{21}H_{34}N_2O_3S_2$[c]	426.2009 (426.1977)		
18	5	$NHCH_2CH_2OH$	C_1	84	Oil			$C_{19}H_{31}N_3O_3$[c]	349.2364 (349.2380)		
19	5	OCH_2CH_2OH	B	84	Oil			$C_{19}H_{30}N_2O_4$[c]	350.2204 (350.2180)		
20	5	$CH_2CH_2CH_2OH$	B	96	Oil			$C_{20}H_{32}N_2O_3$[c]	348.2411 (348.2424)		
21	5	$CH_2SCH_2CH_2OH$	A	82	Oil			$C_{20}H_{32}N_2O_3S$[c]	380.2132 (380.2125)		
22	5	$CH_2CH_2SCH_2CH_2OH$	A	69	Oil			$C_{21}H_{34}N_2O_3S$[c]	394.2290 (394.2264)		

a) Reference 4*a*. *b*) *p*-Nitrobenzyl ammonium bromide. *c*) High-resolution MS analysis. *d*) The structures were confirmed by only IR and NMR spectra.

or 1,4-oxathian-2-one[11] which gave **8** in 90 and 83% yields, respectively (methods A and B). Alkylation of **25** with 2-mercaptoethanol and of **26** with 2-chloroethanol gave **8** in 82 and 88% yields, respectively (methods C_1 and C_2). Among these procedures method A was the most economical for the large scale preparation of **8**.

Biological Screening Methods The compounds were evaluated for gastric acid antisecretory activity in animal models. The conscious rat with gastric fistula was used as the primary screen to assess gastric acid antisecretory activity.[12] In this test, the compounds were administered at a 30 mg/kg dose intraduodenally (i.d.) and the reduction in acid output was measured after 5 h. The secondary model was the inhibition of histamine-stimulated gastric acid secretion in the conscious dog with Heidenhain pouch. The compounds were first administered intravenously (i.v.) and the reduction in acid output, relative to the non-drug-treated control value, in the same animal was measured.[13]

Antiulcer activity of the compounds were tested in a water-immersion stress-induced ulcer model in the rat according to the method of Takagi and Okabe.[14] In this test, the compounds were administered orally (*p.o.*) 5 min before stress load and the effect of the drug was measured on the basis of the sum of the length (mm) of all lesions.

The compounds were tested for gastrointestinal cytoprotective activity in the rat.[15] In this test, the compound was orally (*p.o.*) administered 30 min before oral administration of HCl·ethanol. The effect of the compound against HCl·ethanol-induced ulcer was measured.

That the gastric acid antisecretory efficacy was based on

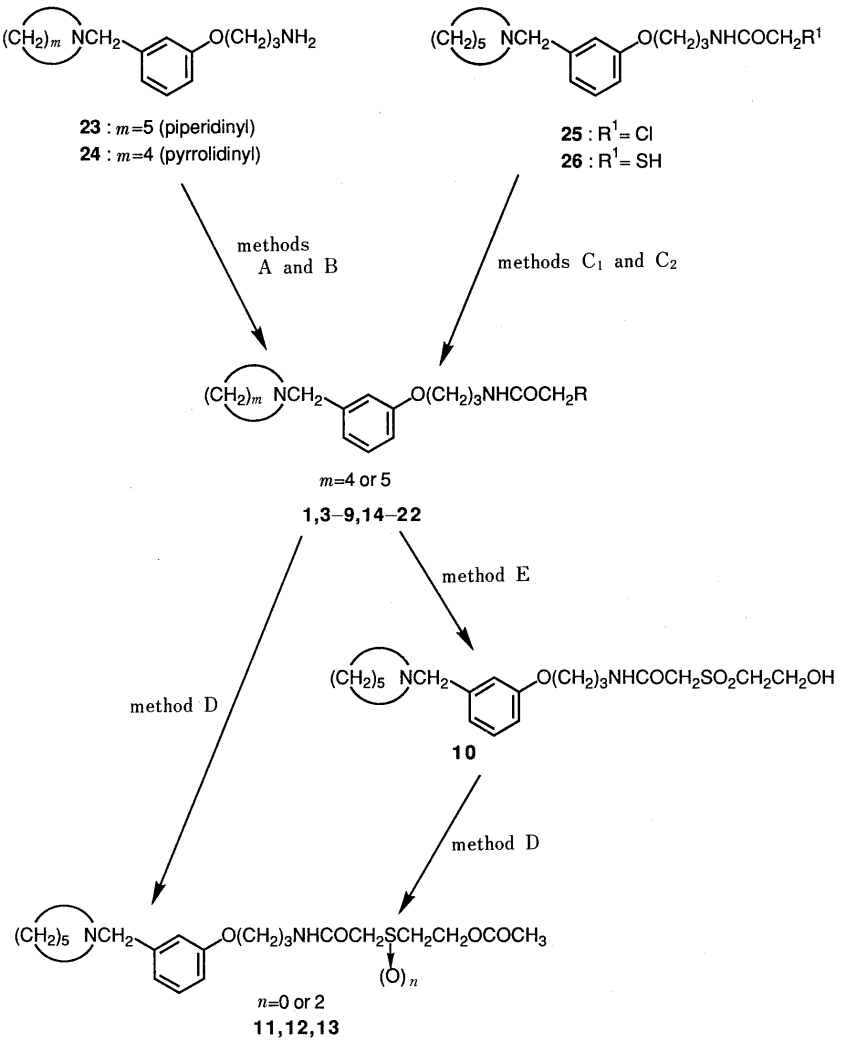


Chart 2

H_2 antagonist properties was confirmed by using the isolated guinea pig right atrial assay.[16]

Results and Discussion

The gastric acid antisecretory activity determined for the compounds prepared in this series in the rat model is described in Table II. Compounds having a function of –$NHCOCH_2S$– exhibited significant gastric acid antisecretory activity in the conscious rat with gastric fistula. Of these compounds, **8** was the most active compound.

Pharmacological properties of **8** are shown along with those of reference compounds, ranitidine and roxatidine, in Table III. As seen in Table III, the efficacy of **8**, in terms of ED_{50} value in the conscious rat with gastric fistula, was superior to that of ranitidine and roxatidine. However, in an inhibition test of histamine-stimulated acid secretion in the dog, **8** was slightly less effective than the reference compounds. The order of antagonistic activity to histamine H_2-receptor as determined by pA_2 value was roxatidine > **8** > ranitidine. These data show that gastric acid antisecretory activity of **8** is equivalent to that of ranitidine and roxatidine. The cytoprotective activity of **8** and roxatidine was found to be comparable; the oral cytoprotective ED_{50}s determined in the rat were 43.7 mg/kg for **8** and 37.1 mg/kg for roxatidine, respectively. The cytoprotective ED_{50} determined for ranitidine was 284.0 mg/kg. The efficacy of **8** in the water-immersion stress-induced ulcer which is similar to the human ulcer was also superior to that of ranitidine and roxatidine. ED_{50} values for **8** and ranitidine were 13.3 and 22.0 mg/kg, respectively. The ED_{50} value for roxatidine was not determined because the dose–response curve for this compound was not established. As can be seen in Fig. 1, **8** exhibited a significant level of gastric acid antisecretory activity upon intravenous administration of 1.0 mg/kg in the dog with long duration. Acute toxicity of **8** is shown to be $LD_{50} > 7000$ mg/kg at oral dose in rats.

Structure–Activity Relationships The histamine-stimulated rat data described in Table II suggested the following structure–activity relationships.

Bioisosteric Replacement of Acyl Side Chain The relationships between the structural features on the acyl side chain and the gastric acid antisecretory activity were not clear. However, the free hydrogen on the nitrogen of the amido group is essential in imparting the desired level of gastric acid antisecretory activity. The –NHCO– function appears to be a minimum structural requirement for the gastric acid antisecretory activity of this series.

It became apparent after the introduction of a considerable number of acyl side chains, –$COCH_2$-R with

widely varying physical and chemical properties of R, that the $-NHCOCH_2S-$ group was effective in imparting the desired level of gastric acid antisecretory activity. Comparison of the compounds in this series reveals large differences in gastric acid anti-secretory activity, which appears to be related to the electron-withdrawing power of the attached group R. As seen in Table II, compounds **1** and **3**—**5** having an electron-withdrawing group as R exhibited significant gastric acid antisecretory activity. On the other hand, compounds **6** and **7** which had an electron-releasing group as R exhibited diminished gastric acid antisecretory activity compared to that of compounds having an electron-withdrawing group as R. It was very interesting that a substituent of the mild electron-withdrawing sulfur atom in **8** resulted in the most enhanced gastric acid antisecretory activity.

TABLE II. Gastric Acid Antisecretory Activity of *N*-Phenoxypropylacetamide Derivatives in Rats with Gastric Fistula

Compd. No.	Salt[a]	π[b]	F[b]	Activity[c]
1	$C_4H_4O_4$	−0.57	0.51	52.7
2	$C_4H_4O_4$	−0.64	0.41	68.8
3	HCl	−0.55	0.32	52.7
4	HCl	−1.49	0.24	65.2
5	HCl	−1.49	0.24	58.2
6	HCl	−1.68	0.07[d]	25.5
7	HCl	−0.78	0.01	(Stimulation)
8	HCl	−0.52[e]	0.23[f]	79.5
9	HCl	—	—	70.9
10	HCl	—	—	59.4
11	$C_4H_4O_4$	—	—	76.7
12	$C_4H_4O_4$	—	—	55.4
13	$C_4H_4O_4$	—	—	73.6
14	HCl	—	—	71.4
15	HCl	—	—	65.5
16	HCl	—	—	37.7
17	HCl	—	—	38.0
18	2HCl	—	—	(Stimulation)
19	HCl	—	—	(Stimulation)
20	HCl	—	—	68.5
21	HCl	—	—	41.3
22	HCl	—	—	19.8
Roxatidine				68.8
Ranitidine				72.1

a) Hydrochloride or maleate was used for the test. *b*) Reference 19. *c*) % inhibition at the dose of 30 mg/kg (i.d.). Each value represents a mean of three rats. *d*) σ_p of CH_2CONH_2. *e*) Calculated from each value of SC_2H_5, CH_3 and CH_2OH. *f*) *F* value of SCH_2CH_3.

Homologation Extension of the alkylene side chain in the function of $-NHCO(CH_2)_n-$ was examined. The function of $-NHCOCH_2-$ in **8** was homologated by increasing (**21** and **22**) the number of methylene groups

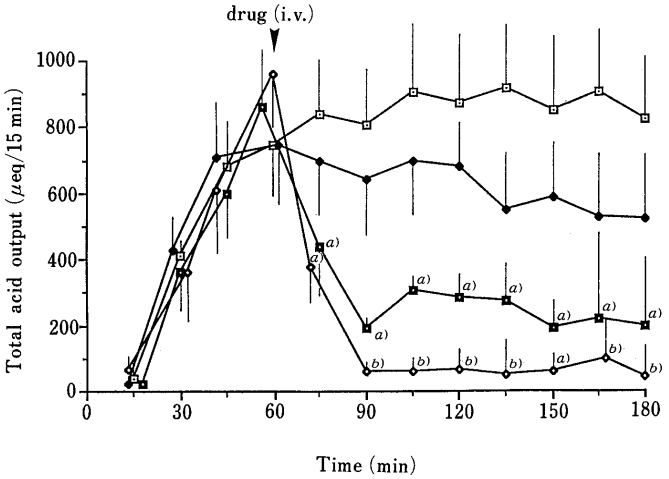


Fig. 1. Gastric Acid Antisecretory Effect of **8** on Histamine-Stimulated Gastric Acid Secretion in Dogs with Heidenhain Pouch

—□—, control; —◆—, 0.25 mg/kg; —■—, 0.5 mg/kg; —◇—, 1.0 mg/kg. Data indicate the mean value of four dogs. *a*) $p<0.05$; *b*) $p<0.01$: significantly different from the control value.

TABLE III. Pharmacological Properties of **8** and Reference Compounds, Ranitidine and Roxatidine

Compd.	Gastric acid antisecretory activity in the conscious rat with gastric fistula, i.d., ED_{50} mg/kg	Gastric acid antisecretory activity in the conscious dog with Heidenhain pouch, i.v., ED_{50} mg/kg	Antiulcer activity in stress-exposed rat, *p.o.*, ED_{50} mg/kg	Antiulcer activity in HCl·EtOH-treated rat, *p.o.*, ED_{50} mg/kg	H_2-Receptor antagonist activity (guinea pig atrium) pA_2
8	12.9	0.38	13.3	43.7	6.7
Ranitidine	17.7	0.15	22.0	284.0	6.6
Roxatidine	14.1	0.20	(25.7)[a]	37.1	7.0

a) Estimated value, because dose–response curve was not obtained.

TABLE IV. Alkylthioalkanoic Acid Ester Derivatives

$R_2S(CH_2)_nCOOR_1$

Compd. No.	R_1	*n*	R_2	Solvent	Base	Temperature	Time (h)	Yield (%)
27	CH_3	1	CH_2CH_2OH	MeOH	Et_3N	RT	3	91
28	CH_3	1	CH_2CH_2SH	MeOH	Et_3N	RT	2	73
29	CH_3	1	$CH_2CH_2CH_2OH$	Acetone	K_2CO_3	Rf	3	81
30	CH_3	1	$CH_2CH(OH)CH_3$	MeOH	Et_3N	RT	4	75
31	C_2H_5	3	CH_2CH_2OH	MeOH	Et_3N	RT	4	85
32	CH_3	3	CH_2CH_2OH	MeOH	NaOMe	Rf	3	62
33	CH_3	1	$CH_2CH_2SCH_2CH_2OH$	MeOH	NaOMe	RT	24	88

RT, room temperature; Rf, refluxing solvent.

TABLE V. Spectral Data for Alkylthioalkanoic Acid Ester Derivatives

Compd. No.	IR ν (neat) cm^{-1}	NMR ($CDCl_3$) δ (ppm)
27	3450, 2940, 1730, 1280	2.71 (1H, br s, OH), 2.84 (2H, t, J=6.0 Hz, CH_2), 3.29 (2H, s, CH_2), 3.75 (3H, s, CH_3), 3.78 (2H, t, J=6.0 Hz, CH_2)
28	2940, 1735, 1435, 1275, 1150	2.70—2.95 (4H, m, CH_2CH_2), 3.25 (2H, s, CH_2), 3.74 (3H, s, CH_3)
29	3400, 2945, 1730, 1430, 1210	1.72 (1H, br s, OH), 1.78—2.08 (2H, m, CH_2), 2.77 (2H, t, J=7.0 Hz, CH_2), 3.24 (3H, s, CH_2), 3.74 (3H, s, CH_3), 3.76 (2H, t, J=5.0 Hz, CH_2)
30	3430, 2960, 1730, 1280	1.26 (3H, d, J=6.0 Hz, CH_3), 2.43—2.94 (3H, m, CH_2 and OH), 3.29 (2H, s, CH_2), 3.75 (3H, s, CH_3), 3.66—4.07 (1H, br, CH)
31	3400, 2925, 1725, 1245	1.27 (3H, t, J=7.0 Hz, CH_3), 2.49—3.04 (7H, m, $CH_2CH_2SCH_2$ and OH), 3.74 (2H, t, J=5.0 Hz, CH_2), 4.17 (2H, q, J=7.0 Hz, CH_2OCO)
32	3430, 2945, 1730, 1435, 1210	1.72—2.91 (9H, m, $CH_2CH_2CH_2SCH_2$ and OH), 3.68 (2H, t, J=7.0 Hz, CH_2), 3.68 (3H, s, CH_3)
33	3400, 2945, 1730, 1435, 1280	1.88—2.39 (1H, br, OH), 2.57—3.08 (6H, m, $CH_2CH_2SCH_2$), 3.26 (2H, s, CH_2), 3.73 (2H, t, J=7.0 Hz, CH_2), 3.73 (3H, s, CH_3)

between the –NHCO– and the $-SCH_2CH_2OH$ groups. Analogues (**21** and **22**) exhibited reduced gastric acid antisecretory activity. These results may indicate that the methylene function is necessary to minimize disturbance to other biologically important molecular properties such as stereochemistry and lipid-water interactions.

***S*-2-Hydroxyethyl Group** The *S*-2-hydroxyethyl group was most uniquely effective in imparting the desired level of gastric acid antisecretory activity. Compound **14** bearing $-SCH_2CH_2CH_2OH$ instead of $-SCH_2CH_2OH$ retained gastric acid antisecretory activity comparable to that of **8**. Compound **15**, an isomer of **14**, also exhibited reduced activity as did dihydroxypropyl analogue (**16**). Compound **17** exhibited one-half the potency of **8**.

Heteroatom Substitution Replacement of the sulfur atom in $-NHCOCH_2-S-CH_2CH_2OH$ of **8** with a nitrogen atom, an oxygen atom and a methylene group resulted in analogues **18**, **19** and **20**. The gastric acid antisecretory activity of **20** was comparable to that of **14**. On the other hand, nitrogen and oxygen analogues (**18** and **19**) were devoid of any significant gastric acid antisecretory activity. Compound **18** showed increasing acid secretion which was about double compared with basal acid secretion. Oxidation of the sulfur atom of **8** gave sulfonyl analogue (**10**) which exhibited reduced gastric acid antisecretory activity compared to **8**.

In conclusion, compound **8**, which is representative of a competitive histamine H_2-receptor antagonist exhibiting both gastric acid antisecretory and cytoprotective properties, was selected for further development and clinical evaluation.

Experimental

Melting points were measured in a Gallenkamp melting point apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 Model infrared spectrophotometer and proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a Hitachi R-90H (90 MHz) spectrometer for 5—10% (w/v) with tetramethylsilane as an internal standard. Chemical shifts are given as δ values (ppm); s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. All spectra were consistent with the assigned structures. Mass spectra (MS) and high-resolution MS were obtained on a JMS-DX 300 spectrometer operating at an ionization potential of 70 eV. Combustion analyses were performed on a Perkin-Elmer Model 240C elemental analyzer.

Alkyl mercaptanes were commercially available. 1,4-Dioxan-2-one[17] and 1,4-oxathian-2-one[11] were prepared according to procedures described in the literatures. Amines **23** and **24** were prepared by procedures in the patent literatures.[9,10]

Preparation of Methyl *S*-(2-Hydroxyethyl)thioglycolate (27) and Related Compounds. General Procedure Triethylamine (121.2 g, 1.2 mol) was added dropwise to a solution of methyl monochloroacetate (108.5 g, 1.0 mol) and 2-mercaptoethanol (78.0 g, 1.0 mol) in MeOH (400 ml) over 30 min at room temperature with stirring. The resulting mixture was stirred for an additional 3 h. After removal of the solvent, the residue was dissolved into AcOEt (250 ml) and insoluble materials were removed by filtration. The AcOEt layer was evaporated to give an oily product which was distilled under reduced pressure to give **27** (136.1 g, 90.7%), bp 82—84 °C (0.25 mmHg). Related compounds were prepared by a procedure similar to that used for **27**. The results are summarized in Table IV and the spectral data are shown in Table V.

Preparation of *N*-[3-{3-(1-Piperidinylmethyl)phenoxy}propyl]-2-chloroacetamide (25) This was prepared by modification of the procedure described in the patent literature.[18] A solution of monochloroacetyl chloride (489 mg, 4.4 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a solution of **23** (1.0 g, 4.0 mmol) and BSA (1.5 ml, 6 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The resulting mixture was allowed to stand at room temperature for 30 min with stirring and poured into ice-water. The mixture was made alkaline with $NaHCO_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give an oily material **25** (1.3 g, quantitative yield). This was employed for the following step without purification.

General Procedure for Synthesizing *N*-Phenoxypropylacetamide Derivatives. Method A A solution of **23** (74.4 g, 0.3 mol) and ester **27** (54 g, 0.36 mol) in toluene (300 ml) was heated for 15 h under refluxing toluene. After removal of the solvent, the residue was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with 10% NaOH (200 ml × 2), successively by brine, and then extracted with 3 N HCl (200 ml × 3). The acidic aqueous layer was made alkaline with 3 N NaOH (800 ml) under cooling with ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give **8** as an oil (92.5 g). Compounds **3**—**7**, **9**, **14**—**17**, **21** and **22** were prepared by a procedure similar to that used for **8**.

2-(4-Hydroxybenzoyl)benzoate of **8**: A mixture of **8** (3.67 g, 10 mmol) and 2-(4-hydroxybenzoyl)benzoic acid (2.42 g, 10 mmol) in EtOH (10 ml) was stirred overnight at room temperature. The crystalline powder precipitated was collected and recrystallized from EtOH to give an analytical pure sample (5.90 g, 97%). NMR (DMSO-d_6) δ: 1.22—1.62 (6H, br s, piperidine-3,4,5-CH_2), 1.85 (2H, q, J=6.0 Hz, $OCH_2-C\underline{H}_2-CH_2N$), 2.14—2.54 (6H, m, piperidine-2,6-CH_2 and OH × 2), 2.64 (2H, t, J=6.5 Hz, $S-C\underline{H}_2-CH_2OH$), 3.12 (2H, s, $CO-CH_2-S$), 3.22 (2H, q, J=6.0 Hz, $OCH_2CH_2-C\underline{H}_2-N$), 3.51 (2H, s, $Ar-CH_2$), 3.54 (2H, t, J=6.5 Hz, $SCH_2-C\underline{H}_2-OH$), 3.96 (2H, t, J=6.0 Hz, $O-C\underline{H}_2-CH_2N$), 6.64—8.18 (14H, Ar–H, CO–NH, =NH–). IR ν (KBr): 3320, 1650, 1640 cm^{-1}.

p-Nitrobenzyl Ammonium Bromide of **8**: A solution of **8** (550 mg, 1.5 mmol) and *p*-nitrobenzyl bromide (0.32 mg, 1.5 mmol) in CH_2Cl_2 (10 ml) was stirred for 5 d at room temperature. After removal of the solvent, the residue obtained was purified by column chromatography on silica gel with a (4:: 1) mixture of $CHCl_3$ and MeOH to give *p*-nitrobenzyl ammonium bromide of **8** (783 mg, 90%) which was recrystallized from

acetone–MeOH to give a pure sample, mp 172.6—173.8 °C. NMR (DMSO-d_6) δ: 1.40—1.55 (2H, m, piperidine-4-CH_2), 1.88—1.92 (2H, m, OCH_2–CH_2–CH_2N), 2.00—2.12 (4H, m, piperidine-3,5-CH_2), 2.63 (2H, t, J=6.3 Hz, S–CH_2–CHO), 3.12 (2H, s, $COCH_2$), 3.21—3.38 (6H, m, piperidine-2,6-CH_2 and CO–CH_2–S), 3.54 (2H, t, J=6.6 Hz, SCH_2–CH_2–O), 4.05 (2H, t, J=6.3 Hz, ArO–CH_2), 4.70 and 4.91 (each 2H, s, Ar–CH_2–N^+), 4.82 (1H, br s, OH), 7.08—7.16 (3H, m, Ar-H), 7.41 (1H, m, Ar-H), 7.93 (2H, d, J=9.0 Hz, Ar-H), 8.11 (1H, m, NH), 8.33 (2H, d, J=9.0, Ar–H). IR ν (KBr): 3430, 3200, 1640 cm^{-1}. *Anal.* Calcd for $C_{19}H_{30}N_2O_3S \cdot C_7H_6BrNO_2 \cdot H_2O$: C, 52.00; H, 6.04; N, 7.00. Found: C, 52.27; H, 5.84; N, 7.02. *p*-Nitrobenzyl ammonium bromides of **1**, **3**, **7**, **10** and **16** were prepared by a procedure similar to that of **8** (Table I).

Method B A mixture of **23** (1.24 g, 5 mmol) and 1,4-oxathian-2-one,[11] prepared from ethyl chloroacetate (613 mg, 5 mmol) and 2-mercaptoethanol (391 mg, 5 mmol) in the presence of NaOEt (10 mmol) in dry EtOH (54 ml), was heated at 70 °C with stirring for 1 h. After removal of the solvent, the residue was treated with a mixture of H_2O and benzene. The benzene and aqueous layers were separated and the aqueous layer was extracted with benzene. The benzene layers were combined, washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo* to give an oily material. The oil was purified by column chromatography on silica gel with a (15 : 1) mixture of $CHCl_3$ and MeOH to give pure **8** as a viscous oil (1.5 g, 83%). Compounds **19** and **20** were prepared by a procedure similar to that used for **8**.

Method C_1 A mixture of **25** (2.4 g, 7.4 mmol), 2-mercaptoethanol (0.64 g, 7.7 mmol) and 85% KOH (0.64 g, 9.7 mmol) in MeOH (30 ml) was stirred at room temperature for 1 h. After removal of the solvent, the residue was treated with a mixture of H_2O and $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over $MgSO_4$ and evaporated to give an oily material. The oil was purified by column chromatography on silica gel with a (4 : 1) mixture of $CHCl_3$ and MeOH as a solvent to give pure **8** as a viscous oil (2.2 g, 82%).

Compound **18** was prepared from **25** and 2-hydroxyethylamine by a procedure similar to that used for **8**.

Method C_2 Compound **26** (1.8 g, 5 mmol) and 2-chloroethanol (403 mg, 5 mmol) were added successively to a solution of MeONa in dry MeOH, prepared from Na (115 mg) and dry MeOH (30 ml). The resulting mixture was stirred at room temperature for 24 h. The reaction product isolated was purified by a procedure similar to that used for method C_1, yielding **8** in 88% yield as a viscous oil.

Method D Compound **8** (1.03 g, 3.1 mmol) was added to a solution of acetic anhydride (1.19 g, 11.7 mmol) in dry pyridine (981 mg). The mixture was heated for 2 h at a bath temperature of 60 °C, and then poured into a mixture of H_2O (10 ml) and saturated $NaHCO_3$ (10 ml) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo* to give an oily material. The oil was purified by column chromatography on silica gel with a (4 : 1) mixture of $CHCl_3$ and MeOH to give pure **11** (637 mg, 56%) as an oil. NMR ($CDCl_3$) δ: 1.35—1.75 (6H, m, piperidine-3,4,5-CH_2), 2.05 (3H, s, $COCH_3$), 1.80—2.20 (2H, m, OCH_2–CH_2–CH_2N), 2.80 (2H, t, S–CH_2–CH_2O), 3.27 (2H, s, $COCH_2$–S), 3.30—3.70 (4H, m, Ar–CH_2–N and OCH_2CH_2–CH_2–N), 3.80—4.40 (4H, m, ArO–CH_2 and SCH_2–CH_2–CO), 6.65—7.50 (5H, m, Ar–H and NH). IR ν (neat): 3280, 1735, 1650, 1240 cm^{-1}. MS *m/z*: 409 (M^++1), 321, 218, 107.

Compounds **12** and **13** were also prepared from **9** and **10**, respectively, by a procedure similar to that used for **11**.

12: An oil (71%). NMR ($CDCl_3$) δ: 1.45—2.30 (6H, m, pyrrolidine-3,4-CH_2 and OCH_2–CH_2–CH_2N), 2.10 (3H, s, $COCH_3$), 2.30—3.00 (6H, m, pyrrolidine-2,5-CH_2 and S–CH_2–CH_2O), 3.20—3.85 (6H, m, $COCH_2$, OCH_2CH_2–CH_2–N and Ar–CH_2), 3.95—4.40 (4H, m, ArO–CH_2 and SCH_2–CH_2–OCO), 6.65—7.00 (5H, m, Ar–H and NH). IR ν (neat): 3280, 1730, 1640 cm^{-1}.

13: An oil (59%). NMR ($CDCl_3$) δ: 1.35—1.85 (6H, m, piperidine-3,4,5-CH_2), 2.10 (3H, s, $COCH_3$), 1.85—2.25 (2H, m, OCH_2–CH_2–CH_2N), 2.25—2.60 (4H, m, piperidine-2,6-CH_2), 3.25—3.80 (6H, m, Ar–CH_2, SO_2–CH_2–CH_2O, and OCH_2CH_2–CH_2–N), 3.80—4.25 (4H, m, $COCH_2$–SO_2 and ArO–CH_2), 4.55 (2H, t, SCH_2–CH_2–OCO), 6.65—7.55 (5H, Ar–H and NH). IR ν (neat) 3350, 1745, 1675, 1325, 1125 cm^{-1}. MS *m/z*: 441 (M^++1), 305, 204, 107, 84.

Method E Thirty percent H_2O_2 solution (14 ml) was added to a solution of **8** (3.63 g, 10 mmol) in AcOH (12 ml). The mixture was heated for 2 h at 65 °C with stirring and diluted with H_2O (30 ml). After removal of the solvent, the residue was treated with a mixture of saturated $NaHCO_3$ solution (50 ml) and $CHCl_3$ (50 ml). The $CHCl_3$ and aqueous layers were separated and the aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layers were combined, washed with chilled brine, dried over $MgSO_4$ and evaporated *in vacuo* to give a brown oil. The oil was purified by column chromatography on silica gel with a (5 : 1) mixture of $CHCl_3$ and MeOH to give pure **10** (1.40 g, 36%) as an oil.

Compounds prepared by methods A—E are summarized with elemental and high-resolution MS analyses in Table I.

Biological Screening Methods The free bases of the compounds were each dissolved in an equimolar of HCl or maleic acid and used for tests.

Animals Male Sprague Dawley rats weighing 180—200 g, male Hartley strain guinea pigs weighing 530—700 g and male beagle dogs (LR strain) weighting 9—10 kg with a Heidenhain pouch were used. Both rats and dogs were deprived of food for 24 h, being allowed free access to water prior to the experiments.

Gastric Acid Antisecretory Activity in the Conscious Rat with Gastric Fistula[12] Rats were divided into groups of 3 or 8 animals each and anesthetized with ether. The abdomen was opened and an acute gastric fistula was prepared by placing a polyethylene tube in the forestomach with a ligature around the neck of the pylorus. The incision was closed, and the rats recovered from the anesthesia. The animals were first administered histamine by i.v. infusion. A dose of histamine of 8 mg/kg per hour was selected as the most appropriate stimulant. Gastric juice was collected at 60-min intervals for 5 h following the start of histamine infusion, and the volume was measured. Five collections were taken from each rat during the experiment. Acid concentration was determined by titrating 0.1 ml of gastric juice to a pH value of 7.0 with 0.1 N aqueous sodium hydroxide. The animals were administered the test compounds at the dose of 30 mg/kg and a specified dose in milligram per kilogram or control vehicle alone, *via* the i.d. route of administration, at 60 min following the start of the histamine infusion. The respective 60-min acid outputs were summated for 5 h after drug administration. The acid output collected over the 5-h period after drug administration was divided by the 5-h acid output collected in the control experiments. This value times 100 yields the percentage of control acid output. Percent inhibition = 100 − percent of control. The doses inhibiting histamine-stimulated gastric acid secretion by 50% (ED_{50}) were calculated by linear regression analysis.

Gastric Acid Antisecretory Activity in the Conscious Dog with Heidenhain Pouch[13] Dogs were divided into groups of 4 animals each and administered histamine in order to stimulate acid output by i.m. injection at 15-min intervals for 3 h with a dose of histamine of 20 μg/kg. The animals were administered the test compounds at a specified dose in milligrams per kilogram, respectively, or the control vehicle alone, *via* the i.v. route of administration, at 60 min following the start of the histamine injection. Gastric juice was collected at 15-min intervals for 2 h after the administration of the test compound. Acid concentration and percent inhibition were determined according to the procedure described in the rat's experiment.

Antiulcer Activity in Rats Rats were divided into groups of 8 animals each, immobilized in individual stress cages, and immersed in a water bath of which the temperature was thermostatically regulated at 21 ± 1 °C, up to the level of the xiphoid process according to the procedure of Takagi and Okabe.[14] After exposure to stress for 7 h, the animals were then immediately killed and the stomach of each was removed to estimate the lesions. The ulcer index was expressed as the sum of the length (mm) of all lesions. The animals were administered the test compounds orally 5 min before the load of stress. The doses inhibiting gastric lesion by 50% (ED_{50}) were calculated by linear regression analysis.

Gastrointestinal Cytoprotective Activity in Rats Rats were divided into groups of 10 animals each. The compound was given to the rats orally 30 min prior to oral administration of 1 ml of a HCl·ethanol solution which was prepared according to the procedure described by Mizui and Doteuchi.[15] One hour after the administration of the HCl·ethanol solution the rats were immediately killed and the stomachs were removed to examine the lesions. The ulcer index was expressed as the sum of the length (mm) of all lesions. The doses inhibiting gastric lesions by 50% (ED_{50}) were calculated by linear regression analysis.

Histamine H_2-Receptor Antagonist Activity The procedure is a modification of that described by Reinhardt *et al.*[16] Guinea pigs were killed rapidly with a blow to the head. The hearts were removed and the right atria were freely dissected. Atria under a 1-g tension load were placed in a temperature-controlled (37 ± 2 °C) organ bath containing oxygenated (95% O_2 ± 5% CO_2) Krebs–Henseleit buffer of which the composition was as follows: 118 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM $NaHPO_4$, 25 mM $NaHCO_3$, 11 mM glucose. Individual atrial contractions were followed with a gross force-displacement transducer connected to a dynograph recorder. A dose–response curve to histamine was

obtained by the cumulative application of histamine into the organ bath. The test compounds were added to the organ bath 10 min before the application of histamine. Results were expressed as a percentage of the maximal response established in the absence of the antagonists for each preparation. The H_2-receptor antagonist potency was reported as a pA_2 value determined from the Schild plots method.

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