Anti-*Helicobacter pylori* Agents. 4. 2-(Substituted guanidino)-4-phenylthiazoles and Some Structurally Rigid Derivatives

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In order to find a new class of anti-*Helicobacter pylori* (*H. pylori)* agents, a series of 4-[(3-acetamido)phenyl]-2-(substituted guanidino)thiazoles and some structurally rigid analoges were synthesized and evaluated for antimicrobial activity against *H. pylori*. Among the compounds obtained, high anti-*H. pyrori* activities were observed in benzyl derivative **34** (MIC = 0.025 μg/mL) and phenethyl derivatives **35** and **36** (MIC = 0.037 μg/mL and 0.017 μg/mL). Though alkyl derivatives generally showed lower activity, the 2-methoxyethyl derivative **28** preserved significant activity (MIC = 0.32 μg/mL) and also exhibited more potent gastric antisecretory activity than ranitidine. Structural restriction by bridging between the thiazole and the phenyl rings with an alkyl chain did not improve the activity in this series.

Introduction

In our previous papers,[1−3] we reported the structure−activity relationships (SARs) of a series of furylthiazoles as a novel class of bactericidal agents for *Helicobacter pylori* (*H. pylori*) which has been widely accepted as a major causative factor in peptic ulcer diseases.[4−22] To investigate further the SAR in this class of compounds, we next tried to replace the furan ring with a phenyl ring in expectation of a successful bioisosteric conversion. In this publication, we describe the synthesis and the pharmacological evaluation of a series of 4-[3-(acetamidomethyl)phenyl]-2-(substituted guanidino)-thiazoles and some structurally rigid derivatives.

Chemistry

The target compounds listed in Table 1 were synthesized by the routes outlined in Scheme 1. 3-Cyanoacetophenone (**1**) was treated with boron trifluoride etherate in the presence of ethylene glycol to generate 3-(2-methyl-1,3-dioxolan-2-yl)benzonitrile (**2**). Reduction of the nitrile group with lithium alminium hydride followed by cleavage of the ketal with 1 N hydrochloric acid and then treatment with acetyl chloride afforded 3-(acetamidomethyl)acetophenone (**3**). Bromination of **3** and subsequent cyclization with thiourea provided the 2-aminothiazole derivative **4**. Treatment of **4** 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 appropriate amines afforded the desired 4-[3-(acetamidomethyl)phenyl]-2-(substituted guanidino)thiazoles (**24**−**44**). Unsubstituted guanidino derivatives **22** and **23** were prepared from (acetamidomethyl)acetophenones (**3** or **7**) by bromination followed by cyclization with amidinothiourea.

The tricyclic derivatives **45**−**52** in Table 2 were prepared by the routes shown in Scheme 2. Alkylation of acetamido- (**8**) or (acetamidomethyl)phenols (**10a** and **10b**) with ethyl 4-bromobutylate followed by hydrolysis with sodium hydroxide gave the phenoxybutylic acid derivatives **12a**−**c**, which were cyclized with polyphosphoric acid (PPA) to afford the benzoxepinones (**14a**−**c)**. Hydrogenation of 3-(4-cyanophenoxy)propionic acid (**13**)[23] with palladium on carbon followed by treatment with acetic anhydride and then cyclization with PPA afforded the benzopyranone derivative **14d**. Bromination of the cyclic ketones (**14a**−**d**) and subsequent cyclization with the appropriate amidinothioureas[3] afforded the desired compounds with the oxomethylene bridge (**45**−**49** and **52**).

4-Nitrobenzylbromide (**15**) was converted to 4-(acetamidomethyl)nitrobenzene (**17**) via Gabriel amine synthesis followed by treatment with acetic anhydride. Reduction of the nitro group on **17** gave the aniline derivative **18**, which was successively treated with sodium nitrite and thioglycolic acid to afford 3-[4-(acetmidomethyl)phenylthio]propionic acid (**20b**). 3-[4-(Acetamido)phenylthio]propionic acid (**20a**) was obtained by the reaction of 4-(acetamido)thiophenol (**19**) with β-propiolactone. The carboxylic acids (**20a** and **20b**) were converted to acid chlorides by treatment with thionyl chloride and then were cyclized in the presence of aluminum chloride to provide the benzothiopyranone derivatives **21a** and **21b**. The synthesis of the target compounds with thiomethylene bridge (**50** and **51**) was carried out in a manner similar to those of the oxomethylene bridged derivatives.

Results and Discussion

The compounds obtained were evaluated for antimicrobial activity against *H. pylori.* Several derivatives with minimum inhibitory concentration (MIC) less than 1 μg/mL were also tested for H2 antagonist and gastric

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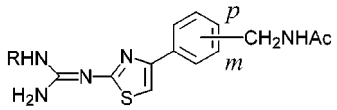
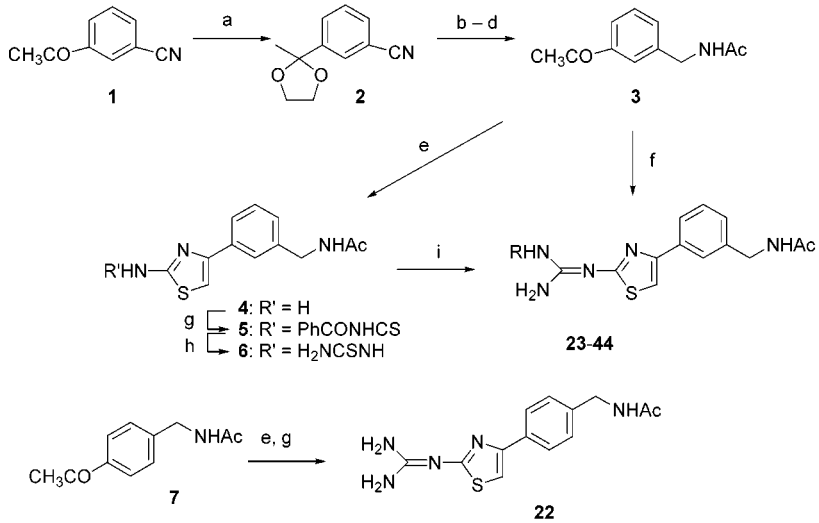
Table 1. Physical Properties for 2-(Substituted guanidino)-4-phenylthiazoles



compd	R	position	mp (°C)	recryst solvent[a]	yield (%)	formula
22	H	*p*	248−249	EA/M	76	$C_{13}H_{15}N_5OS\cdot 2HCl$
23	H	*m*	240−241	I/M/T	44	$C_{13}H_{15}N_5OS$
24	Me	*m*	162−163	EA/T	89	$C_{14}H_{17}N_5OS$
25	Et	*m*	167−169	A/E	50	$C_{15}H_{19}N_5OS$
26	*n*-C_4H_9	*m*	154−155	EA	69	$C_{17}H_{23}N_5OS$
27	$HO(CH_2)_2$	*m*	148−150	A	61	$C_{15}H_{19}N_5O_2S$
28	$MeO(CH_2)_2$	*m*	123−124	EA	42	$C_{16}H_{21}N_5O_2S$
29	$MeO(CH_2)_3$	*m*	154−155	EA	48	$C_{17}H_{23}N_5O_2S$
30	$NC(CH_2)_2$	*m*	150−151	A/W	15	$C_{16}H_{18}N_6OS$
31	$Me_2N(CH_2)_2$	*m*	138−140	EA	40	$C_{17}H_{24}N_6OS\cdot 1/2H_2O$
32	EtO	*m*	115−117	A/I	36	$C_{15}H_{19}N_5O_2S\cdot HCl\cdot H_2O$
33	Ph	*m*	185−186	A/W	34	$C_{19}H_{19}N_5OS$
34	$PhCH_2$	*m*	124−125	A/W	57	$C_{20}H_{21}N_5OS\cdot 1/2H_2O$
35	$Ph(CH_2)_2$	*m*	118−119	A/I	56	$C_{21}H_{23}N_5OS$
36	2-$MeOPh(CH_2)_2$	*m*	155−156	A/I	33	$C_{22}H_{25}N_5O_2S$
37	4-$MeOPh(CH_2)_2$	*m*	110−111	EA	20	$C_{22}H_{25}N_5O_2S$
38	$Ph(CH_2)_3$	*m*	135−136	M/W	17	$C_{22}H_{25}N_5OS$
39	$Ph_2CH(CH_2)_2$	*m*	162−163	A	26	$C_{28}H_{29}N_5OS\cdot H_2O$
40	$PhO(CH_2)_2$	*m*	164−165	EA/M	17	$C_{21}H_{23}N_5O_2S$
41	$PhCH_2O(CH_2)_2$	*m*	143−144	A/I	17	$C_{22}H_{25}N_5O_2S$
42	$PhCONH(CH_2)_2$	*m*	126−127	A/W	13	$C_{22}H_{24}N_6O_2S\cdot H_2O$
43	2-pyridyl-$(CH_2)_2$	*m*	139−140	EA	51	$C_{20}H_{22}N_6OS$
44	4-imidazolyl-$(CH_2)_2$	*m*	163−164	A/EA	50	$C_{18}H_{21}N_7OS$

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

Scheme 1[a]



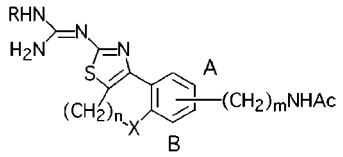
[a] Reagents: (a) $HO(CH_2)_2OH/BF_3\cdot Et_2O$; (b) $LiAlH_4$; (c) 1 N HCl/MeOH; (d) $AcCl/Et_3N$; (e) (1) Br_2, (2) H_2NCSNH_2; (f) (1) Br_2, (2) $(H_2N)_2C{=}NCSNH_2$; (g) PhCONCS; (h) NaOH/aq MeOH; (i) (1) MeI, (2) RNH_2.

antisecretory activities since the prototype compound in this series was obtained from a study of H2 antagonists.[24] The results are summarized in Tables 3 and 4.

Regarding the position of the acetamidomethyl group on the phenyl ring, the *meta* substituted derivative **23** showed anti-*H. pylori* activity, whereas the *para* positional isomer **22** did not show any activity. Therefore, for the substituted guanidino derivatives, we have prepared only the *meta* positional isomer.

Introduction of alkyl substituents (**24**−**26**) enhanced the anti-*H. pylori* activity. Replacement of one methylene on **26** with an oxygen (**28**) did not produce a marked change in the activity. However, elongation of the alkyl chain (**29**) resulted in a decrease in activity. In the phenyl alkyl series, benzyl (**34**) and phenethyl (**35**) were preferable to phenyl (**33**) and phenylpropyl (**38**). Similarly to the alkyl series, replacement of the methylene in **38** with an oxygen (**40**) showed little effect on activity, and extension of the alkyl spacer (**41**) reduced the activity. Incorporation of an additional phenyl (**39**) onto the phenylpropyl on **38** displayed a considerable decrease in activity. Remarkable reduction in the activities was caused by introduction of an ionizable hydrogen (**27**, **42**, and **44**). Introduction of nitrile (**30**) or amine (**31**) also resulted in a great loss of activity. A similar reduction in potency was observed when an ethoxy was

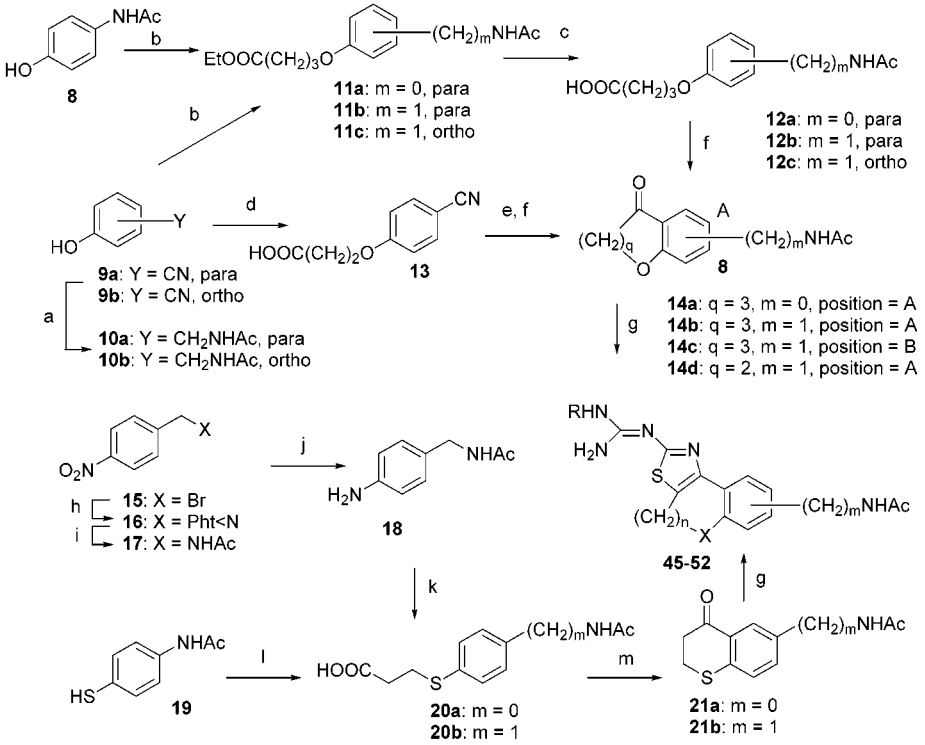
Table 2. Physical Properties for Tricyclic Derivatives



compd	R	*m*	*n*	X	position	mp (°C)	recryst solvent[a]	yield (%)	formula[b]
45	H	0	2	O	A	262−263	D/W	17	$C_{14}H_{15}N_5O_2S\cdot 1/2H_2O$
46	H	1	1	O	A	238−239	D/I/M	19	$C_{14}H_{15}N_5O_2S$
47	H	1	2	O	A	>250	D/W	42	$C_{15}H_{17}N_5O_2S$
48	*n*-C_4H_9	1	2	O	A	110−112	I/M	46	$C_{19}H_{25}N_5O_2S$
49	2-MeOPh$(CH_2)_2$	1	2	O	A	202−204	I/M/T	31	$C_{24}H_{27}N_5O_3S$
50	H	0	1	S	A	255−256	I/M	58	$C_{13}H_{13}N_5OS_2\cdot 1/2H_2O$
51	*n*-C_4H_9	1	1	S	A	218−220	E/EA/M	30	$C_{18}H_{23}N_5OS_2\cdot HCl$
52	H	1	2	O	B	>250	I/T/M	23	$C_{15}H_{17}N_5O_2S$

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

Scheme 2[a]



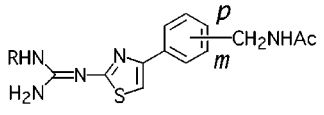
[a] Reagents: (a) (1) $LiAlH_4$, (2) Ac_2O; (b) $EtOOC(CH_2)_3Br/K_2CO_3$; (c) 1 N NaOH/MeOH; (d) β-propiolactone; (e) (1) H_2/Pd-C, (2) Ac_2O; (f) (1) PPA; (g) (1) Br_2, (2) $RHNC(=NH_2)NCSNH_2$; (h) potassium phthalimide; (i) (1) $H_2NNH_2\cdot H_2O$, (2) Ac_2O; (j) Fe/NH_4Cl; (k) (1) $NaNO_2$, (2) $HOOC(CH_2)_2SH$; (1) $HOOC(CH_2)_2Br$; (m) (1) $SOCl_2$, (2) $AlCl_3$.

directly introduced onto the guanidine (**32**). These results indicate that the potency is regulated by both the steric bulk and the lipophilic nature in this area of the molecule, and benzyl and phenethyl are the optimal substituents.

The unique feature of this class of compounds is the replacement of the flexible alkyl chain in conventional H2 antagonists with an aromatic moiety. Though we observed the lack of anti-*H. pylori* activity in the marketed H2 antagonist,[24,25] we also examined the compounds consisting of a guanidinothiazole ring and acetamidoalkyl function as the next referenced compounds for this series (Chart 1). The compounds **53** and **54**, which replace the phenyl ring of **23** with a flexible alkyl chain, did not show any activity (MIC > 200 μg/mL). This result, indicating the importance of structural rigidity in the spacer group between the thiazole and acetamidomethyl moieties, prompted us to further investigate a series of compounds with a more conformationally restrained structure (**45**−**52**). The results are summarized in Table 4. The activity of **47** was only 3-fold less potent than that of the appropriate rotatable analogue **23**. However, contrary to our expectation, the introduction of substitution onto the guanidino moiety did not contribute to improvement of the activity, and the activities of **48** and **49** were 35-fold and 1100-fold weaker than those of the corresponding rotatable analogues **26** and **36**, respectively.

Concerning the H2 antagonist and antisecretory activities, alkyl derivatives are generally more potent

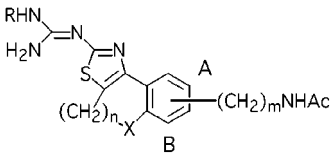
Table 3. Pharmacological Activities of 2-(Substituted guanidino)-4-phenylthiazoles



compd	R	position	MIC (mg/μL)[a] mean	MIC (mg/μL)[a] range	inhibition, % gastric secretion[b] (rat, 1 mg/kg iv)	inhibition, % H_2 antagonism[c] (1×10^{-6} g/mL)
22	H	*p*	>100			
23	H	*m*	16.5	3.13−50		
24	Me	*m*	14.4	3.13−25		
25	Et	*m*	3.6	1.56−6.25		
26	*n*-C_4H_9	*m*	0.22	0.1−0.39	74	84
27	$HO(CH_2)_2$	*m*	20	6.25−50		
28	$MeO(CH_2)_2$	*m*	0.32	0.2−0.39	87	83
29	$MeO(CH_2)_3$	*m*	0.96	0.39−1.56	87	54
30	$NC(CH_2)_2$	*m*	19.3	6.25−25		
31	$Me_2N(CH_2)_2$	*m*	57	12.5−100		
32	EtO	*m*	29	12.5−50		
33	Ph	*m*	0.52	0.2−0.78	24	23
34	$PhCH_2$	*m*	0.025	0.00625−0.05	50	77
35	$Ph(CH_2)_2$	*m*	0.037	0.0125−0.1	59	65
36	2-$MeOPh(CH_2)_2$	*m*	0.017	0.0030−0.05	58	72
37	4-$MeOPh(CH_2)_2$	*m*	0.32	0.2−0.78	10	34
38	$Ph(CH_2)_3$	*m*	0.39	0.2−0.78	57	35
39	$Ph_2CH(CH_2)_2$	*m*	2.5	1.56−3.13		
40	$PhO(CH_2)_2$	*m*	0.49	0.39−0.78	18	52
41	$PhCH_2O(CH_2)_2$	*m*	2.5	0.78−6.25		
42	$PhCONH(CH_2)_2$	*m*	23	3.13−50		
43	2-pyridyl-$(CH_2)_2$	*m*	0.49	0.39−0.78	14	39
44	4-imidazolyl-$(CH_2)_2$	*m*	27	6.25−50		
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.

Table 4. Antimicrobial Activity of Tricyclic Derivatives against *Helicobacter pylori*



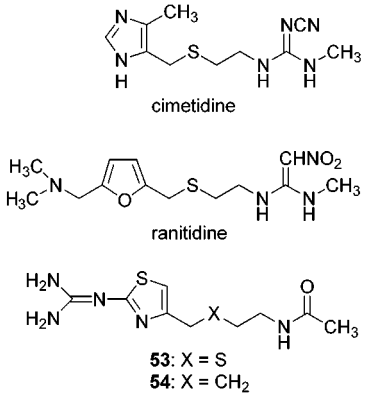
compd	R	m	n	X	position	MIC (μg/mL)[a] mean	MIC (μg/mL)[a] range
45	H	0	2	O	A	>100	
46	H	1	1	O	A	62	25−100
47	H	1	2	O	A	50	12.5−100
48	*n*-C_4H_9	1	2	O	A	7.7	3.13−12.5
49	2-$MeOPh(CH_2)_2$	1	2	O	A	18.9	6.25−50
50	H	0	1	S	A	>100	
51	*n*-C_4H_9	1	1	S	A	22	6.25−50
52	H	1	2	O	B	>100	

[a] See Table 3.

than arylalkyl derivatives. Among them, both activities of methoxyethyl (**28**) and methoxypropyl (**29**) derivatives are superior to those of ranitidine.

Finally, we have assessed the specificity of antimicrobial activity for *H. pylori* of two representative compounds (**28** and **36**) (Table 5). The clinically available drugs for the treatment of *H. pylori* eradication, bismuth salicylate, metronidazole, and amixicillin,

Chart 1



showed susceptibility for a variety of organisms. On the other hand, the antimicrobial activities of **28** and **36** were specific for *H. pylori*.

In conclusion, we have described our experimental results in a novel phenylthiazole series as anti-*H. pylori* agents. Among the compounds obtained, 2-(2-methoxyphenyl)ethyl derivative **36** exhibited the highest anti-*H. pylori* activity in this series, and the potency was superior to that of amoxicillin. On the other hand, though methoxyethyl derivative **28** showed less potent anti-*H. pylori* activity than **36**, this compound had more potent antisecretory activity than ranitidine. Regarding

Table 5. Antimicrobial Activity of **28**, **36**, and the Reference Compounds against Various Organisms

	MIC (μg/mL) (range)				
organisms (*n*)	**28**	**36**	bismuth salicylate	metronidazole	amoxicillin
H. pylori (10)	0.32 (0.2−0.39)	0.017 (0.0030−0.05)	8.7	5.4 (1.56−25)	0.021 (0.0063−0.1)
C. jejuni (8)	>100	20.5 (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. gonorrheas (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)

the mode of anti-*H. pylori* action, both compounds (**28** and **36**) showed bactericidal effect (data to be published elsewhere). We selected **28** and **36** as candidates for further pharmacological evaluation, and the results on one of them, **28** (FR145175), have been reported in a journal of pharmacology.[26]

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.

3-(2-Methyl-1,3-dioxolan-2-yl)benzonitrile (2). A mixture of 3-acetylbenzonitrile (**1**) (50 g, 0.34 mol), boron trifluoride etherate (1 mL, 8 mmol), and ethylene glycol (30 mL, 0.55 mol) in benzene (200 mL) was refluxed for 5 h under water removing with a Dean−Stark apparatus. The resulting solution was washed with saturated aqueous $NaHCO_3$ (200 mL), dried, and concentrated to afford **2** (65 g, 99%) as an oil. IR (film): 2230 cm^{-1}. ^{1}H NMR: δ 1.64 (3H, s), 3.73−3.79 (2H, m), 4.04−4.11 (2H, m), 7.46 (1H, t, J = 7.5 Hz), 7.59 (1H, dt, J = 7.5 and 1.5 Hz), 7.73 (1H, dt, J = 7.5 and 1.5 Hz), 7.80 (1H, t, J = 1.5 Hz). MS: m/z 190 ($M^+ + 1$).

3-(Acetamidomethyl)acetophenone (3). A solution of **2** (65 g, 0.34 mol) in tetrahydrofuran (THF) (400 mL) was added dropwise to a suspension of $LiAlH_4$ (26.3 g, 0.69 mol) in THF (400 mL) at 5−10 °C with stirring under a N_2 atmosphere. The mixture was stirred for 2 h at room temperature. AcOEt (200 mL) was added dropwise to the reaction mixture under cooling in an ice bath, and then ice−water (200 mL) was carefully added. After the resulting precipitate was removed by filtration, the filtered solution was concentrated and the residue was dissolved in $CHCl_3$. The solution was washed with water, dried, and concentrated to give 2-[3-(aminomethyl)-phenyl]-2-methyl-1,3-dioxolan (57.2 g) as an oil. IR (film): 3300, 3250 cm^{-1}. ^{1}H NMR: δ 1.66 (3H, s), 3.72−3.82 (2H, s), 4.01−4.08 (2H, m), 7.23−7.42 (4H, m).

A solution of 2-[3-(aminomethyl)phenyl]-2-methyl-1,3-dioxolan (57 g) in 1 N HCl (500 mL)−MeOH (500 mL) was stirred at room temperature for 2 h. After removal of the solvent, the residue was washed with MeOH (50 mL) to give 3-(aminomethyl)acetophenone hydrochloride (31.2 g): mp 145−146 °C. IR (Nujol): 3180, 1680 cm^{-1}. ^{1}H NMR: δ 2.61 (3H, s), 4.11 (2H, s), 7.58 (1H, t, J = 7.5 Hz), 7.76 (1H, d, J = 7.5 Hz), 7.97 (1H, d, J = 7.5 Hz), 8.15 (1H, s), 8.50 (3H, br s).

Acetyl chloride (32 g, 0.17 mol) was added dropwise to a suspension of 3-(aminomethyl)acetophenone hydrochloride (31 g, 0.17 mol) and Et_3N (37 g, 0.34 mol) in CH_2Cl_2 (300 mL) at 5−10 °C, and the mixture was stirred for 1 h at room temperature. After removal of the solvent, the residue was dissolved in water (600 mL). 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 afford **3** (20 g, 31%) as an oil. IR (film): 3250, 1680, 1640 cm^{-1}. ^{1}H NMR: δ 1.88 (3H, s), 2.57 (3H, s), 4.31 (2H, d, J = 6 Hz), 7.43−7.54 (2H, m), 7.82−7.87 (2H, m), 8.43 (1H, t, J = 6 Hz). MS: m/z 192 ($M^+ + 1$).

4-[3-(Acetamidomethyl)phenyl]-2-aminothiazole (4). Bromine (7.9 g, 50 mmol) was added dropwise to a solution of **3** (9.0 g, 50 mmol) in dioxane (100 mL) at room temperature with stirring. After being stirred for 2 h, the solution was concentrated to dryness. A solution of the residue and thiourea (3.8 g, 50 mmol) in EtOH (100 mL) was refluxed for 2 h with stirring. After removal of the solvent, the residue was dissolved in water (100 mL). 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 MeOH/diisopropyl ether (IPE) to afford **4** (8.0 g, 69%): mp 172−173 °C. IR (Nujol): 3300, 3120, 1640, 1610 cm^{-1}. ^{1}H NMR: δ 1.87 (3H, s), 4.26 (2H, d, J = 6 Hz), 6.97 (1H, s), 7.06 (2H, s), 7.13 (1H, d, J = 7.5 Hz), 7.30 (1H, t, J = 7.5 Hz), 7.64−7.68 (2H, m), 8.35 (1H, t, J = 6 Hz). Anal. ($C_{12}H_{13}N_3OS$) C, H, N.

4-[3-(Acetamidomethyl)phenyl]-2-(3-benzoylthioureido)thiazole (5). A suspension of **4** (2.0 g, 8.0 mmol) and benzoyl isothiocyanate (1.3 g, 8.0 mmol) in Me_2CO (40 mL) was refluxed for 5 h. The resulting precipitate was collected by filtration to afford **5** (2.9 g, 89%): mp 225−226 °C. IR (Nujol): 3260, 1680, 1640 cm^{-1}. ^{1}H NMR: δ 1.89 (3H, s), 4.31 (2H, d, J = 6 Hz), 7.24 (1H, d, J = 7.5 Hz), 7.40 (1H, t, J = 7.5 Hz), 7.57 (2H, t, J = 7.5 Hz), 7.67−7.84 (4H, m), 8.03 (2H, dd, J = 1.5 and 7 Hz), 8.41 (1H, t, J = 6 Hz), 12.21 (1H, s), 14.27 (1H, s). Anal. ($C_{20}H_{18}N_4O_2S_2$) C, H, N.

4-[3-(Acetamidomethyl)phenyl]-2-(thioureido)thiazole (6). A solution of NaOH (5 g, 125 mmol) in water (40 mL) was added to a suspension of **5** (20 g, 50 mmol) in MeOH (400 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 resulting precipitate was collected by filtration to afford **6** (13.5 g, 90%): mp 230−231 °C. IR (Nujol): 3400, 3300, 1620 cm^{-1}. ^{1}H NMR: δ 1.89 (3H, s), 4.29 (2H, d, J = 6 Hz), 7.20 (1H, d, J = 7.5 Hz), 7.37 (1H, t, J = 7.5 Hz), 7.50 (1H, s), 7.73 (1H, d, J = 7.5 Hz), 7.74 (1H, s), 8.37 (1H, t, J = 6 Hz), 8.78 (1H, br s), 11.73 (1H, s). Anal. ($C_{13}H_{14}N_4OS_2$) C, H, N.

4-[5-(Acetamidomethyl)phenyl]-2-[2-(2-methoxyphenyl)-ethyl]guanidino]thiazole (36). General Procedure. A suspension of **6** (5.8 g, 12 mmol) and MeI (2.0 g, 14 mmol) in MeOH (40 mL) was refluxed for 3 h with stirring. After removal of the solvent, 2-(2-methoxyphenyl)ethylamine (7.2 g, 48 mmol) and EtOH (100 mL) were added to the residue,

and the resulting mixture was refluxed for 40 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 **36** (1.6 g, 33%). IR (Nujol): 3310, 3280, 1620 cm^{-1}. ^1H NMR: δ 1.88 (3H, s), 2.77−2.85 (2H, t, J = 7 Hz), 3.37−3.43 (2H, m), 3.80 (3H, s), 4.28 (2H, d, J = 6 Hz), 6.84−6.99 (2H, m), 7.14−7.24 (4H, m), 7.32 (1H, t, J = 7.5 Hz), 7.44 (2H, br s), 7.63−7.68 (2H, m), 8.36 (1H, t, J = 6 Hz).

Ethyl 4-[4-(Acetamidomethyl)phenyloxy]butylate (11b). A mixture of 4-(acetamidomethyl)phenol (8.6 g, 52 mmol), ethyl 4-bromobutylate (10.2 g, 52 mmol), and fine granule K_2CO_3 (7.2 g, 52 mmol) in *N*,*N*-dimethylformamide (80 mL) was stirred at 70 °C for 10 h. After removal of the solvent, the residue was added to water−AcOEt, and the organic layer was separated. The solution was washed with water, dried, and concentrated to give a residue, which was chromatographed on silica gel eluting with $CHCl_3$/MeOH (50/1) to afford **11b** (10.5 g, 71%). An analytical sample was obtained by recrystallization from AcOEt−hexane: mp 67−68 °C. IR (Nujol): 3275, 1715, 1630 cm^{-1}. ^1H NMR: δ 1.07 (3H, t, J = 7 Hz), 1.85 (3H, s), 1.95 (2H, quint, J = 7 Hz), 2.44 (2H, t, J = 7 Hz), 3.96 (2H, t, J = 7 Hz), 4.13 (2H, q, J = 7 Hz), 4.24 (2H, d, J = 7 Hz), 6.86 (2H, d, J = 7.5 Hz), 7.16 (2H, d, J = 7.5 Hz), 8.26 (1H, t, J = 7 Hz). MS: m/z 280 ($M^+ + 1$).

4-[4-(Acetamidomethyl)phenyloxy]butyric Acid (12b). A mixture of **11b** (9.6 g, 35 mmol) and 1 N NaOH (35 mL) in MeOH (100 mL) was stirred at room temperature for 7 h. After removal of the solvent, the residue was added to water-CH_2Cl_2. The aqueous layer was separated, made acidic with 1N HCl, and extracted with AcOEt. The extract was washed with water, dried, and concentrated to afford **12b** (6.3 g, 73%). An analytical sample was obtained by recrystallization from MeOH/IPE: mp 135−136 °C. IR (Nujol): 3320, 1690, 1610 cm^{-1}. ^1H NMR: δ 1.84 (3H, s), 1.90 (2H, quint, J = 7 Hz), 2.37 (2H, t, J = 7 Hz), 3.94 (2H, t, J = 7 Hz), 4.16 (2H, d, J = 6 Hz), 6.86 (2H, d, J = 8 Hz), 7.15 (2H, d, J = 8 Hz), 8.26 (1H, t, J = 6 Hz), 12.14 (1H, br s). MS: m/z 252 ($M^+ + 1$).

7-(Acetamidomethyl)-2,3,4,5-tetrahydro-1-benzoxepin-5-one (14b). Compound **12b** (4.5 g, 18 mmol) was added portionwise to polyphospholic acid (PPA), fleshly prepared from H_3PO_4 (10.5 g, 108 mmol) and P_2O_5 (17.8 g, 126 mmol), and the mixture was stirred at 80 °C for 4 h. The reaction mixture was carefully added to cold water under cooling in an ice bath and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$, dried, and concentrated to afford **14b** (0.9 g, 22%) as an oil. IR (Film): 1760, 1655 cm^{-1}. ^1H NMR: δ 1.85 (3H, s), 2.10 (2H, quint, J = 6.5 Hz), 2.77 (2H, t, J = 6.5 Hz), 4.18 (2H, t, J = 6.5 Hz), 4.21 (2H, d, J = 6 Hz), 7.06 (1H, d, J = 8 Hz), 7.38 (1H, dd, J = 8 and 2 Hz), 7.51 (1H, d, J = 2 Hz), 8.35 (1H, t, J = 6 Hz). MS: m/z 244 ($M^+ + 1$).

4-[4-(Acetamidomethyl)phenylthio]propionic Acid (20b). A solution of $NaNO_2$ (3.2 g, 46 mmol) in water (10 mL) was added dropwise to a solution of 4-(acetamidomethyl)-aniline (**18**) (6.3 g, 38 mmol) and concentrated HCl (10 mL, 114 mmol) in water (60 mL) at 0−5 °C, and the mixture was stirred for 3 h. A solution of 2-mercaptopropionic acid (4.1 g, 38 mmol) and NaOH (7.7 g, 190 mmol) in water (60 mL) was added dropwise to the mixture at 0−5 °C. The resulting mixture was stirred at room temperature for 30 min and then at 70 °C for 4 h. The reaction mixture was washed with AcOEt, made acidic with 6 N HCl, 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 (9/1) to afford **20b** (3.6 g, 38%): mp 119−120 °C. IR (Nujol): 3260, 1690, 1655 cm^{-1}. ^1H NMR: δ 1.86 (3H, s), 2.50 (2H, t, J = 7 Hz), 3.10 (2H, t, J = 7 Hz), 4.21 (2H, d, J = 6 Hz), 7.20 (2H, d, J = 8 Hz), 7.30 (2H, d, J = 8 Hz), 8.33 (1H, t, J = 6 Hz), 12.38 (1H, br s). MS: m/z 253 ($M^+ + 1$).

6-(Acetamidomethyl)benzothiopyran-4-one (21b). Thionyl chloride (4.9 mL, 65 mmol) was added dropwise to a solution of **20b** (3.4 g, 13 mmol) in THF (30 mL) at room temperature, and the mixture was stirred for 3 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (30 mL), and $AlCl_3$ (3.6 g, 26 mmol) was added portionwise to the solution. After being stirred for 2 h at room temperature, the mixture was added to cold water. 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 **21b** (1.2 g, 39%): mp 109−111 °C. IR (Nujol): 3280, 1660, 1645 cm^{-1}. ^1H NMR: δ 1.86 (3H, s), 2.86−2.92 (2H, m), 3.27−3.35 (2H, m), 4.21 (2H, d, J = 6 Hz), 7.31 (1H, d, J = 8 Hz), 7.37 (1H, dd, J = 8 and 1 Hz), 7.86 (1H, d, J = 1 Hz), 8.39 (1H, t, J = 6 Hz). MS: m/z 236 ($M^+ + 1$).

9-(Acetamidomethyl)-2-[2-(2-methoxyphemyl)ethyl]-guanidino-4,5-dihydrothiazolo-[5,4-*d*]benzoxepin (49). General Procedure. A solution of bromine (550 mg, 3.4 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of **14b** (800 mg, 3.4 mmol) in CH_2Cl_2 (8 mL) at room temperature with stirring. After being stirred for 5 h, the solution was concentrated to dryness. A solution of the residue, [2-(2-methoxyphenyl)ethylamidino]thiourea[3] (860 mg, 3.4 mmol), and $NaHCO_3$ (580 mg, 6.8 mmol) in EtOH (10 mL) was refluxed for 4 h with stirring. After removal of the solvent, the residue was added to water−AcOEt. The resulting precipitate was collected by filtration and recrystallized from MeOH/IPE to afford **49** (550 mg, 35%): mp 202−204 °C. IR: 3440, 3300, 1650 cm^{-1}. ^1H NMR: δ 1.86 (3H, s), 2.81 (2H, t, J = 7.5 Hz), 3.11 (2H, t, J = 5 Hz), 3.33−3.43 (2H, m), 3.80 (3H, s), 4.21 (4H, d, J = 5 Hz), 6.84−6.99 (3H, m), 7.03 (1H, dd, J = 2 and 8 Hz), 7.17−7.24 (2H, m), 7.37 (2H br s), 7.95 (1H, d, J = 2 Hz), 8.32 (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 then suspended in buffered saline to give the turbidity equivalent to McFarland No. 1. Next, 10^2-fold dilutions 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.

The MICs for *C. jejuni*, *C. difficile*, *C. perfrigens*, *B. fragilis*, *N. gonorrheas*, and *N. meningitidis* were determined according to the Japan Society of Chemotherapy Guidelines.[27]

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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Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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