Anti-*Helicobacter pylori* Agents. 1. 2-(Alkylguanidino)-4-furylthiazoles and Related Compounds

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A series of 2-(alkylguanidino)-4-[5-(acetamidomethyl)furan-2-yl]thiazoles and related compounds were synthesized and evaluated for antimicrobial activity against *Helicobacter pylori*, inhibitory effect on gastric acid secretion, and histamine H_2-receptor antagonist activity. Introduction of alkyl substituents on the guanidino moiety resulted in a significant increase in antimicrobial activity, which was associated with the alkyl chain length. Of the compounds obtained, the *n*-hexylguanidino derivative **13** demonstrated a 250-fold improvement in activity (MIC = 0.11 μg/mL) over the unsubstituted guanidino derivative **7**. Alkyl-substituted guanidino derivatives also displayed gastric antisecretion and H_2-antagonist activities. However, a simple correlation between the alkyl chain length and the activities was not found in these assays. Replacement of the guanidine with other bioisosteric groups (thiourea, urea, or (dimethylamino)methyl) resulted in loss of all activities tested. Thus the guanidino moiety was found to be essential for activity in this series of compounds.

Since the initial isolation from gastric disease patients,[1] the clinical importance of *Helicobacter pylori* (*H. pylori*) has been pursued for over 10 years. As a result, it is now widely accepted that *H. pylori* is a major causative factor in peptic ulcer disease, and eradication of the organism results in a dramatic decrease in the recurrence rate in peptic ulcer patients.[2−14] Recently, the National Institutes of Health consensus conference on *H. pylori* stated that all ulcer patients with *H. pylori* infection should be treated with antimicrobial agents in addition to gastric antisecretory drugs.[15] Although the optimal protocol for eradication has not been established, a variety of drugs with susceptibility for *H. pylori*, such as antibiotics (amoxicillin and clarithromycin), bactericidal agents (bismuth salt), and antiprotozoal agents (metronidazole), have been effective in the clinic. On the other hand, adverse effects (e.g., nausea, vomiting, and diarrhea) and acquired resistance have been problematic in these drugs.[9−14] Therefore the development of novel types of anti-*H. pylori* agents is of importance.

In the course of research on novel histamine H_2-receptor antagonists (H_2-antagonists), we found compound 7 possessed significant anti-*H. pylori* activity[16] which had not been observed in known H_2-antagonists before the report was published.[17] As a novel chemical lead consisting of a different structure from known antimicrobial agents, we focused on **7** to carry out chemical modifications to improve the antimicrobial potency. In this paper we describe the synthesis and the pharmacological evaluation, antimicrobial activity against *H. pylori* and the effects on gastric acid secretion and H_2-antagonism, of some 2-(alkylguanidino)-4-furylthiazoles and related compounds.

Chemistry

The synthetic pathways to the target compounds are shown in Scheme 1. Compounds **2**−**4** were obtained by cyclization of halo ketones (**1a**[18] or **1b**) with thioamide, amidinothiourea, or (dimethylamino)methylthioamide,[19] respectively. Treatment of **2** with benzoyl isothiocyanate gave the benzoylthiourea derivative **5**, which was hydrolyzed with sodium hydroxide to yield the thiourea derivative **6**. After methylation of **6** with methyl iodide, reaction with amine or diamine afforded the guanidine (**8**−**13**) and imidazolidine (**14**) derivatives, respectively. The urea derivative **15** was prepared by reacting **2** with *n*-butyl isocyanate.

Results and Discussion

The compounds obtained were evaluated for antimicrobial activity against *H. pylori*, antisecretory activity on histamine-stimulated gastric acid secretion in lumen-perfused anesthetized rats, and H_2-antagonist activity using the histamine-stimulated chronotoropic response of the isolated guinea pig right atrium.[16] The results are summarized in Table 1. In anti-*H. pylori* activity, compound **3** which introduced a methyl group on the thiazole nucleus showed 3-fold less activity than the lead compound **7**. In contrast, introduction of a methyl group to the guanidino moiety (**8**) resulted in a 2-fold increase in activity over **7**. This encouraging result led us to prepare a series of compounds which contained an alkyl group on the guanidino moiety. The anti-*H. pylori* activity was enhanced as the alkyl chain length increased, and the improvement in activity was as follows: 9-fold for ethyl (**9**), 9-fold for isopropyl (**11**), 16-fold for *n*-propyl (**10**), 129-fold for *n*-butyl (**12**), and 250-fold for *n*-hexyl (**13**) in comparison with **7**. The potencies of these compounds were superior to those of the bactericidal drugs bismuth salt and metronidazole, which have been widely used for eradication therapy in *H. pylori* infection. On the other hand, imidazolidine derivative **14**, a structural rigid analog of **9**, dramatically decreased the activity. Flexibility at this position was required to show the activity.

Concerning gastric acid antisecretory activity, ethyl (**9**) and *n*-propyl (**10**) derivatives showed strong activity over **7** and the referenced H_2-antagonist cimetidine.

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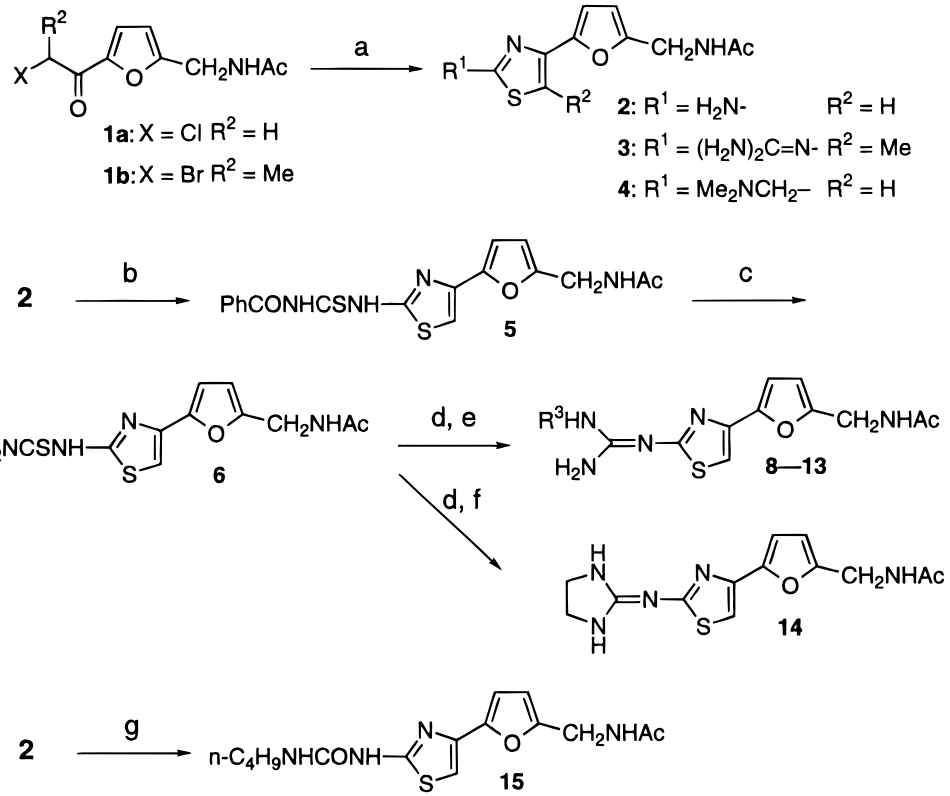
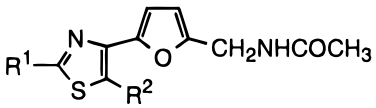
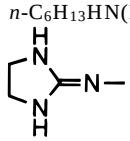
Scheme 1[a]



[a] Reagents: (a) $R^1C(=S)NH_2$/EtOH/reflux; (b) PhCONCS/acetone/reflux; (c) NaOH/MeOH (90%)−H_2O (10%)/60 °C; (d) MeI/MeOH/reflux; (e) R^3-NH_2/EtOH/reflux; (f) $H_2N(CH_2)_2NH_2$/EtOH/reflux; (g) *n*-C_4H_9NCO/DMF/60 °C.

Table 1. Antimicrobial Activity against *H. pylori*



compd	R^1	R^2	MIC (μg/mL)[b] mean	MIC (μg/mL)[b] range	inhibition (%) gastric secretion[c] (rat, 1 mg/kg iv)	inhibition (%) H_2-antagonism[d] (1×10^{-6} g/mL)
3	$(H_2N)_2C=NH-$	CH_3	76	25−200	3	10
4	$(CH_3)_2NCH_2-$	H	>200		4	6
6	$H_2NCSNH-$	H	>200		11	0
7[a]	$(H_2N)_2C=N-$	H	27	25−50	68	85
8	$CH_3HN(H_2N)C=N-$	H	12.5	12.5	24	25
9	$C_2H_5HN(H_2N)C=N-$	H	3.13	1.56−6.25	79	51
10	*n*-$C_3H_7HN(H_2N)C=N-$	H	1.67	0.78−3.13	97	81
11	*i*-$C_3H_7HN(H_2N)C=N-$	H	2.9	1.56−6.25	32	27
12	*n*-$C_4H_9HN(H_2N)C=N-$	H	0.21	0.1−0.39	45	78
13	*n*-$C_6H_{13}HN(H_2N)C=N-$	H	0.11	0.05−0.2	44	79
14		H	>100		18	8
15	*n*-$C_4H_9NHCONH-$	H	>100		9	0
bismuth subcitrate			18	12.5−25		
metronidazole			5.4	1.56−25		
cimetidine			1130	800−1600	53	43

[a] Reference 16. [b] Minimum inhibitory concentration (MIC) was determined as the lowest drug concentration that inhibited macroscopic colonial growth. Mean MIC and range of MICs were obtained from the results of 10 different strains. [c] Inhibition of histamine-stimulated gastric acid secretion in lumen-perfused stomach of anesthetized rats ($n = 2$). [d] Inhibition of the histamine-stimulated chronotoropic response in the isolated guinea pig right atrium.

n-Butyl (**12**) and *n*-hexyl (**13**) derivatives exhibited marginal activity despite having potent H_2-antagonist activity. Methyl (**8**) and isopropyl (**11**) derivatives showed weak activities on both gastric secretion and H_2-antagonism assays. Thus in contrast with the result in the anti-*H. pylori* activity, lengthening the alkyl chain on the guanidino moiety was not crucial for gastric acid antisecretory and H_2-antagonist activities.

In order to identify the importance of the guanidino moiety, we prepared and examined the compounds in

which the guanidine was replaced by nonbasic bioisosteric functional groups: thiourea (**6**) or urea (**15**). We also tried to investigate the derivative with a (dimethylamino)methyl group (**4**) which has been known as a surrogate base for guanidine that could be found in the relationship between nizatidine[20] and famotidine.[21] However, these derivatives displayed a dramatic decrease in the activities for all assays tested. This result seems to be in contrast with that of our previous study on the conversion of the acetamido part at the 5-position of the furan ring. The acetamido group could be replaced by other functions such as cyanoguanidine or urea without a marked decrease in the activities.[16] Therefore it is conceivable that the guanidino moiety is essential for the anti-*H. pylori*, gastric acid antisecretory, and H_2-antagonist activities in these types of compounds.

Conclusions

In conclusion, some structure−activity relationships for anti-*H. pylori*, gastric acid antisecretory, and H_2-antagonist activities in a novel series of 4-furyl-2-modified thiazoles have been obtained. Introduction of several alkyl substituents on the guanidino moiety at the 2-position of the thiazole ring enhanced the anti-*H. pylori* activity in order of increasing alkyl chain length in the range of the investigation, C_1 to C_6. Of the compounds obtained, the *n*-hexyl (**13**) derivative demonstrated the highest activity (MIC = 0.11 μg/mL). Alkylguanidino derivatives also showed gastric acid antisecretory and H_2-antagonist activities. However, no simple correlation between the alkyl chain length and the activities was observed. Replacement of the guanidino moiety with other bioisosteric functional groups resulted in loss of all activities tested. These data indicate that the guanidino moiety is essential for the activity and provide information on a promising chemical modification to potentiate the anti-*H. pylori* activity of prototype compound **7**. Further extensive structure−activity relationships in this type of compound will be reported in due course.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were taken in Nujol using a Hitachi 260−10 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in dimethyl sulfoxide-d_6 (DMSO) with tetramethylsilane as the internal standard on a Bruker AC-200P spectrometer. Mass spectral measurements (MS) were made on a JEOL JMS D-300 mass spectrometer. Analytical results were within ±0.4% of the theoretical values unless otherwise indicated.

2-(Acetamidomethyl)-5-(2-bromopropionyl)furan (1b). $AlCl_3$ (23.0 g, 170 mmol) was added portionwise to a solution of 2-(acetamidomethyl)furan (10.0 g, 72 mmol) and 2-bromopropionyl bromide (23.0 g, 110 mmol) in CH_2Cl_2 (150 mL) at 10 °C, and the mixture was refluxed for 1 h with stirring. The reaction mixture was poured into ice−water, and the organic layer that separated was washed with water, dried over $MgSO_4$, and concentrated to dryness to give **1b** (16.2 g, 82%) as an oil: IR (film) 1730, 1660 cm^{-1}; ^{1}H NMR δ 1.71 (3H, d, J = 7 Hz), 1.85 (3H, s), 4.30 (2H, d, J = 5 Hz), 5.43 (1H, q, J = 7 Hz), 6.48 (1H, d, J = 4 Hz), 7.57 (1H, d, J = 4 Hz), 8.46 (1H, t, J = 5 Hz).

4-[5-(Acetamidomethyl)furan-2-yl]-2-guanidino-5-methylthiazole (3). A solution of **1b** (16.0 g, 58 mmol) and amidinothiourea (5.7 g, 49 mmol) in EtOH (150 mL) was refluxed for 2 h with stirring. After removal of the solvent, the residue was dissolved in AcOEt−water, and the mixture was acidified to pH 1 with 6 N HCl. The aqueous layer that separated was basified to pH 10 with 4 N NaOH and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated to give a residue, which was recrystallized from MeOH−dioxane to afford **3** (3.5 g, 21%): mp 247−248 °C; IR 3420, 3350, 1660 cm^{-1}; ^{1}H NMR δ 1.85 (3H, s), 2.40 (3H, s), 4.24 (2H, d, J = 5 Hz), 6.22 (1H, d, J = 3 Hz), 6.72 (4H, s), 8.20 (1H, t, J = 5 Hz). Anal. ($C_{12}H_{15}N_5O_2S$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-[(dimethylamino)-methyl]thiazole (4). A solution of 2-(acetamidomethyl)-5-(chloroacetyl)furan (**1a**)[18] (12.0 g, 56 mmol) and (dimethylamino)methylthioamide[19] (7.9 g, 67 mmol) in EtOH (120 mL) was refluxed for 2.5 h with stirring. After removal of the solvent, the residue was added to AcOEt−water, and the resulting mixture was acidified to pH 1 with 6 N HCl. The aqueous layer that separated was basified to pH 9 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$−MeOH (40/1) and recrystallized from AcOEt−hexane−IPE to afford **4** (2.6 g, 17%): mp 111−113 °C; IR 1630 cm^{-1}; ^{1}H NMR δ 1.89 (3H, s), 2.30 (6H, s), 3.76 (2H, s), 4.29 (2H, d, J = 5 Hz), 6.31 (1H, d, J = 3 Hz), 6.66 (1H, d, J = 3 Hz), 7.61 (1H, s), 8.28 (1H, br s); MS m/z 279 (M^+). Anal. ($C_{13}H_{17}N_3O_2S$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-(3-benzoylthioureido)thiazole (5). Benzoyl chloride (2.7 mL, 23 mmol) was added dropwise to a solution of NH_4SCN (1.9 g, 25 mmol) in Me_2CO (50 mL) under reflux, and the mixture was refluxed for a further 1 h. 4-[5-(Acetamidomethyl)furan-2-yl]-2-aminothiazole (**2**)[18] (5.2 g, 22 mmol) was added portionwise to the mixture, and the resulting mixture was refluxed for 2 h. After removal of the solvent, the residue was added to AcOEt−water. The resulting precipitate was collected by filtration and recrystallized from MeOH−IPE to give **5** (5.5 g, 62%): mp 213−214 °C; IR 3270, 1675, 1630 cm^{-1}; ^{1}H NMR δ 1.90 (3H, s), 4.37 (2H, d, J = 6 Hz), 6.40 (1H, d, J = 3 Hz), 6.80 (1H, d, J = 3 Hz), 7.42 (1H, s), 7.58−8.17 (5H, m), 8.40 (1H, t, J = 6 Hz), 12.00 (1H, s), 14.08 (1H, s). Anal. ($C_{18}H_{16}N_4O_3S_2$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-thioureidothiazole (6). A solution of NaOH (0.55 g, 14 mmol) in water (5 mL) was added to a suspension of **5** (5.4 g, 14 mmol) in MeOH (50 mL), and the mixture was stirred at 60 °C for 1 h. After removal of the solvent, the residue was added to AcOEt−water. The resulting precipitate was collected by filtration and recrystallized from MeOH−IPE to give **6** (3.0 g, 74%): mp 231−232 °C; IR 3270, 3190, 3140, 1635 cm^{-1}; ^{1}H NMR δ 1.86 (3H, s), 4.27 (2H, d, J = 6 Hz), 6.30 (1H, d, J = 3 Hz), 6.61 (1H, d, J = 3 Hz), 7.10 (1H, s), 8.28 (1H, t, J =6 Hz), 8.33 (2H, br s), 11.81 (1H, s). Anal. ($C_{11}H_{12}N_4O_2S_2$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-(*n*-butylguanidino)thiazole (12). General Procedure. A suspension of **6** (1.5 g, 5 mmol) and MeI (0.32 mL, 5 mmol) in MeOH (30 mL) was refluxed for 4 h with stirring. After removal of the solvent, *n*-butylamine (5 mL) and EtOH (30 mL) were added to the residue, and the resulting mixture was refluxed for 42 h. The solution was concentrated to dryness, and the residue was dissolved in water. The solution was basified to pH 10 with 20% aqueous K_2CO_3 and extracted with AcOEt−THF. The extract was dried over $MgSO_4$ and concentrated to give a residue, which was recrystallized from AcOEt to afford **12** (0.3 g, 20%): mp 147−148 °C; IR 3460, 3310, 3200, 1640 cm^{-1}; ^{1}H NMR δ 0.91 (3H, t, J = 7 Hz), 1.29−1.48 (4H, m), 1.85 (3H, s), 3.16 (2H, q, J = 7 Hz), 4.26 (2H, d, J = 5.5 Hz), 6.30 (1H, d, J = 3 Hz), 6.54 (1H, d, J = 3 Hz), 6.77 (1H, s), 7.32 (2H, br s), 8.34 (1H, t, J = 5.5 Hz); MS m/z 335 (M^+). Anal. ($C_{15}H_{21}N_5O_2S$) C, H, N.

The following compounds were prepared according to a similar procedure.

4-[5-(Acetamidomethyl)furan-2-yl]-2-(methylguanidino)thiazole (8): yield 34%, mp 188−189 °C (EtOH); IR 3380, 3260, 1635 cm^{-1}; ^{1}H NMR δ 1.85 (3H, s), 2.74 (3H, d, J = 5 Hz), 4.26 (2H, d, J = 5.5 Hz), 6.29 (1H, d, J = 3 Hz), 6.60 (1H, d, J = 3 Hz), 6.77 (1H, s), 7.42 (1H, s), 7.42 (1H, s), 7.42 (2H, br s), 8.35 (1H, t, J = 5.5 Hz). Anal. ($C_{12}H_{15}N_5O_2S$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-(ethylguanidino)-thiazole (9): yield 45%, mp 170−171 °C (EtOH−IPE); IR 3470, 3280, 3100, 1650 cm^{-1}; ^1H NMR δ 1.10 (3H, t, $J = 7$ Hz), 1.85 (3H, s), 3.12−3.25 (2H, m), 4.26 (2H, d, $J = 5.5$ Hz), 6.29 (1H, d, $J = 3$ Hz), 6.56 (1H, d, $J = 3$ Hz), 6.77 (1H, s), 7.38 (2H, br s), 8.35 (1H, t, $J = 5.5$ Hz). Anal. ($C_{13}H_{17}N_5O_2S$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-(*n*-propylguanidino)thiazole (10): yield 48%, mp 155−156 °C (EtOH−IPE); IR 3460, 3320, 3210, 1640 cm^{-1}; ^1H NMR δ 0.91 (3H, t, $J = 7$ Hz), 1.42−1.60 (2H, m), 1.85 (3H, s), 3.08−3.17 (2H, m), 4.26 (2H, d, $J = 5.5$ Hz), 6.30 (1H, d, $J = 3$ Hz), 6.55 (1H, d, $J = 3$ Hz), 6.77 (1H, s), 7.33 (2H, br s), 8.35 (1H, t, $J = 5.5$ Hz). Anal. ($C_{14}H_{19}N_5O_2S$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-(isopropylguanidino)thiazole (11): yield 43%, mp 104−105 °C (EtOH−IPE); IR 3420, 3350, 3220, 1630 cm^{-1}; ^1H NMR δ 1.13 (6H, d, $J =$ 6.5 Hz), 1.86 (3H, s), 3.81−3.91 (1H, m), 4.27 (2H, d, $J = 5.5$ Hz), 6.30 (1H, d, $J = 3$ Hz), 6.55 (1H, d, $J = 3$ Hz), 6.77 (1H, s), 7.33 (2H, br s), 8.35 (1H, t, $J = 5.5$ Hz). Anal. ($C_{14}H_{19}N_5O_2S$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-(*n*-hexylguanidino)thiazole (13): yield 47%, mp 138−139 °C (AcOEt); IR 3470, 3340, 3225, 1635 cm^{-1}; ^1H NMR δ 0.87 (3H, t, $J = 6.5$ Hz), 1.05−1.60 (8H, m), 1.85 (3H, s), 3.16 (2H, q, $J = 6.5$ Hz), 4.26 (2H, d, $J = 5.5$ Hz), 6.29 (1H, d, $J = 3$ Hz), 6.54 (1H, d, $J = 3$ Hz), 7.06 (1H, s), 7.32 (2H, s), 8.34 (1H, t, $J = 5.5$ Hz). Anal. ($C_{17}H_{25}N_5O_2S \cdot {}^1/_2H_2O$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-(imidazolidin-2-ylimino)thiazole (14): yield 33%, mp 239−240 °C (MeOH−THF); IR 3290, 3105, 1630 cm^{-1}; ^1H NMR δ 1.88 (3H, s), 3.57 (4H, s), 4.33 (2H, d, $J = 6$ Hz), 6.33 (1H, d, $J = 3$ Hz), 6.82 (1H, s), 6.85 (1H, d, $J = 3$ Hz), 7.68 (2H, s), 8.33 (1H, t, $J = 6$ Hz); MS *m*/*z* 305 (M^+). Anal. ($C_{13}H_{15}N_5O_2S$) C, H, N.

4-[5-(Acetamidomethyl)furan-2-yl]-2-(3-*n*-butylureido)-thiazole (15). A solution of **2** (0.50 g, 2.1 mmol) and *n*-butyl isocyanate (0.23 g, 2.3 mmol) in DMF (5 mL) was stirred at 70 °C for 15 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed several times with water, dried over $MgSO_4$, and concentrated to dryness. The residue was triturated with Et_2O and recrystallized from MeOH−AcOEt to give **15** (0.53 g, 75%): mp 186−188 °C; IR 3340, 1645, 1635 cm^{-1}; ^1H NMR δ 0.89 (3H, t, $J =$ 7 Hz), 1.23−1.46 (4H, m), 1.85 (3H, s), 3.08−3.17 (2H, m), 4.27 (2H, d, $J = 5.5$ Hz), 6.31 (1H, d, $J = 3$ Hz), 6.48 (1H, t, $J = 6$ Hz), 6.55 (1H, d, $J = 3$ Hz), 7.05 (1H, s), 8.35 (1H, t, $J = 6.5$ Hz); MS *m*/*z* 337 ($M^+ + 1$). Anal. ($C_{15}H_{20}N_4O_3S$) C, H, N.

Antimicrobial Activity. *In vitro* antimicrobial activity against *H. pylori* was determined by the agar dilution method. Test strain was precultured in Brucella agar containing 3% horse serum and 2% starch at 37 °C for 3 days and suspended in buffered saline to give the turbidity equivalent to McFarland no. 1; 10^2-fold dilution of the bacterial suspensions was inoculated with a multipoint replicator onto a Brucella agar plus 7% lysed horse blood plate containing serial 2-fold dilutions of each drug at 37 °C for 3 days. Incubation was carried out in an atmosphere of 10% CO_2. Minimum inhibitory concentration (MIC) was read after incubation as the lowest drug concentration that inhibited macroscopic colonial growth. Mean MIC was determined from the MICs in 10 strains: *H. pylori* 8001, 8003, 8004, 8007, 8008, 8009, 8011, 9005, FP1530, and FP1532.

Gastric Antisecretory Activity in Lumen-Perfused Rats. Male Sprague−Dawley rats weighing about 250 g were used. Rats were deprived of food for 24 h. The animals were anesthetized with 1.25 g/kg urethane intraperitoneally. The abdomen was opened, and the gastric lumen was perfused with saline throughout the experiment. The perfusate was titrated by an autotitrator with 25 mM NaOH as a titrant. Gastric secretion was stimulated by intravenous infusion with histamine (3 mg/kg/h). After reaching a plateu, the test compound (1 mg/kg) was given intravenously. The effect of the drug was expressed as maximal inhibition by acid output.

Histamine H_2-Receptor Antagonist Activity. The atrial strip isolated from guinea pig was suspended under an initial tension of 0.3−0.6 g in an organ bath containing Thyrode solution at 30 °C and aerated by 95% O_2−5% CO_2 gas. The beating rate and the amplitude of contraction of the atrium were recorded by means of a transducer and a polygraph. Histamine hydrochloride (1×10^{-6} g/mL) was added to the beating fluid, and the increase in the beating rate after dosing was measured. Addition of test compounds (1×10^{-6} g/mL) was done 30 min after washing out the histamine hydrochloride. The percent inhibitory effect of the test compound was calculated by comparing histamine-induced increases in beating rate before and 30 min after dosing with the test compounds.

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