A Novel Histamine 2(H$_2$) Receptor Antagonist with Gastroprotective Activity. II.[1] Synthesis and Pharmacological Evaluation of 2-Furfuryl-thio and 2-Furfurylsulfinyl Acetamide Derivatives with Heteroaromatic Rings

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We recently found that *N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide derivatives with a thioether function showed gastric anti-secretory and gastroprotective activities and that the thioether function (particularly furfurylthio or furfurylsulfinyl) was essential for gastroprotection. In the present study, a series of 2-furfurylthio and 2-furfurylsulfinyl acetamide derivatives were synthesized and evaluated for histamine H$_2$ receptor antagonistic activity, gastric anti-secretory activity and gastroprotective action. Based on the structure of *N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide, we designed compounds, in which the 3-(piperidinomethyl)phenoxy part is substituted with many types of heteroaromatic ring attached to the tertiary amine and the propyl group is replaced with other carbon linkages. Structure–activity relationships are discussed. 2-Furfurylsulfinyl-*N*-[4-[4-(piperidinomethyl)-2-pyridyloxy]-(*Z*)-2-butenyl]acetamide was the most potent among the tested compounds and was given the code designation FRG-8813.

Key words FRG-8813; histamine H$_2$ receptor antagonist; gastroprotection; furfurylsulfinyl group; *N*-[4-[4-(piperidinomethyl)-2-pyridyloxy]-(*Z*)-2-butenyl]acetamide derivative

Peptic ulcer often recurs after healing by long-term H$_2$ receptor antagonist therapy.[2–4] Therefore, patients are treated with an H$_2$ antagonist in combination with defensive factor-potentiating agents to prevent recurrence. In the course of our study on anti-ulcer agents with gastroprotective activity, we found that *N*-[3-[3-(piperidinomethyl)phenoxy]propyl]acetamide derivatives with a thioether function (whether oxidized or not) showed gastric anti-secretory activity based on H$_2$ receptor antagonistic activity, as well as gastroprotective activity against necrotizing agents in rat.[1] These compounds are novel H$_2$ receptor antagonists with the combined actions of reducing aggressive factors and enhancing defensive factors. FRG-8701 (Fig. 1), which possesses a furfurylsulfinyl group as its thioether function, showed particularly potent activities. Although the mechanisms of gastroprotection of FRG-8701 are not clear, we were interested in the effect of the thioether function. In this study the effect of this functional group in combination with a partial structure of a known histamine H$_2$ receptor antagonist was examined by means of measurements of histamine H$_2$ receptor antagonistic activity, gastric anti-secretory activity and gastroprotective activity.

A tertiary amino group attached to a heteroaromatic ring is thought to be essential for the H$_2$ receptor antagonistic activity. Based on a comparison of the structure of FRG-8701 and those of knowen H$_2$ receptor antagonists, it is assumed that side chain A (Fig. 1) is important for gastric anti-secretory activity based on H$_2$ receptor antagonistic action and the thioether part (δ) is important for gatroprotective activity. The structure of FRG-8701 consists of 4 parts; α (amine part), β (aromatic part), γ (chain part) and δ (thioether part) as shown in Fig 1. In our previous work,[1] the structural requirements for activity were examined by altering the thioether part

(δ) while other three parts were fixed (piperidino group, phenyl group, and propylene group respectively). Thus, we decided to synthesize 2-furfurylthio and 2-furfurylsulfinylacetamide derivatives to examine the effect of the side chain A (α, β, γ; Fig. 1, $p=0$, 1): several tertiary amino groups were examined as the amine part (α), various heteroaromatic rings (imidazole, furan, thiazole, *etc.*) as the aromatic ring part (β) and various carbon linkages as the chain part (γ).
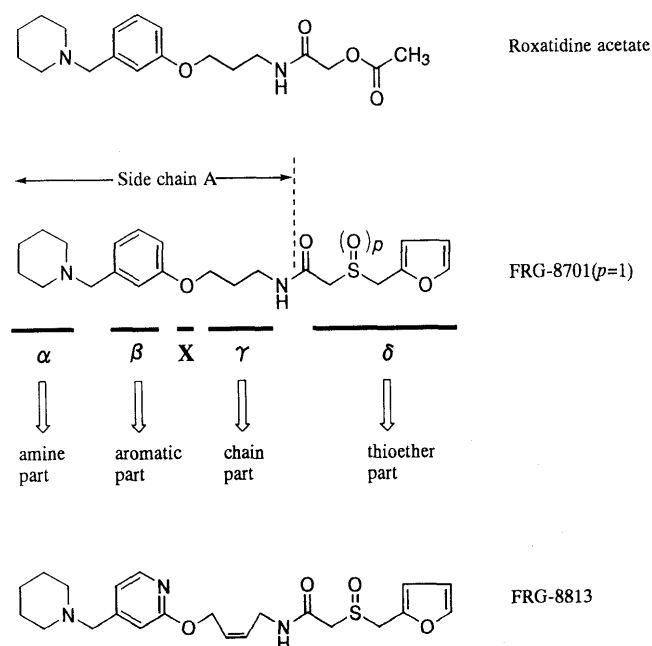

Fig. 1. Structures of Roxatidine Acetate, FRG-8701, FRG-8813 and Related Compounds

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Chemistry

Compounds **1—15, 17** were synthesized by condensation of primary amines with 2-furfurylthioacetic acid or 2-furfurylsulfinylacetic acid in the presence of condensation reagents (Chart 1). Compounds **16, 19—24** were synthesized as shown in Chart 2. Tetrahydropyranyl derivatives (**27**) were synthesized by reaction of protected pyridine derivatives (**25**) with 4-(2-tetrahydropyranyloxy)-(Z)-2-butenol (**26**). The products **27** were converted into alcohol derivatives (**28**) by partial hydrolysis. Chlorination of compound **28** followed by reaction with potassium phthalimide gave protected amines (**29**), which were converted into amino acetal derivatives (**30**). Condensation of compound **30** with p-nitrophenyl-2-furfurylsulfinyl acetate (**31**) followed by removal of the protecting group gave aldehyde derivatives (**33**). Reaction of **33** with secondary amines followed by reduction with NaBH₄ afforded the desired products. Compound **18**, the *trans*

isomer of **16** was synthesized by the same method as above from 4-(2-tetrahydropyranyloxy)-(E)-2-butenol.

Pharmacological Results and Discussion

Compounds synthesized in the present study were tested for *in vitro* inhibition of H_2 receptor in guinea pig atrium and for anti-secretory and gastroprotective actions. For comparison, cimetidine and roxatidine acetate were included in the biological determinations. The structure and pharmacological activities of the compounds are shown in Tables 1 and 2.

First, we examined the effect of the combination of tertiary amino group attached to the heteroaromatic ring (α-β part) and thioether function among the 2-furfurylthio acetamide derivatives (**1—14**, Table 1). Compounds **1, 3, 13** and **14** showed H_2 receptor antagonistic and gastric anti-secretory activities. Compound **9**, which has a partial structure of famotidine, showed
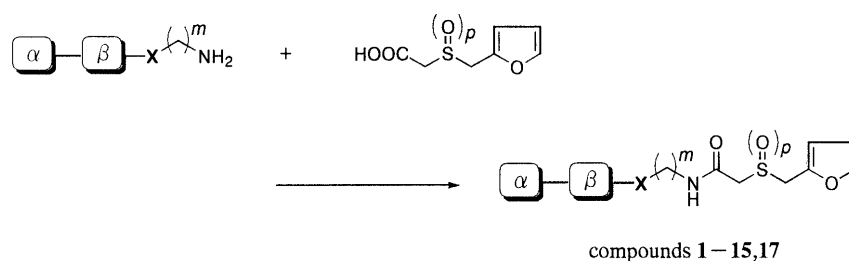

compounds 1 — 15, 17

Chart 1. Synthetic Route to 2-Furfurylthio and 2-Furfurylsulfinyl Acetamide Derivatives
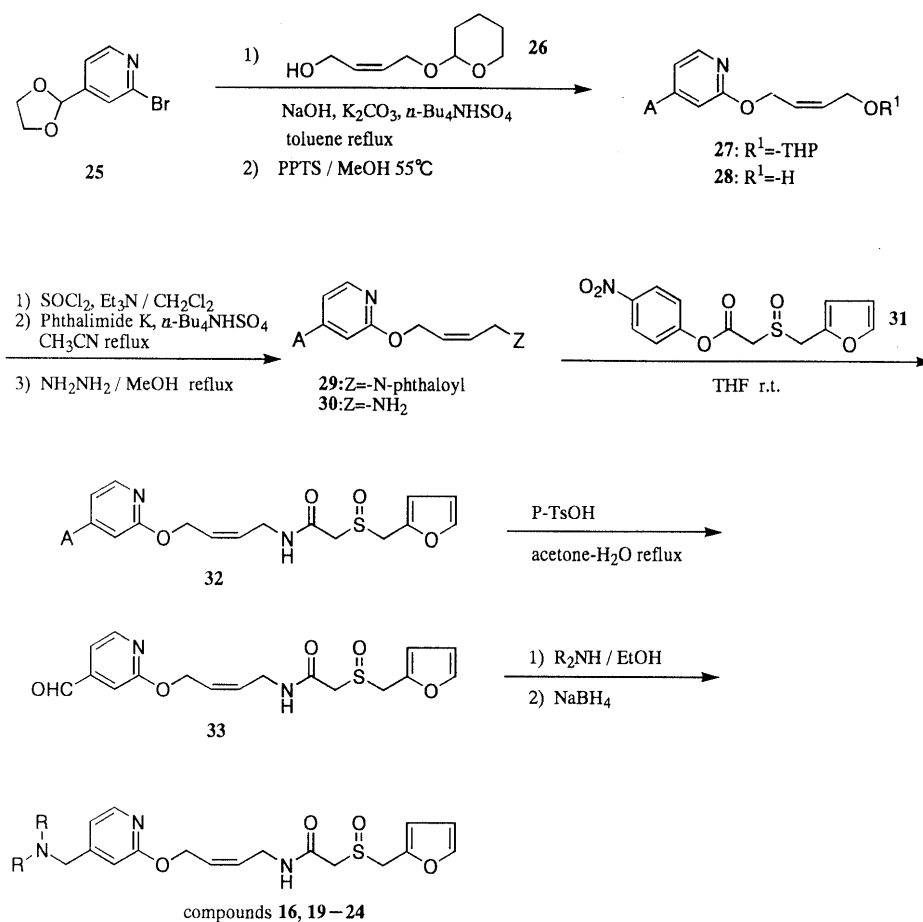

Chart 2. Synthetic Route to 2-Furfurylsulfinyl Acetamide Derivatives

Table 1. Structures and Pharmacological Activities of 2-Furfurylthio Acetamide Derivatives

Compound	α—β—	X	m	H_2	GSR	GP	LD_{50} (mg/kg)
1	Me2N—furan	–S–	2	+	+	–	67
2	piperidine—furan	–S–	2	+ +	–	+	
3	pyrrolidine—thienyl	–S–	2	+	+	+	30
4	piperidine—thienyl	–S–	2	+	–		
5	piperidine—thiazole	–S–	2	–	–		
6	Me/Me pyrimidine	–O–	3	–	–		
7	HN—Me imidazole	–S–	2	–	–		
8	piperidine—oxazole	–S–	2	–	–		
9	H2N/H2N guanidine—thiazole	–S–	2	+ +	+ + +	–	65
10	pyridine	–S–	2	–			
11	Me2N—pyridine	–S–	2	+	–	–	
12	piperidine—pyridine	–S–	2	–			
13	Me2N—pyridine	–O–	3	+	–		
14	piperidine—pyridine	–O–	3	+	+	+	67
Roxatidine acetate				+ + +	+	–	
Cimetidine				+ +	+	–	

H_2; histamine H_2 receptor antagonistic activity, GSR; gastric acid anti-secretory activity, GP; Gastroprotective activity. Degree of activity; see experimental section.

potent gastric anti-secretory activity. Further, gastroprotective activity was observed with compounds 3 and 14. In contrast, compound 9, which has potent anti-secretory activity, did not show gastroprotection. Compound 3 having a 5-[3-(1-pyrrolidinyl)-1-propenyl]-2-thienyl group and compound 14 having a 4-(piperidinomethyl)-2-pyridyl group as the amine part showed all the above activities.

The α, β and X parts in Fig. 1 were fixed as piperidine, pyridyl and an oxygen atom respectively, and we examined the effect of the distance between the oxygen atom (X) and the nitrogen atom. Compound 15, having a cis double bond as a linkage, showed more potent gastric anti-secretory and gastroprotective actions than 14 (propylene chain). Further, compound 16 obtained by monooxidation of 15 showed the most potent gastric anti-secretory action, together with more potent H_2 receptor antagonistic activity and somewhat less gastroprotective activity than 15. In the trans double bond isomer (18) H_2 receptor antagonistic activity was reduced. Conversion of the cis double bond into a butylene chain (compound 17) afforded gastric anti-secretory action equal to that of 16, but reduced gastroprotection. The activities are greatly influenced by the length and bond form of carbon linkage, and a cis double bond is the optimum structure.

Therefore, β, X, and γ were fixed as pyridyl, oxygen and cis-2-butene, respectively. Finally, the effect of the tertiary amino group (α) was also studied. Compound 19,

Table 2. Structures and Pharmacological Activities of 2-Furfurylthio and 2-Furfurylsulfinylacetamide Derivatives

Compound	α	γ	p	H₂	GSR	GP	LD₅₀ (mg/kg)
15	piperidino	(Z)-butene	0		+ +	+ +	40
16	piperidino		1	+ +	+ + + +	+	90
17	piperidino		1	+	+ + + +	–	
18	piperidino		1	+			
19	Me₂N		1	+ +	+ + +	–	100
20	3-methylpiperidino		1		+ + +		70
21	pyrrolidino		1		+ + +		35
22	morpholino		1		+ +	+	100
23	tetrahydropyridino		1		+ + +		65
24	azepano		1		+ +		50

H₂; histamine H₂-receptor antagonistic activity, GSR; gastric acid anti-secretory activity, GP, gastroprotective activity. Degree of activity, see experimental section.

which has a dimethylamino moiety instead of piperidine, inhibited gastric secretion without gastroprotective action and compound 22, which is substituted with morpholine as the basic part, showed gastroprotective action equal to that of 16, but had no inhibitory effect on gastric secretion.

Studies designed to investigate the gastroprotective effect of 16 are in progress. It appears that gastroprotection by 16 is independent of antisecretory activity and capsaicin-sensitive nerves may be involved in the gastroprotective mechanism.[5] Compound 16 stimulated mucin biosynthesis in rat gastric mucosa and this effect is not directly due to histamine H₂ receptor antagonism.[6]

In summary, suructure activity relationships of FRG-8701-related compounds for H₂ receptor antagonistic, anti-secretory and gastroprotective activities are discussed. These activities were influenced by the aromatic part, by the distance between the oxygen atom and the nitorgen atom of the γ part, and by the amine part (α part). Among these compounds, FRG-8813 (16), 2-furfurylsulfinyl-N-[4-[4-(piperidinomethyl)pyridyl-2-oxy]-(Z)-2-butenyl]acetamide, which was named "lafutidine" (INN), was found to be the most potent with respect to all three activities in the rat model.

Experimental

Chemistry Melting points were measured on a Mettler FR800 instrument without correction. NMR spectra were recorded on a Varian

XL-300 in CDCl₃ solution using tetramethylsilane as an internal standard. IR spectra were obtained 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-Furfurylthio-N-[4-[4-(piperizinomethyl)-2-pyridyloxy]-(Z)-2-butenyl]acetamide (15) 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.15 g, 0.8 mmol) was added to a solution of 4-[4-(piperidinomethyl))pyridyl-2-oxy]-(Z)-2-butenamine (0.17 g, 0.6 mmol) and 2-furfurylthioacetic acid (0.11 g, 0.6 mmol) in CH₂Cl₂ (20 ml) and the mixture was stirred for 18 h, then CH₂Cl₂ (20 ml) and water (20 ml) were added. The organic layer was separated and washed with water. The extract was dried over anhydrous MgSO₄, and evaporated in vacuo. The residue was purified by silica gel column chromatography (2% MeOH–CH₂Cl₂) to give 15 (0.18 g, 68%). ¹H-NMR (CDCl₃) δ: 1.40—1.50 (2H, m), 1.50—1.65 (4H, m), 2.30—2.45 (4H, m), 3.23 (2H, s), 3.41 (2H, s), 3.74 (2H, s), 3.99 (2H, td, J=6.10, 6.10 Hz), 4.91 (2H, d, J=6.10 Hz), 5.55—5.70 (1H, m), 5.80—5.90 (1H, m), 6.20 (1H, d, J=3.2 Hz), 6.30 (1H, dd, J=3.2, 1.4 Hz), 6.74 (1H, s), 6.80—6.95 (1H, br s), 6.88 (1H, d, J=4.30 Hz), 7.36 (1H, d, J=1.40 Hz), 8.06 (1H, d, J=4.30 Hz). IR (film) cm⁻¹ : 1655 (C=O). HR-MS m/z: Calcd for C₂₂H₂₉N₃O₃S (M⁺): 415.1930. Found: 415.1931.

Similarly, compounds 1—14 and 17 were synthesized by condensation of the corresponding amine and 2-furfurylthioacetic acid (Chart 1).

2-Furfurylthio-N-[2-[5-dimethylaminomethyl-2-furfurylthio]ethyl-acetamide (1): ¹H-NMR (CDCl₃) δ: 2.25 (6H, s), 2.64 (2H, t, J=6.5 Hz), 3.20 (2H, s), 3.35 (2H, dt, J=6.5, 6.5 Hz), 3.43 (2H, s), 3.72 (2H, s), 3.78 (2H, s), 6.13 (1H, d, J=3.5 Hz), 6.15 (1H, d, J=3.5 Hz), 6.22 (1H, d, J=3.5 Hz), 6.30 (1H, d, J=3.5, 2.0 Hz), 7.05—7.15 (1H, m), 7.36 (1H, d, J=2.0 Hz). IR (film) cm⁻¹: 1665 (C=O). HR-MS m/z: Calcd for C₁₇H₂₄N₂O₃S₂ (M⁺): 368.1227. Found: 368.1216.

2-Furfurylthio-N-[2-[5-piperidinomethyl-2-furfurylthio]ethyl]acet-amide (2): ¹H-NMR (CDCl₃) δ: 1.36—1.76 (6H, m), 2.32—2.46 (4H, m), 2.64 (2H, t, J=6.5 Hz), 3.21 (2H, s), 3.37 (2H, dt, J=6.5, 6.5 Hz), 3.47 (2H, s), 3.72 (2H, s), 3.77 (2H, s), 6.11 (1H, d, J=3.0 Hz), 6.14 (1H,

d, $J=3.0$ Hz), 6.22 (1H, d, $J=3.5$ Hz), 6.30 (1H, dd, $J=3.5$, 2.0 Hz), 7.03—7.10 (1H, m), 7.36 (1H, d, $J=2.0$ Hz). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{20}H_{28}N_2O_3S_2$ (M$^+$): 408.1542. Found: 408.1557.

2-Furfurylthio-N-[2-[[5-[3-(1-pyrrolidinyl)-1-propenyl]-2-thienyl]-methylthio]ethyl]acetamide (**3**): ^{1}H-NMR (CDCl$_3$) δ: 1.75—1.88 (4H, m), 2.50—2.61 (4H, m), 2.62 (2H, dt, $J=6.5$ Hz), 3.20 (2H, s), 3.22 (2H, d, $J=7.0$ Hz), 3.37 (2H, dd, $J=6.5$, 6.5 Hz), 3.76 (2H, s), 3.87 (2H, s), 6.09 (1H, dt, $J=15.5$, 7.0 Hz), 6.20 (1H, d, $J=3.0$ Hz), 6.29 (1H, dd, $J=3.0$, 2.0 Hz), 6.59 (1H, d, $J=15.5$ Hz), 6.72 (1H, d, $J=3.5$ Hz), 6.78 (1H, d, $J=3.5$ Hz), 6.96—7.05 (1H, m), 7.34 (1H, d, $J=2.0$ Hz). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{21}H_{28}N_2O_2S_3$ (M$^+$): 436.1312, Found: 436.1240.

2-Furfurylthio-N-[2-[(5-piperidinomethyl-2-thienyl)methylthio]-ethyl]acetamide (**4**): ^{1}H-NMR (CDCl$_3$) δ: 1.36—1.73 (6H, m), 2.37—2.54 (4H, m), 2.63 (2H, t, $J=6.5$ Hz), 3.21 (2H, s), 3.38 (2H, dt, $J=6.5$, 6.5 Hz), 3.66 (2H, s), 3.77 (2H, s), 3.89 (2H, s), 6.21 (1H, d, $J=3.5$ Hz), 6.30 (1H, dd, $J=3.5$, 2.0 Hz), 6.72 (1H, d, $J=3.5$ Hz), 6.78 (1H, d, $J=3.5$ Hz), 6.96—7.08 (1H, m), 7.35 (1H, d, $J=2.0$ Hz). IR (film) cm^{-1}: 1660 (C=O). HR-MS m/z: Calcd for $C_{20}H_{28}N_2O_2S_3$ (M$^+$): 424.1313, Found: 424.1310.

2-Furfurylthio-N-[2-[(2-piperidinomethyl-4-thiazolyl)methylthio]-ethyl]acetamide (**5**): ^{1}H-NMR (CDCl$_3$) δ: 1.40—1.50 (2H, m), 1.50—1.70 (4H, m), 2.40—2.60 (2H, m), 2.65 (2H, t, $J=6.5$ Hz), 3.21 (2H, s), 3.42 (2H, q, $J=6.5$ Hz), 3.77 (4H, s), 3.83 (2H, s), 6.21 (1H, d, $J=3.5$ Hz), 6.29 (1H, dd, $J=3.5$, 2.0 Hz), 7.08 (1H), 7.15—7.25 (1H), 7.35 (1H, d, $J=2.0$ Hz). IR (film) cm^{-1}: 1660 (C=O). HR-MS m/z: Calcd for $C_{19}H_{27}N_3O_2S_3$ (M$^+$): 425.1266, Found: 425.1272.

2-Furfurylthio-N-[3-[(4,6-dimethyl-2-pyrimidinyl)oxy]propyl]acet-amide (**6**): ^{1}H-NMR (CDCl$_3$) δ: 1.93 (2H, t, $J=6.5$ Hz), 2.41 (6H, s), 3.17 (2H, t, $J=6.5$ Hz), 3.22 (2H, s), 3.35 (2H, q, $J=6.5$ Hz), 3.76 (2H, s), 6.21 (1H, d, $J=3.0$ Hz), 6.30 (1H, dd, $J=3.0$, 2.0 Hz), 6.70 (1H, s), 6.80—7.00 (1H), 7.35 (1H, d, $J=2.0$ Hz). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{16}H_{21}N_3O_2S_2$ (M$^+$): 351.1076, Found: 351.1076.

2-Furfurylthio-N-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]acet-amide (**7**): ^{1}H-NMR (CDCl$_3$) δ: 2.23 (3H, s), 2.61 (2H, t, $J=6.5$ Hz), 3.22 (2H, s), 3.43 (2H, d, $J=6.5$ Hz), 3.73 (2H, s), 3.78 (2H, s), 6.20 (1H, d, $J=3.5$ Hz), 6.28 (1H, dd, $J=3.5$, 2.0 Hz), 7.34 (1H, d, $J=2.0$ Hz), 7.55 (1H, br s). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{14}H_{19}N_3O_2S_2$ (M$^+$): 325.0918, Found: 325.0808.

2-Furfurylthio-N-[2-[(2-piperidinomethyl-4-oxazolyl)methylthio]-ethyl]acetamide (**8**): ^{1}H-NMR (CDCl$_3$) δ: 1.40—1.50 (2H, m), 1.55—1.65 (4H, m), 2.40—2.50 (4H, m), 2.67 (2H, t, $J=6.5$ Hz), 3.22 (2H, s), 3.44 (2H, dt, $J=6.5$, 6.5 Hz), 3.63 (2H, s), 3.64 (2H, s), 3.78 (2H, s), 6.21 (1H, d, $J=3.0$ Hz), 6.29 (1H, dd, $J=3.0$, 2.0 Hz), 7.18 (1H, br s), 7.36 (1H, d, $J=2.0$ Hz), 7.54 (1H, s). IR (film) cm^{-1}: 1660 (C=O). HR-MS m/z: Calcd for $C_{19}H_{27}N_3O_3S_2$ (M$^+$): 409.1493, Found: 409.1482.

2-Furfurylthio-N-[2-[[2-(diaminomethyleneamino)-4-thiazolyl]meth-ylthio]ethyl]acetamide (**9**): ^{1}H-NMR (CDCl$_3$) δ: 2.66 (2H, t, $J=6.5$ Hz), 3.21 (2H, s), 3.39 (2H, dt, $J=6.5$, 6.5 Hz), 3.67 (2H, s), 3.76 (2H, s), 6.21 (1H, d, $J=3.0$ Hz), 6.30 (1H, dd, $J=3.0$, 2.0 Hz), 6.46 (1H, s), 6.98—7.07 (1H, m), 7.36 (1H, d, $J=2.0$ Hz). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{14}H_{19}N_5O_2S_3$ (M$^+$): 385.0701, Found: 385.0710.

2-Furfurylthio-N-[2-[(2-pyridyl)methylthio]ethyl]acetamide (**10**): ^{1}H-NMR (CDCl$_3$) δ: 2.65 (2H, t, $J=6.5$ Hz), 3.20 (2H, s), 3.43 (2H, dt, $J=6.5$, 6.5 Hz), 3.77 (2H, s), 3.86 (2H, s), 6.21 (1H, d, $J=3.5$ Hz), 6.27 (1H, dd, $J=3.5$, 2.0 Hz), 7.19 (1H, ddd, $J=7.5$, 4.5, 1.0 Hz), 7.35 (1H, d, $J=2.0$ Hz), 7.36 (1H, d, $J=7.5$ Hz), 7.67 (1H, dd, $J=7.5$, 2.0 Hz), 8.55 (1H, d, $J=4.5$ Hz). IR (film) cm^{-1}: 1650 (C=O). HR-MS m/z: Calcd for $C_{15}H_{18}N_2O_2S_2$ (M$^+$): 322.0809, Found: 322.0808.

2-Furfurylthio-N-[2-[(4-dimethylaminomethyl-2-pyridyl)methylthio]-ethyl]acetamide (**11**): ^{1}H-NMR (CDCl$_3$) δ: 2.25 (6H, s), 2.66 (2H, t, $J=6.5$ Hz), 3.20 (2H, s), 3.42 (2H, s), 3.44 (2H, dt, $J=6.5$, 6.5 Hz), 3.77 (2H, s), 3.85 (2H, s), 6.21 (1H, d, $J=2.5$ Hz), 6.30 (1H, dd, $J=3.5$, 2.5 Hz), 7.15 (1H, d, $J=4.9$ Hz), 7.25 (1H, s), 7.35 (1H, d, $J=3.5$ Hz), 8.47 (1H, d, $J=5.0$ Hz). IR (film) cm^{-1}: 1660 (C=O). HR-MS m/z: Calcd for $C_{18}H_{25}N_3O_2S_2$ (M$^+$): 379.1389, Found: 379.1391.

2-Furfurylthio-N-[2-[(4-piperidinomethyl-2-pyridyl)methylthio]eth-yl]acetamide (**12**): ^{1}H-NMR (CDCl$_3$) δ: 1.40—1.50 (2H, m), 1.50—1.65 (4H, m), 2.30—2.45 (4H, m), 2.66 (2H, t, $J=6.5$ Hz), 3.20 (2H, s), 3.44 (2H, dt, $J=6.5$, 6.5 Hz), 3.45 (2H, s), 3.77 (2H, t, $J=6.5$ Hz), 3.84 (2H, s), 6.21 (1H, d, $J=3.5$ Hz), 6.29 (1H, dd, $J=3.5$, 2.5 Hz), 7.17 (1H, d, $J=5.0$ Hz), 7.31 (1H, s), 7.35 (1H, d, $J=2.5$ Hz), 8.45 (1H, d, $J=5.0$ Hz).

IR (film) cm^{-1}: 1660 (C=O). HR-MS m/z: Calcd for $C_{21}H_{29}N_3O_2S_2$ (M$^+$): 419.1701, Found: 419.1711.

2-Furfurylthio-N-[3-[(4-dimethylaminomethyl)-2-pyridyloxy]pro-pyl]acetamide (**13**): ^{1}H-NMR (CDCl$_3$) δ: 1.96 (2H, tt, $J=6.5$, 6.5 Hz), 3.24 (2H, s), 3.38 (2H, s), 3.39 (2H, td, $J=6.5$, 6.5 Hz), 3.75 (2H, s), 4.39 (2H, t, $J=6.5$ Hz), 6.19 (1H, d, $J=1.5$ Hz), 6.28 (1H, dd, $J=1.5$ Hz), 6.75 (1H, s), 6.89 (1H, d, $J=6.0$ Hz), 7.30 (1H, d, $J=1.5$ Hz), 8.09 (1H, d, $J=6.6$ Hz). IR (film) cm^{-1}: 1660 (C=O). HR-MS m/z: Calcd for $C_{18}H_{25}N_3O_3S$ (M$^+$): 363.1616, Found: 363.1600.

2-Furfurylthio-N-[3-[(4-piperidinomethyl)-2-pyridyloxy]propyl]acet-amide (**14**): ^{1}H-NMR (CDCl$_3$) δ: 1.40—1.50 (2H, m), 1.50—1.65 (4H, m), 1.90—2.05 (4H, m), 1.96 (2H, tt, $J=6.5$, 6.5 Hz), 2.30—2.45 (4H, m), 3.24 (2H, s), 3.39 (2H, td, $J=6.5$ Hz, 6.5Hz), 3.41 (2H, s), 3.75 (2H, s), 4.39 (2H, t, $J=6.5$ Hz), 6.19 (1H, d, $J=3.0$ Hz), 6.28 (1H, dd, $J=3.0$, 2.0 Hz), 6.78 (1H, s), 6.89 (1H, d, $J=5.5$ Hz), 7.33 (1H, d, $J=2.0$ Hz), 8.07 (1H, d, $J=5.5$ Hz). IR (film) cm^{-1}: 1660 (C=O). HR-MS m/z: Calcd for $C_{21}H_{28}N_2O_3S$ (M$^+$): 436.1312, Found: 436.1240.

2-Furfurylsulfinyl-N-[4-[4-(piperidinomethyl)-2-pyridyloxy]butyl]-acetamide (**17**): ^{1}H-NMR (CDCl$_3$) δ: 1.40—1.65 (6H, m), 1.65—1.90 (4H, m), 2.30—2.45 (4H, m), 3.31 (1H, d, $J=14.5$ Hz), 3.40 (2H, s), 3.41 (2H, td, $J=6.1$, 6.1 Hz), 3.58 (1H, d, $J=14.5$ Hz), 4.16 (1H, d, $J=13.9$ Hz), 4.26 (1H, d, $J=13.9$ Hz), 4.30 (2H, d, $J=6.1$ Hz), 6.40 (1H, dd, $J=3.5$, 2.0 Hz), 6.47 (1H, d, $J=3.5$ Hz), 6.90 (1H, s), 6.85 (1H, dd, $J=5.4$, 1.3 Hz), 6.95 (1H, br s), 7.44 (1H, d, $J=2.0$ Hz), 8.03 (1H, d, $J=5.4$ Hz). IR (film) cm^{-1}: 1050 (S→O), 1647 (C=O). HR-MS m/z: Calcd for $C_{22}H_{31}N_3O_4S$ (M$^+$): 433.3036, Found: 433.2037.

2-[4-(2-Tetrahydropyranyloxy)-(Z)-2-buten-1-yloxy]-4-(1,3-dioxolan-2-yl)-pyridine (27) A suspension of **25** (9.9 g, 43.0 mmol), **26** (9.7 g, 56.3 mmol), powded NaOH (7.0 g, 175 mmol), K_2CO_3 (9.7 g, 70 mmol) and tetra-n-butylammonium hydrogen sulfate (1.3 g, 3.8 mmol) in toluene (150 ml) was refluxed for 18 h. After cooling, the mixture was diluted with benzene, washed with water, and dried over anhydrous MgSO$_4$. The solvent was evaporated *in vacuo* to give **27** (12.1 g, 87%). ^{1}H-NMR (CDCl$_3$) δ: 1.46—1.92 (6H, m), 3.46—3.56 (1H, m), 3.82—3.91 (1H, m), 4.04 (4H, d, $J=2$ Hz), 4.20 (1H, dd, $J=12.5$, 5.4 Hz), 4.37 (1H, dd, $J=12.5$, 5.4 Hz), 4.65—4.68 (1H, m), 4.93 (2H, d, $J=5.4$ Hz), 5.70—5.90 (2H, m), 5.79 (1H, s), 6.96 (1H, d, $J=5.5$ Hz), 8.15 (1H, d, $J=5.5$ Hz). HR-MS m/z: Calcd for $C_{17}H_{23}NO_5$ (M$^+$): 321.1577, Found: 321.1591.

4-[4-(1,3-Dioxolan-2-yl)-2-pyridyloxy]-(Z)-2-buten-1-ol (28) Pyridini-um p-toluenesulfonate (1.5 g, 5.9 mmol) was added to a solution of **27** (12.1 g, 37.6 mmol) in EtOH (250 ml), and the mixture was stirred at 55 °C (bath temperature) for 18 h. Saturated NaHCO$_3$ solution was added to render the reaction mixture basic, then the whole was concentrated and the residue was taken up in AcOEt. This solution was washed with water and dried over anhydrous MgSO$_4$. The solvent was evaporated *in vacuo* to give **28** (9.2 g, 90%). ^{1}H-NMR (CDCl$_3$) δ: 4.01—4.08 (4H, m), 4.32 (2H, d, $J=6.4$ Hz), 5.01 (2H, d, $J=7.4$ Hz), 5.69—5.78 (1H, m), 5.78 (1H, s), 5.83—5.92 (1H, m), 6.86 (1H, s), 6.98 (1H, d, $J=4.5$ Hz), 8.10 (1H, d, $J=4.5$ Hz). IR (film) cm^{-1}: 3424, 2896, 1620, 1566, 1426, 1316, 1032. HR-MS m/z: Calcd for $C_{12}H_{15}NO_4$ (M$^+$): 237.1001, Found: 237.0998.

N-[4-[(1,3-Dioxolan-2-yl)-2-pyridyloxy]-(Z)-2-butenyl]phthalimide (29) Thionyl chloride (6 g, 50.4 mmol) was added dropwise to a solution of **28** (10 g, 42.1 mmol) and triethylamine (6 g, 59.2 mmol) in CH$_2$Cl$_2$ (250 ml) under ice cooling, and the mixture was stirred for 1 h. Ice-cooled NaHCO$_3$ solution was added to render the solution basic. The organic layer was washed with water, and dried over anhydrous MgSO$_4$, and evaporated *in vacuo*. The residue was dissolved in acetonitrile (250 ml), then potassium phthalimide (8 g, 43.1 mmol) and tetra-n-butylammonium hydrogen sulfate (1.4 g, 4.12 mmol) were added, and the mixture was refluxed for 18 h. It was allowed to cool, the insoluble material was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was taken up in AcOEt. This solution was washed with a 1 N-NaOH and then with water, and dried over anhydrous MgSO$_4$. Removal of the solvent *in vacuo* gave a crude solid, which was recrystallized from EtOH to give **29** (8 g, 53%). mp 96.9—97.9 °C. ^{1}H-NMR (CDCl$_3$): 4.00—4.09 (4H, m), 4.47 (2H, d, $J=7.2$ Hz), 5.12 (2H, d, $J=7.2$ Hz), 5.64—5.74 (1H, m), 5.80 (1H, s), 5.88—5.96 (1H, m), 6.86 (1H, s), 6.98 (1H, d, $J=5.3$ Hz), 7.72 (2H, dd, $J=6.3$, 3.7 Hz), 7.85 (2H, dd, $J=6.3$, 3.7 Hz), 8.17 (1H, d, $J=5.3$ Hz). IR (KBr) cm^{-1}: 2496, 1770, 1716, 1614, 1568, 1120, 1092. HR-MS m/z: Calcd for $C_{20}H_{18}N_2O_5$ (M$^+$): 366.1216, Found: 366.1221.

4-[4-(1,3-Dioxolan-2-yl)-2-pyridyloxy]-(Z)-2-butenamine (30) Hydra-zine hydrate (2.3 g, 45.9 mmol) was added to a solution of **29** (8.5 g,

23.1 mmol) in MeOH (200 ml) was added , and the mixture was refluxed for 10 h. It was allowed to cool then, the insoluble matter was removed by filtration, and the filtrate was concentrated. On standing, the residue crystallized to give 30 (10.3 g, 78%).

^{1}H-NMR (CDCl$_3$) δ: 3.45 (2H, d, J=4.8 Hz), 4.01—4.07 (4H, m), 4.90 (2H, d, J=4.8 Hz), 5.68—5.76 (2H, m), 5.78 (1H, s), 6.85 (1H, s), 6.97 (1H, d, J=4.8 Hz), 8.15 (1H, d, J=4.8 Hz). IR (KBr) cm^{-1}: 3068, 1666, 1082.

2-Furfurylsulfinyl-N-[4-[4-(1,3-dioxolan-2-yl)-2-pyridyloxy]-(Z)-2-butenyl]acetamide (32) A solution of 30 (10.3 g, 43.6 mmol) in tetrahydrofuran (THF) (100 ml) was added to a suspension of 31 (13.5 g, 43.6 mmol) in THF (300 ml) was added dropwise under ice cooling. The mixture was kept at this temperature for 1 h, then stirred at room temperature for 18 h and concentrated *in vacuo*. The residue was taken up in AcOEt. This solution was washed with a 1 N-NaOH and water, dried over anhydrous MgSO$_4$, evaporated *in vacuo* to give 32 (16.1 g, 91%). ^{1}H-NMR (CDCl$_3$) δ: 3.34 (1H, d, J=14.2 Hz), 3.59 (1H, d, J=14.2 Hz), 4.01—4.07 (4H, m), 4.10 (2H, t, J=6.6 Hz), 4.18 (1H, d, J=14.2 Hz), 4.27 (1H, d, J=14.2 Hz), 4.95 (2H, d, J=6.9 Hz), 5.63—5.72 (1H, m), 5.78 (1H, s), 5.79—5.90 (1H, m), 6.39 (1H, dd, J=2.4, 2.8 Hz), 6.47 (1H, dd, J=2.8 Hz), 6.98 (1H, d, J=5.5 Hz), 7.10—7.20 (1H, br s), 7.44 (1H, d, J=2.4 Hz), 8.15 (1H, d, J=5.5 Hz). IR (film) cm^{-1}: 1660, 1618, 1566, 1310, 1034. HR-MS m/z: Calcd for C$_{19}$H$_{22}$N$_2$O$_6$S (M$^+$): 406.1199, Found: 406.1208.

N-[4-(4-Formyl-2-pyridyloxy)-(Z)-2-butenyl]-2-(furfurylsulfinyl)acetamide (33) p-Toluenesulfonic acid monohydrate (5.6 g, 29.4 mmol) was added to a solution of 32 (10.0 g, 24.6 mmol) in a 1:1 mixture of water and acetone (200 ml), and the mixture was refluxed for 18 h. It was allowed to cool, then made basic with saturated NaHCO$_3$ solution and concentrated *in vacuo*. The residue was taken up in AcOEt. This solution was washed with water, dried over anhydrous MgSO$_4$, and evaporated *in vacuo*. The residue was subjected to column chromatography (1% MeOH–CHCl$_3$) to give 33 (4.6 g, 52%). mp 67.6—69.9 °C. ^{1}H-NMR (CDCl$_3$) δ: 3.34 (1H, d, J=14.1 Hz), 3.59 (1H, d, J=14.1 Hz), 4.12 (2H, d, J=6.3 Hz), 4.18 (1H, d, J=14.3 Hz), 4.27 (1H, d, J=14.3 Hz), 5.00 (2H, d, J=6.4 Hz), 5.66—5.76 (1H, m), 5.82—5.92 (1H, m), 6.40 (1H, dd, J=3.5, 3.0 Hz), 6.47 (1H, d, J=3.5 Hz), 7.08 (1H, br s), 7.16 (1H, s), 7.30 (1H, d, J=4.6 Hz), 7.45 (1H, d, J=3 Hz), 8.36 (1H, d, J=4.6 Hz), 10.00 (1H, s). IR (KBr) cm^{-1}: 3236, 1712, 1624, 1564, 1036. HR-MS m/z: Calcd for C$_{17}$H$_{18}$N$_2$O$_5$S (M$^+$): 362.0937, Found: 362.0934.

2-Furfurylsulfinyl-N-[4-[4-(piperidinomethyl)-2-pyridyloxy]-(Z)-2-butenyl]acetamide (16) Piperidine (2.0 g, 23.4 mmol) was added to a solution of 33 (4.0 g, 11.0 mmol) in EtOH (100 ml) under ice cooling. After 3 h, NaBH$_4$ (0.5 g, 13.2 mmol) was added under ice cooling, and the mixture was stirred for 16 h. Acetic acid was added to decompose the excess hydride, and the reaction mixture was concentrated *in vacuo*. The residue was taken up in AcOEt and extracted with 20% acetic acid twice. The aqueous layer was washed with AcOEt, made basic with K$_2$CO$_3$ and extracted with AcOEt. The organic layer was washed with water, dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was recrystallized from ether–hexane to give 16 (2.2 g, 46%). mp 92.7—94.9 °C. ^{1}H-NMR (CDCl$_3$) δ: 1.40—1.50 (2H, m), 1.50—1.65 (4H, m), 2.30—2.45 (4H, m), 3.34 (1H, d, J=14.2 Hz), 3.40 (2H, s), 3.96 (1H, d, J=14.2 Hz), 4.15 (2H, dd, J=6.1, 6.1 Hz), 4.14 (1H, d, J=14.2 Hz), 4.38 (1H, d, J=14.2 Hz), 4.93 (2H, t, J=6.1 Hz), 5.60—5.75 (1H, m), 5.80—5.90 (1H, m), 6.40 (1H, dd, J=3.1, 1.6 Hz), 6.47 (1H, d, J=3.1 Hz), 6.73 (1H, s), 6.87 (1H, d, J=5.1 Hz), 7.15—7.25 (1H, br s), 7.44 (1H, d, J=1.6 Hz), 8.04 (1H, d, J=5.1 Hz). IR (KBr) cm^{-1}: 1645 (C=O), 1041 (S→O). HR-MS m/z: Calcd for C$_{22}$H$_{29}$N$_3$O$_4$S (M$^+$): 431.1879, Found: 431.1883. *Anal.* Calcd for C$_{22}$H$_{29}$N$_3$O$_4$S: C, 61.23%; H, 6.77%; N, 9.74%; S, 7.43%. Found: C, 60.89%; H, 6.72%; N, 9.51%; S, 7.43%.

Similarly, compounds 19—24 were synthesized from the corresponding amine and compound 32 (Chart 2).

2-Furfurylsulfinyl-N-[4-[4-(dimethylaminomethyl)-2-pyridyloxy]-(Z)-2-butenyl]acetamide (19): ^{1}H-NMR (CDCl$_3$) δ: 2.24 (6H, s), 3.33 (1H, d, J=14.2 Hz), 3.37 (2H, s), 3.59 (1H, d, J=14.2 Hz), 4.11 (2H, dd, J=6.8, 6.1 Hz), 4.19 (1H, d, J=13.3 Hz), 4.26 (1H, d, J=13.3 Hz), 4.93 (2H, d, J=6.4 Hz), 5.62—5.74 (1H, m), 5.80—5.90 (1H, m), 6.39 (1H, dd, J=2.9, 2.1 Hz), 6.47 (1H, d, J=2.9 Hz), 6.71 (1H, s), 6.87 (1H, d, J=5.6 Hz), 7.11 (1H, br s), 7.44 (1H, d, J=2.1 Hz), 8.07 (1H, d, J=5.6 Hz). IR (film) cm^{-1}: 1666 (C=O), 1040 (S→O). HR-MS m/z: Calcd for C$_{19}$H$_{25}$N$_3$O$_4$S (M$^+$): 391.1556, Found: 391.1500.

2-Furfurylsulfinyl-N-[4-[4-(3-methylpiperidinomethyl)-2-pyridyloxy]-(Z)-2-butenyl]acetamide (20): ^{1}H-NMR (CDCl$_3$) δ: 0.84 (3H, d,

J=5.6 Hz), 1.54—1.73 (6H, m), 1.84—1.94 (1H, m), 2.69—2.78 (2H, m), 3.33 (1H, d, J=14.1 Hz), 3.40 (2H, s), 3.59 (1H, d, J=14.1 Hz), 4.11 (1H, dd, J=7.0, 5.0 Hz), 4.19 (1H, d, J=13.4 Hz), 4.26 (1H, d, J=13.4 Hz), 4.93 (2H, d, J=7.1 Hz), 5.66—5.72 (1H, m), 5.82—5.90 (1H, m), 6.39 (1H, dd, J=3.4, 2.0 Hz), 6.47 (1H, d, J=3.4 Hz), 6.73 (1H, s), 6.87 (1H, d, J=5.4 Hz), 7.15 (1H, br s), 7.44 (1H, d, J=2.0 Hz), 8.05 (1H, d, J=5.4 Hz). IR (film) cm^{-1}: 1666 (C=O), 1036 (S→O). HR-MS m/z: Calcd for C$_{23}$H$_{31}$N$_3$O$_4$S (M$^+$): 445.2034, Found: 445.2029.

2-Furfurylsulfinyl-N-[4-[4-(pyrroridinylmethyl)-2-pyridyloxy]-(Z)-2-butenyl]acetamide (21): ^{1}H-NMR (CDCl$_3$) δ: 1.75—1.84 (4H, m), 2.48—2.55 (4H, m), 3.35 (1H, d, J=14.9 Hz), 4.10 (1H, dd, J=6.3, 5.9 Hz), 4.19 (2H, d, J=14.2 Hz), 4.27 (2H, d, J=14.2 Hz), 4.93 (2H, d, J=6.6 Hz), 5.62—5.72 (1H, m), 5.80—5.90 (1H, m), 6.39 (1H, dd, J=2.9, 1.8 Hz), 6.47 (1H, d, J=2.9 Hz), 6.88 (1H, d, J=5.1 Hz), 7.28 (1H, s), 7.43 (1H, d, J=1.8 Hz), 8.05 (1H, d, J=5.1 Hz). IR (film) cm^{-1}: 1672 (C=O), 1040 (S→O). HR-MS m/z: Calcd for C$_{21}$H$_{27}$N$_3$O$_4$S (M$^+$): 417.1722, Found: 417.1716.

2-Furfurylsulfinyl-N-[4-[4-(morphorinomethyl)-2-pyridyloxy]-(Z)-2-butenyl]acetamide (22): ^{1}H-NMR (CDCl$_3$) δ: 2.44 (4H, t, J=4.4 Hz), 3.32 (1H, d, J=14.5 Hz), 3.44 (2H, s), 3.59 (2H, d, J=14.5 Hz), 3.72 (4H, t, J=4.4 Hz), 4.11 (2H, dd, J=6.4, 6.1 Hz), 4.18 (1H, d, J=14.1 Hz), 4.26 (1H, d, J=14.1 Hz), 4.93 (2H, d, J=7.0 Hz), 5.62—5.72 (1H, m), 5.80—5.90 (1H, m), 6.39 (1H, dd, J=3.5, 1.7 Hz), 6.47 (1H, d, J=3.5 Hz), 6.74 (1H, s), 6.88 (1H, d, J=5.1 Hz), 7.05—7.15 (1H, m), 7.44 (1H, d, J=1.7 Hz), 8.06 (1H, d, J=5.1 Hz). IR (film) cm^{-1}: 1672 (C=O), 1040 (S→O). HR-MS m/z: Calcd for C$_{21}$H$_{27}$N$_3$O$_5$S (M$^+$): 433.1671, Found: 433.1671.

2-Furfurylsulfinyl-N-[4-[4-(1,2,3,6-tetrahydro-pyridylmethyl)-2-pyridyloxy]-(Z)-2-butenyl]acetamide (23): ^{1}H-NMR (CDCl$_3$) δ: 2.18 (4H, dt, J=5.6, 2.5 Hz), 2.55 (2H, t, J=5.6 Hz), 2.97 (2H, dt, J=2.6, 2.5 Hz), 3.33 (1H, d, J=14.0 Hz), 3.52 (2H, s), 3.59 (2H, d, J=14.0 Hz), 4.11 (2H, dd, J=6.6, 5.9 Hz), 4.18 (1H, d, J=13.9 Hz), 4.93 (2H, d, J=6.6 Hz), 5.60—5.90 (4H, m), 6.39 (1H, dd, J=3.1, 1.2 Hz), 6.47 (1H, d, J=3.1 Hz), 6.91 (1H, d, J=5.4 Hz), 7.15 (1H, br s), 7.44 (1H, d, J=1.2 Hz), 8.06 (1H, d, J=5.4 Hz). IR (film) cm^{-1}: 1668 (C=O), 1040 (S→O). HR-MS m/z: Calcd for C$_{22}$H$_{27}$N$_3$O$_4$S (M$^+$): 429.1722, Found: 429.1708.

2-Furfurylsulfinyl-N-[4-[4-(perhydroazepinylmethyl)-2-pyridyloxy]-(Z)-2-butenyl]acetamide (24): ^{1}H-NMR (CDCl$_3$) δ: 1.55—1.78 (8H, m), 2.55—2.62 (4H, m), 3.33 (1H, d, J=15.1 Hz), 3.58 (2H, s), 3.59 (1H, d, J=15.1 Hz), 4.11 (2H, dd, J=6.4, 5.8 Hz), 4.18 (1H, d, J=14.4 Hz), 4.26 (1H, d, J=14.4 Hz), 4.93 (2H, d, J=6.4 Hz), 5.64—5.73 (1H, m), 5.80—5.91 (1H, m), 6.39 (1H, dd, J=2.8, 1.4 Hz), 6.47 (1H, d, J=2.8 Hz), 6.75 (1H, s), 6.90 (1H, d, J=5.5 Hz), 7.16 (1H, br s), 7.44 (1H, d, J=1.4 Hz), 8.04 (1H, d, J=5.5 Hz). IR (film) cm^{-1}: 1668 (C=O), 1040 (S→O). HR-MS m/z: Calcd for C$_{23}$H$_{31}$N$_3$O$_4$S (M$^+$): 445.2034, Found: 445.2018.

2-Furfurylsulfinyl-N-[4-[4-(piperidinomethyl)-2-pyridyloxy]-(E)-2-butenyl]acetamide (18): mp 108.5—109.2 °C. ^{1}H-NMR (CDCl$_3$) δ: 1.37—1.50 (2H, m), 1.50—1.65 (4H, m), 2.25—2.45 (4H, m), 3.32 (1H, d, J=14.3 Hz), 3.39 (2H, s), 3.60 (1H, d, J=14.3 Hz), 3.98 (2H, dd, J=5.9, 5.4 Hz), 4.16 (1H, d, J=14.2 Hz), 4.25 (1H, d, J=14.0 Hz), 4.80 (1H, d, J=5.4 Hz), 5.85 (1H, dt, J=15.5, 5.4 Hz), 5.98 (1H, dt, J=15.5, 5.4 Hz), 6.39 (1H, dd, J=3.3, 1.9 Hz), 6.47 (1H, d, J=3.3 Hz), 6.71 (1H, s), 6.86 (1H, d, J=5.3 Hz), 6.78—6.88 (1H, m), 7.44 (1H, d, J=2.0 Hz), 8.03 (1H, d, J=5.3 Hz). IR (KBr) cm^{-1}: 1642 (C=O), 1040 (S→O). HR-MS m/z: Calcd for C$_{22}$H$_{29}$N$_3$O$_4$S (M$^+$): 431.1879, Found: 431.1884.

Pharmacology. Histamine H$_2$ Receptor Antagonistic Activity The right atrium was removed from a male Hartley guinea pig weighing between 300 and 500 g, 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 and allowed to become constant. After the heart rate was returned to the basal rate by washing with fresh medium, a test compound was added to medium and the preparation was incubated for 10 min. In the presence of a test compound, induction of the 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 the following 4 groups: −, no effect at 1×10^{-5} M; +, under 70% inhibition at 1×10^{-6} M; ++, 70—90% inhibition at 1×10^{-6} M; +++, over 90% inhibition 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.[7] 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 rise of pH of the 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; $+++$, marked rise of pH at a dose of 3 mg/kg; $++++$, rise of pH at a dose of 0.3 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% EtOH and killed for evaluation of 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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