Synthesis and Antiulcer Activity of *N*-Substituted *N'*-[3-[3-(Piperidinomethyl)phenoxy]propyl]ureas: Histamine H_2-Receptor Antagonists with a Potent Mucosal Protective Activity

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As an aim toward developing new antiulcer agents, new N-substituted *N'*-[3-[3-(piperidinomethyl)phenoxy]propyl]ureas were synthesized and evaluated for histamine H_2-receptor antagonistic, gastric antisecretory, and gastric mucosal protective activities. A QSAR study showed that the most favorable N-substituents were electron-donating straight-chain alkyl groups of short length such as ethyl group from the viewpoint of dual action, i.e., gastric antisecretory and mucosal protective actions. Among the ureas studied, compounds **4**, **5**, and **8–10** were selected as candidates for further study.

Introduction

Peptic ulcers have been considered to result from an imbalance between the aggressive factors and the defensive factors in gastric mucosa[1] and have been treated with either acid-reducing or mucosal protective drugs.

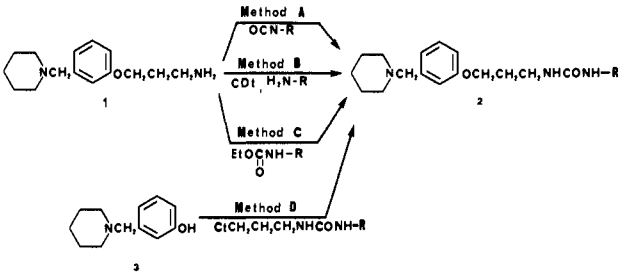
Although histamine H_2-receptor antagonists have been shown to be highly effective in the treatment of peptic ulcer,[2,3] a serious problem has been described by the unusually high relapse rate after cessation.[4-7] On the other hand, mucosal protective drugs were inferior or comparable to histamine H_2-receptor antagonists for ulcer healing, but the former showed a lower relapse rate than the latter.[7-10]

In addition, the combination of histamine H_2-receptor antagonist and mucosal protective drug was found to be more effective than each type individually[11-16] in experimental models. However, antiulcer agents which exhibit both histamine H_2-receptor antagonistic and gastric mucosal protective activities have scarcely been known. So, we have tried to develop the new histamine H_2-receptor antagonist having a potent mucosal protective activity. We selected the 3-[3-(piperidinomethyl)phenoxy]propyl moiety as a lead moiety, which was essential for some potent histamine H_2-receptor antagonists such as TZU-0460 (roxatidine acetate), BMY-25368, and L-643441 (Figure 1).[17]

On the other hand, it has been reported that the thiourea structure in metiamide was closely correlated with its potent histamine H_2-receptor antagonistic activity.[18] This prompted us to attach the thiourea structure to the 3-[3-(piperidinomethyl)phenoxy]propyl moiety to create an original potent histamine H_2-antagonist structure. Compound **32** (Figure 2), our first compound, had very weak histamine H_2-receptor antagonistic activity and minimal gastric antisecretory activity, but had moderate gastric mucosal protective activity (Table II). So, we replaced thiourea with urea by utilizing the concept of bioisosterism. Compound **22** (Table I) showed a moderate histamine H_2-receptor antagonistic and potent gastric antisecretory activity with moderate gastric mucosal protective activity (Table II). Ureas were further extended to get more potent histamine H_2-receptor antagonists with a more potent gastric mucosal protective activity.

Quantitative structure–activity relationships were studied to show the correlation between physicochemical properties of the urea substituents and antiulcer activities (histamine H_2-receptor antagonistic, gastric antisecretory, and gastric mucosal protective activities) and to demonstrate candidates for further study from the viewpoint of gastric antisecretory and mucosal protective activities.

Scheme I



† Technical Center of Organic Syntheses.
‡ Central Research Laboratories.

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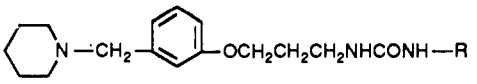
Table I. *N*-Substituted-*N'*-[3-[3-(piperidinomethyl)phenoxy]propyl]ureas (**2**)



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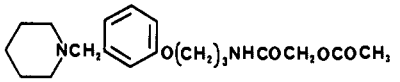
no.	R	% yield	mp, °C	formula	method[a]	recryst solv
4	CH_3	57	73–75	$C_{17}H_{27}N_3O_2 \cdot 0.1H_2O$	A, D[b]	pet. ether
5	C_2H_5	89	80–81.5	$C_{18}H_{29}N_3O_2$	A, D[b]	pet. ether
6	CH_2CH_2F	28	98–101	$C_{18}H_{28}FN_3O_2 \cdot 0.4H_2O$	B	AcOEt–Et_2O
7	c-C_3H_5	33	75–77	$C_{19}H_{29}N_3O_2 \cdot 0.2H_2O$	B	Et_2O
8	*n*-C_3H_7	74	99–101	$C_{19}H_{31}N_3O_2$	A	AcOEt
9	$CH(CH_3)_2$	65	93–95	$C_{19}H_{31}N_3O_2$	B, D[b]	AcOEt–pet. ether
10	*n*-C_4H_9	63	88–91	$C_{20}H_{33}N_3O_2$	A	EtOH
11	$CH_2CH(CH_3)_2$	87	68–71	$C_{20}H_{33}N_3O_2 \cdot 0.2H_2O$	B	AcOEt–pet. ether
12	$CH(CH_3)CH_2CH_3$	84	148–158	$C_{20}H_{33}N_3O_2 \cdot HCl \cdot 0.3H_2O$	B	pet. ether
13	C_6H_5	73	109–111	$C_{22}H_{29}N_3O_2$	A	EtOH
14	3-$NH_2C_6H_4$	88	116–118	$C_{22}H_{30}N_4O_2$	E	EtOH
15	3-$NO_2C_6H_4$	69	64–66	$C_{22}H_{28}N_4O_4 \cdot 0.1H_2O$	A	pet. ether
16	4-$NO_2C_6H_4$	20	oil	$C_{22}H_{28}N_4O_4 \cdot 0.5H_2O$	A	*c*
17	3-$CH_3OC_6H_4$	67	114–118	$C_{23}N_{31}N_3O_3 \cdot HCl \cdot H_2O$	A	EtOH–Et_2O
18	3,4-$(OCH_2O)C_6H_3$	67	128–130	$C_{23}H_{29}N_3O_4$	B	EtOH
19	$CH_2C_6H_5$	59	109–112	$C_{23}H_{31}N_3O_2$	A	EtOH
20	3-ClC_6H_4	92	58–61	$C_{22}H_{28}ClN_3O_2 \cdot 0.2H_2O$	A	AcOEt–pet. ether
21	4-ClC_6H_4	77	131–133	$C_{22}H_{28}ClN_3O_2$	A	EtOH
22	4-$CH_3OC_6H_4$	66	111–112	$C_{23}H_{31}N_3O_3$	A	EtOH
23	2-$CH_3OC_6H_4$	83	92–94	$C_{23}H_{31}N_3O_3$	A	AcOEt
24	3-$CF_3C_6H_4$	100	oil	$C_{23}H_{28}F_3N_3O_2 \cdot 0.2H_2O$	A	*c*
25	2,4-$(CH_3O)_2C_6H_3$	88	80–83	$C_{24}H_{33}N_3O_4$	A	Et_2O
26	4-$CF_3C_6H_4$	85	114–116	$C_{23}H_{28}F_3N_3O_2$	A	EtOH
27	4-$CH_3CH_2OC_6H_4$	11	109–111	$C_{24}H_{33}N_3O_3$	C	EtOH
28	2,5-$(CH_3O)_2C_6H_3$	75	95–98	$C_{24}H_{33}N_3O_4$	A	Et_2O
29	$C(CH_3)_3$	56	94–95	$C_{20}H_{33}N_3O_2$	A	AcOEt
30	c-C_6H_{11}	57	94–96	$C_{22}H_{35}N_3O_2$	A	EtOH–pet. ether
31	4-$CH_3C_6H_4$	67	103–105	$C_{23}H_{31}N_3O_2$	A	AcOEt

[a] See the Chemistry section. [b] The yields of products were 53% (R = CH_3), 36% (R = C_2H_5), and 26% (R = $CH(CH_3)_2$), respectively. [c] Purified by column chromatography on silica gel.

Chemistry

Most of N-substituted *N'*-[3-[3-(piperidinomethyl)-phenoxy]propyl]ureas (**2**) were synthesized by four methods (A–D) as shown in Scheme I.



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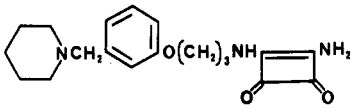

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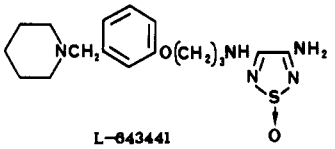

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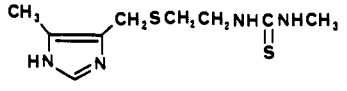
Figure 1.



Metiamide

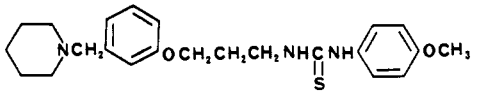


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Figure 2.

In the first route (method A), ureas **2** were prepared by the reaction of 3-[3-(piperidinomethyl)phenoxy]propyl-

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Table II. Biological Properties of Ureas 2

no.[a]	in vitro[b] pA_2	in vivo (% inhibn)[b] antisecretory activity[c]	AS[d]	mucosal protective activity[e]	MP[f]	predicted AS[g]	predicted MP[h]
4	6.81	93.3	3	64.7 ± 5.9	3	3	3
5	7.39	71.8 ± 1.7	3	77.9 ± 8.0	3	3	3
6	7.07	98.7 ± 1.3	3	36.0 ± 11.3	2	3	2
7	7.32	87.5 ± 6.1	3	49.4 ± 11.9	2	3	2
8	7.01	96.6 ± 2.0	3	73.5 ± 7.0	3	3	3
9	7.36	71.3 ± 7.7	3	72.9 ± 3.0	3	3	2
10	7.09	83.0 ± 3.7	3	67.5 ± 11.0	3	3	3
11	6.77	40.3 ± 20.9	2	43.3 ± 20.5	2	2	2
12	7.02	55.1 ± 33.1	2	17.7 ± 20.7	1	2	2
13	6.90	12.6	1	44.3 ± 18.5	2	2	2
14	6.81	95.0	3	47.2 ± 13.5	2	3	2
15	6.57	−23.9	1	40.9 ± 15.2	2	1	2
16	6.75	9.0 ± 14.5	1	23.4 ± 7.7	1	1	1
17	6.70	53.2 ± 20.8	2	48.2 ± 14.4	2	2	2
18	6.54	48.9 ± 4.8	2	47.1 ± 13.1	2	2	2
19	6.46	54.2	2	61.0 ± 9.0	3	2	3
20	6.50	−44.9	1	43.3 ± 9.9	2	1	2
21	6.20	28.2	1	33.9 ± 10.9	2	1	2
22	6.20	73.5 ± 8.3	3	40.9 ± 7.2	2	2	2
23	6.11	−57.4	1	31.7 ± 7.9	2	1	2
24	6.09	7.8 ± 17.1	1	−4.9 ± 12.7	1	1	2
25	5.65	13.1	1	55.7 ± 10.5	2	1	2
26	5.77	3.8	1	51.0 ± 5.5	2	1	2
27	6.31	54.1 ± 7.7	2	32.7 ± 8.4	2	2	2
28	6.80	−30.8	1	34.7 ± 10.1	2	2	2
29	5.68	−56.0 ± 52.8	1	28.5 ± 15.7	1	1	2
30	7.36	77.9 ± 6.7	3	39.3 ± 4.4	2	3	2
31	6.20	−45.5	1	40.1 ± 10.7	2	1	2
32[i]	5.36	−5.5		51.6 ± 12.9			
cimetidine	6.58	51.4 ± 10.1[j]		−42.2 ± 18.6[k]			
famotidine	7.00	90.7 ± 6.8[l]		7.9 ± 7.1[k]			
ranitidine	7.19	not tested		−16.8 ± 9.0[k]			
teprenone		not tested		42.7 ± 7.3[k]			

[a] Number corresponding to that of Table I. [b] See the experimental section for biological test methods. [c] Mean ± SE from three or four animals at 10 mg/kg id (except two animals). [d] The gastric antisecretory activities classified according to the percent inhibition. See the QSAR section. [e] Mean ± SE from 5–10 animals at 25 mg/kg po. [f] The gastric mucosal protective activities classified according to the percent inhibition value. See the QSAR section. [g] Using eq 2. [h] Using eq 3. [i] Number corresponding to that of Figure 2. [j] 12.5 mg/kg id. [k] 200 mg/kg po. [l] 5 mg/kg id.

amine[19] (1) with the corresponding isocyanates in EtOH. In the second route (method B), ureas 2 were prepared by the reaction of compound 1 with the corresponding amines in the presence of 1,1-carbonyldiimidazole (CDI) in CH_2Cl_2. In the third route (method C), ureas 2 were prepared in 3-methoxy-1-butanol by the reaction of compound 1 with the intermediary carbonates which were synthesized by the reaction of the corresponding amines with ethyl chlorocarbonate in the presence of Et_3N in CH_2Cl_2. In the fourth route (method D), ureas 2 were also prepared by the reaction of 3-(piperidinomethyl)phenol[19] (3) with the corresponding *N*-(3-chloropropyl)ureas in the presence of NaH in DMF.

N-(3-Aminophenyl)-*N'*-[3-[3-(piperidinomethyl)phenoxy]propyl]urea (14) was synthesized by the reductive reaction of 15 with tin in concentrated HCl–EtOH under reflux (method E).

The structures, methods of preparation, and yields of these compounds are given in Table I.

Pharmacology

The N-substituted *N'*-[3-[3-(piperidinomethyl)phenoxy]propyl]ureas (2) were assayed by (1) in vitro histamine H_2-receptor antagonistic activity (pA_2) in isolated guinea pig right atria, (2) in vivo gastric antisecretory activity (percent inhibition) in acute fistula rats, and (3) in vivo gastric mucosal protective activity (percent inhibition)[20] against gastric mucosal lesions induced by 0.6 N HCl in rats (see Table II).

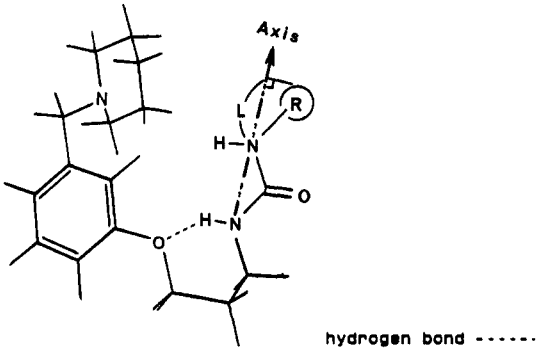

Figure 3.

Cimetidine, ranitidine, and famotidine were selected as reference compounds for gastric antisecretion. Teprenone was selected as a reference compound for gastric mucosal protection.[21,22]

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Table III. Physicochemical Parameters[a] of N-Substituents of Ureas 2

no.[b]	π	σ	L	B_1	B_4	VW	D
4	0.56	−0.17	3.01	0.89	2.37	0.18	1
5	1.02	−0.15	4.31	1.84	2.32	0.33	1
6	0.41	0.00	4.88	1.85	2.35	0.38	1
7	1.00	−0.21	4.32	1.86	2.91	0.38	−1
8	1.55	−0.13	5.37	1.63	2.71	0.49	1
9	1.53	−0.15	4.31	1.86	3.57	0.49	−1
10	2.07	−0.16	5.44	1.69	3.64	0.64	1
11	2.06	−0.12	5.46	1.93	3.06	0.64	−1
12	2.04	−0.12	5.37	1.91	3.34	0.64	−1
13	1.96	−0.01	5.25	1.09	5.19	0.72	0
14	0.67	−0.02	5.24	1.08	3.74	0.82	0
15	2.07	0.17	6.05	1.18	4.36	0.92	0
16	1.85	0.23	6.54	1.08	5.05	0.92	0
17	2.08	0.05	5.33	1.24	4.46	0.96	0
18	1.90	−0.04	6.33	1.23	5.43	0.93	0
19	2.01	−0.09	6.06	1.22	4.64	0.87	1
20	2.84	0.09	5.67	1.04	4.00	0.89	0
21	2.84	0.08	6.70	1.07	5.20	0.89	0
22	1.93	−0.09	6.60	1.23	5.42	0.96	0
23	1.63	0.00	5.30	1.12	4.73	0.96	0
24	3.06	0.12	6.50	1.13	4.46	1.01	0
25	1.60	−0.09	7.24	1.12	4.54	1.19	0
26	3.01	0.17	7.00	1.07	5.75	1.00	0
27	2.51	−0.09	6.53	1.13	6.31	1.11	0
28	1.75	0.05	5.99	1.17	5.79	1.19	0
29	1.98	−0.20	4.25	2.00	3.45	0.64	−1
30	2.51	−0.22	5.58	1.92	4.40	0.85	−1
31	2.69	−0.07	6.53	1.10	4.68	0.87	0

[a] See the Quantitative Structure–Activity Relationships section. [b] Number corresponding to that of Table I.

Quantitative Structure–Activity Relationships (QSAR)

The compounds and biological activities used in this study are respectively listed Tables I and II. Table III summarizes the values of the physicochemical parameters of substituents employed in this work.

The physicochemical parameters of substituents were chosen to reflect the hydrophobic, electronic, and bulk effects for N-substituents. The hydrogen-bonding ability of compound 2 was pointed out in the literature.[23] So, we built a three-dimensional structure model having a hydrogen bond between the NH and the side chain ether oxygen of compound 2 by use of AM1 molecular orbital method[24] and assumed it as active conformer (Figure 3). We measured bulk parameters of substituents from its structure. The axis was decided as the direction toward a straight line binding two nitrogens in the urea moiety. Along to the axis we measured the length (L) of substituents, and in the plane perpendicular to the axis we measured the STERIMOL width (B_1 and B_4)[25] of substituents. van der Waals volume (VW)[26] was also examined as descriptor of bulk. The parameter of electronic effect (σ) was calculated from the Hammett parameter.[27] The hydrophobic effect (π) was calculated from hydrophobic substituent constant values.[27] Indicator variable D was modeled as a structural indicator variable to give the diversity in the parameters. D was given the value 1 for straight-chain alkyl substituents, 0 for aromatic substituents, and −1 for branch-chain alkyl substituents.

The in vivo activities were classified into three grades for structure–activity relationship analysis. Gastric antisecretory activity (AS) values were classified on the basis of the percent inhibition value at a dose of 10 mg/kg (id): class 1, −30%; class 2, 30–60%; class 3, 60–100%. Gastric mucosal protective activity (MP) values were classified on the basis of the percent inhibition value at a dose of 25 mg/kg (po): class 1, −30%; class 2, 30–60%; class 3, 60–100%.

Statistical methods were employed on QSAR. The Hansch–Fujita method[28] was employed for in vitro histamine H_2-receptor antagonistic activity (pA_2) using π, σ, L, B_1, B_4, VW, and squared values of these parameters. For in vivo antiulcer activities, the ALS method (adaptive least-squares classification)[29] was employed, because of the large variance of activities in some compounds (see Table

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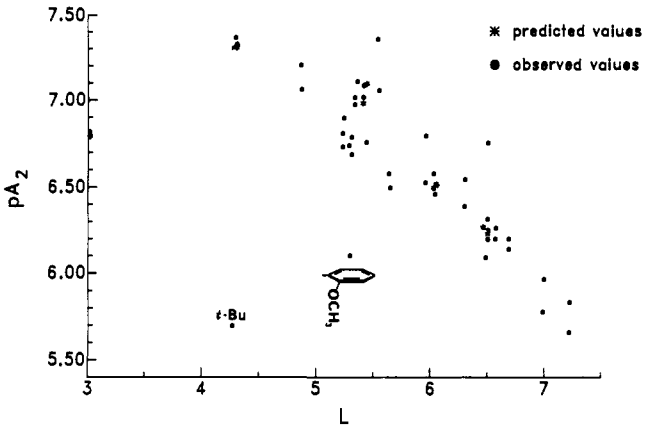

Figure 4. Relationship between observed pA_2 and L together with predicted pA_2 calculated from eq 1.

II). π, σ, L, B_1, B_4, VW, and D parameters and pA_2 were used in ALS method.

QSAR were analyzed using the all possible subsets method (up to four possible subsets of parameters).

From QSAR for in vitro and in vivo antiulcer activities, the following statistically significant relationships were derived:

(1) histamine H_2-receptor antagonism (compound **29** was removed)

$$pA_2 = 0.707L - 0.094L^2 + 0.504B_1 + 5.054 \quad (1)$$

$$R = 0.89, F_{3,23} = 30.65, s = 0.23, N = 27$$

(2) gastric antisecretion

$$AS = 1.028pA_2 - 0.502\pi - 3.181\sigma - 5.981 \quad (2)$$

$$R_s = 0.93, N_{mis} = 3, N = 28$$

(3) gastric mucosal protection

$$MP = -3.619\sigma + 0.927D - 0.222 \quad (3)$$

$$R_s = 0.79, N_{mis} = 4, N = 28$$

where N, R, R_s, N_{mis}, and s represent the number of compounds, correlation coefficient, Spearman's rank correlation, the number of compounds misclassified, and standard deviation, respectively. The correlation between observed pA_2 and L is shown in Figure 4 together with predicted pA_2 values calculated from eq 1. The predicted values of gastric antisecretory and mucosal protective activities calculated from eqs 2 and 3 are listed in Table II.

Discussion

As shown in Table II, the rank order of efficacy of antisecretory activity was famotidine ≥ compounds **4–10**, **14**, **22**, and **30** > cimetidine. Moreover, in contrast to cimetidine, famotidine, and ranitidine, compounds **4**, **5**, **8–10**, and **19** had much more potent mucosal protective activity than terprenone. Compounds **4**, **5**, and **8–10** were expected to be new histamine H_2-receptor antagonists with mucosal protective activities.

QSAR for Histamine H_2-Receptor Antagonism. A good correlation was found between the observed pA_2 values and length L (eq 1 and Figure 4). Moreover, B_1 has slight influence on histamine H_2-receptor antagonistic activity. B_1 values of alkyl substituents were larger than those of aryl substituents. The optimum L value was estimated as 3.8. It was predicted that the most favorable N-substituents for antagonistic activity were short-length alkyl groups such as ethyl (L = 4.31) and c-propyl (L = 4.32) groups, when the contribution of B_1 in eq 1 was taken into consideration. In QSAR, compound **29** was removed because the difference between predicted and observed pA_2 values was considerably large compared with differences for other compounds in eq 1 (see Figure 4). It was estimated that some bulk factor exerted negative effect on activity because the *tert*-butyl group is the most bulky substituent in the space close to the nitrogen of the ureas. The same tendency was also observed in compound **23** in which the methoxy group was in the space close to the nitrogen of the urea. The observed pA_2 of compound **23** was lower than the predicted pA_2 value (see Figure 4).

QSAR for Gastric Antisecretion. A good correlation was observed in the combination of histamine H_2-receptor antagonistic activity (pA_2) and parameters π and σ for gastric antisecretion (eq 2). The coefficient of pA_2 was positive and large, so histamine H_2-receptor antagonistic activity appeared to be a main factor contributing to gastric antisecretion in these ureas. Selected parameters π and σ might represent the effects of substituents on the pathway (absorption, distribution, etc.) reaching receptor site. It was suggested that better N-substituents for gastric antisecretion were more hydrophilic and electron-donating substituents such as methyl and ethyl groups because the coefficients of parameters π and σ were negative.

QSAR for Gastric Mucosal Protection. Though the value of Spearman's rank correlation was lower in eq 3 than in eq 2, eq 3 was well worth using in order to predict gastric mucosal protection. The gastric antisecretory action of ureas **2** was simply correlated with histamine H_2-receptor antagonism (eq 2), whereas the pharmacological actions of mucosal protective drugs have been known to be associated with several actions, i.e., increases in blood flow,[30] prostaglandin levels,[31] and mucus secretion[22,32] in gastric mucosa. So, the correlation between physicochemical parameters and mucosal protective activity was considered to be lower than that for antisecretory activity. If we could find a main action for mucosal protection in these ureas, the correlation would be better. Physicochemical effects of N-substituents on gastric mucosal protective activity seemed to be different from those on gastric antisecretory activity because the combination of parameters in the selected equations differed between gastric antisecretion and gastric mucosal protection. The coefficient of σ was negative, and those of indicator variable D was positive. Although the value of Spearman's rank correlation was low, it was suggested that better N-substituents for gastric mucosal protection were more electron-donating straight-chain alkyl groups.

From QSAR for histamine H_2-receptor antagonistic and gastric antisecretory and gastric mucosal protective activities, electron-donating straight-chain alkyl groups of short length were extracted as the common features for the most favorable N-substituents.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. Elemental analyses for C, H, and N were measured on a Perkin-Elmer 240C analyzer. Analytical values of all compounds were within ±0.4% of theo-

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retical values. Compounds were checked by IR spectra on a Hitachi 270-3, by mass spectra on an ESCO EMD-05B, and by ^1H NMR spectra on a JEOL JNM-PMX60 (Me_4Si as an internal standard). The calculations of AM1 were made on an IBM 4361. The conformations were examined on an IBM 5550 personal computer using the program Molecular Design Support System (IBM).

General Method of Synthesis. Method A. To an ice-cooled solution of 3-[3-(piperidinomethyl)phenoxy]propylamine (1) in ethanol was added the required isocyanate dropwise with stirring. The mixture was stirred at room temperature for 2.5 h and concentrated in vacuo. The resulting residue was extracted with CH_2Cl_2, and the extracts were washed with water and dried ($MgSO_4$). The solvent was removed in vacuo. If necessary, the crude material was chromatographed. The product was recrystallized from the solvent indicated in Table I.

Method B. To a solution of CDI in CH_2Cl_2 was added a solution of 1 in CH_2Cl_2 dropwise at 0–5 °C. The mixture was stirred at the same temperature for 1 h and then at room temperature for 1 h. A solution of the required amine in CH_2Cl_2 was added dropwise with stirring at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then at room temperature for 1 h. The resulting mixture was washed with water and dried ($MgSO_4$). The solvent was removed in vacuo. If necessary, the crude material was chromatographed. The product was recrystallized from the solvent indicated in Table I.

Method C. To a mixture of the required amine and Et_3N in CH_2Cl_2 was added ethyl chlorocarbonate dropwise with cooling and the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was washed with water and dried ($MgSO_4$). The solvent was removed in vacuo. The resulting precipitate was triturated with petroleum ether and collected by the filtration to give the intermediate carbamate. The mixture of 1 and the carbamate in 3-methoxy-1-butanol was refluxed for 6 h and concentrated in vacuo. The resulting residue was extracted with CH_2Cl_2. The extracts were washed with water, dilute HCl, water, saturated $NaHCO_3$, and water, successively. The extracts were dried ($MgSO_4$) and concentrated in vacuo. If necessary, the crude material was chromatographed. The product was recrystallized from the solvent indicated in Table I.

Method D. To an ice-cooled solution of NaH in DMF was added dropwise a solution of 3-(piperidinomethyl)phenol (3) in DMF and the mixture was stirred at room temperature for 1 h. The appropriate *N*-(3-chloropropyl)urea was added and stirred at room temperature for 3 h, and then poured into water and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated in vacuo. If necessary, the crude material was chromatographed. The product was recrystallized from the solvent indicated in Table I.

Method E. *N*-(3-Aminophenyl)-*N'*-[3-[3-(piperidinomethyl)phenoxy]propyl]urea (14). To a solution of 15 (4.6 g, 0.01 mol) in EtOH (46 mL) were added concentrated HCl (1.9 mL) and tin (2.6 g, 0.02 mol) dropwise at room temperature with stirring. After further concentrated HCl (18.2 mL) was added dropwise under heating, and the reaction mixture was refluxed for 6 h and then cooled. The resulting mixture was added to water (100 mL) and alkalized with 10% NaOH while being cooled and then extracted with CH_2Cl_2. The extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The product was recrystallized from the solvent indicated in Table I. Anal. ($C_{22}H_{30}N_4O_2$) C, H, N.

***N*-(4-Methoxyphenyl)-*N'*-[3-[3-(piperidinomethyl)phenoxy]propyl]thiourea (32).** To an ice-cooled solution of 3-[3-(piperidinomethyl)phenoxy]propylamine (1) (3.0 g, 0.012 mol) in ethanol (30 mL), 4-methoxyphenylisothiocyanate (2.0 g, 0.012 mol) was added dropwise with stirring. The mixture was stirred at room temperature for 2.5 h and concentrated in vacuo. The resulting residue was extracted with CH_2Cl_2, and the extracts were washed with water and dried ($MgSO_4$). The solvent was removed in vacuo and the crude material was recrystallized from EtOH to give 2.8 g (56%) of 32, mp 107–108 °C. Anal. ($C_{23}H_{31}N_3O_2S$) C, H, N.

Biological Test Methods. Histamine H_2-Receptor Antagonistic Activity in Guinea Pigs. Male Hartley guinea pigs were killed by a blow to the head. The right atria were dissected and suspended at 0.5-g tension in a 10-mL organ bath containing Krebs–Henseleit solution, kept at 34 °C and bubbled with a 95% O_2 and 5% CO_2 gas mixture. The chronotroic response of the atrium was recorded with a force-displacement transducer through a strain gauge. After constant control cumulative concentration–response curves had been constructed by sequential addition of histamine in the range of 3×10^{-8} and 10^{-3} M, further curves were obtained with compounds (10^{-6} M) being added to the bath 5 min before the sequential addition of histamine. The pA_2 values of compounds were calculated by each preparation.

Antisecretory Activity in Rats. The acute fistula rat was used as the primary screen to assess antisecretory activities of compounds. Male Donryu or Wistar rats, weighing 170–310 g, were fasted for 24 h before the experiment. Under urethane anesthesia, the abdomen was incised and the pylorus was ligated. The gastric cannula was implanted in the forestomach. The gastric lumen was continuously perfused with saline through the cannula. Gastric juice from cannula was collected into test tubes every hour and titrated against 0.01 N NaOH to determine the acid output. Histamine (10 mg/kg) was given intramuscularly after the first collection of gastric juice. Compounds suspended in vehicle (1% gum arabic solution) were given intraduodenally after the second collection of gastric juice. Two to five animals were used for each compound and vehicle. The acid output in each compound was compared to the mean acid output in the vehicle, and the percent inhibition was presented as mean ± SE.

Mucosal Protective Activity in Rats. Male Donryu or Wistar rats, weighing 150–230 g, were deprived of food and water for 24 h prior to the experiments. One milliliter of 0.6 N HCl was given orally, and 1 h later the animals were sacrificed with ether. The stomach was removed and slightly inflated by injecting 10 mL of 0.5% formalin to fix the inner and outer layer of the gastric walls. The stomach was then incised along the greater curvature and examined for gastric lesions in the glandular portion. Compounds as the primary screen were given orally 1.5 h before the administration of a 0.6 N HCl solution. Each lesion length per 5–10 animals for each compound was compared to the mean lesion length for the vehicle, and the percent inhibition of gastric lesions was presented as mean ± SE.

Registry No. 1, 73278-98-5; 3, 73279-04-6; 4, 120958-94-3; 5, 120958-90-9; 6, 140835-31-0; 7, 120959-27-5; 8, 120958-82-9; 9, 120959-24-2; 10, 140835-32-1; 11, 120959-26-4; 12, 140835-33-2; 13, 120958-76-1; 14, 120959-31-1; 15, 120958-88-5; 16, 120958-89-6; 17, 140835-34-3; 18, 120959-23-1; 19, 120958-83-0; 20, 120958-81-8; 21, 120958-80-7; 22, 120958-75-0; 23, 120958-84-1; 24, 120958-79-4; 25, 120958-85-2; 26, 120958-78-3; 27, 120959-22-0; 28, 120958-86-3; 29, 120958-95-4; 30, 120958-92-1; 31, 120958-77-2; 32, 120958-93-2; $EtOCONHC_6H_4$-*p*-OEt, 5255-65-2; $Cl(CH_2)_3NHCONHMe$, 13107-99-8; $Cl(CH_2)_3NHCONHEt$, 140835-35-4; $Cl(CH_2)_3NHCONHPr$-*i*, 140835-36-5.