Anti-*Helicobacter pylori* Agents. 3. 2-[(Arylalkyl)guanidino]-4-furylthiazoles

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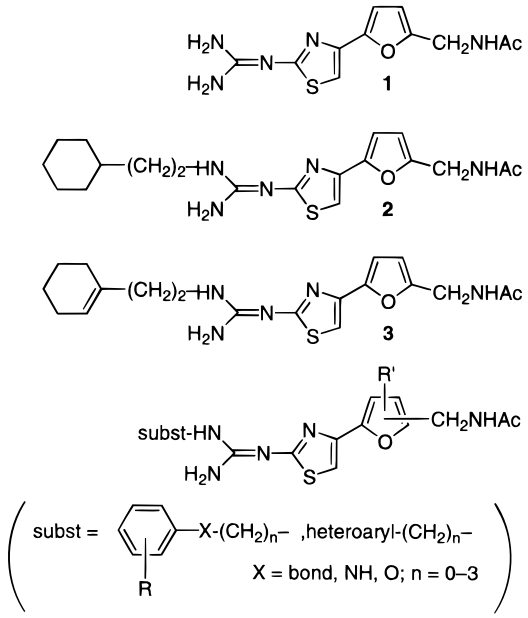
A series of 2-[(arylalkyl)guanidino]-4-[(5-acetamidomethyl)furan-2-yl]thiazoles and some 4-acetamidomethyl positional isomers were synthesized and evaluated for antimicrobial activity against *Helicobacter pylori*. Among the compounds that had potent antimicrobial activity (MIC < 0.1 μg/mL), compounds **31** and **36** additionally possessed H2 antagonist and gastric antisecretory activities. Though compound **51**, an analogue incorporating a methyl group onto the furan nucleus of **36**, and compound **54**, a positional isomer of **51**, also showed potent anti-*H. pylori* activity, the H2 antagonism profile was eliminated from these compounds. Thus, two types of potent anti-*H. pylori* agents could be derived from the same scaffold.

Introduction

Peptic ulcers are caused by an imbalance between gastrointestinal defensive factors (forces of mucosal resistance) and aggresive factors (gastric acid and pepsin secretion), a concept known as Shay's balance theory. In light of this theory, many antiulcer drugs which have gastroprotective effects and/or gastric antisecretory effects have been developed over the last three decades. Among them, strong antisecretory agents, such as histamine H2-receptor antagonists (H2 antagonists) and proton−potassium ATPase inhibitors, dramatically increased the healing ratio for peptic ulcers to 90−95%. On the other hand, the high ratio of recurrence of the ulcers following the cessation of treatment with such antisecretory agents has been problematic. Therefore recurrence has gained recognition as a part of the natural history of peptic ulcers.

The discovery of a new spiral organism in stomach named *Helicobacter pylori* (*H. pylori*)[1] dramatically changed the concept of pathology in peptic ulcers. After numerous studies on the pathogenic role, it is now widely accepted that *H. pylori* is a major causative factor in peptic ulcer diseases, and eradication of this bacteria results in a dramatic decrease in the recurrence rate in peptic ulcer patients.[2−14] A variety of drugs with susceptibility for *H. pylori*, such as antibiotics (β-lactams, macrolides, and quinolones), bactericidal agents (bismuth salts), and an antiprotozoal agent (metronidazole), have been clinically useful. However, several adverse effects (e.g., nausea, vomiting, and diarrhea) have been problematic in these drugs.[9−14] Besides, as these drugs possess a wide bactericidal spectrum, the prescription of them for elimination of *H. pylori* would disturb the treatment in various systematic infectious diseases because of acquired resistance to the other bacteria. Therefore the development of novel types of anti-*H. pylori* agents is needed.

In the course of research on a novel class of H2 antagonists, we have prepared several series of compounds with new structural features. Among them, compound **1**, a structurally rigid analogue of traditional H2 antagonists, demonstrated a significant antimicrobial activity against *H. pylori* (MIC = 27 μg/mL), which was roughly comparable to that of bismuth subcitrate (MIC = 18 μg/mL).[15] With this finding as the starting point of the research program exploring anti-*H. pylori* agents, we have carried out several kinds of modifications of **1** to obtain more potent anti-*H. pylori* agents.



In our previous papers,[16,17] we described some structure−activity relationships (SARs) in a series of compounds incorporating alkyl substituents into the guanidino moiety of **1**. Among the compounds obtained, a cyclohexylethyl derivative (**2**) showed strong anti-*H. pylori* activity (MIC = 0.069 μg/mL) and compound **3**, an unsaturated analogue of **2**, also maintained strong activity (MIC = 0.052 μg/mL). In pursuing further extensive SAR study in this series, these findings

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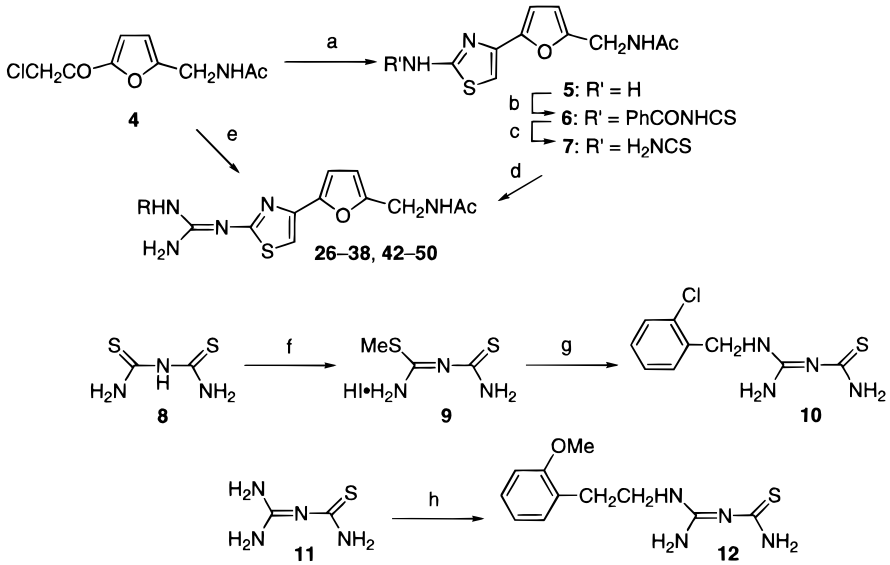
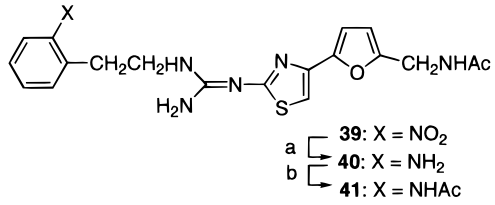
Scheme 1[a]



[a] Reagents: (a) H_2NCSNH_2/EtOH; (b) PhCONCS/Me_2CO; (c) NaOH/aq MeOH; (d) (i) MeI/MeOH, (ii) R-NH_2/EtOH; (e) **10** or **12**/EtOH; (f) MeI/MeOH; (g) 2-ClPhCH_2NH_2/EtOH; (h) 2-MeOPh$(CH_2)_2NH_2$/EtOH−AcOH.

Scheme 2[a]



[a] Reagents: (a) H_2/Pd−C/MeOH; (b) Ac_2O−Et_3N/CH_2Cl_2−DMF.

encouraged us to prepare a new series of compounds with an aromatic group in place of the alicyclic part. In this paper we describe the synthesis and the pharmacological evaluations of a series of 2-[(arylalkyl)guanidino]-4-furylthiazoles.

Chemistry

Most of the targeted compounds were synthesized by treatment of the thiourea derivative **7** with methyl iodide followed by reaction with the appropriate amines as previously described.[16] 2-[(Chlorobenzyl)guanidino]- and 2-[(methoxyphenethyl)guanidino]thiazoles (**34** and **36**) were obtained by cyclization of the chloroacetyl derivative **4** with the substituted guanidines **10** and **12** which were prepared from dithiobeulet (**8**) or amidinothiourea (**11**) as the starting material, respectively (Scheme 1). Reduction of the nitro group on **39** gave the 2-[(aminophenethyl)guanidino] derivative **40**, which was treated with acetic anhydride to afford the 2-(acetamidophenethyl) derivative **41** (Scheme 2).

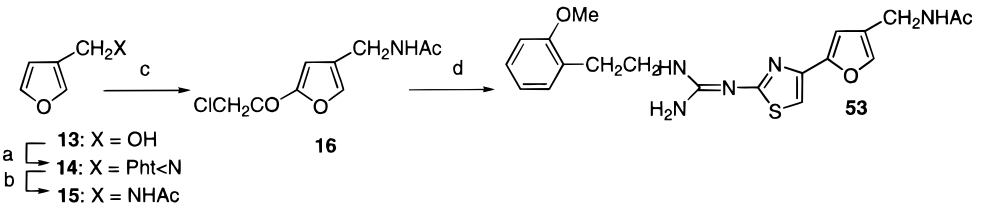
The synthetic pathways for the acetamidomethyl positional isomer of **36** and the derivatives incorporating a methyl or phenyl on the furan ring are shown in Schemes 3−5. Mitsunobu reaction of 3-(hydroxymethyl)-furan (**13**) with potassium phthalimide followed by treatment successively with hydrazine, acetic anhydride, and chloroacetyl chloride gave 2-(chloroacetyl)-4-acetamidofuran (**16**), which was cyclized with **12** to afford the desired compound **53**. Amidation of the methyl 2- or 3-methylfurancarboxylate (**17a** and **17b**) followed by successive reduction and acetylation yielded the 2- or 3-acetamidomethyl derivatives **19a** and **19b**. Friedel−Crafts acylation of **19a** and **19b** gave the chloroacetyl derivatives **20a** and **20b**, which were condensed with **12** to afford the required compounds **51** and **54**. Introduction of phenyl group on the furan ring was achieved by Suzuki coupling reaction on 3-furylborate, which was obtained from 3-bromofuran, with phenyl triflate. 3-Phenylfuran (**22**) was treated with chlorosulfonyl isocyanate to give the nitrile derivative **23**. Reduction of **23** followed by acetylation and then Friedel−Crafts acylation gave the chloroacetyl derivative **25**, which was condensed with **12** to afford the desired compound **52**.

Results and Discussion

The compounds obtained were evaluated for antimicrobial activity against *H. pylori*. Several derivatives with minimum inhibitory concentration (MIC) under 1 μg/mL were also tested for H2 antagonist and gastric antisecretory activities with a few exceptions. The results are summarized in Table 2.

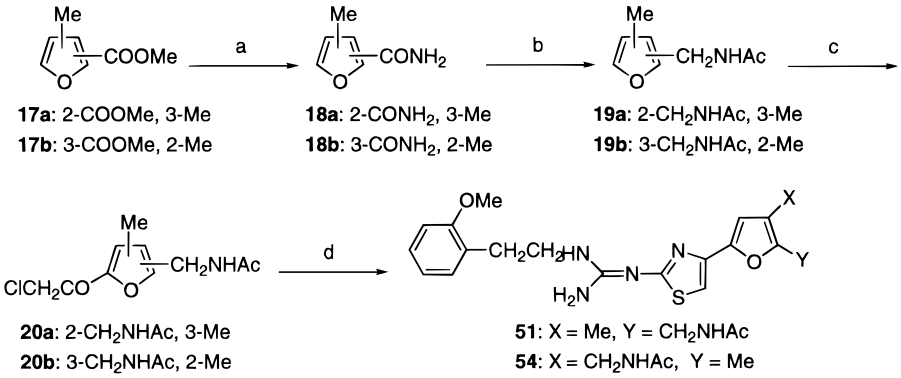
The anti-*H. pylori* activities of the benzyl (**27**) and phenethyl (**35**) derivatives were more potent than that of the phenylpropyl analogue **44**. Introduction of a 2-methoxy group (**28** and **36**) to the benzyl and phenethyl substituents increased the activity. The phenyl analogue **26** was less potent than **28** and **36**. Thus, regarding the length (n) of the alkyl chain connecting the phenyl and guanidino parts, $n = 1$ and 2 are preferable to $n = 0$ and 3. In the methoxy positional isomers, the order of potency was as follows: 2-methoxy (**28** and **36**) > 3-methoxy (**29** and **37**) > 4-methoxy (**30** and **38**). Conversion of the 2-MeO on **28** and **36** to EtO (**31**), Me (**33**), Cl (**34**), or NO_2 (**39**) did not produce a marked change in activity. On the other hand, conversion to substituents with an ionizable hydrogen, OH (**32**), NH_2 (**40**), and AcNH (**41**), displayed a considerable decrease in activity. Incorporation of a heteroatom into the connecting alkyl chain (**42** and **43**) also resulted in great loss of activity. In the heteroaryl series, the order

Scheme 3[a]



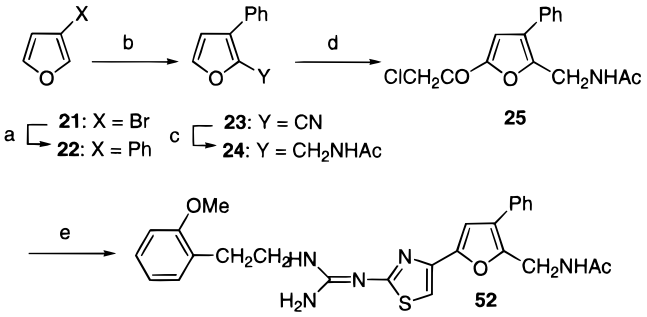
[a] Reagents: (a) potassium phthalimide/EtOOCN=NCOOEt/PPh_3/THF; (b) (1) H_2HNH_2/EtOH, (2) Ac_2O; (c) $ClCH_2COCl/AlCl_3/CH_2Cl_2$; (d) **12**/EtOH.

Scheme 4[a]



[a] Reagents: (a) $HCONH_2$/NaOMe; (b) (1) $LiAlH_4$/THF, (2) Ac_2O; (c) $ClCH_2COCl/AlCl_3/CH_2Cl_2$; (d) **12**/EtOH.

Scheme 5[a]



[a] Reagents: (a) (1) $B(i\text{-}C_3H_7O)_3/n$-BuLi/THF, (2) PhOTf/Pd-$(PPh_3)_4/Et_3N$/DMF; (b) $ClSO_2NCO/CH_2Cl_2$−DMF; (c) (1) $LiAlH_4$/Et_2O, (2) Ac_2O; (d) $ClCH_2COCl/AlCl_3/CH_2Cl_2$; (e) **12**/EtOH.

of potency roughly seems to follow the lipophilic nature of aromatics; i.e., thiophene (**47**) > furan (**46**) > pyridine (**48**). Similarly to the phenylalkyl series, the imidazolyl derivative **50** which has an ionizable hydrogen dramatically decreased the activity. From these SARs in anti-*H. pylori* activity, it can be concluded that (a) a one- or two-methylene length between the aryl and guanidino moieties is preferable as the connecting group, (b) the incorporation of a heteroatom to the connecting group is disadvantageous, and (c) an ionizable hydrogen is not tolerated in the arylalkyl substituent region.

To extend the SAR study within this series, we have also investigated the effects of an additional substitution on the furan ring and the acetamidomethyl positional isomers. Introduction of a methyl (**51**) to the adjacent position of the acetamidomethyl group on **36** maintained the activity; however, replacement of the methyl with phenyl (**52**) led to a dramatic decrease in activity. Compound **54**, the acetamidomethyl positional isomer of **51**, maintained high activity. On the other hand, compound **53**, the positional isomer of **36**, did not show any significant activity contrary to our expectation.

Concerning the gastric antisecretory and H2 antagonist activities, three compounds (**31**, **36**, and **37**) showed comparable potency to the referenced H2 antagonist, cimetidine. However, no clear correlations between these pharmacological activities and the structural features could be observed.

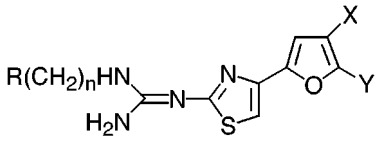
Finally, we have assessed the selectivity of two representative compounds from this study toward *H. pylori* (Table 3). The therapeutically useful drugs for the treatment of *H. pylori* eradication, bismuth salicylate, metronidazole, and amoxicillin, showed susceptibility for a variety of organisms. On the other hand, the antimicrobial activities of the representative compounds (**31** and **54**) were specific for *H. pylori*.

In conclusion, a series of 2-[(arylalkyl)guanidino]-4-furylthiazoles were prepared and evaluated as new structural anti-*H. pylori* agents. The anti-*H. pylori* activity strictly depends on the nature of the arylalkyl moiety. Especially, the existence of an ionizable hydrogen on the arylalkyl moiety caused a remarkable decrease in the anti-*H. pylori* activity. Therefore, it is conceivable that a lipophilic nature is required for the guanidino substituent region. Among the compounds tested, several compounds demonstrated potent anti-*H. pylori* activity with an MIC under 0.1 μg/mL. From the viewpoint of the pharmacological profile, these compounds could be categorized into two types: compounds with H2 antagonist activity (**31** and **36**) and compounds without H2 antagonist activity (**51** and **54**). The interesting conversion of the pharmacological profile was possible with only minor alteration of the substitution on the same scaffold.

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)

Table 1. Physical Properties for 2-[(Arylalkyl)guanidino]-4-furylthiazoles



compd	R	*n*	X	Y	mp (°C)	recryst solvent[a]	yield (%)	formula[b]
26	2-MeOPh	0	H	CH_2NHAc	132−133	E/M	48	$C_{18}H_{19}N_5O_3S$
27	Ph	1	H	CH_2NHAc	189−191	E/M	56	$C_{18}H_{19}N_5O_2S$
28	2-MeOPh	1	H	CH_2NHAc	159−160	E/M	60	$C_{19}H_{21}N_5O_3S$
29	3-MeOPh	1	H	CH_2NHAc	178−179	EA/M	54	$C_{19}H_{21}N_5O_3S\cdot C_2H_2O_4$
30	4-MeOPh	1	H	CH_2NHAc	154−156	I/M	71	$C_{19}H_{21}N_5O_3S\cdot 1/2H_2O$
31	2-EtOPh	1	H	CH_2NHAc	151−153	E/M	79	$C_{20}H_{23}N_5O_3S$
32	2-HOPh	1	H	CH_2NHAc	213−214	E/M	47	$C_{18}H_{19}N_5O_3S$
33	2-MePh	1	H	CH_2NHAc	143−145	E/M	71	$C_{19}H_{21}N_5O_2S$
34	2-Cl Ph	1	H	CH_2NHAc	164−165	E/EA	52	$C_{17}H_{16}ClN_5O_2S$
35	Ph	2	H	CH_2NHAc	100−102	EA	79	$C_{19}H_{21}N_5O_2S$
36	2-MeOPh	2	H	CH_2NHAc	188−190	EA/M	85	$C_{20}H_{23}N_5O_3S\cdot C_2H_2O_4$
37	3-MeOPh	2	H	CH_2NHAc	125−128	E/M	77	$C_{20}H_{23}N_5O_3S$
38	4-MeOPh	2	H	CH_2NHAc	147−148	E/M	34	$C_{20}H_{23}N_5O_3S$
39	2-NO_2Ph	2	H	CH_2NHAc	133−134	I/M	74	$C_{29}H_{20}N_6O_4S$
40	2-NH_2Ph	2	H	CH_2NHAc	161−162	E/EA	86	$C_{19}H_{22}N_6O_2S$
41	2-AcNHPh	2	H	CH_2NHAc	224−225	EA/M	57	$C_{21}H_{24}N_6O_3S\cdot 1/2H_2O$
42	PhNH	2	H	CH_2NHAc	113−115	M	51	$C_{19}H_{22}N_6O_2S$
43	2-MeOPhO	2	H	CH_2NHAc	170−171	E/EA	68	$C_{20}H_{23}N_5O_4S$
44	Ph	2	H	CH_2NHAc	117−118	E/EA	38	$C_{20}H_{23}N_5O_2S$
45	furan-2-yl	2	H	CH_2NHAc	182−183	T/M	53	$C_{16}H_{17}N_5O_3S$
46	furan-2-yl	2	H	CH_2NHAc	134−135	T/M	33	$C_{17}H_{19}N_5O_3S$
47	thiophen-2-yl	2	H	CH_2NHAc	163−164	T/M	54	$C_{17}H_{19}N_5O_2S_2$
48	pyridin-2-yl	2	H	CH_2NHAc	67−68	T/M	68	$C_{18}H_{20}N_6O_2S\cdot H_2O$
49	pyridin-4-yl	2	H	CH_2NHAc	237−239	M	80	$C_{18}H_{20}N_6O_2S$
50	imidazol-4-yl	2	H	CH_2NHAc	189−191	T/M	23	$C_{16}H_{19}N_7O_2S\cdot 1/2H_2O$
51	2-MeOPh	2	Me	CH_2NHAc	187−188	A/EA	91	$C_{21}H_{25}N_5O_3S\cdot HCl$
52	2-MeOPh	2	Ph	CH_2NHAc	161−163	E/M	26	$C_{26}H_{27}N_5O_3S$
53	2-MeOPh	2	CH_2NHAc	H	180−186	I/M	54	$C_{20}H_{23}N_5O_3S\cdot 1/4H_2O$
54	2-MeOPh	3	CH_2NHAc	Me	185−186	I/M	77	$C_{21}H_{25}N_5O_3S\cdot HCl$

[a] A = EtOH, E = Et_2O, EA = ethyl acetate, I = $(i\text{-Pr})_2O$, M = MeOH, T = toluene. [b] Analyses for C, H, and N are within ±0.4% of the theoretical values.

spectra were recorded in dimethyl sulfoxide-d_6 (DMSO) with tetramethylsilane as an internal standard on a Bruker AC-200P spectrometer. Mass spectral measurements (MS) were made on a JEOL JMS D-300 mass spectrometer. Analytical results are within ±0.4% of the theoretical values unless otherwise indicated. All extracted solutions were dried over magnesium sulfate and concentrated to dryness on a rotary evaporator under reduced pressure.

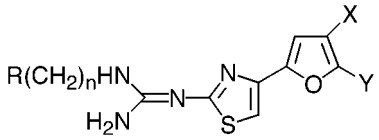
[(2-Chlorobenzyl)amidino]thiourea (10). A mixture of dithiobeulet (**8**) (3.7 g, 25 mmol) and MeI (1.6 mL, 25 mmol) in MeOH (50 mL) was refluxed for 3 h with stirring. After removal of the solvent, 2-chlorobenzylamine (14.1 g, 100 mmol) and EtOH (50 mL) were added to the residue, and the resulting mixture was refluxed for 3 h. The solution was concentrated to dryness. The residue was added to AcOEt−water, and the resulting mixture was acidified to pH 3 with 6 N HCl. The aqueous layer was separated, saturated with NaCl, and then extracted with AcOEt. The extract was made basic to pH 9 with 20% aqueous K_2CO_3. The resulting obtained organic layer was dried and concentrated to give a residue, which was recrystallized from AcOEt/Et_2O to afford **10** (4.9 g, 79%): mp 176−178 °C. IR: 3300, 3150, 1700, 1640 cm^{-1}. ^1H NMR: δ 4.68 (2H, d, J = 4.5 Hz), 7.30−7.60 (4H, m), 8.8 (1H, br s), 9.20−9.50 (3H, m), 10.00 (1H, br s), 11.80 (1H, br s). MS: m/z 243 and 245 ($M^+ + 1$). Anal. ($C_9H_{11}N_4ClS$) C, H, N.

[2-(2-Methoxyphenyl)ethylamidino]thiourea (12). A mixture of amidinothiourea (**11**) (20.6 g, 0.17 mol), 2-(2-methoxyphenyl)ethylamine (52.7 g, 0.34 mol), and AcOH (30 mL) in EtOH (100 mL) was refluxed for 22 h with stirring. The solution was poured into EtOH (80 mL)/water (720 mL), and the resulting precipitate was collected by filtration. A suspension of the material in water was adjusted to pH 8.5 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was dried and concentrated to give a residue, which was recrystallized from AcOEt/diisopropyl ether (IPE) to afford **12** (13.2 g, 30%): mp 102−103 °C. IR: 3460, 3325, 1645, 1620 cm^{-1}. ^1H NMR: δ 2.75 (2H, t, J = 7.5 Hz), 3.25−3.35 (2H, m), 3.79 (3H, s), 6.88 (1H, t, J = 7.4 Hz), 6.96 (1H, d, J = 7.4 Hz), 7.00 (4H, br s), 7.19 (1H, d, J = 7.4 Hz), 7.21 (1H, t, J = 7.4 Hz), 7.90 (1H, br s). MS: m/z 253 ($M^+ + 1$). Anal. ($C_{11}H_{16}N_4OS$) C, H, N.

3-(Phthalimidomethyl)furan (14). Diethyl azodicarboxylate (17.7 mL, 0.11 mol) was added dropwise to a solution of 3-(hydroxymethyl)furan (**13**) (10 g, 0.10 mol), phthalimide (15 g, 0.10 mol), and triphenylphosphine (29.4 g, 0.10 mol) in tetrahydrofuran (THF) (100 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. After removal of the solvent, the residue was added to water and extracted with AcOEt. The extract was dried and concentrated to give a residue, which was added to AcOEt/hexane, and the resulting insoluble material was removed by filtration. The filtered solution was concentrated to give a residue, which was chromatographed on silica gel eluting with AcOEt/hexane (1/4) to afford **14** (19.8 g, 85%). An analytical sample was obtained by recrystallization from aqueous DMF: mp 165−167 °C. IR: 1770, 1710 cm^{-1}. ^1H NMR: δ 4.62 (2H, s), 6.43−6.44 (1H, m), 7.59−7.61 (1H, m), 7.69 (1H, s), 7.82−7.92 (4H, m). MS: m/z 228 ($M^+ + 1$).

3-(Acetamidomethyl)furan (15). A solution of **14** (39 g, 0.17 mol) and hydrazine hydrate (10 mL, 0.20 mol) in EtOH (500 mL) was refluxed for 2 h with stirring. After cooling, the resulting insoluble material was removed by filtration. The filtered solution was concentrated, and the residue was added to AcOEt (100 mL). Ac_2O (35 mL, 0.37 mol) was added dropwise to the mixture at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. After removal of the insoluble material by filtration, the filtered solution was concentratred to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$/MeOH (95/5) to afford **15** (4.6 g, 25%) as an oil. IR (film): 3275, 1630 cm^{-1}. ^1H NMR: δ 1.83

Table 2. Pharmacological Activities of 2-[(Arylalkyl)guanidino]-4-furylthiazoles



compd	R	*n*	X	Y	MIC (μg/mL)[a] mean	MIC (μg/mL)[a] range	inhibition (%) gastric secretion (rat,[b] 1 mg/kg iv)	inhibition (%) H_2 antagonism[c] (1×10^{-6} g/mL)
26	2-MeOPh	0	H	CH_2NHAc	0.24	0.1−0.39		
27	Ph	1	H	CH_2NHAc	0.085	0.025−0.2	8	35
28	2-MeOPh	1	H	CH_2NHAc	0.035	0.0125−0.1	40	26
29	3-MeOPh	1	H	CH_2NHAc	0.074	0.025−0.2	37	28
30	4-MeOPh	1	H	CH_2NHAc	0.28	0.1−0.78		
31	2-EtOPh	1	H	CH_2NHAc	0.026	0.0125−0.05	62	42
32	2-HOPh	1	H	CH_2NHAc	5.8	1.56−12.5		
33	2-MePh	1	H	CH_2NHAc	0.091	0.025−0.2	41	88
34	2-Cl Ph	1	H	CH_2NHAc	0.11	0.025−0.2	11	50
35	Ph	2	H	CH_2NHAc	0.13	0.05−0.2	24	71
36	2-MeOPh	2	H	CH_2NHAc	0.052	0.025−0.1	54	67
37	3-MeOPh	2	H	CH_2NHAc	0.36	0.1−0.78	65	70
38	4-MeOPh	2	H	CH_2NHAc	0.90	0.39−1.56	5	27
39	2-NO_2Ph	2	H	CH_2NHAc	0.14	0.025−0.39	39	66
40	2-NH_2Ph	2	H	CH_2NHAc	1.01	0.39−0.13		
41	2-AcNHPh	2	H	CH_2NHAc	4.1	0.78−12.5		
42	PhNH	2	H	CH_2NHAc	1.79	0.78−3.13		
43	2-MeOPhO	2	H	CH_2NHAc	2.5	0.78−6.25		
44	Ph	3	H	CH_2NHAc	0.27	0.1−0.39	0	40
45	furan-2-yl	1	H	CH_2NHAc	0.48	0.2−0.78	0	46
46	furan-2-yl	2	H	CH_2NHAc	0.24	0.1−0.39	0	63
47	thiophene-2-yl	2	H	CH_2NHAc	0.112	0.025−0.2	21	83
48	pyridin-2-yl	2	H	CH_2NHAc	0.73	0.2−1.56		0
49	pyridin-4-yl	2	H	CH_2NHAc	1.92	0.39−6.25		
50	imidazol-4-yl	2	H	CH_2NHAc	31	12.5−50		
51	2-MeOPh	2	Me	CH_2NHAc	0.030	0.0125−0.1		0[d]
52	2-MeOPh	2	Ph	CH_2NHAc	9.47	3.13−12.5		
53	2-MeOPh	2	CH_2NHAc	H	2.21	0.78−6.25		
54	2-MeOPh	2	CH_2NHAc	Me	0.046	0.025−0.1		0[d]
clarithromycin					0.057	0.025−0.1		
metronidazole					5.4	1.56−25		
bismuth subcitrate					18	12.5−25		
cimetidine					1130	800−1600	53	43

[a] 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. [b] Inhibition of histamine-stimulated gastric acid secretion in lumen-perfused stomach of anesthetized rats ($n = 2$). [c] Inhibition of histamine-stimulated chronotropic response in isolated guinea pig right atrium. [d] No significant inhibition (<10%) was observed at the concentration of 1×10^{-4} g/mL.

Table 3. Antimicrobial Activity of **31**, **54**, and the Reference Compounds against Various Organisms

organisms (*n*)	MIC (range) **31**	**54**	bismuth salicylate	metonidazole	amoxicillin
H. pylori (10)	0.026 (0.0125−0.05)	0.046 (0.025−0.1)	8.7	5.4 (0.56−25)	0.021 (0.0063−0.1)
C. jejuni (8)	23 (12.5−50)	23 (12.5−50)	7.4 (6.25−12.5)	30 (0.78−100)	2.2 (0.39−6.25)
C. difficile (4)	>100	>100	50	0.2 (0.1−0.39)	0.28 (0.1−0.78)
C. perfrigens (6)	>100	>100	>100	1.75 (0.78−3.13)	0.027 (0.025−0.05)
B. fragilis (10)	>100	>100	50	0.59 (0.39−0.78)	2.1 (0.2−12.5)
N. gonorrhoeas (10)	>100	>100	4.7 (3.13−6.25)	>100	7.7 (0.39−100)
N. meningitidis (10)	>100	>100	12.5 (3.13−100)	>100	0.056 (0.05−0.1)

(3H, s), 4.07 (2H, d, $J = 8.5$ Hz), 6.40 (1H, d, $J = 1.5$ Hz), 7.54 (1H, d, $J = 1.5$ Hz), 7.57−7.59 (1H, m), 8.16 (1H, br s). MS: m/z 140 ($M^+ + 1$).

3-Methyl-2-furancarboxamide (18a). A solution of methyl 3-methylfuran-2-carboxylate (**14**) (50 g, 0.36 mol) and NaOMe (75 g, 1.4 mol) in $HCONH_2$ was stirred at 100 °C for 30 min. The reaction mixture was poured into ice−water (400 mL) and extracted with AcOEt. The extract was dried and concentratred to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$ to afford **18a** (27.9 g, 63%): mp 89−90 °C. IR: 3315, 3200, 1650 cm^{-1}. ^1H NMR: δ 2.27 (3H, s), 6.48 (1H, d, $J = 1.6$ Hz), 7.27 (1H, br s), 7.51 (1H, br s), 7.64 (1H, d, $J = 1.6$ Hz). MS: m/z 126 ($M^+ + 1$).

2-(Acetamidomethyl)-3-methylfuran (19a). A solution of **18a** (27.8 g, 0.22 mol) in THF (250 mL) was added dropwise to a suspension of $LiAlH_4$ (12.6 g, 0.33 mol) in THF (250 mL)

at 5−10 °C with stirring under a N_2 atmosphere. The mixture was stirred for 5 h at 50−60 °C. After cooling, 50% aqueous THF (60 mL) was added dropwise to the mixture at 5−10 °C. The resulting precipitate was removed by filtration, and the filtered solution was dried and concentrated to give an oil. Ac_2O (19 mL, 0.2 mol) was added dropwise to a solution of the oil in AcOEt (100 mL), and the mixture was stirred for 1 h at room temperature. After removal of the solvent, the residue was distilled under reduced pressure to give **19a** (22.3 g, 87%): $bp_{1.5}$ = 120−124 °C. IR: 3250, 1650 cm^{-1}. ^1H NMR: δ 1.80 (3H, s), 1.96 (3H, s), 4.18 (2H, d, J = 8.5 Hz), 6.26 (1H, d, J = 2.6 Hz), 7.46 (1H, d, J = 2.6 Hz), 8.21 (1H, br s). MS: m/z 154 ($M^+ + 1$).

2-(Acetamidomethyl)-5-(chloroacetyl)-3-methylfuran (20a). Chloroacetyl chloride (17.2 mL, 0.22 mol) was added dropwise to a solution of $AlCl_3$ (38 g, 0.28 mol) in CH_2Cl_2 (150 mL) at room temperature, and the mixture was stirred for 1 h. A solution of **19a** (22.3 g, 0.14 mol) in CH_2Cl_2 (30 mL) was added dropwise to the mixture at 0 °C, and the resulting mixture was stirred for 2 h. The reaction mixture was poured into ice−water, and the organic layer was separated. The solution was washed with water, dried, and concentrated to give a residue, which was washed with Et_2O to afford **20a** (24.8 g, 75%): mp 105−108 °C. IR: 3340, 1675, 1640 cm^{-1}. ^1H NMR: δ 1.82 (3H, s), 2.04 (3H, s), 4.27 (2H, d, J = 8.5 Hz), 4.80 (1H, s), 7.45 (1H, s), 8.44 (1H, br s). MS: m/z 230 and 232 ($M^+ + 1$).

4-[2-(Acetamidomethyl)-3-methylfuran-5-yl]-2-[[2-(2-methoxyphenyl)ethyl]guanidino]thiazole Hydrochloride (51). A mixture of **20a** (0.69 g, 3 mmol) and **12** (0.76 g, 3 mmol) in EtOH (10 mL) was stirred at room temperature for 5 h. After removal of the solvent, the residue was recrystallized from EtOH/AcOEt to give **51** (1.3 g, 91%): mp 187−188 °C. IR: 3425, 3230, 1685, 1630 cm^{-1}. ^1H NMR: δ 1.82 (3H, s), 2.02 (3H, s), 2.91 (2H, t, J = 6.6 Hz), 3.63−3.66 (2H, m), 3.76 (3H, s), 4.24 (2H, d, J = 5.4 Hz), 7.27 (1H, br s), 6.87 (1H, t, J = 7.5 Hz), 6.96 (1H, t, J = 7.5 Hz), 7.18−7.29 (3H, m), 8.34 (1H, t, J = 5.2 Hz), 8.58 (2H, br s), 9.14 (1H, br s).

4-[5-(Acetamidomethyl)furan-2-yl]-2-[[(2-nitrophenyl)-ethyl]guanidino]thiazole (39). A suspension of 4-[5-(acetamidomethyl)furan-2-yl]-2-thioureidothiazole (**7**)[16] (3.6 g, 12 mmol) and MeI (0.77 mL, 12 mmol) in MeOH (70 mL) was refluxed for 4 h with stirring. After removal of the solvent, 2-(2-nitrophenyl)ethylamine (7 g, 42 mmol) and EtOH (60 mL) were added to the residue, and the resulting mixture was refluxed for 72 h. The solution was concentrated to dryness, and the residue was dissolved in water. The solution was made basic to pH 10 with 20% aqueous K_2CO_3 and extracted with AcOEt/THF. The extract was dried and concentrated to give a residue, which was recrystallized from MeOH/IPE to afford **39** (3.8 g, 74%): mp 133−134 °C. IR: 3400, 3330, 1660, 1520 cm^{-1}. ^1H NMR: δ 1.85 (3H, s), 3.07 (2H, t, J = 7 Hz), 3.44−3.54 (2H, m), 4.26 (2H, d, J = 5.5 Hz), 6.29 (1H, d, J = 3 Hz), 6.55 (1H, d, J = 3 Hz), 6.80 (1H, s), 7.44−7.56 (5H, m), 7.63−7.71 (1H, m), 7.96 (1H, d, J = 8 Hz), 8.34 (1H, t, J = 5.5 Hz).

4-[5-(Acetamidomethyl)furan-2-yl]-2-[[(2-aminophenyl)-ethyl]guanidino]thiazole (40). A solution of **39** (3.3 g, 7.7 mmol) in MeOH (50 mL) was hydrogenated over 10% Pd−C (0.5 g) under atomospheric pressure of H_2 at room temperature. After removal of the solvent and catalyst, the residue was recrystallized from AcOEt/Et_2O to give **40** (2.2 g, 73%): mp 161−162 °C. IR: 3400, 3350, 3275, 3250, 1650 cm^{-1}. ^1H NMR: δ 1.86 (3H, s), 2.63−2.71 (2H, m), 3.20−3.40 (2H, m), 4.27 (2H, d, J = 5.5 Hz), 5.18 (2H, br s), 6.30 (1H, d, J = 3 Hz), 6.48 (1H, t, J = 7 Hz), 6.59 (1H, d, J = 3 Hz), 6.60−6.71 (1H, m), 6.83 (1H, s), 6.88−6.96 (2H, m), 7.53 (3H, br s), 8.38 (1H, t, J = 5.5 Hz).

4-[5-(Acetamidomethyl)furan-2-yl]-2-[[(2-acetamido-phenyl)ethyl]guanidino]thiazole (41). Acetic anhydride (0.7 mL, 7.4 mmol) was added dropwise to a solution of **40** (2 g, 5 mmol) and Et_3N (0.7 mL, 5 mmol) in CH_2Cl_2 (40 mL)/DMF (13 mL), and the mixture was stirred for 1 h at room temperature. The resulting precipitate was collected by filtration and recrystallized from MeOH/AcOEt to give **41** (1.3 g, 57%): mp 224−225 °C. IR: 3300, 3250, 1625 cm^{-1}. ^1H NMR: δ 1.85 (3H, s), 2.06 (3H, s), 2.73−2.89 (2H, m), 3.35−3.42 (2H, m), 4.26 (2H, d, J = 5.5 Hz), 6.29 (1H, d, J = 3 Hz), 6.55 (1H, d, J = 3 Hz), 6.79 (1H, s), 7.14−7.40 (7H, m), 8.35 (1H, t, J = 5.5 Hz), 9.37 (1H, s).

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 were 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. 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.

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 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 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.

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 plateau, the test compound (1 mg/kg) was given intravenously. The effect of the drug was expressed as maximal inhibition by acid output.

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