Antiulcer Agents. II. Synthesis and Gastric Acid Antisecretory Activity of *N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]-4-(1-methyl-1*H*-tetrazol-5-ylthio)butanamide and Related Compounds

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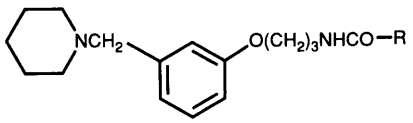
***N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]butanamides having a 1-methyl-1*H*-tetrazol-5-ylthio moiety as a pharmacophore and related compounds were prepared and tested for their antisecretory activity against histamine-induced gastric acid secretion in conscious rats with gastric fistulas. Most of the compounds showed antisecretory activity. Among them, *N*-[3-{3-(piperidinomethyl)phenoxy}propyl]-4-(1-methyl-1*H*-tetrazol-5-ylthio)butanamide (5f) was found to possess the most potent activity, and a possibility of isosteric replacement of the methoxycarbonyl group with 1-methyl-1*H*-tetrazol-5-yl group was indicated. The structure–activity relationships are also discussed.**

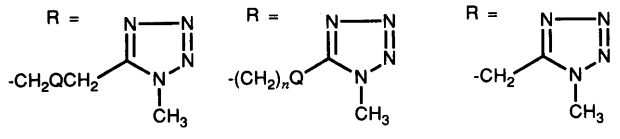
Keywords gastric acid antisecretory activity; antiulcer activity; *N*-[3-{3-(piperidinomethyl)phenoxy}propyl]-4-(1-methyl-1*H*-tetrazol-5-ylthio)butanamide; 5-mercapto-1-methyl-1*H*-tetrazole; structure–activity relationship; histamine H_2-receptor antagonist

In the previous paper,[1] we reported that *N*-[3-{3-(piperidinomethyl)phenoxy}propyl]-2-(2-hydroxyethylthio)-acetamide (**1**) showed potential gastric acid antisecretory and gastrointestinal cytoprotective activities. Compounds **2** and **3**, which are analogues of **1**, were also found to possess significant gastric acid antisecretory activity.[1,2] It has been suggested that successive bioisosteric replacement of key positions of a biologically important molecule results in an improvement of its biological effects.[3]

Structual Alteration of Compounds 2 and 3 The similarity between the spatial and acidic properties of the tetrazole ring and the carboxylic acid group has prompted a search for tetrazoles with pharmacological application.[3,4] We are now estimating the possibility of bioisosteric replacement of the methoxycarbonyl ($-COOCH_3$) group with 1-methyl-1*H*-tetrazol-5-yl group. Structural alteration of **2** was tried on the basis of bioisosterism principles. Isosteric replacement of the $-COOC_2H_5$ group by a 1-methyl-1*H*-tetrazol-5-yl group brought compound **4**. As the $-CH_2SCH_2-$ ($-CH_2SO_2CH_2-$) group may be substituted for the $-CH_2CH_2S-$ ($-CH_2CH_2SO_2-$) group with similar electronic structures, **4** will be changeable into compounds **5d** and **5e**. And it has been shown that the $-NHCOCH_2S-$ group was effective in imparting the desired level of gastric acid antisecretory activity.[1] Thus, *N*-[3-{3-(piperidinomethyl)phenoxy}propyl]-2-(1-methyl-1*H*-tetrazol-5-ylthio)-acetamide (**5a**) was the first target compound in this series. Secondly, the replacement of the methoxycarbonyl group of **3** with a 1-methyl-1*H*-tetrazol-5-yl group led to *N*-[3-{3-(piperidinomethyl)phenoxy}propyl]-2-(1-methyl-1*H*-tetrazol-5-yl)acetamide (**5k**). Both compounds **5a** and **5k** exhibited significant antisecretory activity against histamine-induced gastric acid secretion in conscious rats with gastric fistulas. The inhibition percent upon intraduodenal administration of the dose of 30 mg/kg was 66.9% for **5a** and 77.4% for **5k**, respectively. These results led us to prepare compounds illustrated in a general formula **5** having a 1-methyl-1*H*-tetrazol-5-yl moiety as its pharmacophore (Chart 2). One of these compounds, *N*-[3-{3-(piperidinomethyl)phenoxy}propyl]-4-(1-methyl-1*H*-tetrazol-5-ylthio)-butanamide (**5f**), in terms of its ED_{50} value, was shown to be 1.5 times more potent than **1**. In this paper, we describe the synthesis, histamine-induced gastric acid antisecretory activity of **5f** and related compounds, and determination of structure–activity relationships with gastric acid antisecretory activity data.



1 : R = -$CH_2SCH_2CH_2OH$ (79.5)
2 : R = -$CH_2SO_2CH_2COOC_2H_5$ (39.7)
3 : R = -CH_2COOCH_3 (46.9)



4 : Q=S or SO_2

5a : n=1, Q=S
5d : n=2, Q=S
5e : n=2, Q=SO_2

5k

( ) : %inhibition of gastric acid secretion in conscious rats with gastric fistulas at the dose of 30 mg/kg (i.d.)

Chart 1

Synthesis Compounds illustrated in a general formula **5** were prepared according to methods A—E (Chart 2). In this series, most compounds were prepared by the reaction of 3-{3-(piperidino(or pyrrolidino)methyl)phenoxy}propanamine [**6**[5] (or **7**[6])] with an ester derivative (**12**) in good yields (method A). Compound **5d** was synthesized by treatment of **6** with 3-(1-methyl-1*H*-tetrazol-5-ylthio)propionyl chloride (method B). *N*-[3-{3-(piperidinomethyl)phenoxy}-propyl]-2-(1-methyl-1*H*-tetrazol-5-ylthio)acetamide (**5a**) was prepared by the reaction of *N*-[3-{3-(piperidinomethyl)phenoxy}propyl]-2-chloroacetamide[1] (**8**) with 5-mercapto-1-methyl-1*H*-tetrazole (TzSH) in the presence of a base in a good yield (method C). Variation of the piperidino group was conveniently achieved by the use of *N*-[3-(3-chloromethylphenoxy)propyl]-4-(1-methyl-1*H*-tetrazol-5-ylthio)butanamide (**10**) as a starting material. Compound **10**, which was prepared by the reaction of *N*-[3-(3-hydroxymethylphenoxy)propyl]-4-(1-methyl-1*H*-

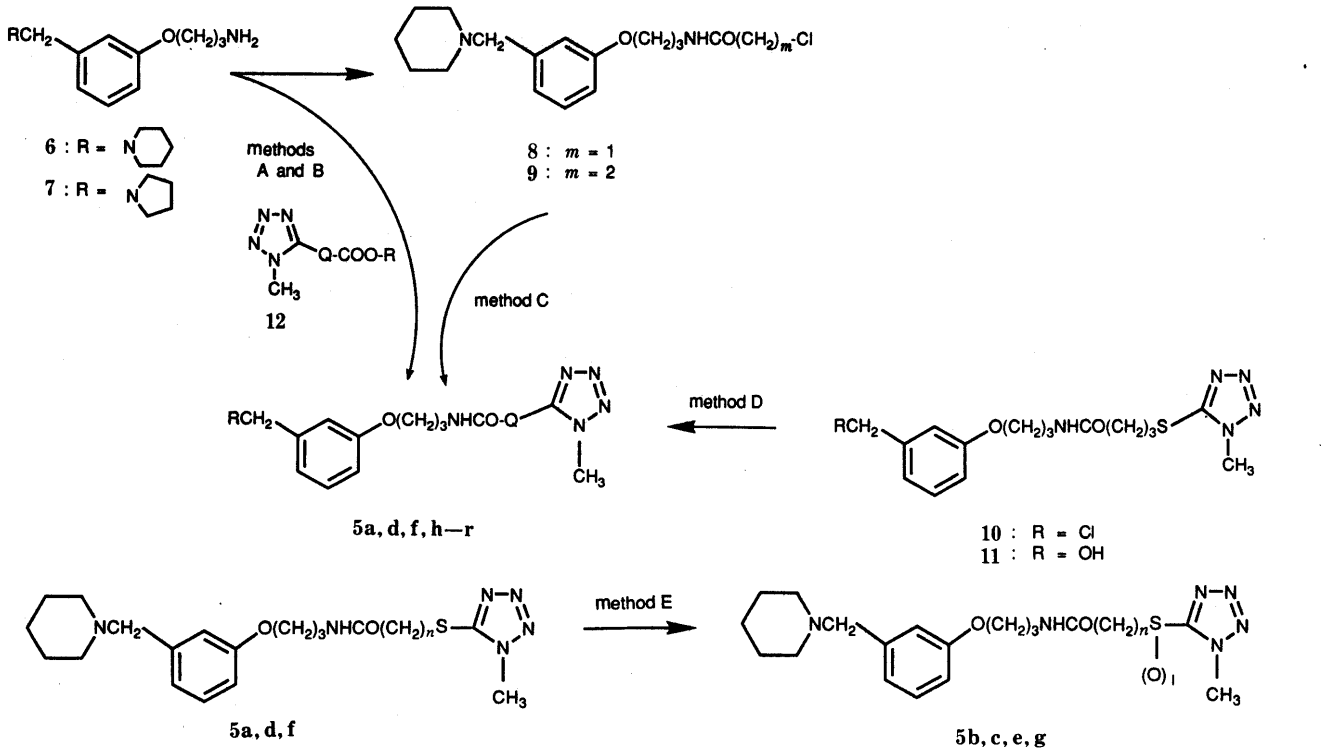
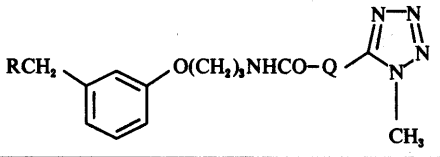


Chart 2

TABLE I. *N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]-4-(1-methyl-1*H*-tetrazol-5-ylthio)butanamide and Related Compounds



Compd. No.	R[a]	Q	Method	Yield (%)	mp °C [Recryst. solv.]	Formula	Analysis (%) Calcd (Found) C	H	N	Activity[c] (%)
5a	P	CH_2S–[b]	A, C	88	90.0—90.5 [IPE]	$C_{19}H_{28}N_6O_2S$	56.41 (56.60	6.98 6.75	20.77 20.81)	66.9
5b	P	CH_2SO_2–[b]	E	58	Oil	$C_{19}H_{28}N_6O_4S$	436.1893 (436.1909)[g]			19.6
5c	P	CH_2SO–[b]	E	63	Oil	$C_{19}H_{28}N_6O_3S$	420.1944 (420.1953)[g]			51.6
5d	P	CH_2CH_2S–[b]	B	70	Oil	$C_{20}H_{30}N_6O_2S$	418.2149 (418.2178)[g]			63.1
5e	P	$CH_2CH_2SO_2$–[b]	E	81	Oil	$C_{20}H_{30}N_6O_4S$	450.2049 (450.2037)[g]			35.5
5f	P	$CH_2CH_2CH_2S$–[b]	A	94	87.0—88.0 [EtOH–Et_2O]	$C_{21}H_{32}N_6O_2S\cdot HCl$	53.78 (53.81	7.09 7.21	17.94 18.06)	86.1 (9.5)[d]
5g	P	$CH_2CH_2CH_2SO_2$–[b]	A, E	34	76.5—77.5 [IPE]	$C_{21}H_{32}N_6O_4S$	54.29 (54.53	6.94 6.79	18.09 18.12)	50.4
5h	P	$CH_2SCH_2CH_2S$–[b]	A	61	Oil	$C_{21}H_{32}N_6O_2S_2$	464.2026 (464.2030)[g]			68.9
5i	P	$CH_2OCH_2CH_2S$–[b]	A	75	Oil	$C_{21}H_{32}N_6O_3S$	448.2257 (448.2243)[g]			13.9
5j	P	$CH_2SCH_2CH_2$–[b]	A	60	Oil	$C_{21}H_{32}N_6O_2S$	432.2306 (432.2272)[g]			18.4
5k	P	CH_2	A	63	95.0—95.9 [C_6H_6–hexane]	$C_{19}H_{28}N_6O_2$	61.27 (61.37	7.58 7.39	22.56 22.45)	77.4
5l[e]	P	CH_2	A	56	126—127 (dec.) [EtOH–Et_2O]	$C_{19}H_{28}N_6O_2\cdot HCl \cdot 1/3H_2O$	55.00 (55.15	7.21 7.39	20.25 19.95)	19.5
5m	P	—[f]	A	84	Oil	$C_{18}H_{26}N_6O_2$	358.2117 (358.2119)[g]			−23.9
5n[e]	P	—[f]	A	76	Oil	$C_{18}H_{26}N_6O_2$	358.2117 (358.2101)[g]			17.7
5o	Py	$CH_2CH_2CH_2S$–[b]	B, D	86	Oil	$C_{20}H_{30}N_6O_2S$	418.2149 (418.2138)[g]			66.7
5p	PyOH	$CH_2CH_2CH_2S$–[b]	D	86	Oil	$C_{20}H_{30}N_6O_3S$	434.2100 (434.2106)[g]			41.8
5q	DM	$CH_2CH_2CH_2S$–[b]	D	82	Oil	$C_{18}H_{28}N_6O_2S$	392.1993 (392.1996)[g]			61.1
5r	HE	$CH_2CH_2CH_2S$–[b]	D	88	Oil	$C_{19}H_{30}N_6O_3S$	422.2100 (422.2126)[g]			−2.4
1[h]										79.5 (12.9)[d]
Ranitidine[h]										72.1 (17.7)[d]

a) P: piperidino, Py: pyrrolidino, PyOH: 3-hydroxypyrrolidino, DM: *N*,*N*-dimethylamino, HE: *N*-2-hydroxyethyl-*N*-methylamino. *b*) Binding site to tetrazole ring. *c*) % inhibition at the dose of 30 mg/kg (i.d.) in rats. Each value represents the mean of three rats. *d*) ED_{50} value; mg/kg. *e*) 1*H*-2-Methyltetrazole analogue. *f*) Direct binding to tetrazole ring. *g*) High-resolution MS analysis. *h*) See ref. 1.

tetrazol-5-ylthio)butanamide (**11**) with thionyl chloride, was treated with various amines to give the corresponding derivatives (**5o—r**) (method D). Sulfinyl compound (**5c**) and sulfonyl compounds (**5b**, **5e** and **5g**) were synthesized from methane sulfonates of corresponding thio derivatives (**5a**, **5d** and **5f**) and *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 (method E). Derivatives of **5** prepared in this series are summarized with their antisecretory activity in Table I. Infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectral data for **5** are shown in Table II (Experimental section).

In the course of synthesizing **5**, some interesting reactions were observed. When methyl 2-(1-methyl-1*H*-tetrazol-5-ylsulfonyl)acetate (**12b**) was allowed to react with **6** in refluxing toluene for 5 h, *N*-(1-methyl-1*H*-tetrazol-5-yl)-*N*-[3-{3-(piperidinomethyl)phenoxy}propyl]acetamide (**13**) was obtained in a 68% yield. The structure of **13** was confirmed by spectral data and high-resolution mass spectral analysis and conversion of **13** into 5-[*N*-[3-{3-(piperidinomethyl)phenoxy}propyl]]amino-1-methyl-1*H*-tetrazole[7] (**16**). In order to estimate the reaction pathway to **13** in this reaction, both reactions of 5-methoxycarbonyl-1methyl-1*H*-tetrazole[8] (**14**) with **6**, and 5-methylsulfonyl-1-methyl-1*H*-tetrazole[8] (**15**) with **6** were carried out as model reactions. When **14** was allowed to react with **6** for 1 h at 120 °C, 3-{3-(piperidinomethyl)phenoxy}-*N*-(1-methyl-1*H*-tetrazol-5-ylcarbonyl)propanamine (**5m**) was obtained in an 84% yield. On the other hand, the reaction of **15** with **6** for 48 h in refluxing toluene gave **16** in a 22% yield. These results suggest that, in the reaction of **12b** having two reaction sites of $-COOCH_3$ and CH_3SO_2-Tz in the molecule with **6**, amidation proceeds preferentially, compared with replacement of the CH_3SO_2- group. Additionally, treatment of **5b** in refluxing toluene for 13 h gave compound **13** in a 73% yield. These observations suggest that first **12b** reacts with **6**, yielding amide **5b**, followed by the Smiles rearrangement of **5b** to give **13**. Studies on the Smiles rearrangement of **5b** will be reported elsewhere.[9] The reaction of respective ethyl 3-(1-methyl-1*H*-tetrazol-5-ylthio)-propionate (**12c**) and its sulfonyl derivative (**12d**) with **6** gave the same product of ethyl 3-[*N*-[3-{3-(piperidinomethyl)phenoxy}propyl]]aminopropionate (**17**) in good yields without giving corresponding amides (**5d** and **5e**). Compound **17** was also obtained in a 58% yield by the reaction of **6** with ethyl acrylate in toluene at 70 °C. When *N*-[3-{3-(piperidinomethyl)phenoxy}propyl]-3-chloropropanamide (**9**) was allowed to react with TzSH in the presence of NaH, *N*-[3-{3-(piperidinomethyl)phenoxy}propyl]-acrylamide (**18**) was obtained in an 88% yield as a main product without yielding amide **5d**. These findings indicate that **17** was produced by the reaction of **6** with ethyl acrylate, which was produced from **12c** and **12d**, respectively.

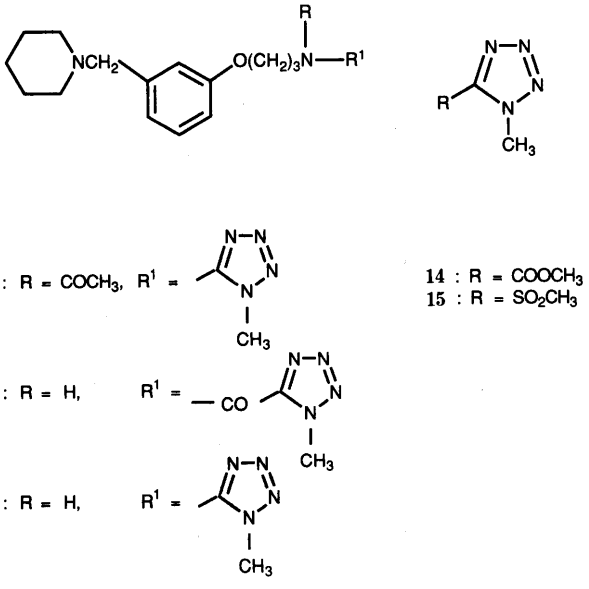


Chart 3

Results and Discussion

The compounds were evaluated for their antisecretory activity against histamine-induced gastric acid secretion in conscious rats with gastric fistulas as a primary screen. In this test, the compounds were administered intraduodenally (i.d.) at a dose of 30 mg/kg, and the reduction in acid output was measured at 1-h intervals for 5 h after administration of the test compound. The gastric acid antisecretory activity determined for the compounds in the rat model is described in Table I. The compounds having a 1-methyl-1*H*-tetrazol-5-yl moiety exhibited significant antisecretory activity. Among these compounds, **5f** was the most active compound. The potency of **5f**, in terms of ED_{50} value, was superior to that of **1** and the reference compound, ranitidine; Each ED_{50} value was 9.5 mg/kg for **5f**, 12.9 mg/kg for **1** and 17.7 mg/kg for ranitidine, respectively.

Structure–Activity Relationships Gastric acid antisecretory activity data described in Table I suggested the following structure–activity relationships.

Extension of the alkylene side chain (Q) in a function of –HNCO-Q-Tz, in which Tz is tetrazole ring, was examined. The function of $-CH_2S-$ in $-HNCOCH_2S-$ of **5a** was homologated by increasing (**5d** and **5f**) the number of methylene groups and by incorporation of $-CH_2SCH_2CH_2S-$ (**5h**) and $-CH_2OCH_2CH_2S-$ (**5i**) instead of $-CH_2S-$. In this case, **5d** showed a tendency to reduce antisecretory activity, compared to **5a**. Compound **5f** was the most active, and **5h** retained its antisecretory activity. As observed in **5i**, isosteric replacement of one of the sulfur atoms in **5h** by an oxygen atom reduced the activity. Compound **5j**, an isomer of **5f**, exhibited diminished antisecretory activity compared to **5f**. The order of activity was **5f**≫**5h**>**5a**, **5d**≫**5j**≒**5i**. These results suggest that the distance of about 8 Å between the –HNCO– and Tz ring brings a maximum potency. As observed in compounds **5k—n**, the shorter distance between –NHCO– group and Tz ring gave variable effects on antisecretory activity. Compound **5k** exhibited an enhanced antisecretory activity relative to that of **1**, while compound **5m** showed a tendency to increase acid secretion. It was difficult to rationalize the pattern of structure–activity relationships within the shorter distance between the –NHCO– and Tz ring.

Oxidation of the sulfur atom in **5a** gave sulfonyl derivative (**5b**) and sulfinyl derivative (**5c**), both of which exhibited reduced antisecretory activity. Compound **5e**, prepared by oxidation of **5d**, was also less active than **5d**. The increase

of hydrophilicity by oxidation of the sulfur atom may be a cause of the reduction in activity. A similar tendency has been observed among **1** and related compounds.[1] Regarding the position of the methyl group of the Tz ring, the data indicates that the 1-methyl derivative (**5k**) is superior to the 2-methyl derivative (**5l**) in antisecretory activity.

At present, it is difficult to discuss structure–toxicity relationships, because there is not enough data on these relationships. As is seen in certain cases,[10,11] toxicity may be reduced by increasing hydrophilicity suitably. Then, we attempted to change the piperidino group on the benzene ring to pyrrolidino, 3-hydroxypyrrolidino, *N*,*N*-dimethylamino and *N*-2-hydroxyethyl-*N*-methylamino groups. The pyrrolidino compound (**5o**) retained antisecretory activity and 3-hydroxypyrrolidino compound (**5p**) was less active than **5o**. The activity of the *N*,*N*-dimethylamino compound (**5q**) was comparable to that of **5o**, but the *N*-2-hydroxyethyl-*N*-methylamino compound (**5r**) was devoid of antisecretory activity.

In conclusion, we were able to show that isosteric replacement of the methoxycarbonyl group with a 1-methyl-1*H*-tetrazol-5-yl group achieved an improvement in biological effect. Since an increase of hydrophilicity resulted in reducing antisecretory activity, toxicological study of compounds **5o**, **5p**, **5q** and **5r** was not carried out.

Experimental

Melting points were measured in a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 Model infrared spectrophotometer and ^{1}H-NMR spectra were measured on Hitachi R-90H (90 MHz) and Bruker AM 360 (360 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are given as δ values (ppm); s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; br, broad; m, multiplet. All spectra were consistent with the assigned structures. Mass spectra (MS) were obtained on a JMS-DX 300 spectrometer. Combustion analyses were performed on a Perkin–Elmer Model 240C elemental analyzer and high-resolution MS analyses were used for oily products.

Solvents used were dried over molecular sieves 4A overnight. 3-Hydroxypyrrolidine, 3-hydroxymethylphenol and 3-chloropropanamine were commercially available. Compounds **14** and **15** were prepared according to the procedure described in the literature.[8]

Typical procedures for the preparation of **5** are shown:

Method A ***N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]-4-(1-methyl-1*H*-tetrazol-5-ylthio)butanamide (5f)** Amine **6**[5] (2.40 g, 9.7 mmol) and **12e** (3.15 g, 14.6 mmol) were added to a solution of $NaOCH_3$ in MeOH (sodium; 222 mg, dry MeOH; 40 ml). The mixture was refluxed for 5 h with stirring. After removal of the solvent, the residue obtained was treated with 3 N HCl and washed with Et_2O, and then made alkaline with 3 N NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give an oil. The oil was purified by column chromatography on silica gel with a (10 : 1) mixture of $CHCl_3$ and MeOH to give pure **5f** as an oil. Compounds **5a** and **5g**—**n** were prepared by a procedure similar to that used for **5f**.

Method B ***N*-[3-{3-Piperidinomethyl)phenoxy}propyl]-3-(1-methyl-1*H*-tetrazol-5-ylthio)propanamide (5d)** 3-(1-Methyl-1*H*-tetrazol-5-ylthio)propionyl chloride, prepared from 3-(1-methyl-1*H*-tetrazol-5-ylthio)propionic acid[12] (1.05 g, 5.6 mmol) and thionyl chloride (3 ml, 41 mmol), was added to a solution of **6** (1.24 g, 5 mmol) and pyridine (600 mg, 7.6 mmol) in CH_3CN (15 ml). The resulting mixture was stirred for 3 h at room temperature. After removal of the solvent, the obtained residue dissolved in CH_2Cl_2 was washed with saturated aqueous $NaHCO_3$ and then extracted with 1 N HCl. The aqueous layer was made alkaline with 4 N NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give an oil. The oil was purified by column chromatograpy on silica gel with a (14 : 1) mixture of $CHCl_3$ and MeOH to give pure **5d**. Compound **5o** was prepared by a procedure similar to that used for **5d**.

Method C ***N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]-2-(1-methyl-1*H*-tetrazol-5-ylthio)acetamide (5a)** Compound **8**[1] (1.31 g, 4 mmol) and TzSH (581 mg, 5 mmol) were added to a solution of KOH (85% purity; 396 mg, 6 mmol) in MeOH (15 ml). The resulting mixture was stirred for 3 h at room temperature. After removal of the solvent, the obtained residue dissolved in CH_2Cl_2 was extracted with 1 N HCl. The aqueous layer was made alkaline with $NaHCO_3$. The oil obtained was extracted with C_6H_6, and the C_6H_6 layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give crude crystals. The crystals were recrystallized from IPE to give pure **5a**.

Method D ***N*-[3-[3-{(3-Hydroxy)pyrrolidinomethyl}phenoxy]propyl]-4-(1-methyl-1*H*-tetrazol-5-ylthio)butanamide (5p)** Chloro derivative (**10**), prepared from **11** (547 mg, 1.5 mmol) and thionyl chloride (196 mg, 1.6 mmol) in CH_2Cl_2, was added to a mixture of 3-hydroxypyrrolidine (191 mg, 2.1 mmol) and K_2CO_3 (416 mg, 3 mmol) in acetone (10 ml). The resulting mixture was refluxed for 3 h with stirring and filtered for the removal of inorganic materials. The filtrate and washing were combined and evaporated *in vacuo* to give an oil. The oil in CH_2Cl_2 was extracted with 1 N HCl, and the acidic aqueous layer was made alkaline with 3 N NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give an oil. The oil was purified by column chromatography on silica gel with a (10 : 1) mixture of $CHCl_3$ and MeOH to give pure **5p** as an oil. Compounds **5o**, **5q** and **5r** were prepared by a procedure similar to that used for **5p**.

***N*-[3-{(3-Hydroxymethyl)phenoxy}propyl]-4-(1-methyl-1*H*-tetrazol-5-ylthio)butanamide (11)** *N*-(3-Chloropropyl)-4-(1-methyl-1*H*-tetrazol-5-ylthio)butanamide (**19**) was prepared from 4-(1-methyl-1*H*-tetrazol-5-ylthio)butyryl chloride[12] and 3-chloropropanamine under a Schotten–Baumann reaction condition. Oily material **19**: ^{1}H-NMR ($CDCl_3$) δ: 1.86—2.58 (6H, m), 3.29—3.71 (6H, m), 3.92 (3H, s), 6.21—6.74 (1H, br s). IR ν (neat): 3300, 1650, 1540 cm^{-1}.

A mixture of **19** (278 mg, 1 mmol) with sodium (3-hydroxymethyl) phenolate, prepared from 3-hydroxymethylphenol (125 mg, 1 mmol) and NaOH (40 mg, 1 mmol) in a mixed solvent of dimethyl sulfoxide (DMSO) (3 ml) and C_6H_6 (2 ml) was heated for 3 h at 150 °C with stirring. The reaction mixture dissolved in CH_2Cl_2 was washed with H_2O, followed by 3 N HCl and brine. After removal of the solvent, the residue obtained was purified by column chromatography on silica gel with a (15 : 1) mixture of $CHCl_3$ and MeOH to give pure **11** (311 mg) as a viscous oil in an 85% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.42 (6H, m), 2.49—3.68 (1H, br), 3.16—3.54 (4H, m), 3.85 (3H, s), 3.99 (2H, t, J = 6.0 Hz), 4.61 (2H, s), 6.48—7.39 (5H, m). IR ν (neat): 1655, 1440, 1260 cm^{-1}.

Method E ***N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]-2-(1-methyl-1*H*-tetrazol-5-ylsulfonyl)acetamide (5b)** *m*-CPBA (80% purity; 1.19 g, 5.5 mmol) was added to a mixture of **5a** (1.03 g, 2.5 mmol) and methane sulfonic acid (244 mg, 2.5 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred for 18 h at room temperature and then washed with 10% aqueous $Na_2S_2O_3$, followed by saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$ and evaporated *in vacuo* to give an oil. The oil was purified by column chromatography on silica gel with a (6 : 1) mixture of $CHCl_3$ and MeOH to give pure **5b** as an oil. Compound **5e** was prepared from **5d** by a procedure similar to that used for **5b**.

***N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]-2-(1-methyl-1*H*-tetrazol-5-ylsulfinyl)acetamide (5c)** **5c** was prepared from **5a** (505 mg, 1.3 mmol), methane sulfonic acid (120 mg, 1.3 mmol) and *m*-CPBA (80% purity; 297 mg, 1.42 mmol) at −10 °C. Work-up by a procedure similar to that used for **5b** gave **5c**. IR and ^{1}H-NMR spectral data for **5** are shown in Table II.

***N*-(1-Methyl-1*H*-tetrazol-5-yl)-*N*-[3-{3-(piperidinomethyl)phenoxy}-propyl]acetamide (13)** 1. A solution of **6** (2.0 g, 8.0 mmol) and **12b** (1.9 g, 9.5 mmol) in toluene (40 ml) was refluxed for 5 h with stirring. After removal of the solvent, the residue obtained was purified by column chromatography on silica gel with a (10 : 1) mixture of $CHCl_3$ and MeOH to give pure **13** (2.0 g) as an oil in a 68% yield. High-resolution MS: 372.2247 (Calcd for $C_{19}H_{28}N_6O_2$: 372.2273). IR ν (neat): 1690 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.55 (2H, m, 4-CH_2 of piperidine), 1.62—1.69 (4H, m, 3,5-CH_2 of piperidine), 2.21 (2H, m, OCH_2–$\underline{CH_2}$–CH_2N), 2.41—2.49 (7H, m, $COCH_3$ and 2,6-CH_2 of piperidine), 3.52 (2H, s, $ArCH_2O$), 3.92—4.03 (5H, br s, CH_3 and CH_2N), 4.10 (2H, t, J = 6.0 Hz, OCH_2), 6.79—7.31 (4H, m, ArH).

2. A solution of **5b** (500 mg, 1.1 mmol) in toluene (50 ml) was refluxed for 13 h with stirring. Work-up by a procedure similar to that described above gave **13** (310 mg) as an oil in a 73% yield. The structure of the product was assigned on the basis of IR, ^{1}H-NMR and MS spectral data.

5-[*N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]]amino-1-methyl-1*H*-tetrazole (16) A aqueous solution of **13** (500 mg) in 1 N HCl (25 ml) was

TABLE II. IR and ^{1}H-NMR Spectral Data for **5**

Compd. No.	IR[c] cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
5a[a]	k: 3300, 1640, 1565, 1265	1.39—1.47 (2H, m), 1.53—1.62 (4H, m), 1.98 (2, qt, J=6.0 Hz), 2.33—2.41 (4H, m), 3.43 (2H, s), 3.47 (2H, q, J=6.0, 6.5 Hz), 3.90 (3H, s), 3.93 (2H, s), 3.98 (2H, t, J=6.0 Hz), 6.71—7.23 (5H, m)
5b[a]	c: 1690, 1355, 1260	1.40—1.78 (6H, m), 2.01—2.27 (2H, m), 2.31—2.65 (4H, m), 3.38—3.67 (4H, m), 3.97 (3H, s), 4.05 (2H, t, J=6.0 Hz), 4.32 (2H, s), 6.63—7.58 (5H, m)
5c[a]	n: 1660, 1445, 1255, 1065	1.38—1.74 (6H, m), 1.74—2.13 (2H, m), 2.23—2.57 (4H, m), 3.27—3.73 (2H, m), 3.48 (2H, s), 3.99 (2H, t, J=6.0 Hz), 4.26 (3H, s), 4.37 (2H, dd, J=4.0 Hz), 6.62—7.53 (5H, m)
5d[a]	c: 3440, 1665, 1520, 1260	1.39—1.50 (2H, m), 1.54—1.66 (4H, m), 1.99 (2H, qt, J=6.3 Hz), 2.37—2.49 (4H, m), 2.79 (2H, t, J=6.5 Hz), 3.47 (2H, q, J=6.3 Hz), 3.48 (2H, s), 3.60 (2H, t, J=6.5 Hz), 3.86 (3H, s), 4.02 (2H, t, J=6.3 Hz), 6.47 (1H, br s), 6.64—7.21 (4H, m)
5e[b]	c: 3420, 1660, 1340, 1260, 1135	1.21—2.44 (12H, m), 2.84—3.35 (6H, m), 3.80—4.15 (4H, m), 4.34 (3H, s), 6.68—7.31 (4H, m), 8.01—8.22 (1H, br)
5f[a]	n: 3300, 1650, 1440, 1260	1.38—1.48 (2H, m), 1.52—1.63 (4H, m), 2.02 (2H, qt, J=6.0 Hz), 2.17 (2H, qt, J=7.0 Hz), 2.32—2.44 (6H, m), 3.38 (2H, t, J=7.0 Hz), 3.45 (2H, s), 3.48 (2H, q, J=6.0 Hz), 3.90 (3H, s), 4.04 (2H, t, J=6.0 Hz), 6.38—7.22 (5H, m)
5g[a]	k: 3320, 1640, 1580, 1345	1.43—1.53 (2H, m), 1.61—1.70 (4H, m), 1.99 (2H, qt, J=6.0 Hz), 2.25 (2H, qt, J=7.0 Hz), 2.44 (2H, t, J=7.0 Hz), 2.48—2.56 (4H, m), 3.45 (2H, q, J=6.0 Hz), 3.57 (2H, s), 3.78 (2H, t, J=7.0 Hz), 4.06 (2H, t, J=6.0 Hz), 4.34 (3H, s), 6.43 (1H, br s), 6.78—7.23 (4H, m)
5h[b]	n: 3290, 1645, 1445, 1365	1.37—1.66 (6H, m), 2.02 (2H, qt, J=6.0 Hz), 2.26—2.48 (4H, m), 3.10 (2H, t, J=7.0 Hz), 3.30 (2H, s), 3.44 (2H, s), 3.52 (2H, q, J=6.0 Hz), 3.85 (3H, s), 4.07 (2H, t, J=6.0 Hz), 4.49 (2H, t, J=7.0 Hz), 6.68—7.33 (5H, m)
5i[b]	n: 3400, 1665, 1275, 1255, 1110	1.29—1.72 (6H, m), 2.03 (2H, qt, J=6.0 Hz), 2.26—2.48 (4H, m), 3.43 (2H, s), 3.55 (4H, t, J=6.0 Hz), 3.88 (3H, s), 3.90—4.17 (4H, m), 4.00 (2H, s), 6.65—7.28 (5H, m)
5j[b]	n: 3320, 1650, 1445, 1255	1.33—1.74 (6H, m), 2.02 (2H, qt, J=6.0 Hz), 2.27—2.53 (4H, m), 3.08 (4H, br s), 3.23 (2H, s), 3.47 (2H, s), 3.51 (2H, q, J=6.0 Hz), 3.98 (3H, s), 4.07 (2H, t, J=6.0 Hz), 6.71—7.34 (5H, m)
5k[b]	c: 3320, 1685, 1475, 1265	1.38—1.72 (6H, m), 2.03 (2H, qt, J=6.0 Hz), 2.22—2.46 (4H, m), 3.43 (2H, s), 3.46 (2H, q, J=6.0 Hz), 3.88 (2H, s), 3.99 (2H, t, J=6.0 Hz), 4.07 (3H, s), 6.64—7.59 (5H, m)
5l[b]	n: 3290, 1655, 1485, 1260	1.38—1.69 (6H, m), 1.99 (2H, qt, J=6.0 Hz), 2.23—2.48 (4H, m), 3.43 (2H, s), 3.49 (2H, q, J=6.0 Hz), 3.87 (2H, s), 4.02 (2H, t, J=6.0 Hz), 4.28 (3H, s), 6.67—7.31 (5H, m)
5m[b]	n: 3290, 1685, 1550, 1445, 1255	1.33—1.71 (6H, m), 2.12 (2H, qt, J=6.0 Hz), 2.29—2.47 (4H, m), 3.43 (2H, s), 3.71 (2H, q, J=6.0 Hz), 4.11 (2H, t, J=6.0 Hz), 4.36 (3H, s), 6.70—7.32 (4H, m), 7.89—8.18 (1H, br)
5n[b]	n: 3320, 1680, 1545, 1440, 1250	1.31—1.73 (6H, m), 2.13 (2H, qt, J=6.0 Hz), 2.23—2.48 (4H, m), 3.44 (2H, s), 3.74 (2H, q, J=6.0 Hz), 4.13 (2H, t, J=6.0 Hz), 4.42 (3H, s), 6.70—7.30 (4H, m), 7.52—7.83 (1H, br)
5o[b]	c: 3450, 1665, 1515, 1450, 1265	1.67—2.73 (14H, m), 3.29—3.63 (6H, m), 3.89 (3H, s), 4.05 (2H, t, J=6.0 Hz), 6.38—6.61 (1H, br), 6.69—7.32 (4H, m)
5p[b]	c: 3450, 1660, 1450, 1265	1.92—2.63 (12H, m), 2.99 (1H, br), 3.27—3.59 (6H, m), 3.88 (3H, s), 4.03 (2H, t, J=6.0 Hz), 4.19—4.42 (1H, m), 6.54—7.34 (5H, m)
5q[b]	n: 3300, 1645, 1445, 1265	1.84—2.48 (6H, m), 2.23 (6H, s), 3.25—3.67 (6H, m), 3.89 (3H, s), 4.05 (2H, t, J=6.0 Hz), 6.18—6.42 (1H, br), 6.63—7.38 (4H, m)
5r[b]	n: 3280, 1645, 1445, 1260	1.94—2.64 (12H, m), 3.29—3.68 (8H, m), 3.89 (3H, s), 4.04 (2H, t, J=6.0 Hz), 6.38—6.57 (1H, br), 6.67—7.29 (4H, m)

a) 360 MHz. *b*) 90 MHz. *c*) c: $CHCl_3$, k: KBr, n: neat.

stirred at room temperature for 30 min. The resulting mixture was made alkaline with 10% NaOH, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O and dried over $MgSO_4$. After removal of the solvent, the crystalline materials obtained were recrystallized from a mixture of C_6H_6 and hexane to give pure **16** (440 mg) in a quantitative yield. mp 124.5 °C. *Anal.* Calcd for $C_{17}H_{26}N_6O$: C, 61.79; H, 7.93; N, 25.44. Found: C, 61.96; H, 8.03; N, 25.17. IR ν (KBr): 3280 (NH), 1630 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.46 (2H, m, 4-CH_2 of piperidine), 1.53—1.59 (4H, m, 3,5-CH_2 of piperidine), 2.16 (2H, qt, J=6.0 Hz, OCH_2-$\underline{CH_2}$-CH_2N), 2.31—2.41 (4H, m, 2,6-CH_2 of piperidine), 3.42 (2H, s, $ArCH_2$), 3.67 (2H, q, J=6.0 Hz, CH_2NH), 3.73 (3H, s, CH_3), 4.09 (2H, t, J=6.0 Hz, OCH_2), 5.47 (1H, t, J=6.0 Hz, NH), 6.70—7.20 (4H, m, ArH).

Ethyl 3-[*N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]aminopropionate (17) 1. A mixture of **6** (418 mg, 1.7 mmol) and ester **12c** (410 mg, 1.9 mmol) in toluene (5 ml) was stirred for 4 h in refluxing toluene. The resulting mixture was extracted twice with 3 N HCl. The acidic aqueous layer was made alkaline with 4 N NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, followed by brine, dried over $MgSO_4$ and evaporated *in vacuo* to give an oil. The oil was purified by column chromatography on silica gel with a (10 : 1) mixture of $CHCl_3$ and MeOH to give pure **17** (223 mg) as an oil in a 38% yield. High-resolution MS: 348.2420 (Calcd for $C_{20}H_{32}N_2O_3$: 348.2413). MS m/z 348 (M^+). IR ν (neat): 2925, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.0 Hz), 1.41—1.44 (2H, m), 1.54—1.63 (4H, m), 1.96 (2H, q, J=6.7, 6.0 Hz), 2.36—2.42 (4H, m), 2.52 (2H, t, J=6.4 Hz), 2.82 (2H, t, J=6.7 Hz), 2.91 (2H, t, J=6.4 Hz), 3.46 (2H, s), 4.03 (2H, t, J=6.0 Hz), 4.13 (2H, q, J=7.0 Hz), 6.74—7.23 (4H, m).

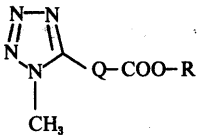
2. A mixture of **6** (1.03 g, 4.1 mmol), ester **12c** (1.80 g, 8.3 mmol) and C_2H_5ONa [Na (95 mg)] in dry EtOH (20 ml) was stirred for 1 h at room temperature. After removal of the solvent, the residue obtained was dissolved in 3 N HCl and extracted with CH_2Cl_2. Work-up in a procedure similar to procedure 1 gave **17** (608 mg) in a 42% yield.

3. The reaction of **6** (703 mg, 2.8 mmol) with ester **12d** (781 mg, 3.1 mmol) in toluene (10 ml) according to procedure 1 gave **17** (271 mg) in a 27% yield.

4. A mixture of **6** (146 mg, 0.59 mmol) and ethyl acrylate (60 mg, 0.61 mmol) in toluene (5 ml) was stirred for 10 h at 70 °C. Work-up in procedure 1 gave **17** (119 mg) in a 58% yield. Compound **17**, prepared by procedures 2—4, was assinged on the basis of IR, ^{1}H-NMR and MS spectral data, compared with those of **17** prepared by procedure 1.

***N*-[3-{3-(Piperidinomethyl)phenoxy}propyl]acrylamide (18)** A mixture of TzSH (581 mg, 5 mmol) and 60% NaH (203 mg, 5 mmol) in dry dimethylformamide (DMF) (10 ml) was stirred for 10 min at room temperature. A mixture of **9** (1.52 g, 4.5 mmol) and KI (747 mg, 4.5 mmol) in DMF (10 ml) was added dropwise to the above mixture at room temperature. The resulting mixture was stirred for 5 h at 70 °C and evaporated *in vacuo* to give an oil. The oil dissolved in C_6H_6 was extracted with 1 N HCl. The acidic aqueous layer was made alkaline with 4 N NaOH and extracted C_6H_6. The C_6H_6 layer was washed with brine and H_2O, dried over $MgSO_4$ and evaporated *in vacuo* to crude oil **18**, which was purified by column chromatography on silica gel with a (5 : 1) mixture of $CHCl_3$ and MeOH to give pure **18** (1.21 g) as an oil in an 88% yield. High-resolution MS: 302.2009 (Calcd for $C_{18}H_{26}N_2O_2$: 302.1994). MS m/z (M^+) 302. IR ν (neat): 3270, 2420, 1650, 1440 cm^{-1}. ^{1}H-NMR

TABLE III. 1-Methyl-1*H*-tetrazolylalkanoic Acid Ester (**12**)



Compd. No.	R	Q	Formula	Ref.
12a	CH_3	CH_2S–[a]	$C_5H_8N_4O_2S$	2
12b	CH_3	CH_2SO_2–[a]	$C_5H_8N_4O_4S$	2
12c	C_2H_5	CH_2CH_2S–[a]	$C_7H_{12}N_4O_2S$	12
12d	C_2H_5	$CH_2CH_2SO_2$–[a]	$C_7H_{12}N_4O_4S$	This work
12e	CH_3	$CH_2CH_2CH_2S$–[a]	$C_7H_{12}N_4O_2S$	12
12f	CH_3	$CH_2CH_2CH_2SO_2$–[a]	$C_7H_{12}N_4O_4S$	This work
12g	CH_3	CH_2	$C_5H_8N_4O_2$	13
12h[b]	CH_3	CH_2	$C_5H_8N_4O_2$	13
12i	CH_3	$CH_2SCH_2CH_2S$–[a]	$C_7H_{12}N_4O_2S_2$	This work
12j	CH_3	$CH_2OCH_2CH_2S$–[a]	$C_7H_{12}N_4O_3S$	This work
12k	CH_3	$CH_2SCH_2CH_2$–[a]	$C_7H_{12}N_4O_2S$	12
12l	C_2H_5	—[c]	$C_5H_8N_4O_2$	8
12m[b]	C_2H_5	—[c]	$C_5H_8N_4O_2$	8

a) Binding site to tetrazole ring. *b*) 1*H*-2-Methyltetrazole analogue. *c*) Direct binding to tetrazole ring.

($CDCl_3$) δ: 1.43—1.46 (2H, m), 1.55—1.60 (4H, m), 2.05 (2H, dd, J=6.0 Hz), 2.38 (4H, br s), 3.44 (2H, s), 3.54 (1H, t, J=6.0 Hz), 3.56 (1H, t, J=6.0 Hz), 4.07 (2H, t, J=6.0 Hz), 5.63 (1H, dd, J=10.2 Hz), 6.10 (1H, dd, J=10.2 Hz), 6.06—6.13 (1H, br s), 6.26 (1H, dd, J=1.8, 17.2 Hz), 6.77—7.21 (4H, m).

Preparation of 1-Methyl-1*H*-tetrazolylalkanoic Acid Esters 12 **Methyl 4-(1-Methyl-1*H*-tetrazol-5-ylsulfonyl)butyrate (12f)** A solution of **12e** (2.17 g, 0.01 mol) and *m*-CPBA (4.33 g, 0.02 mol) in C_6H_6 (40 ml) was stirred for 1 h at 70 °C. The reaction mixture was allowed to stand overnight at room temperature, yielding crystalline materials. After removal of the crystalline materials by filtration, the C_6H_6 layer was washed with 10% $Na_2S_2O_3$, followed by saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. After removal of the solvent, the residue obtained was purified by column chromatography with a (10 : 1) mixture of $CHCl_3$ and MeOH to give pure **12f** (2.36 g) in a 95% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (2H, q, J=7.0 Hz), 2.58 (2H, t, J=7.0 Hz), 3.70 (3H, s), 3.78 (2H, t, J=7.0 Hz), 4.36 (3H, s). IR ν (neat): 1730, 1340, 1145 cm^{-1}.

Ethyl 3-(1-Methyl-1*H*-tetrazol-5-ylsulfonyl)propionate (12d) **12d** was prepared in a 65% yield from **12c** and *m*-CPBA by a procedure similar to that used for **12f**.

Methyl 2-[2-(1-Methyl-1*H*-tetrazol-5-ylthio)ethoxy]acetate (12j) A mixture of 5-(2-hydroxyethylthio)-1-methyl-1*H*-tetrazole[12] (2.23 g, 0.014 mol) and NaH (60% purity; 561 mg, 0.014 mol) in dry DMF (20 ml) was stirred for 10 min at room temperature. Then, methyl 2-bromoacetate (2.30 g, 0.015 mol) was added to the reaction mixture. The resulting mixture was stirred for 2 h at room temperature and poured into ice-water. The mixture was made acidic with 1 N HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine and evaporated to give **12j** (1.94 g) as an oil in a 60% yield. ^{1}H-NMR ($CDCl_3$) δ: 3.57 (2H, t, J=5.5 Hz), 3.75 (3H, s), 3.93 (2H, t, J=5.5 Hz), 3.94 (3H, s), 4.13 (2H, s). IR ν (neat) 1750, 1275, 1210, 1130 cm^{-1}.

Methyl 2-[2-(1-Methyl-1*H*-tetrazol-5-ylthio)ethylthio]acetate (12i) **12i** was prepared from 5-(2-chloroethylthio)-1-methyl-1*H*-tetrazole[12] (100 mg, 0.56 mmol) and methyl thioglycolate (73 mg, 0.68 mmol) by a procedure similar to that used for **12j** in a 78% yield. ^{1}H-NMR ($CDCl_3$) δ: 3.18 (2H, t, J=7.0 Hz), 3.34 (2H, s), 3.76 (3H, s), 3.90 (3H, s), 4.54 (2H, t, J=7.0 Hz). IR ν (neat): 1735, 1365, 1300 cm^{-1}.

Methyl 2-(1-methyl-1*H*-tetrazol-5-ylthio)acetate (**12a**)[2] and its sulfonyl (**12b**),[2] ethyl 3-(1-methyl-1*H*-tetrazol-5-ylthio)propionate (**12c**),[12] 4-(1-methyl-1*H*-tetrazol-5-ylthio)butyrate (**12e**),[12] 1-methyl- and 2-methyl-5-methoxycarbonylmethyl-1*H*-tetrazoles (**12g** and **12h**),[13] 2-[2-(1-methyl-1*H*-tetrazol-5-ylethyl)thio]acetate (**12k**)[12] and 1-methyl- and 2-methyl-5-ethoxycarbonyl-1*H*-tetrazoles (**12l** and **12m**)[8] were prepared by procedures descibed in the literature, respectively. The structure of **12** is shown in Table III.

Biological Method Gastric acid antisecretory activity in rats was tested by the reported method.[1]

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