A Novel Histamine 2(H_2) Receptor Antagonist with Gastroprotective Activity. I. Synthesis and Pharmacological Evaluation of *N*-Phenoxypropylacetamide Derivatives with Thioether Function

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In an attempt to develop new types of anti-ulcer agents, a series of *N*-(phenoxypropyl)acetamide derivatives with a thioether moiety and their sulfur-oxidized analogues were synthesized and evaluated for histamine H_2-receptor antagonistic activity, Ca antagonistic activity and gastric anti-secretory activity in the lumen-perfuseed rat. Selected compounds were also tested for gastroprotective activity, which was expected to be based on Ca antagonistic activity. Structure–activity relationships are discussed. As a thioether moiety, $-CH_2-S(O)p-CH_2-Ar$ (Ar; phenyl or furyl) was found to be optimal for the above activities. Especially, *N*-[3-[(3-(piperidinomethyl) phenoxy]propyl]acetamide with a benzyl sulfinyl, benzylsulfonyl, furfurylsulfinyl or furfurylsulfonyl group showed potent gastroprotective activity upon oral administration in a rat model. These compounds are candidates for novel anti-ulcer drugs with gastric anti-secretory and gastroprotective activities. 2-Furfurylsulfinyl-*N*-[3-[(piperidinomethyl)phenoxy]propyl]-acetamide was the most potent among the compounds tested and was given the code designation FRG-8701.

Key words FRG-8701; histamine H_2-receptor antagonist; gastroprotection; *N*-(phenoxypropyl)acetamide with thioether moiety; furfurylsulfinyl group

Various histamine H_2-receptor antagonists, such as cimetidine,[1] famotidine,[2] roxatidine acetate,[3] ranitidine,[4] tiotidine,[5] oximetidine[6] and etintidine,[7] have been developed, since the discovery of metiamide by Black *et al.*[8] The anti-ulcer effect of these agents is considered to be due only to gastric anti-secretory activity. It has been demonstrated that the recurrence ratio of peptic ulcer is relatively high after healing by long-term H_2 antagonist therapy.[9-11] Therefore, patients are treated with an H_2 antagonist in combination with defensive factor-potentiating agents to prevent recurrence of the ulcer. An optimum agent would possess the combined actions of reducing aggressive factors. Thus, our research was focused on finding H_2-receptor antagonists that exert both anti-secretory and gastroprotective activities.

Calcium plays an important role in the pathogenesis of chemically induced gastric lesion, and Ca antagonists protect against chemically induced gastric lesions.[12] Therefore, we expected that a new type of H_2-receptor antagonist with a weak Ca antagonistic action would show combined anti-secretory and gastroprotective activities. We focused on the aminoethylthio unit ($-S-CH_2-CH_2-NH-$) which is a common structural feature of H_2-receptor antagonist except roxatidine acetate. Roxatidine acetate has a 3-oxypropylamino moiety ($-O-CH_2-CH_2-CH_2-NH-$) instead.

Based on the above considerations, two [(piperidinomethyl)phenoxy]propylamine derivatives (compounds **1**, **2** in Fig. 1) bearing a partial structure of KB-944,[13] which is a Ca antagonist, were synthesized. Compound **1** showed 32% H_2-receptor antagonistic activity and 15% Ca antagonistic activity at a concentration of 10^{-5} M, while compound **2** showed no H_2-receptor antagonistic activity at the same concentration. Therefore, four thioether derivatives (compounds **3**, **4**, **5** and **6** in Fig. 1) which have other aromatic rings instead of the 4-(2-benzothiazolyl)phenylmethyl function in compound **1** were synthesized. Among them, compound **6** showed potent H_2-receptor antagonistic activity, weak Ca antagonistic activity and gastroprotective action. Compound **6** was selected as a lead compound, and it was decided to synthesize compounds with the general structures V and VI (Chart 1) and to elucidate the structure–activity relationship.

Chemistry

The desired compounds with a thioether linkage were synthesized through the general reaction sequence depicted in Chart 1. The key intermediates (III, X) were suitable for the synthesis of small amounts samples.

The intermediates (III) were obtained by the reactioen of primary amines (I) with ω-chlorocarboxylic acids (II; $m=1, 3, 5$) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) in quantitative yield. The condensed products (III) were converted to thioether derivatives (V) by reaction with thiol derivatives (XI; $n=0, 1, 3, 5$) in the presence of K_2CO_3 and KI (route 1). The condensation of primary amines (I) with carboxylic acid derivatives (IV; $m=1, 3, 5$) having an acetylthio group, followed by hydrolysis with aqueous NaOH at room temperature afforded the desired thiols (X) in excellent yield. The thiols (X) were converted into the desired products (V) by reaction with chlorides (IX; $n=0, 1, 3, 5$) (route 2). Further thioether derivatives (V) were directly derived from the reaction of primary amines (I) with carboxylic acids bearing a thioether linkage (VII) in the presence of EDC (route 3). Oxidation of thioether derivatives (V) with an oxidizing reagent (*e.g.*, $NaIO_4$ or H_2O_2) gave sulfoxides ($p=1$) or sulfones ($p=2$) in acceptable yields. The oxidized products (VI) were also ob-

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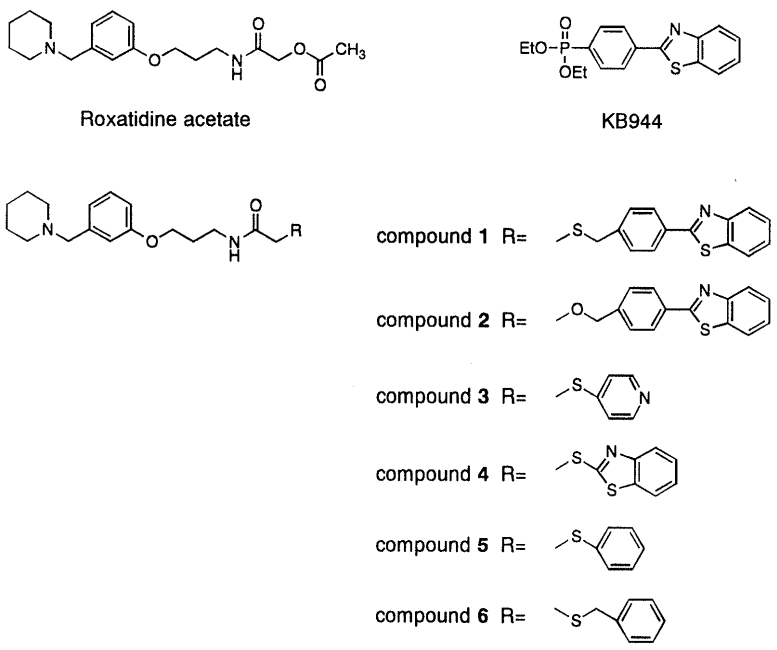

Fig. 1. Chemical Structures of Roxatidine Acetate, KB944 and Compounds **1**—**6**

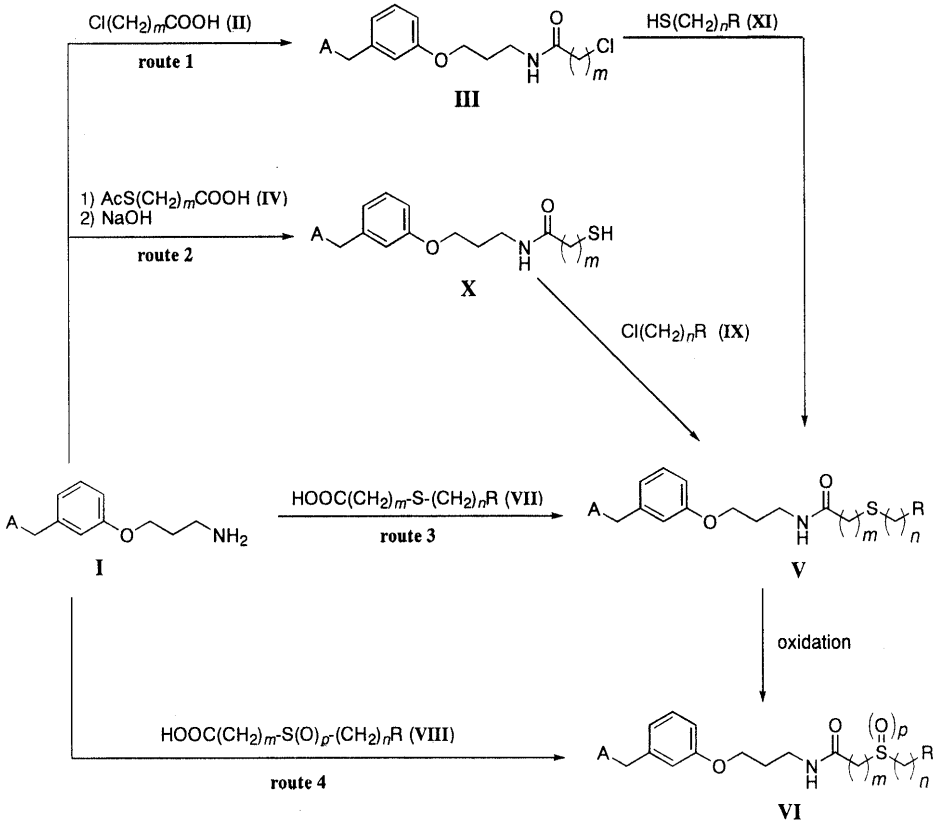

Chart 1. Synthetic Routes to *N*-Phenoxypropylacetamide Derivatives

tained by condensation of primary amines (I) with carboxylic acid derivatives (VIII) in the presence of EDC at room temperature (route 4).

Pharmacological Results and Discussion

All compounds synthesized in the present study were tested for *in vitro* inhibition of H_2-receptor using guinea pig right atrium. For the compounds that showed histamine H_2-receptor antagonistic action at a concentration of 10^{-6} M in the first screening test, their properties of Ca antagonistic, anti-secretory and gastroprotective activities were also examined. For comparison, cimetidine and roxatidine acetate were included in the biological determinations. The structures and pharmacological activities of synthesized compounds are shown in Tables 1 and 2 .

The effect of the length of the thioether unit was examined in a series of thioether derivatives having a

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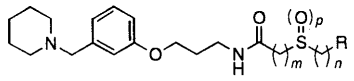
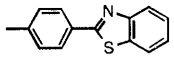
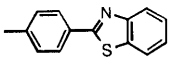
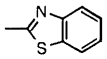
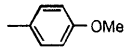
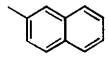
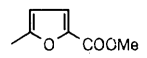
Table 1. Structures and Pharmacological Activities of *N*-[3-[3-(Piperidinomethyl)phenoxy]propyl]acetamide Derivatives



Compound	*m*	*n*	*p*	R	H_2	Ca	GSR	GP
1	1	1	0		+	+		
2	1	1			−	−		
3	1	0	0		+	+	−	
4	1	0	0		+++	−		
5	1	0	0		+	+	−	
6	1	1	0		+++	+	+++	++
7	3	1	0		+	+	++	++
8	5	1	0		+	++	+	++
9	1	3	0		++	++	+	++
10	1	5	0		+	+	+	+
11	1	1	1		++	+	+++	+++
12	1	1	2		+++	+	+++	+++
13	1	1	0		+++	+	+	−
14	1	1	0		+++	+		++
15	1	1	0		+++	+	+	−
16	1	1	0		++	+	++	++
17	1	1	0		++	+	+++	+
18	1	1	0		+	−	+++	+
19	1	1	0		+++	++	+++	++
20	1	1	0		+++	+	+++	++
21	1	1	1		+++	+	+++	+++
22	1	1	2		+++	+	+++	+++
23	1	1	0		+++	+	+	
24	1	1	0		+++	+++	+++	+
Roxatidine acetate					+++	−	+	−
Cimetidine					++	−	+	−

H_2; Histamine H_2-receptor-antagonistic activity, Ca; Ca-antagonistic activity, GSR; gastric acid anti-secretory activity, GP; gastroprotective activity. Degree of activity; see experimental section.

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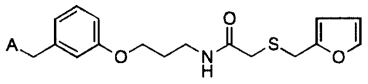
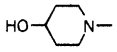
Table 2. Structures and Pharmacological Properties of Furfurylthio Acetamide Derivatives



Compound	A	H_2	Ca	GSR	GP
20		+++	+	+++	++
25		+	+		
26		+	+		
27		+	+		

H_2; Histamine H_2-receptor-antagonistic activity, Ca; Ca-antagonistic activity, GSR; gastric acid anti-secretory activity, GP; gastroprotective activity. Degree of activity; see experimental section.

benzene ring as the aromatic function (R = phenyl; Table 1; **5**—**12**). With respect to the number of methylenes (*m*) between the carbonyl group and the sulfur atom chain, the relative potency of H_2-receptor antagonistic and anti-secretory activity of these compounds is generally in the following order: $m=1>3>5$. In addition, the effect of H_2-receptor antagonistic activity in the *N*-(3-phenoxypropyl)acetamide derivatives was also influenced by the number of methylenes (*n*) between sulfur and the benzene ring ($n=1>3>5>0$), and the relative potencies on anti-secretory activity were in the order: $n=1>3>5>0$. The Ca antagonistic activity was not influenced by the length of the thioether unit. Oxidation of the sulfur atom tended to increase the anti-secretory action, but did not alter the H_2-receptor antagonistic and Ca antagonistic actions. As a consequence, the compounds having a thioether unit ($m=n=1$), such as **6**, **11**, **12**, showed potent H_2-receptor antagonistic and anti-secretory activities.

In order to examine the effect of the R group (Table 1) the benzene ring of the side chain of **6** was replaced with other aromatic rings and alkyl groups. An H_2-receptor antagonistic activity equal to that of **6** was obtained with the R groups such as cyclohexyl (**15**), 2-naphthyl (**14**), 2- or 3-furyl (**20** or **19**) and 2-thienyl (**24**), but lower activity was obtained with a pyridyl group (**16**—**18**). Ca antagonistic activity was increased in the 2-thienyl (**24**) and 3-furyl group (**19**) compounds, but other groups had no effect. Anti-secretory activity equal to that of **6** was obtained with heteroaromatic groups such as pyridyl (**17**, **18**), furyl (**19**, **20**) and thienyl (**24**) group, but this activity was reduced in the cyclohexyl (**15**) and 2-naphthyl (**14**) compounds. Introduction of a substituent onto the benzene ring significantly reduced the anti-secretory activity, and a similar tendency was observed with the 2-furyl group (**6** *vs.* **13**, **20** *vs.* **23**).

Replacement of the piperidinyl group with other amine groups such as dimethylamino (**25**), pyrrolidinyl (**26**) and 4-hydroxypiperidinyl (**27**) reduced the H_2-receptor antagonistic activity (Table 2).

Finally, gastroprotective activities were examined. The effect of the carbon chain length linking to sulfur was considered first. The relative potency of these compounds was in the order **6**≒**7**≒**8**≧**9**>**10**. Thus, the potency did not depend upon the number of methylene groups (*m*) between sulfur and the carbonyl group, but upon the number of methylene groups (*n*) between sulfur and the aromatic ring: $n=1\geqq3>5$. Aromatic rings such as benzene, furan and naphthalene were favorable for gastroprotective activity. In addition, oxidation of sulfur atom tended to strengthen gastroprotective action (**6** *vs.* **11**, **12** and **20** *vs.* **21**, **22**). In comparison with the structure of roxatidine acetate, these data suggest that the thioether moiety contributes to gastroprotective activities.

The relation of Ca antagonistic action to gastroprotection is uncertain, although several mechanisms have been proposed.[12] Further studies are in progress.[14]

In summary, we found that phenoxypropylacetamide derivatives with a thioether function showed H_2-receptor antagonistic, anti-secretory and gastroprotective activities. These compounds are novel H_2-receptor antagonists with gastroprotective activity and among them, FRG-8701, 2-furfurylsulfinyl-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**21**), is a candidate for further development.[15]

Experimental

Chemistry NMR spectra were recorded on a Varian XL-300 in $CDCl_3$ solution using tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi 270-30. Mass spectra were recorded on a JEOL DX-300. In silica gel column chromatography, WAKO gel C-200 was used as the stationary phase.

[2-Benzylthio-*N*-[3-[3-(piperidinomethyl)phenoxypropyl]acetamide (6) Route 1] Chloroacetic acid (1.0 g, 10.5 mmol) and EDC (1.92 g, 10.0 mmol) were added to a solution of 3-[3-(piperidinomethyl)phenoxy]-propylamine (Ia: 2.4 g, 9.6 mmol) in CH_2Cl_2 (50 ml) at under 5 °C and the solution was stirred for 30 min. Stirring was continued for 12 h at room temperature, then water (30 ml) and CH_2Cl_2 (30 ml) were added to the reaction mixture . The organic layer was separated, dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to afford 2-chloro-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (IIIa: 1.97 g, 63%). α-Toluenethiol (0.46 g, 3.7 mmol), K_2CO_3 (0.51 g, 3.7 mmol) and KI (0.061 g, 0.3 mmol) were added to a solution of IIIa (1.0 g, 3.0 mmol) in acetonitrile (20 ml) were added at room temperature and the mixture was refluxed for 4 h, then cooled. Water (50 ml) and CH_2Cl_2 (50 ml) were added and the organic phase was separated, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give a crude residue, which was submitted to column chromatography (2% $CHCl_3$–MeOH) to afford **6** (0.68 g, 54%).

[2-(5-Methoxycarbonyl)furfurylthio-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (23) Route 2] 2-(Acetylthio)acetic acid (1.60 g, 11.9 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.26 g, 11.7 mmol) were added to a solution of Ia (2.94 g, 11.8 mmol) in CH_2Cl_2 (80 ml) under ice cooling and the solution was stirred for 30 min., then for 12 h at room temperature. Water (100 ml) and CH_2Cl_2 (50 ml) were added and the organic layer was separated, washed with water, dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was submitted to column chromatography (2% $CHCl_3$–MeOH) to afford 2.23 g of the acetylthioacetamide derivative. A solution of the above acetamide in MeOH (30 ml) and water (3 ml) was treated with 85% KOH solution (0.48 g, 8.5 mmol) under ice cooling, and the mixture was stirred for 1.5 h. It was neutralized with 2 N HCl, then CH_2Cl_2 (100 ml) and water (50 ml) were added. The orgainc layer was separated, washed with water, dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give 2-mercapto-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (Xa: 1.86 g, 48% from Ia) as a colorless oil. A solution of Xa (0.70 g, 2.1 mmol) in DMF (10 ml) was treated with 60% NaH dispersed in mineral oil (0.087 g, 2.1 mmol) under ice cooling and the solution was stirred for 10 min, then for 10 min at room temperature.

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It was cooled in an ice-water bath, then was added dropwise methyl 5-chloromethyl-2-furan-carboxylate (0.38 g, 2.1 mmol) in DMF (5 ml) and the whole was stirred for 20 min. Stirring for 12 h at room temperature, and the reaction mixture was poured into ice-water and extracted with benzene twice. The combined benzene layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. Purification of the residue by column chromatography (2% $CHCl_3$–MeOH) gave compound **23** (0.40 g, 41%).

[2-Furfurylthio-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (20) Routes 3 and 4] 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.56 g, 2.9 mmol) was added to a solution of 3-[3-(piperidinomethyl)phenoxy]propyl-amine (Ia, 0.72 g, 2.9 mmol) and 2-(furfurylthio)acetic acid (VIIa, 0.59 g, 3.4 mmol) in CH_2Cl_2 (30 ml) was added at room temperature, and the solution was stirred for 12 h. Water (30 ml) and CH_2Cl_2 (30 ml) was added, and the organic layer was separated, washed with water, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was submitted to column chromatography (2% $CHCl_3$–MeOH) to afford compound **20** (0.58 g, 49%). The sulfoxides (VI) were synthesized *via* the route 4 using 2-(furfurylsulfinyl)-acetic acid (VIIIa) instead of VIIa.

Oxidation of 2-Benzylthio-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]-acetamide (6) (a) 2-Benzylsulfinyl-*N*-[3-[3-(piperidinomethyl)phenoxy]-propyl]acetamide (11) Compound **6** (0.11 g, 0.26 mmol) and KIO_4 (0.063 g, 0.27 mmol) were dissolved in MeOH (4 ml) and water (2 ml) and the solution was stirred at room temperature for 24 h. Water (10 ml) and CH_2Cl_2 (50 ml) were addd, and the organic layer was separated, dried over $MgSO_4$ and evaporated *in vacuo*. Purification of the residue by column chromatography (2% $CHCl_3$–MeOH) on silica gel gave of compound **11** (0.08 g, 71%).

(b) 2-Benzylsulfonyl-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (12) Aqueous 30% H_2O_2 (0.4 ml, 3.50 mmol) was added to a solution of **6** (0.13 g, 0.30 mmol) in acetic acid (2 ml) and the reaction mixture was heated at 100 °C for 1 h. After having been cooled to room temperature, the mixture was neutralized with saturated $NaHCO_3$ solution. Water (20 ml) and CH_2Cl_2 (40 ml) were added, and the organic layer was separated, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was submitted to column chromatography (2% $CHCl_3$–MeOH) to give compound **12** (0.04 g, 30%).

2-(4-Pyridylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**3**): ^{1}H-NMR ($CDCl_3$) δ: 1.3—1.7 (6H, m), 1.89 (2H, tt, J=6, 6 Hz), 2.2—2.5 (4H, m), 3.39 (2H, t, J=6 Hz), 3.40 (2H, s), 3.63 (2H, s), 3.90 (2H, t, J=6 Hz), 6.5—7.4 (7H, m), 8.2—8.4 (2H, m). IR (film) cm^{-1}: 1640 (C=O). HR-MS m/z: Calcd for $C_{22}H_{29}N_3O_2S$ (M^+): 399.1980. Found: 399.1974.

2-Benzothiazolylthio-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]-acetamide (**4**): ^{1}H-NMR ($CDCl_3$) δ: 1.3—1.7 (6H, m), 1.93 (2H, tt, J=6, 6 Hz), 2.2—2.5 (4H, m), 3.41 (2H, t, J=6 Hz), 3.41 (2H, s), 3.94 (2H, t, J=6 Hz), 3.95 (2H, s), 6.47—7.84 (8H, m), 6.80 (1H, br s). IR (film) cm^{-1}: 1655 (C=O). HR-MS m/z: Calcd for $C_{24}H_{29}N_3O_2S_2$ (M^+): 455.1701. Found: 455.1669.

2-Phenylthio-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**5**): ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.77 (6H, m), 1.90 (2H, tt, J=6, 6 Hz), 2.23—2.58 (4H, m), 3.40 (2H, t, J=6 Hz), 3.44 (2H, s), 3.46 (1H, br s), 3.64 (2H, s), 3.90 (2H, t, J=6 Hz), 7.21 (5H, s), 6.57—7.38 (4H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{23}H_{30}N_2O_2S$ (M^+): 398.2027. Found: 398.2024.

2-Benzylthio-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**6**): ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.65 (6H, m), 1.96 (2H, tt, J=6, 6 Hz), 2.3—2.5 (4H, m), 3.16 (2H, s), 3.40 (2H, t, J=6 Hz), 3.45 (2H, s), 3.70 (2H, s), 4.04 (2H, t, J=6 Hz), 6.8—7.35 (10H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{24}H_{32}N_2O_2S$ (M^+): 412.2184. Found: 412.2162.

4-Benzylthio-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]butanamide (**7**): ^{1}H-NMR ($CDCl_3$) δ: 1.3—2.6 (18H, m), 3.36 (2H, t, J=6 Hz), 3.45 (2H, s), 3.61 (2H, s), 4.02 (2H, t, J=6 Hz), 5.8—6.0 (1H, br s), 7—7.3 (8H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{26}H_{36}N_2O_2S$ (M^+): 440.2470. Found: 440.2497.

6-Benzylthio-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]hexanamide (**8**): ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.6 (22H, m), 3.37 (2H, t, J=6 Hz), 3.40 (2H, s), 3.62 (2H, s), 3.98 (2H, t, J=6 Hz), 5.9—6.2 (1H, br s), 6.6—7.4 (9H, m). IR (film) cm^{-1}: 1640 (C=O). HR-MS m/z: Calcd for $C_{28}H_{40}N_2O_2S$ (M^+): 468.2810. Found: 468.2724.

2-(3-Phenylpropylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]-acetamide (**9**): ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.8 (18H, m), 3.15 (2H, s), 3.38 (2H, s), 3.38 (2H, t, J=6 Hz), 3.98 (2H, t, J=6 Hz), 6.6—7.4 (10H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{26}H_{36}N_2O_2S$ (M^+): 440.2497. Found: 440.2475.

2-(5-Phenylpentylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]-acetamide (**10**): ^{1}H-NMR ($CDCl_3$) δ: 1.3—2.7 (12H, m), 2.02 (2H, tt, J=6, 6 Hz), 2.3—2.55 (4H, m), 2.50 (2H, t, J=7 Hz), 2.57 (2H, t, J=7 Hz), 3.22 (2H, s), 3.44 (2H, s), 3.52 (2H, t, J=6 Hz), 4.06 (2H, t, J=6 Hz), 6.8—7.45 (10H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{28}H_{40}N_2O_2S$ (M^+): 468.2810. Found: 468.2796.

2-Benzylsulfinyl-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**11**): ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.65 (6H, m), 2.05 (2H, tt, J=6.3, 6.3 Hz), 3.19 (1H, d, J=13 Hz), 3.44 (2H, s), 3.52 (1H, d, J=13 Hz), 3.56 (2H, t, J=6.3 Hz), 4.06 (2H, t, J=6.3 Hz), 4.09 (1H, d, J=13 Hz), 4.17 (1H, d, J=13 Hz), 6.75—7.40 (10H, m). IR (film) cm^{-1}: 1660 (C=O), 1030 (S–O). HR-MS m/z: Calcd for $C_{24}H_{32}N_2O_3S$ (M^+): 428.2133. Found: 428.2152.

2-Benzylsulfonyl-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**12**): ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.55 (6H, m), 2.03 (2H, tt, J=6.3, 6.3 Hz), 2.3—2.45 (4H, m), 3.45 (2H, s), 3.51 (2H, t, J=6.3 Hz), 3.72 (2H, s), 4.07 (2H, t, J=6.3 Hz), 4.42 (2H, s), 6.7—7.5 (10H, m). IR (film) cm^{-1}: 1660 (C=O), 1120, 1310 (S=O). HR-MS m/z: Calcd for $C_{24}H_{32}N_2O_4S$ (M^+): 444.2083. Found: 444.2102.

2-(4-Methoxybenzylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**13**): ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.5 (2H, m), 1.5—1.65 (4H, m), 1.97 (2H, tt, J=6, 6 Hz), 2.35—2.5 (4H, m), 3.14 (2H, s), 3.44 (2H, t, J=6 Hz), 3.46 (2H, s), 3.66 (2H, s), 3.78 (3H, s), 4.05 (2H, t, J=6 Hz), 6.81 (2H, d, J=8.8 Hz), 6.8—7.0 (2H, m), 7.15 (2H, d, J=8.8 Hz), 7.1—7.3 (2H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{25}H_{34}N_2O_3S$ (M^+): 442.2290. Found: 442.2256.

2-(2-Naphthylmethylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**14**): ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.7 (6H, m), 1.87 (2H, tt, J=6, 6 Hz), 2.3—2.5 (4H, m), 3.17 (2H, s), 3.34 (2H, t, J=6 Hz), 3.46 (2H, s), 3.87 (2H, s), 3.97 (2H, t, J=6 Hz), 6.75—7.85 (12H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{28}H_{34}N_2O_2S$ (M^+): 462.2340. Found: 462.2302.

2-(Cyclohexylmethylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**15**): ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.9 (19H, m), 2.03 (2H, tt, J=6, 6 Hz), 2.3—2.5 (4H, m), 2.39 (2H, d, J=7 Hz), 3.27 (2H, s), 3.48 (2H, s), 3.53 (2H, t, J=6 Hz), 4.08 (2H, t, J=6 Hz), 6.8—7.3 (4H, m), 7.35—7.45 (1H, br s). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{24}H_{38}N_2O_2S$ (M^+): 418.2654. Found: 418.2672.

2-(2-Pyridylmethylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]-acetamide (**16**): ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.65 (6H, m), 2.02 (2H, tt, J=5.9, 5.9 Hz), 2.3—2.45 (4H, m), 3.17 (2H, s), 3.44 (2H, s), 3.47 (2H, dt, J=5.9, 5.9 Hz), 3.84 (2H, s), 4.05 (2H, t, J=5.9 Hz), 6.75—7.0 (3H, m), 7.1—7.3 (3H, m), 7.6—7.8 (2H, m), 8.48 (1H, d, J=5.0 Hz). IR (film) cm^{-1}: 1660 (C=O). HR-MS m/z: Calcd for $C_{23}H_{31}N_3O_2S$ (M^+): 413.2137. Found: 413.2139.

2-(3-Pyridylmethylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]-acetamide (**17**): ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.65 (6H, m), 2.00 (2H, tt, J=6.3, 6.3 Hz), 2.3—2.45 (4H, m), 3.15 (2H, s), 3.44 (2H, s), 3.46 (2H, dt, J=6.3, 6.3 Hz), 4.07 (2H, t, J=6.3 Hz), 6.8—7.0 (3H, m), 7.1—7.3 (3H, m), 7.5—7.6 (1H, m), 8.5—8.6 (2H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{23}H_{31}N_3O_2S$ (M^+): 413.2137. Found: 413.2139.

2-(4-Pyridylmethylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]-acetamide (**18**): ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.80 (6H, m), 1.97 (2H, tt, J=6.4, 6.4 Hz), 2.35—2.70 (4H, m), 3.14 (2H, s), 3.43 (2H, t, J=6.4 Hz), 3.60 (2H, s), 3.68 (2H, s), 4.08 (2H, t, J=6.4 Hz), 6.8—7.4 (7H, m), 8.45—8.6 (2H, m). IR (film) cm^{-1}: 1655 (C=O). HR-MS m/z: Calcd for $C_{23}H_{31}N_3O_2S$ (M^+): 413.2137. Found: 413.2121.

2-(3-Furylmethylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]-acetamide (**19**): ^{1}H-NMR ($CDCl_3$) δ: 1.36—1.72 (6H, m), 2.00 (2H, tt, J=6.0, 6.0 Hz), 2.30—2.46 (4H, m), 3.17 (2H, s), 3.44 (2H, s), 3.47 (2H, dt, J=6.0, 6.0 Hz), 3.56 (2H, s), 4.06 (2H, t, J=6.0 Hz), 6.34 (1H, d, J=1.5 Hz), 6.82 (1H, dd, J=7.5, 2.5 Hz), 6.92 (1H, d, J=7.5 Hz), 6.95 (1H, br s), 7.17—7.27 (1H, m), 7.22 (1H, d, J=7.5 Hz), 7.32 (1H, s), 7.36 (1H, d, J=7.5 Hz). IR (film) cm^{-1}: 1642 (C=O). HR-MS m/z: Calcd for $C_{22}H_{30}N_2O_3S$ (M^+): 402.1977. Found: 402.1969.

2-Furfurylthio-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**20**): ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.7 (6H, m), 1.99 (2H, tt, J=6, 6 Hz), 2.3—2.45 (4H, m), 3.23 (2H, s), 3.43 (2H, t, J=6 Hz), 3.44 (2H, s), 3.73 (2H, s), 4.05 (2H, t, J=6 Hz), 6.18—6.28 (2H, m), 6.75—7.0 (3H, m), 7.15—7.4 (3H, m). IR (film) cm^{-1}: 1655 (C=O). HR-MS m/z:

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Calcd for $C_{22}H_{30}N_2O_3S$ (M^+): 402.1977. Found: 402.1972.

2-Furfurylsulfinyl-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**21**): ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.7 (6H, m), 2.04 (2H, tt, J=6.3, 6.3 Hz), 2.3—2.5 (4H, m), 3.31 (1H, d, J=14.2 Hz), 3.44 (2H, s), 3.55 (2H, dt, J=6.3, 6.3 Hz), 3.58 (1H, d, J=14.2 Hz), 4.05 (2H, t, J=6.3 Hz), 4.16 (1H, d, J=14.2 Hz), 4.26 (1H, d, J=14.2 Hz), 6.39 (1H, t, J=1.5 Hz), 6.46 (1H, d, J=1.5 Hz), 6.75—7.3 (5H, m), 7.43(1H, d, J=1.5 Hz). IR (film) cm^{-1}: 1660 (C=O), 1020 (S–O). HR-MS *m/z*: Calcd for $C_{22}H_{30}N_2O_4S$ (M^+): 418.1926. Found: 418.1922.

2-Furfurylsulfonyl-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**22**): ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.7 (6H, m), 2.03 (2H, tt, J=6.3, 6.3 Hz), 2.3—2.5 (4H, m), 3.44 (2H, s), 3.53 (2H, dt, J=6.3, 6.3 Hz), 3.83 (2H, s), 4.06 (2H, t, J=6.3 Hz), 4.53 (2H, s), 6.43 (1H, t, J=1.5 Hz), 6.59 (1H, d, J=1.5 Hz), 6.7—7.25 (5H, m), 7.49 (1H, d, J=1.5 Hz). IR (KBr) cm^{-1}: 1660 (C=O), 1315 (S=O). HR-MS *m/z*: Calcd for $C_{22}H_{30}N_2O_5S$ (M^+): 434.1875. Found: 434.1871.

2-(5-Methoxycarbonylfurfurylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**23**): ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.65 (6H, m), 2.00 (2H, tt, J=6.5, 6.5 Hz), 2.3—2.45 (4H, m), 3.23 (2H, s), 3.44 (2H, s), 3.45 (2H, dt, J=6.5, 6.5 Hz), 3.77 (2H, s), 3.87 (3H, s), 4.05 (2H, t, J=6.5 Hz), 6.33 (1H, d, J=3.5 Hz), 6.97 (1H, d, J=3.5 Hz), 6.8—7.0 (5H, m). IR (film) cm^{-1}: 1730 (C=O), 1650 (C=O). HR-MS *m/z*: Calcd for $C_{24}H_{32}N_2O_5S$ (M^+): 460.2032. Found: 460.2041.

2-(2-Thienylmethylthio)-*N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide (**24**): ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.7 (6H, m), 1.99 (2H, tt, J=6, 6 Hz), 2.3—2.45 (4H, m), 3.22 (2H, s), 3.44 (2H, s), 3.46 (2H, t, J=6 Hz), 3.94 (2H, s), 4.05 (2H, t, J=6 Hz), 6.75—7.3 (8H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS *m/z*: Calcd for $C_{22}H_{30}N_2O_2S_2$ (M^+): 418.1749. Found: 418.1757.

2-Furfurylthio-*N*-[3-[3-(dimethylaminomethyl)phenoxy]propyl]acetamide (**25**): ^{1}H-NMR ($CDCl_3$) δ: 1.99 (2H, tt, J=6.3, 6.3 Hz), 3.25 (6H, s), 3.40 (2H, s), 3.45 (2H, dt, J=6.3, 6.3 Hz), 3.73 (2H, s), 4.05 (2H, t, J=6.3 Hz), 6.18 (1H, d, J=3.0 Hz), 6.29 (1H, dd, J=3.0, 1.9 Hz), 6.8—7.4 (6H, m). IR (film) cm^{-1}: 1650 (C=O). HR-MS *m/z*: Calcd for $C_{19}H_{26}N_2O_3S$ (M^+): 362.1663. Found: 362.1653.

2-Furfurylthio-*N*-[3-[3-(pyrrolidinylmethyl)phenoxy]propyl]acetamide (**26**): ^{1}H-NMR ($CDCl_3$) δ: 1.8—1.95 (4H, m), 1.99 (2H, tt, J=5.9, 5.9 Hz), 2.5—2.7 (4H, m), 3.23 (2H, s), 3.45 (2H, dt, J=5.9, 5.9 Hz), 3.64 (2H, s), 3.74 (2H, s), 4.06 (2H, t, J=5.9 Hz), 6.18 (1H, d, J=2.8 Hz), 6.28 (1H, dd, J=2.8, 3.1 Hz), 6.8—7.35 (6H, m) IR (film) cm^{-1}: 1650 (C=O). HR-MS *m/z*: Calcd for $C_{21}H_{28}N_2O_3S$ (M^+): 388.1821. Found: 388.1826.

2-Furfurylthio-*N*-[3-[3-(4-hydroxypiperidinomethyl)phenoxy]propyl]acetamide (**27**): ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.8 (3H, m), 1.85—1.95 (2H, m), 1.99 (2H, tt, J=6.0, 6.0 Hz), 2.15—2.25 (2H, m), 2.7—2.85 (2H, m), 3.23 (2H, s), 3.44 (2H, dt, J=6.0, 6.0 Hz), 3.50 (2H, s), 3.73 (2H, s), 3.7—3.8 (1H, m), 4.05 (2H, t, J=6.0 Hz), 6.18 (1H, d, J=3.2 Hz), 6.28 (1H, dd, J=1.1, 3.2 Hz), 6.8—7.0 (3H, m), 7.15—7.3 (2H, m), 7.33 (1H, d, J=1.1 Hz). IR (film) cm^{-1}: 1650 (C=O). HR-MS *m/z*: Calcd for $C_{22}H_{30}N_2O_4S$ (M^+): 418.1926. Found: 418.1910.

Pharmacology. Histamine H_2-Receptor Antagonistic Activity and Ca Antagonistic Activity The right atrium was removed from a male Hartley guinea pig weighing between 300 and 500 g and suspended in Krebs–Henseleit solution maintained at 32 °C and aerated with 95% O_2 and 5% CO_2. The tissue was attached to an isometric transducer and allowed to stabilize for about 1 h. Positive chronotropic response to histamine was established until the response to histamine was constant. After the heart rate had been returned to the basal rate by washing the preparation with fresh medium, test compound was added and the preparation was incubated for 10 min. In the presence of test compound, positive chronotropic response to histamine was repeated. The H_2-receptor antagonistic activity of test compound was evaluated in terms of the degree of inhibition of the response to histamine and divided into following the 4 groups: −, no effect at 1×10^{-5} M; +, less than 70% inhibition at 1×10^{-6} M; ++, 70—90% inhibition at 1×10^{-6} M; +++, over 90% inhibition at 1×10^{-6} M. Ca antagonistic activity of a test compound was evaluated in terms of the degree of suppression on basal heart-rate and divided into the following 4 groups: −, no effect at 1×10^{-5} M; +, 5—10% suppression at 1×10^{-6} M; ++, 10—25% suppression at 1×10^{-6} M; +++, over 25% suppression at 1×10^{-6} M.

Gastric Acid Anti-secretory Activity An anesthetized male Wistar rat weighing between 180 and 300 g was surgically prepared as described by Ghosh and Schild.[16] The stomach of the rat was perfused with warm saline containing 1/2000 N NaOH at the rate of 1 ml/min and the pH of the perfusate was continuously recorded. Tetragastrin (40 g/kg/h) was infused *via* the tail vein to stimulate gastric acid secretion. After gastric acid secretion stimulated by tetragastrin was stabilized, a test compound was intravenously administered to the rat. Gastric acid anti-secretory activity was evaluated in terms of the increase of raising pH of perfusate and divided into the following 4 groups: −, no effect at a dose of 10 mg/kg; +, rise of pH at a dose of 10 mg/kg; ++, rise of pH at a dose of 3 mg/kg; +++, remarked rise of pH at a dose of 3 mg/kg.

Gastroprotective Activity Starved male Donryu rats weighing between 160 and 220 g were orally given 1 ml of 0.4 N HCl + 50% ethanol and killed for examination of sacrificed the gastric lesions 1 h later. A test compound was orally administered to rats 30 min before noxious agent treatment. Gastroprotective activity was evaluated in terms of the degree of inhibition of lesion formation and divided into the following 4 groups: −, no effect at a dose of 30 mg/kg; +, inhibition of lesion formation at doses of 10—30 mg/kg; ++, significant inhibition of lesion formation ($p<0.05$) at a dose of 10 mg/kg; +++, significant inhibition of lesion formation ($p<0.01$) at a dose of 10 mg/kg.

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