Anti-*Helicobacter pylori* Agents. 5. 2-(Substituted guanidino)-4-arylthiazoles and Aryloxazole Analogues

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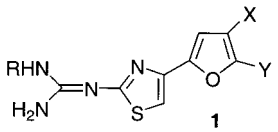
To extend the SAR study of guanidinothiazoles as a structurally novel class of anti-*H. pylori* agents, a series of 2-(substituted guanidino)-4-arylthiazoles and some 4-aryloxazole analogues were synthesized and evaluated for antimicrobial activity against *H. pylori*. Some of them were also subjected to H2 antagonist and gastric antisecretory assays. Several arylthiazoles were identified as potent anti-*H. pylori* agents, and of these, thienylthiazole derivative **44** exhibited the strongest activity (MIC = 0.0065 μg/mL) among the compounds obtained in our guanidinothiazole studies. Although **44** was void of H2 antagonist activity, pyridylthiazole derivative **39** had both potent anti-*H. pylori* and H2 antagonist activities. Thiazolylthiazole derivative **46** also showed potent anti-*H. pylori* activity, but the H2 antagonist activity was weak. On the other hand, no attractive activities were found in pyrimidyl, oxazolyl, isoxazolyl, imidazolyl, and oxadiazolylthiazole derivatives. The anti-*H. pylori* activity of the aryloxazole analogues was weaker than those of the corresponding arylthiazole derivatives, though they had potent H2 antagonist activity.

Introduction

It is well-known that *Helicobacter pylori* (*H. pylori*) is a major causative factor in peptic ulcer diseases.[1−18] Several conventional antibiotics and antiprotozoals, e.g., amoxicillin, clarithromycin, bismuth salt, and metronidazole, have been prescribed for the peptic ulcer patients infected with *H. pylori*. However, various adverse effects, such as nausea, vomiting, and diarrhea, have been problematic in these drugs. Besides, as these drugs have susceptibility to a variety of bacteria, the prescription of them for elimination of *H. pylori* would disturb the treatment in various systemic infectious diseases because of appearance of resistance strains in other pathogenic bacteria. Therefore, the development of novel types of anti-*H. pylori* agents is an important medical need.

As a result of efforts to find a novel class of anti-*H. pylori* agents, we recently reported that some 2-(substituted guanidino)-4-furylthiazoles (**1**) showed potent antimicrobial activities for *H. pylori*.[19−21] In the following study, we also found that 4-phenyl analogues (**2**) maintained potent activities.[22] The success of bioisosteric replacement of the furan ring with a phenyl ring encouraged us to extend the investigation into a wide range of biaryl structural derivatives. In this paper we describe the synthesis and structure−activity relationships (SARs) of various arylthiazoles and some aryloxazole analogues.



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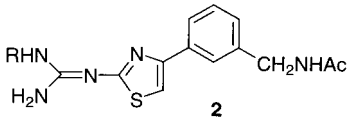

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Chemistry

The guanidinothiazoles linked with a six-membered heteroaromatic ring, pyridine and pyrimidine, were synthesized by the routes shown in Scheme 1. Cyclization of bromoacetylpyridine (**3**)[23] with thiourea provided the 2-aminothiazole derivative **4**. Treatment of **4** with benzoyl isothiocyanate yielded the benzoylthiourea derivative **5**, which was hydrolyzed with sodium hydroxide to give the thiourea derivative **6**. After methylation of **6** with methyl iodide, reaction with appropriate amines afforded the desired 2-(substituted guanidino)-4-pyridylthiazoles (**28**−**30**, **32**−**38**, **40** and **41**) (see Table 1). Of the pyridine series, *n*-butylguanidino and 2-(2-methoxyphenyl)ethylguanidino derivatives (**31** and **39**) were prepared by cyclization of **3** with substituted amidinothioureas.[21]

Bromination of 4-acetyl-2-methylpyrimidine (**7**)[24] with *N*-bromosuccinimide followed by treatment with potassium phthalimide gave 4-acetyl-2-phthalimidomethylpyrimidine (**8**). Reaction of **8** with bromine and subsequent cyclization with *n*-butylamidinothiourea provided pyrimidylthiazole derivative **9**, which was successively treated with hydrazine hydrate and acetic

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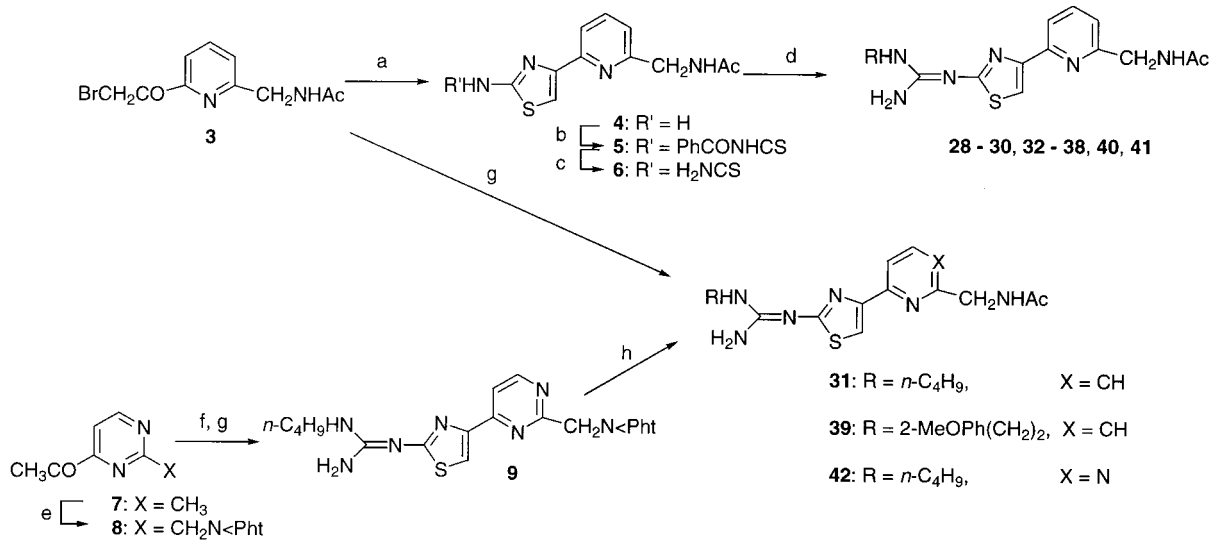
Scheme 1[a]



[a] Reagents: (a) H_2NCSNH_2; (b) PhCONCS; (c) NaOH/aq MeOH; (d) (1) MeI, (2) RNH_2; (e) (1) *N*-bromosuccinimide, (2) potassium phthalimide; (f) Br_2; (g) $RHNC(=NH)NHCSNH_2$; (h) (1) $H_2NNH_2 \cdot H_2O$, (2) Ac_2O.

anhydride to afford the desired pyrimidylthiazole derivative **42**.

The synthetic routes of the guanidinothiazole derivatives linked with a variety of five-membered heteroaromatic rings are shown in Scheme 2. The thienylthiazole derivatives **43** and **44** were obtained by cyclization of chloroacetyl derivative **10**[25] with substituted amidinothiourea. Treatment of acetylthiazole (**11**)[26] with bromine followed by cyclization with substituted amidinothiourea gave the thiazolylthiazole derivatives **45** and **46**. The oxazolylthiazole derivative **47** was prepared from 2-acetyl-5-methyloxazole (**12**)[27] by a method similar to that of the pyrimidyl derivative **42**. Condensation of propanone 1-oxime (**15**) with *N*-acetylpropargylamine provided the key intermediate **16** for the preparation of the isoxazolylthiazole derivative. The key intermediate **20** for the synthesis of the imidazolylthiazole derivative was obtained by the reaction protocols described by Reiter.[28] These intermediates **16** and **20** were converted to the final compounds **48** and **49** by treatment with bromine followed by cyclization with substituted amidinothioureas. Condensation of ethyl bromopyruvate (**21**) with *n*-butylamidinothiourea gave thiazole derivative **22**, which was cyclized with aminoacetaldoxime to afford the desired oxadiazolylthiazole derivative **50**.

Scheme 3 shows the synthetic route to prepare the guanidinoxazoles. Potassium acetate was reacted with haloketones to give the acetoxymethylcarbonyl derivatives **25**. Cyclization of **25** with the appropriate cyanoguanidine (**27**), which were derived from sodium dicyanamide (**26**), afforded the final compounds **51**−**54**.

Results and Discussion

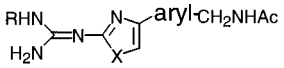
The compounds obtained were evaluated for antimicrobial activity against *H. pylori*. Several derivatives, mainly having minimum inhibitory concentration (MIC) less than 1 μg/mL, were also tested for H2 antagonist and gastric antisecretory activities since the prototype compound in this series was obtained from a study of H2 antagonists.[26] The results are summarized in Table 2.

In the preceding furyl and phenylthiazole series, the *n*-butyl and 2-(2-methoxyphenyl)ethyl groups were found as the favorable substituents on the guanidino moiety. Therefore, to evaluate the new biaryl templates, we have synthesized and compared the activity of the derivatives with those substituents. In the guanidinothiazole series, pyridyl (**31** and **39**), thienyl (**43** and **44**), and thiazolyl (**45** and **46**) derivatives showed potent anti-*H. pylori* activities. Of these, compound **44** demonstrated the strongest activity among the compounds obtained through all our guanidinothiazole studies including our earlier works,[19−22] and the potency (MIC = 0.0065 μg/mL) was 3−10 times higher than those of the referenced antibiotics, amoxicillin (MIC = 0.021 μg/mL) and clarithromycin (MIC = 0.057 μg/mL). On the other hand, pyrimidyl (**42**), isoxazolyl (**48**), imidazolyl (**49**), and oxadiazolyl (**50**) derivatives did not have attractive activities. Though the activity of oxazolyl derivative **47** was significant, the potency was 200 times less than that of the most potent compound **44**. The result of the SAR assessment for the substituents on guanidino moiety in the pyridylthiazole series was the same as the previous observations in the furyl- and phenylthiazole series, i.e., (a) the introduction of bulky substituents tended to increase the activity, (b) the incorporation of a heteroatom (**33**−**35**), a basic function (**36**), or an ionizable hydrogen (**37**) were disadvantageous.

Concerning the H2 antagonist and gastric antisecretory activities, pyridyl derivatives (**31**, **32**, **39**, and **40**) showed potent activities over or comparable to those of the referenced H2 antagonists. On the other hand, the thienyl derivatives **43** and **44** did not have H2 antagonist activity. The thiazole derivatives **45** and **46** and the oxazole derivative **47** showed only weak to moderate activities except for the H2 antagonist activity of **45**.

Next, we evaluated the guanidinoxazole derivatives to consider the possibility of bioisosteric conversion for the guanidinothiazole moiety. Compounds **51**−**54** had moderate to high H2 antagonist and gastric antisecretory activities. However, these compounds were one or

Table 1. Physical Properties for 2-(Substituted guanidino)-4-arylthiazoles and Aryloxazoles



compd	R	X	aryl	mp (°C)	recryst solvent[a]	yield (%)	formula[b]
28	Me	S		189-190	D/I/M	62	$C_{13}H_{16}N_6OS$
29	Et	S		199-200	D/I/M	39	$C_{14}H_{18}N_6OS$
30	*n*-C_3H_7	S		163-164	A/I	33	$C_{15}H_{20}N_6OS$
31	*n*-C_4H_9	S		145-146	D/I/M	41	$C_{16}H_{22}N_6OS$
32	$Me_2CH(CH_2)_2$	S		135-136	E/M	49	$C_{17}H_{24}N_6OS$
33	CF_3CH_2	S		233-234	D/I/M	31	$C_{14}H_{15}F_3N_6OS$
34	$CH_3O(CH_2)_2$	S		162-163	D/I/M	55	$C_{15}H_{20}N_6O_2S$
35	$CH_3S(CH_2)_2$	S		146-147	I/M	50	$C_{15}H_{20}N_6OS_2$
36	$Me_2N(CH_2)_2$	S		228-229	I/M	63	$C_{16}H_{23}N_7OS \cdot 3HCl \cdot 1/3H_2O$
37	$AcNH(CH_2)_2$	S		184-185	D/I/M	60	$C_{16}H_{21}N_7O_2S$
38	$Ph(CH_2)_2$	S		143-144	A/I	41	$C_{20}H_{22}N_6OS$
39	2-MeOPh$(CH_2)_2$	S		127-128	A/I	48	$C_{21}H_{24}N_6O_2S$
40	3-MeOPh$(CH_2)_2$	S		154-155	A/I	48	$C_{21}H_{24}N_6O_2S$
41	4-MeOPh$(CH_2)_2$	S		142-143	EA	34	$C_{21}H_{24}N_6O_2S$
42	*n*-C_4H_9	S		200-201	M	74	$C_{15}H_{21}N_7OS$
43	*n*-C_4H_9	S		173-174	A	53	$C_{15}H_{21}N_5OS_2 \cdot 1/4H_2O$
44	2-MeOPh$(CH_2)_2$	S		172-173	M	43	$C_{20}H_{23}N_5O_2S_2$
45	*n*-C_4H_9	S		177-178	A	79	$C_{14}H_{20}N_6OS_2$
46	2-MeOPh$(CH_2)_2$	S		159-161	EA/M	48	$C_{19}H_{22}N_6O_2S_2$
47	2-MeOPh$(CH_2)_2$	S		165-166	E/EA	53	$C_{19}H_{22}N_6O_3S$
48	2-MeOPh$(CH_2)_2$	S		122-124	M	64	$C_{19}H_{22}N_6O_3S \cdot C_2H_2O_4$
49	2-MeOPh$(CH_2)_2$	S		216-218	EA/M	43	$C_{19}H_{23}N_7O_2S \cdot 2HCl$
50	*n*-C_4H_9	S		150-151	EA/M	22	$C_{13}H_{19}N_7O_2S$
51	*n*-C_4H_9	O		94-95	A/I	26	$C_{15}H_{21}N_5O_3$
52	*n*-C_4H_9	O		145-147	I/M	27	$C_{17}H_{23}N_6O_2$
53	2-MeOPh$(CH_2)_2$	O		193-194	M/W	39	$C_{22}H_{25}N_5O_3 \cdot 1/10H_2O$
54	*n*-C_4H_9	O		181-182	D/I/M	34	$C_{16}H_{22}N_6O_2 \cdot 1/10H_2O$

[a] A = EtOH, D = *N*,*N*-dimethylformamide, E = Et_2O, EA = ethyl acetate, I = diisopropyl ether, M = MeOH, W = H_2O. [b] Analyses for C, H, and N are within ±0.4% of the theoretical values.

two orders of magnitude less potent in anti-*H. pylori* activity than the corresponding guanidinothiazole analogues.[19,21,22]

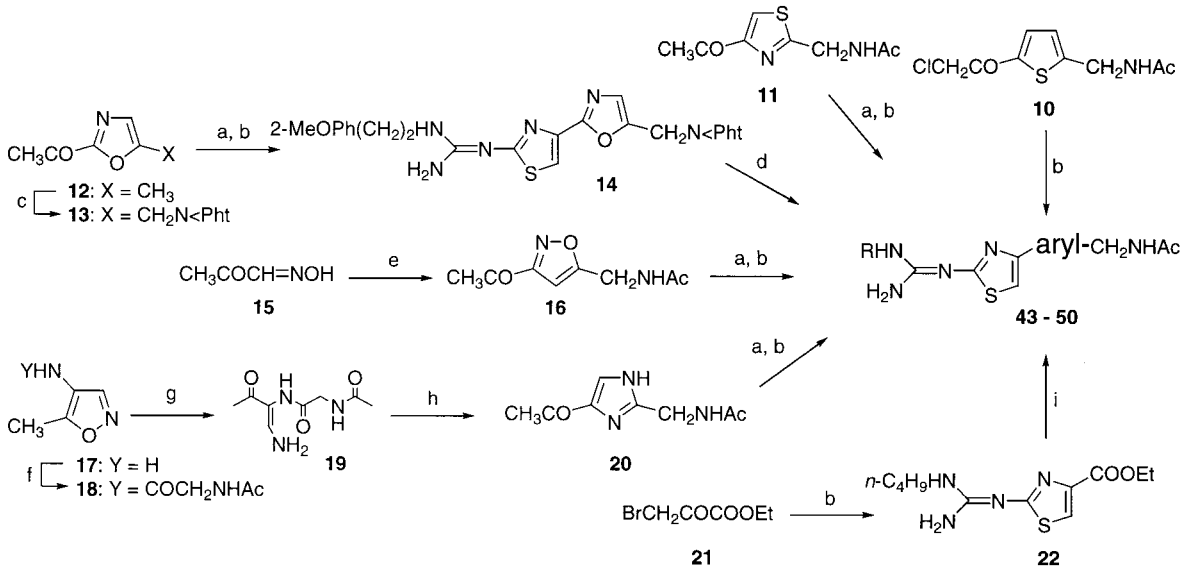
Regarding the antimicrobial selectivity toward *H. pylori*, the clinically available drugs for the eradication therapy, bismuth salicylate, metronidazole, and amoxicillin, showed susceptibility for a variety of microorganisms, which have been reported in our previous publications,[20−22] but the representative compounds in this investigation (**39**, **44**, and **46**) did not have susceptibility for the other organisms at the test dose of 100 μg/mL (see Experimental Section).

The specific target of the compounds in this series is unclear. However, regarding the mode of anti-*H. pylori* action, it was shown that the representative compounds had bactericidal action by measurement of viability in a growth curve test (data to be published elsewhere).

Conclusion

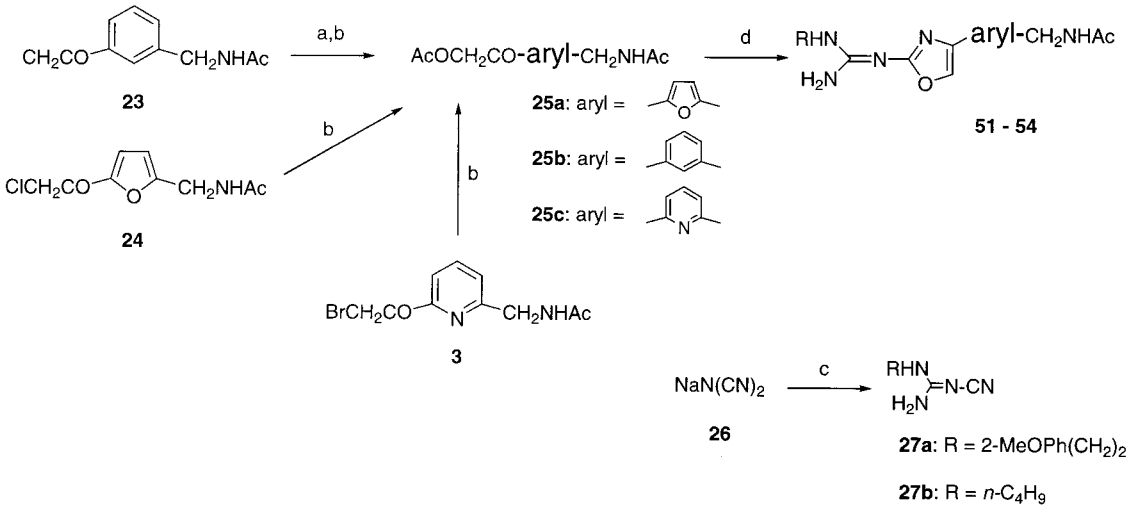
To assess the possibility of bioisosteric conversion for the 2-guanidino-4-furylthiazole template, we have pre-

Scheme 2[a]



[a] Reagents: (a) Br_2; (b) $RHNC(=NH)NHCSNH_2$; (c) (1) *N*-bromosuccinimide, (2) potassium phthalimide; (d) (1) $H_2NNH_2 \cdot H_2O$, (2) Ac_2O; (e) (1) Cl_2, (2) $HC{\equiv}CCH_2NHAc$; (f) $AcNHCH_2COOH$; (g) H_2/Pd-C; (h) NaOH; (i) $AcNHCH_2C(=NOH)NH_2$.

Scheme 3[a]



[a] Reagents: (a) Br_2; (b) MeCOOK; (c) RNH_2; (d) **27**.

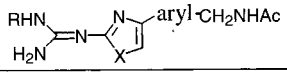
pared a series of 2-guanidino-4-arylthiazole and some 4-aryloxazole derivatives and tested for antimicrobial activity against *H. pylori*. Among the derivatives obtained, the 4-thienylthiazole derivative with a 2-(2-methoxyphenyl)ethyl substituent on the guanidino moiety (**44**) was identified as the most potent compound in all the series of our guanidinothiazole studies. Although compound **44** was void of H2 antagonist activity, the 4-pyridylthiazole analogue **39** possessed both potent antimicrobial and H2 antagonist activities. The 4-thiazolylthiazole analogue **46** also showed potent antimicrobial activity, but the H2 antagonist activity was weak. The other 4-arylthiazole analogues **47**−**49** did not have any attractive activities. In the previous studies, we demonstrated that the guanidino and acetamidomethyl groups were the necessary functions to exhibit potent anti-*H. pylori* or H2 antagonist activities and the substituent on the guanidino moiety modulated the potency of those activities. On the other hand, from the results of this study, it can be concluded that the aryl junction between the guanidinothiazole and acetamidomethyl moieties is not a simple spacer but plays a role in regulating the pharmacological character (antimicrobial and/or H2 antagonist) in this series of compounds.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were taken 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 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 Mg_2SO_4 and concentrated to dryness on a rotary evaporator under reduced pressure.

4-[6-(Acetamidomethyl)pyridin-2-yl]-2-aminothiazole (4). A solution of 2-acetamidomethyl-6-bromoacethylpyridine (**3**)[23] (5.0 g, 18 mmol) and thiourea (1.4 g, 18 mmol) in EtOH (50 mL) was refluxed for 2 h with stirring. After removal of the solvent, the residue was dissolved in water. The solution

Table 2. Pharmacological Activities of 2-(Substituted guanidino)-4-arylthiazoles and Aryloxazoles



compd	R	X	aryl	MIC (μg/mL)[a] mean	MIC (μg/mL)[a] range	inhibition, % gastric secretion[b] (rat, 1 mg/kg iv)	inhibition, % H_2 antagonism,[c] ($1X10^{-6}$ g/mL)
28	Me	S		5.1	3.13-12.5		
29	Et	S		4.7	1.56-12.5		
30	*n*-C_3H_7	S		2.9	0.78-6.25		
31	*n*-C_4H_9	S		0.59	0.2-1.56	76	100
32	$Me_2CH(CH_2)_2$	S		0.1	0.05-0.2	86	80
33	CF_3CH_2	S		13.4	6.25-25		
34	$CH_3O(CH_2)_2$	S		6.7	3.13-12.5		
35	$CH_3S(CH_2)_2$	S		1.1	0.78-1.56		
36	$Me_2N(CH_2)_2$	S		>100			
37	$AcNH(CH_2)_2$	S		11.5	6.25-25		
38	$Ph(CH_2)_2$	S		0.1	0.05-0.2	50	71
39	2-MeOPh$(CH_2)_2$	S		0.037	0.025-0.1	65	78
40	3-MeOPh$(CH_2)_2$	S		0.14	0.025-0.39	68	83
41	4-MeOPh$(CH_2)_2$	S		0.42	0.2-0.78	18	24
42	*n*-C_4H_9	S		4.1	3.13-6.25		n.e.[d]
43	*n*-C_4H_9	S		0.32	0.1-0.78		n.e.[e]
44	2-MeOPh$(CH_2)_2$	S		0.0065	0.003-0.025		n.e.[e]
45	*n*-C_4H_9	S		0.52	0.2-1.56	50	85
46	2-MeOPh$(CH_2)_2$	S		0.043	0.0125-0.1	23	30
47	2-MeOPh$(CH_2)_2$	S		1.1	0.2-3.13	50	37
48	2-MeOPh$(CH_2)_2$	S		4.4	3.13-6.25		n.e.
49	2-MeOPh$(CH_2)_2$	S		10.2	6.25-12.5		
50	*n*-C_4H_9	S		10.9	3.13-12.5		n.e.
51	*n*-C_4H_9	O		19.3	6.25-25	51	82
52	*n*-C_4H_9	O		1.92	0.39-6.25	60	93
53	2-MeOPh$(CH_2)_2$	O		0.3	0.1-0.78	40	65
54	*n*-C_4H_9	O		3.9	0.56-6.25	92	81
clarithromycin				0.057	0.025-0.1		
amoxicillin				0.021	0.00625-0.1		
metronidazole				5.4	1.56-25		
bismuth subcitrate				18	12.5-25		
cimetidine				1130	800-1600	53	43
ranitidine				>1600		72	44

[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] n.e.: less than 10%. [e] At 1×10^{-4} g/mL.

was made basic to pH 10 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 **4** (3.7 g, 80%): mp 179−180 °C. IR (Nujol): 3325, 3250, 3120, 1650 cm^{-1}. ^1H NMR: δ 1.93 (3H, s), 4.36 (2H, d, J = 6 Hz), 7.11 (2H, s), 7.13 (1H, d, J = 7 Hz), 7.26 (1H, s), 7.68 (1H, d, J = 7 Hz), 7.76 (1H, t, J = 7 Hz), 8.45 (1H, t, J = 6 Hz). MS: m/z 249 ($M^+ + 1$).

4-[6-(Acetamidomethyl)pyridin-2-yl]-2-(3-benzoylthioureido)thiazole (5). A suspension of **4** (3.6 g, 15 mmol) and benzoyl isothiocyanate (2.6 g, 16 mmol) in Me_2CO (70 mL) was refluxed for 3 h. The resulting precipitate was collected by filtration to afford **5** (3.8 g, 63%): mp 226−227 °C. IR (Nujol): 3300, 1670, 1640 cm^{-1}. ^1H NMR: δ 1.95 (3H, s), 4.42 (2H, d, J = 6 Hz), 7.19−7.33 (1H, m), 7.49−7.80 (3H, m), 8.02−8.06 (5H, m), 8.50 (1H, t, J = 6 Hz), 12.16 (1H, s), 14.29 (1H, s). MS: m/z 412 ($M^+ + 1$).

4-[6-(Acetamidomethyl)pyridin-2-yl]-2-(thioureido)-thiazole (6). A solution of NaOH (0.36 g, 90 mmol) in water (4 mL) was added to a suspension of **5** (3.7 g, 90 mmol) in MeOH (40 mL), and the mixture was stirred at 60 °C for 2 h. After removal of the solvent, the residue was added to water−AcOEt. The organic layer was separated, washed with water, dried, and concentrated to give a residue, which was recrystallized from AcOEt−IPE to afford **6** (2.4 g, 87%): mp 212−213 °C. IR (Nujol): 3300, 3175, 1640 cm^{-1}. ^1H NMR: δ 1.94 (3H, s), 4.41 (2H, s), 7.21−7.30 (1H, m), 7.75−7.92 (3H, m). MS: m/z 308 ($M^+ + 1$).

4-[6-(Acetamidomethyl)pyridin-2-yl]-2-[2-(2-phenylethyl)guanidino]thiazole (38). A suspension of **6** (1.35 g, 5 mmol) and MeI (0.73 g, 5 mmol) in MeOH (15 mL) was refluxed for 3 h with stirring. After removal of the solvent, β-phenethylamine (4.8 g, 40 mmol) and EtOH (40 mL) were added to the residue, and the resulting mixture was refluxed for 48 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. The extract was dried and concentrated to give a residue, which was recrystallized from EtOH−IPE to afford **38** (0.72 g, 36%). IR (Nujol): 3320, 1645, 1615 cm^{-1}. ^1H NMR: δ 1.93 (3H, s), 2.84 (2H, t, J = 7 Hz), 3.51−3.38 (2H, m), 4.36 (2H, d, J = 6 Hz), 7.50−7.14 (9H, m), 7.70−7.55 (1H, br s), 7.78 (1H, t, J = 7.5 Hz), 8.45 (1H, t, J = 6 Hz).

4-Acetyl-2-(phthalimidomethyl)pyrimidine (8). A mixture of 4-acetyl-2-methylpyrimidine (**7**)[24] (2.0 g, 14.6 mmol), N-bromosuccinimide (2.9 g, 16.2 mmol), and benzoylperoxide (0.2 g, 0.83 mmol) in CCl_4 (60 mL) was refluxed for 3 h with stirring. After cooling, 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 $CHCl_3$/hexane (1/1) to afford 4-acetyl-2-bromomethylpyrimidine (0.96 g, 31%) as an oil. ^1H NMR: δ 2.65 (3H, s), 4.80 (2H, s), 7.80 (1H, d, J = 8 Hz), 9.11 (1H, d, J = 8 Hz). MS: m/z 215, 217 ($M^+ + 1$).

A mixture of 4-acetyl-2-bromomethylpyrimidine (0.84 g, 4 mmol) and potassium phthalimide (0.72 g, 4 mmol) in N,N-dimethylformamide (DMF) (10 mL) was stirred for 1 h at room temperature. After removal of the solvent, the residue was added to water−AcOEt and the organic layer was separated. The solution was dried and concentrated to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$ to afford **8** (0.26 g, 47%): mp 195−198 °C. IR (Nujol): 1770, 1700 cm^{-1}. ^1H NMR: δ 2.47 (3H, s), 5.13 (2H, s), 7.77 (1H, d, J = 7.5 Hz), 7.89−8.00 (4H, m), 9.01 (1H, d, J = 7.5 Hz). MS: m/z 282 ($M^+ + 1$).

4-(2-Acetamidomethylpyrimidin-4-yl)-2-[2-(*n*-butyl)-guanidino]thiazole (42). A mixture of **8** (0.49 g, 1.7 mmol), phenyltrimethylammonium tribromide (0.85 g, 2.3 mmol) in tetrahydrofuran (THF) (10 mL) was stirred for 1 h at room temperature. After removal of the solvent, the residue and n-butylamidinothiourea (0.3 g, 1.7 mmol) were dissolved in MeCN (10 mL), and the solution was refluxed for 1 h. After concentration, the residue was added to AcOEt−saturated aqueous $NaHCO_3$. The organic layer was separated, dried, and concentrated to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$/MeOH (50/1) to afford 2-[2-(*n*-butyl)guanidino]-4-[(2-phthalimidomethyl)pyrimidin-4-yl]-thiazole (**9**). ^1H NMR: δ 0.90 (3H, t, J = 7 Hz), 1.29−1.48 (4H, m), 3.13−3.23 (2H, m), 5.01 (2H, s), 7.36 (3H, brs), 7.47 (1H, s), 7.76 (1H, d, J = 5 Hz), 7.88−8.00 (5H, m), 8.73 (1H, d, J = 5 Hz).

A solution of **9** (250 mg, 0.57 mmol) and hydrazine hydrate (70 mg, 1.4 mmol) in EtOH (10 mL) was refluxed for 1 h. After cooling to room temperature, Ac_2O (1 mL) was added dropwise to the mixture, and the resulting mixture was stirred for 2 h at room temperature. The solution was concentrated, and the residue was added to AcOEt−saturated aqueous $NaHCO_3$. The organic layer was separated, dried, and concentrated to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$/MeOH (95/5) and recrystallized from MeOH to afford **42** (140 mg, 74%). IR (Nujol): 3350, 3150, 1655 cm^{-1}. ^1H NMR: δ 0.92 (3H, t, J = 7 Hz), 1.30−1.50 (4H, m), 1.93 (3H, s), 3.15−3.21 (2H, m), 4.45 (2H, d, J = 6 Hz), 7.38 (2H, brs), 7.72 (1H, d, J = 5 Hz), 7.75 (1H, s), 8.36 (1H, t, J = 6 Hz), 8.76 (1H, d, J = 5 Hz).

5-Acetamidomethyl-3-acetylisoxazole (16). Cl_2 gas was bubbled into a solution of propanone 1-oxime (**15**) (9.5 g, 110 mmol) in $CHCl_3$ (300 mL) at −10 °C for 3 h. After removal of the solvent, the residue was washed with Et_2O−hexane to give a semisolid material (11.1 g). The material was added portionwise to a mixture of N-acetylpropargylamine (8.8 g, 90 mmol) and K_2CO_3 (12.6 g, 90 mmol) in $CHCl_3$ (150 mL) at 0 °C with stirring. The mixture was stirred at room temperature for 5 h and poured into water. The organic layer was separated, washed with water, dried, and concentrated to give a residue, which was chromatographed on silica gel eluting with AcOEt/$CHCl_3$ (9/1) to afford **16** (7.5 g, 37%) as a semisolid material. IR (Nujol): 1700, 1660 cm^{-1}. ^1H NMR: δ 1.88 (3H, s), 2.57 (3H, s), 4.44 (2H, d, J = 6 Hz), 6.62 (1H, s), 8.56 (1H, t, J = 6 Hz). MS: m/z 183 ($M^+ + 1$).

2-[2-(*n*-Butyl)guanidino]-4-ethoxycarbonylthiazole (22). Ethyl bromopyruvate (**21**) (7.15 g, 33 mmol) was added dropwise to a mixture of n-butylamidinothiourea (5.22 g, 30 mmol) and $NaHCO_3$ (10.1 g, 120 mmol) in dimethoxyethane (75 mL) at room temperature. After being refluxed for 20 min, the mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried, and concentrated to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$/MeOH (20/1) and recrystallized from AcOEt−IPE to afford **22** (5.7 g, 70%): mp 102−104 °C. IR (Nujol): 3400, 1695 cm^{-1}. ^1H NMR: δ 0.90 (3H, t, J = 7 Hz), 1.28 (2H, t, J = 7 Hz), 1.24−1.58 (4H, m), 3.15 (2H, q, J = 6.5 Hz), 4.23 (2H, q, J = 7 Hz), 7.42 (2H, br s), 7.60 (1H, s). MS: m/z 271 ($M^+ + 1$).

4-(3-Acetamidomethyl-1,2,4-oxadiazol-5-yl)-2-[2-(*n*-butyl)guanidino]thiazole (50). NaH (60% dispersion in mineral oil) (320 mg, 8 mmol) was added portionwise to a solution of 2-acetamido-1-aminoacetaldoxime (520 mg, 4 mmol) in THF (5 mL) at room temperature, and the mixture was stirred for 30 min. A solution of **22** (540 mg, 2 mmol) in THF (5 mL) was added to the mixture, and the resulting mixture was refluxed for 1 h. After cooling, the reaction mixture was poured into cold water, adjusted to pH 8 with AcOH, and extracted with AcOEt. The extract was dried and concentrated to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$/MeOH (50/1) and recrystallized from AcOEt−MeOH to afford **50** (160 mg, 22%). IR (Nujol): 3350, 3200, 1650 cm^{-1}. ^1H NMR: δ 0.91 (3H, t, J = 7 Hz), 1.18−1.56 (4H, m), 1.88 (3H, s), 3.14−3.23 (2H, m), 4.41 (2H, d, J = 6 Hz), 7.56 (3H, brs), 8.58 (1H, t, J = 6 Hz). MS: m/z 338 ($M^+ + 1$).

1-Cyano-2-[2-(2-methoxyphenyl)ethyl]guanidine (27a). A mixture of 2-(2-methoxyphenyl)ethylamine (29.8 g, 0.20 mol), sodium dicyanamide (19.3 g, 0.22 mol), and concentrated HCl (16.5 mL) was heated at 100 °C for 8 h. After cooling, the reaction mixture was added to saturated aqueous NaCl (100 mL) and extracted with AcOEt. The extract was dried and concentrated to afford **27a** (39.5 g, 92%): mp 104−105 °C. IR (Nujol): 3420, 3300, 3170, 2150, 1660 cm^{-1}. ^1H NMR: δ 2.71

(2H, t, $J = 7.5$ Hz), 3.20−3.30 (2H, m), 3.78 (3H, s), 6.65 (2H, brs), 6.68 (1H, dt, $J = 1$ and 7 Hz), 6.96 (1H, d, $J = 7$ Hz), 7.12−7.25 (2H, m). MS: *m/z* 219 ($M^+ + 1$).

3-(Acetamidomethyl)-α-acetoxyacetophenone (25b). Br_2 (4.4 g, 28 mmol) was added dropwise to a solution of 3-acetamidomethylacetophenone (5.0 g, 26 mmol) in dioxane (50 mL) at room temperature. After being stirred for 5 h, the solution was concentrated and the residue was dissolved in acetone (50 mL). Sodium acetate (4.3 g, 52 mmol) was added to the solution, and the mixture was refluxed for 23 h. After removal of the solvent, the residue was added to water (100 mL). The mixture was made basic to pH 9.5 with 20% aqueous K_2CO_3 and extracted with AcOEt. The extract was dried and concentrated to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$/MeOH (20/1) and recrystallized from AcOEt−IPE to afford **25b** (3.1 g, 48%): mp 72−73 °C. IR (Nujol): 3300, 1740, 1700, 1650 cm^{-1}. ^1H NMR: δ 1.88 (3H, s), 2.15 (3H, s), 4.32 (2H, d, $J = 6$ Hz), 5.45 (2H, s), 7.47−7.59 (2H, m), 7.82−7.87 (2H, m), 8.44 (1H, t, $J = 6$ Hz). MS: *m/z* 250 ($M^+ + 1$).

4-(3-Acetamidomethyl)phenyl-2-[2-[2-(2-methoxyphenyl)ethyl]guanidino]oxazole (53). A suspension of **25b** (3.0 g, 12 mmol), **27a** (5.3 g, 24 mmol), and 6 N HCl (4.4 mL) in dioxane (6 mL) was stirred at room temperature for 24 h. The mixture was added to water (50 mL), made basic to pH 9 with 20% aqueous K_2CO_3, and extracted with AcOEt. The extract was dried and concentrated to give a residue, which was recrystallized from MeOH−water to afford **53** (1.9 g, 39%). IR (Nujol): 3450, 3280, 1680, 1610 cm^{-1}. ^1H NMR: δ 1.88 (3H, s), 2.81 (2H, t, $J = 7$ Hz), 3.34−3.44 (2H, m), 3.80 (3H, s), 4.27 (2H, d, $J = 6$ Hz), 6.85−6.99 (2H, m), 7.12−7.36 (6H, m), 7.53−7.57 (2H, m), 7.89 (1H, s), 8.35 (1H, t, $J = 6$ Hz).

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. A 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. 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.

The susceptibility for *C. jejuni*, *C. difficile*, *C. perfrigens*, *B. fragilis*, *N. gonorrheas*, and *N. meningitidis* were tested according to the Japan Society of Chemotherapy Guidelines.[29]

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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