Chem. Pharm. Bull. **40**(9) 2432—2441 (1992) Vol. 40, No. 9

Studies on Antiulcer Drugs. VI.[1] 4-Furyl-2-guanidinothiazoles and Related Compounds as Potent Histamine H_2-Receptor Antagonists

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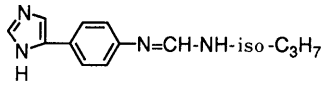
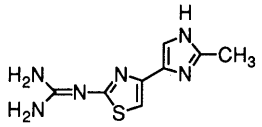
A series of 4-furyl-2-guanidinothiazole derivatives and related compounds were synthesized and evaluated for histamine H_2-receptor antagonist and gastric acid antisecretory activities. Among them, compounds I-17, I-48 and I-49 showed high activities in these tests. In addition, compound I-17 possessed potent inhibitory activities on each of the gastric ulcers induced by stress, ethanol and HCl–aspirin. On the other hand, compound I-48 demonstrated antimicrobial activity against *Helicobacter Pylori* and the potency was far stronger than that of clinically used H_2-antagonists. Some structure–activity relationships are discussed.

Keywords furylthiazole; histamine H_2-receptor antagonist; antisecretory activity; antiulcer activity; cytoprotective activity; antimicrobial activity; *Helicobacter Pylori*; structure–activity relationship

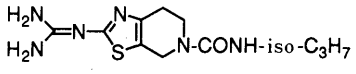
Notable efficacy of cimetidine in the treatment of peptic ulcers has prompted medicinal chemists to investigate novel histamine H_2-receptor antagonists (H_2-antagonists). In regard to the structural aspect, cimetidine and subsequently marketed agents, ranitidine, famotidine, roxatidine acetate and nizatidine, have a common feature consisting of three fundamental components: (A) a basic heteroaromatic ring or aromatic ring substituted by basic moiety, (B) a four-membered flexible alkyl chain as a spacer group and (C) a urea or amidine equivalent group. According to such a scheme, many chemical modifications of this class of compounds have been conventionally performed.[2]



mifentidine (**1**)



zaltidine (**2**)



FCE-23067 (**3**)

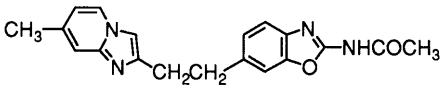


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Chart 1

On the other hand, recent reports have demonstrated some successful approaches for obtaining potent H_2-antagonists in conformationally restricted derivatives, mifentidine (**1**),[3] zaltidine (**2**)[4] and FCE-23067 (**3**).[5] As described in a previous paper,[6] we also obtained a novel class of H_2-antagonist, an imidazo[1,2-*a*]pyridinylethylbenzoxazole derivative (**4**), having a semirigid (aralkyl) spacer group (Chart 1).

Supported by these results, a continuing search for a H_2-antagonist led us to prepare new derivatives by introducing an aralkyl spacer group. The strategy employed here was to replace the $-CH_2SCH_2-$ group existing in the conventional H_2-antagonists with a heteroaromatic moiety. As prototype compounds we selected the guanidinothiazole derivatives represented by tiotidine (**5**),[7] famotidine,[8] ebrotidine[9] and BL-6341A,[10] which possess an attractive efficacy as H_2-antagonists (Chart 2). This paper describes the synthesis and pharmacological profile of a series of 4-furyl-2-guanidinothiazoles and related compounds.

Chemistry

The desired 2-guanidinothiazoles listed in Tables I—III were synthesized by the routes outlined in Charts 3—8. Friedel–Crafts acylation[11] of **9** or **10** and subsequent cyclization with amidinothiourea afforded the two fundamental derivatives (I-**1** and **13**) (Chart 3). Acid hydrolysis of I-**1** gave a key intermediate **14**. Treatment of **14** with several reagents, *e.g.*, (a) reactive carboxylic acid derivatives, (b) imidates, (c) *S*-methylisothioureas, (d) dithioimidocarbonates or 1,1-bis(methylthio)-2-nitroethene, (e) iso-

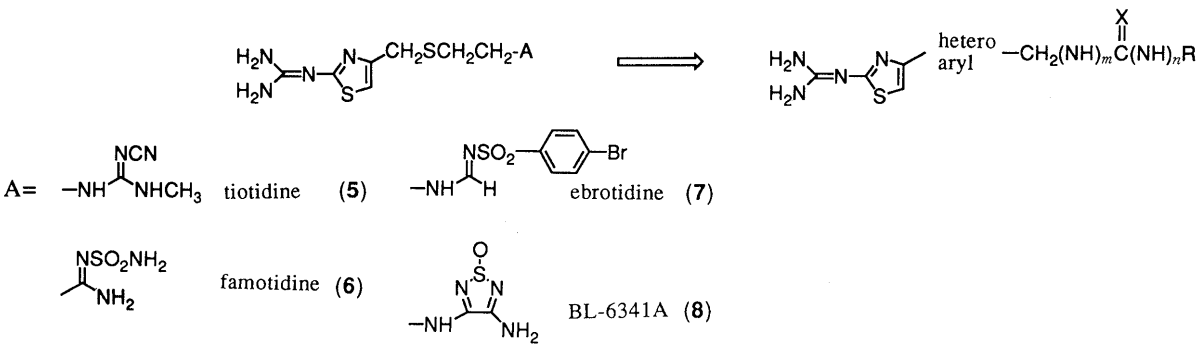


Chart 2

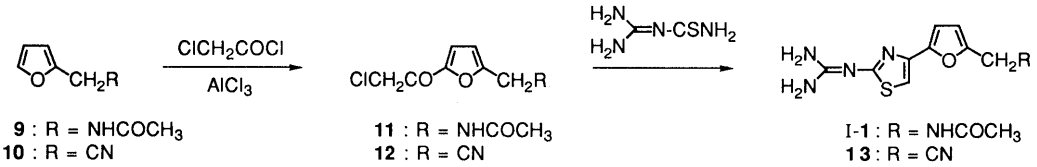


Chart 3

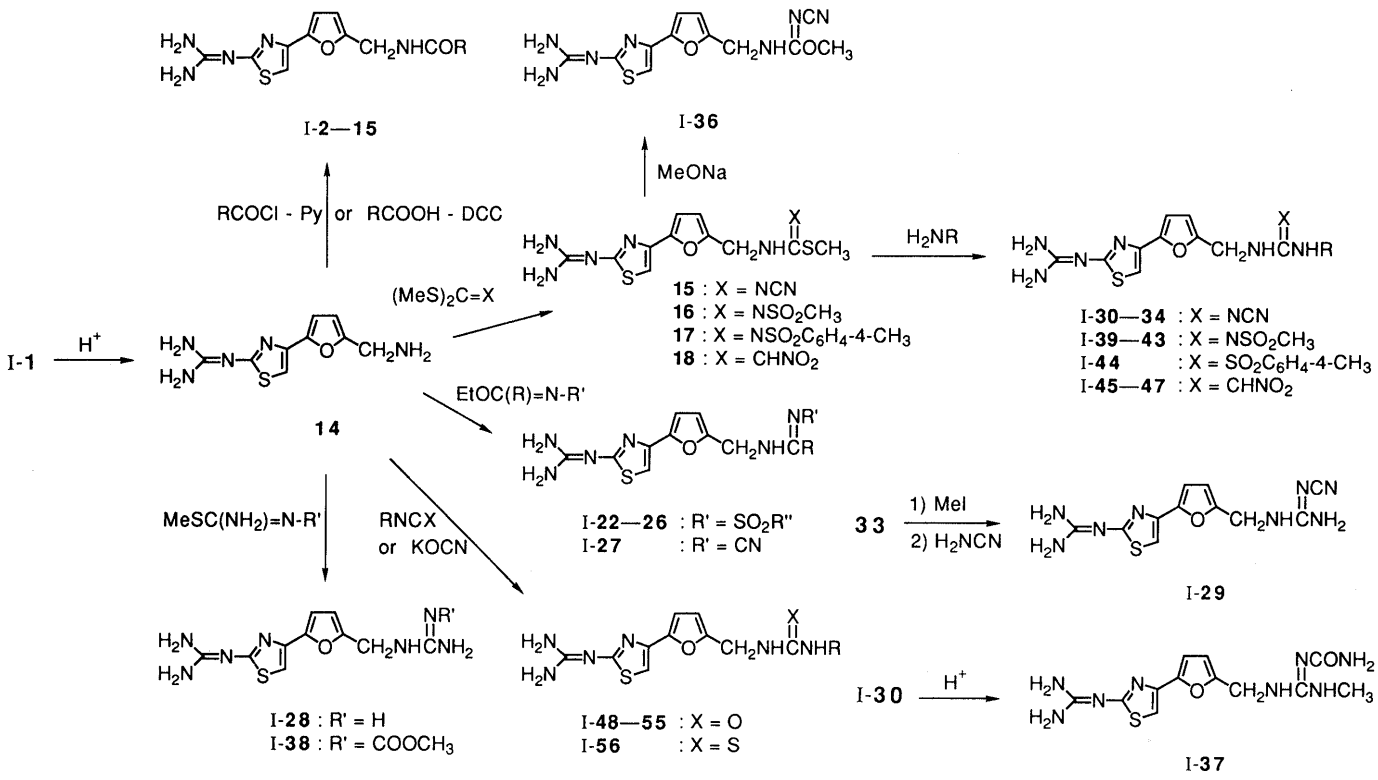
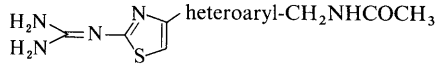


Chart 4

TABLE I. Physical Data of Several Biaryl Derivatives



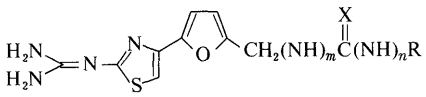
Compd. No.	Heteroaryl	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N
I-1		47	230—231 (I–M–T)	$C_{11}H_{13}N_5O_2S \cdot 1/10H_2O$	46.96 (47.31	4.73 4.71	24.89 24.65)
II[b]							
III		13	225—226 (W)	$C_{10}H_{12}N_6OS_2 \cdot 4/5H_2O$	38.65 (38.51	4.41 4.31	27.04 27.00)
IV		27	218—219 (A–Et)	$C_{10}H_{12}N_6OS_2 \cdot 2HBr$	26.21 (26.33	3.08 3.01	18.34 18.24)
V		29	260—261 (M–W)	$C_9H_{11}N_7O_2S \cdot 1/5H_2O$	37.94 (37.66	4.03 3.95	34.41 34.37)
VI		37	215—217 (Et–W)	$C_9H_{12}N_8OS \cdot HCl \cdot 3/2H_2O$	32.88 (32.93	4.39 4.46	34.08 34.08)

a) A, acetone; Et, EtOH; I, diisopropyl ether; M, MeOH; T, tetrahydrofuran; W, H_2O. *b*) Ref. 17.

cyanates or methylisothiocyanate resulted in the corresponding products, *i.e.*, (a) amides (**I-2**—**15**), (b) *N*-furfurylamidines (**I-22**—**27**), (c) guanidines (**I-28** and **I-38**), (d) *S*-methylisothioureas or isothioamide (**15**—**18**), (e) ureas (**I-48**—**55**) or thiourea (**I-56**), respectively. Compounds **15**—**18** were converted with the appropriate amines to the desired cyanoguanidines (**I-30**—**34**), sulfonylguanidines (**I-39**—**44**) and nitroethenes (**I-45**—**47**). The *O*-methylisourea derivative (**I-36**) was formed by the reaction of **15** with sodium methoxide. Of the guanidines, compound **I-29** was prepared by the reaction of thiourea derivative (**33**) with methyliodide followed by substitution with cyanamide. Compound **I-37** was obtained by the hydrolysis of cyanoguanidine derivative (**I-30**) (Chart 4). The *C*-furfuryl amidines (**I-16**—**21**) were prepared from the imidate (**19**) by treatment with the appropriate sulfonamides (Chart 5).

Charts 6 and 7 show the synthetic routes of the compounds having a heteroaryl moiety as an amidino function. Condensation of furan-2-glyoxal (**20**)[12] with acetaldehyde in the presence of concentrated ammonia gave imidazolylfuran (**21**). Friedel–Crafts acylation of **21**, followed by cyclization with amidinothiourea, afforded the desired compound (**I-57**). Similarly, compound **I-60** was prepared

TABLE II. Physical Data of Furylthiazoles



Compd. No.	*m*	*n*	X	R	Yield (%)	mp (°C) (Recrystn. solvent)[a]	Formula	Analysis (%) Calcd (Found)		
								C	H	N
I-2	1	0	O	C_2H_5	31	192—194 (I–M)	$C_{12}H_{15}N_5O_2S$	49.13 (49.25	5.15 5.26	23.87 23.91)
I-3	1	0	O	*n*-C_3H_7	29	182—183 (M–W)	$C_{13}H_{17}N_5O_2S \cdot H_2O$	47.99 (48.26	5.86 5.97	21.52 21.70)
I-4	1	0	O	iso-C_3H_7	14	211—213 (I–M)	$C_{13}H_{17}N_5O_2S$	47.99 (47.81	5.86 6.02	21.52 21.49)
I-5	1	0	O	*n*-C_4H_9	29	198—199 (M)	$C_{14}H_{19}N_5O_2S$	52.30 (52.15	5.96 6.00	21.79 21.73)
I-6	1	0	O	CH_2OCH_3	28	201—202 (I–M)	$C_{12}H_{15}N_5O_3S$	46.59 (46.60	4.89 5.02	22.64 22.48)
I-7	1	0	O	CH_2SCH_3	35	195—197 (I–M)	$C_{12}H_{15}N_5O_2S_2 \cdot 1/5H_2O$	43.81 (44.17	4.72 5.09	21.28 21.14)
I-8	1	0	O	CH_2OCOCH_3	35	250—253 (I–M)	$C_{13}H_{15}N_5O_4S \cdot HCl$	41.77 (41.70	4.31 4.31	18.73 18.46)
I-9	1	0	O	3-Pyridyl	20	224—225 (M–W)	$C_{15}H_{14}N_6O_2S \cdot H_2O$	49.99 (50.00	4.48 4.50	23.32 23.39)
I-10	1	0	O	2-Furyl	18	246 (M)	$C_{14}H_{13}N_5O_3S$	50.75 (50.69	3.95 3.81	21.14 21.01)
I-11	1	0	O	2-Thienyl	18	217—220 (M–W)	$C_{14}H_{13}N_5O_2S_2 \cdot 1/5H_2O$	47.91 (47.98	3.85 4.13	19.95 20.22)
I-12	1	0	O	C_6H_4-2-NO_2	12	218—220 (EA–I–M)	$C_{16}H_{14}N_6O_4S$	49.74 (49.37	3.65 3.76	21.75 21.57)
I-13	1	0	O	3-Pyridinyloxide	10	217 (DX–I–M)	$C_{15}H_{14}N_6O_3S \cdot 3/4H_2O$	48.45 (48.79	4.20 4.03	22.59 22.22)
I-14	1	0	O	CH_2SCH_2-2-furyl	53	180—181 (DX–I–M)	$C_{16}H_{17}N_5O_3S_2$	49.09 (49.25	4.38 4.40	17.89 17.98)
I-15	1	0	O	$CH_2S(O)CH_2$-2-furyl	46	208—209 (DX–I–M)	$C_{16}H_{17}N_5O_4S_2$	47.16 (47.15	4.21 4.15	17.19 17.02)
I-16	0	1	NSO_2CH_3	H	25	168—169 (M)	$C_{11}H_{14}N_6O_3S_2 \cdot H_2O$	36.66 (36.80	4.47 4.31	23.32 23.44)
I-17	0	1	NSO_2NH_2	H	53	224—225 (D–EA)	$C_{10}H_{13}N_7O_3S_2$	34.98 (35.28	3.82 3.84	28.55 28.26)
I-18	0	1	NSO_2NHCH_3	H	9	219—220 (D–W)	$C_{11}H_{15}N_7O_3S_2$	36.97 (36.93	4.23 4.15	27.43 27.41)
I-19	0	1	$NSO_2N(CH_3)_2$	H	6	161 (Et–I)	$C_{12}H_{17}N_7O_3S_2$	38.80 (38.62	4.61 4.39	26.40 26.42)
I-20	0	1	$NSO_2C_6H_4$-4-CH_3	H	31	207—209 (DX–I–M)	$C_{17}H_{18}N_6O_3S_2$	48.79 (48.44	4.34 4.19	20.08 19.77)
I-21	0	1	$NSO_2C_6H_4$-4-NH_2	H	15	190—191 (A)	$C_{16}H_{17}N_7O_3S_2 \cdot 1/8H_2O$	45.57 (45.92	4.12 4.21	23.25 22.95)
I-22	1	0	NSO_2CH_3	H	22	222—223 (DX–I–M)	$C_{11}H_{14}N_6O_3S_2$	38.59 (38.66	4.12 4.24	24.54 24.85)
I-23	1	0	$NSO_2C_2H_5$	H	26	188 (I–M)	$C_{12}H_{16}N_6O_3S_2$	40.44 (40.49	4.52 4.53	23.58 23.46)
I-24	1	0	$NSO_2C_6H_4$-4-CH_3	H	33	141—142 (I–M–T)	$C_{17}H_{18}N_6O_3S_2 \cdot 7/6H_2O$	46.46 (46.86	4.66 4.59	19.12 18.78)
I-25	1	0	$NSO_2C_6H_4$-4-OCH_3	H	32	185—186 (I–M–T)	$C_{17}H_{18}N_6O_4S_2 \cdot 8/7H_2O$	44.87 (45.25	4.49 4.81	18.47 18.07)
I-26	1	0	$NSO_2C_6H_4$-4-Br	H	28	210—211 (I–M–T)	$C_{16}H_{15}N_6BrO_3S_2$	39.76 (40.17	3.13 3.41	17.39 17.12)
I-27	1	0	NCN	CH_3	18	215—217 (DX–I–M)	$C_{12}H_{13}N_7OS$	47.53 (47.48	4.32 4.33	32.32 31.95)
I-28	1	1	NH	H	49	255 (I–M–T)	$C_{10}H_{13}N_7OS \cdot 2HCl \cdot 1/5H_2O$	33.75 (34.08	4.36 4.29	27.55 27.41)
I-29	1	1	NCN	H	25	224—225 (M–W)	$C_{11}H_{12}N_8OS \cdot 4/5H_2O$	41.46 (41.61	4.30 4.33	35.16 35.08)
I-30	1	1	NCN	CH_3	43	231—232 (I–M–T)	$C_{12}H_{14}N_8OS$	45.27 (45.37	4.43 4.46	35.20 35.19)
I-31	1	1	NCN	$CH_2CH=CH_2$	66	164—165 (A–W)	$C_{14}H_{16}N_8OS$	48.83 (48.86	4.68 4.41	32.54 32.58)
I-32	1	1	NCN	$(CH_2)_2OH$	70	208—209 (DX–I–M)	$C_{13}H_{16}N_8O_2S$	44.82 (45.12	4.63 4.91	32.16 32.10)

TABLE II. (continued)

Compd. No.	*m*	*n*	X	R	Yield (%)	mp (°C) (Recrystn. solvent)[a]	Formula	Analysis (%) Calcd (Found)		
								C	H	N
I-33	1	1	NCN	$(CH_2)_3OH$	57	160—161 (M–W)	$C_{14}H_{18}N_8O_2S$	46.40 (46.52	5.01 4.96	30.92 30.86)
I-34	1	1	NCN	$[NHR=N(CH_3)_2]$	51	205—206 (EA–I–M)	$C_{13}H_{16}N_8OS$	46.98 (47.14	4.85 4.92	33.71 33.66)
I-35	1	1	NCN	SCH_3	90	210 (I–M–T)	$C_{12}H_{13}N_7OS_2$	42.97 (43.08	3.91 3.65	29.23 29.38)
I-36	1	1	NCN	OCH_3	64	205—206 (D–W)	$C_{12}H_{13}N_7O_2S$	45.13 (44.93	4.10 4.33	30.70 30.42)
I-37	1	1	$NCONH_2$	CH_3	56	241—242 (M–W)	$C_{12}H_{16}N_8O_2S \cdot HCl$	35.21 (35.06	4.43 4.29	27.38 27.25)
I-38	1	1	$NCOOCH_3$	H	23	199—200 (I–M)	$C_{12}H_{15}N_7O_3S$	42.72 (42.92	4.48 4.62	29.06 28.82)
I-39	1	1	NSO_2CH_3	CH_3	29	233—234 (I–M)	$C_{12}H_{17}N_7O_3S_2 \cdot HCl$	35.34 (35.11	4.45 4.59	24.04 23.88)
I-40	1	1	NSO_2CH_3	C_2H_5	53	151—152 (I–M–T)	$C_{13}H_{19}N_7O_3S_2 \cdot 2HCl \cdot 1/3H_2O$	33.62 (33.75	4.70 4.53	21.11 21.05)
I-41	1	1	NSO_2CH_3	$(CH_2)_2OH$	60	202—203 (I–M)	$C_{13}H_{19}N_7O_4S_2 \cdot 1/5H_2O$	38.55 (38.89	4.83 5.20	24.21 24.22)
I-42	1	1	NSO_2CH_3	$(CH_2)_2OCH_3$	61	173—174 (I–M)	$C_{14}H_{21}N_7O_4S_2$	40.47 (40.56	5.09 4.94	23.60 23.64)
I-43	1	1	NSO_2CH_3	$(CH_2)_2N(CH_3)_2$	68	183—184 (I–M)	$C_{15}H_{24}N_8O_3S_2$	42.04 (42.32	5.64 5.61	26.15 26.31)
I-44	1	1	$NSO_2C_6H_4$-4-CH_3	CH_3	69	208—209 (D–W)	$C_{18}H_{21}N_7O_3S_2$	48.31 (48.21	4.73 5.00	21.91 21.66)
I-45	1	1	$CHNO_2$	CH_3	16	238—239 (M–W)	$C_{12}H_{15}N_7O_3S$	42.72 (42.77	4.48 4.53	29.06 28.96)
I-46	1	1	$CHNO_2$	*n*-C_4H_9	37	215—217 (M)	$C_{15}H_{21}N_7O_3S$	47.48 (47.44	5.58 5.71	25.84 25.97)
I-47	1	1	$CHNO_2$	$(CH_2)_2OH$	60	182—183 (EA)	$C_{13}H_{17}N_7O_4S \cdot 3/4H_2O$	40.99 (41.04	4.90 5.13	25.74 26.04)
I-48	1	1	O	H	19	214—215 (D–W)	$C_{10}H_{12}N_6O_2S \cdot 1/3H_2O$	41.95 (42.04	4.46 4.53	29.35 29.04)
I-49	1	1	O	CH_3	50	219—220 (DX–I–M)	$C_{11}H_{14}N_6O_2S$	44.89 (45.02	4.79 4.84	28.55 28.51)
I-50	1	1	O	C_2H_5	41	221—223 (DX–I–M)	$C_{12}H_{16}N_6O_2S$	46.74 (46.96	5.23 5.50	27.25 27.33)
I-51	1	1	O	*n*-C_3H_7	37	223 (D–EA)	$C_{13}H_{18}N_6O_2S$	48.43 (48.03	5.63 5.53	26.07 25.90)
I-52	1	1	O	iso-C_3H_7	40	222—224 (I–M)	$C_{13}H_{18}N_6O_2S \cdot 1/3H_2O$	47.55 (47.50	5.73 5.53	25.59 25.62)
I-53	1	1	O	$CH_2CH=CH_2$	50	219—220 (DX–I–M)	$C_{13}H_{16}N_6O_2S$	48.74 (48.51	5.03 5.30	26.23 25.99)
I-54	1	1	O	$(CH_2)_2OCOCH_3$	39	200—202 (DX–I–M)	$C_{14}H_{18}N_6O_4S$	45.89 (45.67	4.95 4.87	22.94 22.72)
I-55	1	1	O	$(CH_2)_2OH$	47	201—203 (DX–I–M)	$C_{12}H_{16}N_6O_3S \cdot 1/5H_2O$	43.95 (43.96	5.04 4.84	25.63 25.51)
I-56	1	1	S	CH_3	18	220 (D–W)	$C_{11}H_{14}N_6OS_2$	42.56 (42.68	4.55 4.70	27.08 26.86)

a) A, acetone; D, *N*,*N*-dimethylformamide; DX, dioxane; EA, ethyl acetate; Et, EtOH; I, diisopropyl ether; M, MeOH; T, tetrahydrofuran; W, H_2O.

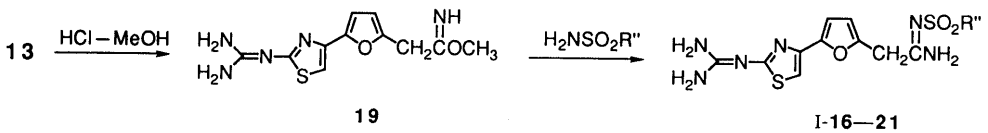
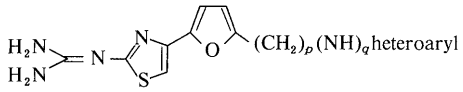
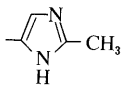
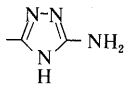
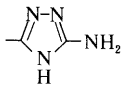
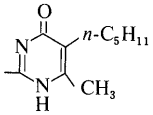
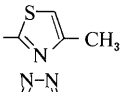
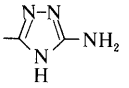
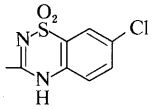


Chart 5

from **30** by acylation and successive cyclization. Hydrolysis of the imidate prepared from **13**, or cyclization[13] of **23** with amidinothiourea yielded the ester derivatives (**24** and **25**). Conversion of these compounds to hydrazide, followed by treatment with *S*-methylisothiourea, and finally, cyclization in the presence of concentrated ammonia, furnished the target compounds (**I-58** and **I-59**). Condensation of the thiourea derivative (**33**), derived from **14** by treatment with benzoylisothiocyanate and subsequent hydrolysis, with chloroacetone provided **I-61**. Compound **I-63** was obtained by the coupling reaction of **14** with **34**. Cyclization of **15** with hydrazine gave the triazole deriva-

TABLE III. Physical Data of Heteroarylsubstituted Furylthiazoles



Compd. No.	p	q	Heteroaryl	Yield (%)	mp (°C) (Recrystn. solvent)[a]	Formula	Analysis (%) Calcd (Found)		
							C	H	N
I-57	0	0		47	>300 (M)	$C_{12}H_{12}N_6OS \cdot 2HCl \cdot 5/4H_2O$	37.56 (37.83	4.33 4.32	21.80 21.73)
I-58	0	0		60	>300 (D–W)	$C_{10}H_{10}N_8OS \cdot 1/3H_2O$	40.53 (40.48	3.63 3.55	37.82 37.61)
I-59	1	0		51	259—261 (D–W)	$C_{11}H_{12}N_8OS \cdot 1/2H_2O$	42.17 (42.12	4.18 4.12	35.76 35.96)
I-60	1	0		45	212—213 (DX–I–M)	$C_{19}H_{24}N_6O_2S$	56.98 (56.72	6.04 5.95	20.98 20.76)
I-61	1	1		75	193—194 (I–M)	$C_{13}H_{14}N_6OS_2 \cdot HCl$	42.10 (41.82	4.08 4.23	22.66 22.53)
I-62	1	1		68	241—242 (D–W)	$C_{11}H_{13}N_9OS \cdot H_2O$	39.16 (38.94	4.48 4.30	37.37 37.30)
I-63	1	1		41	220—221 (D–M)	$C_{16}H_{14}N_7ClO_3S_2 \cdot 3/2H_2O$	40.13 (40.10	3.58 3.56	20.47 20.61)

a) See footnote a) in Tables I and II.

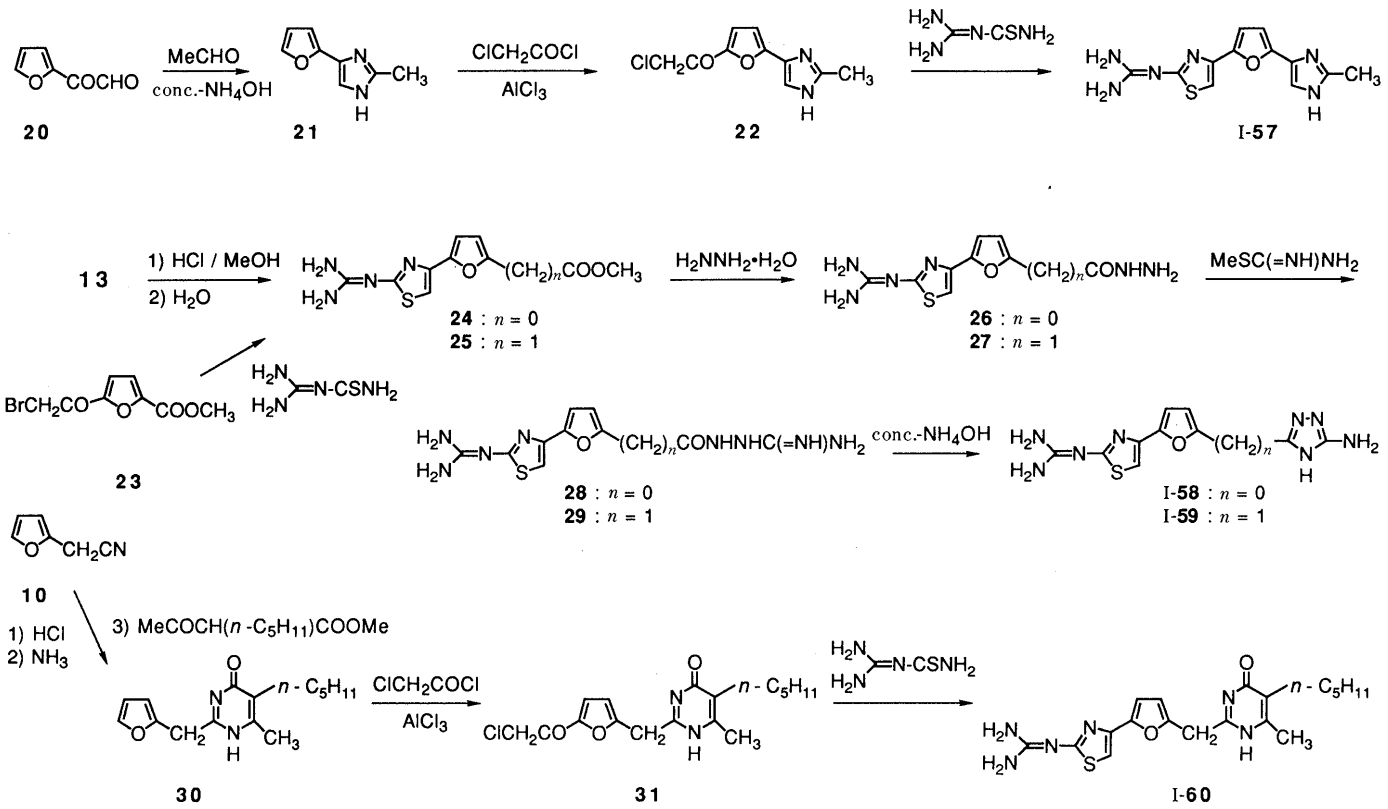


Chart 6

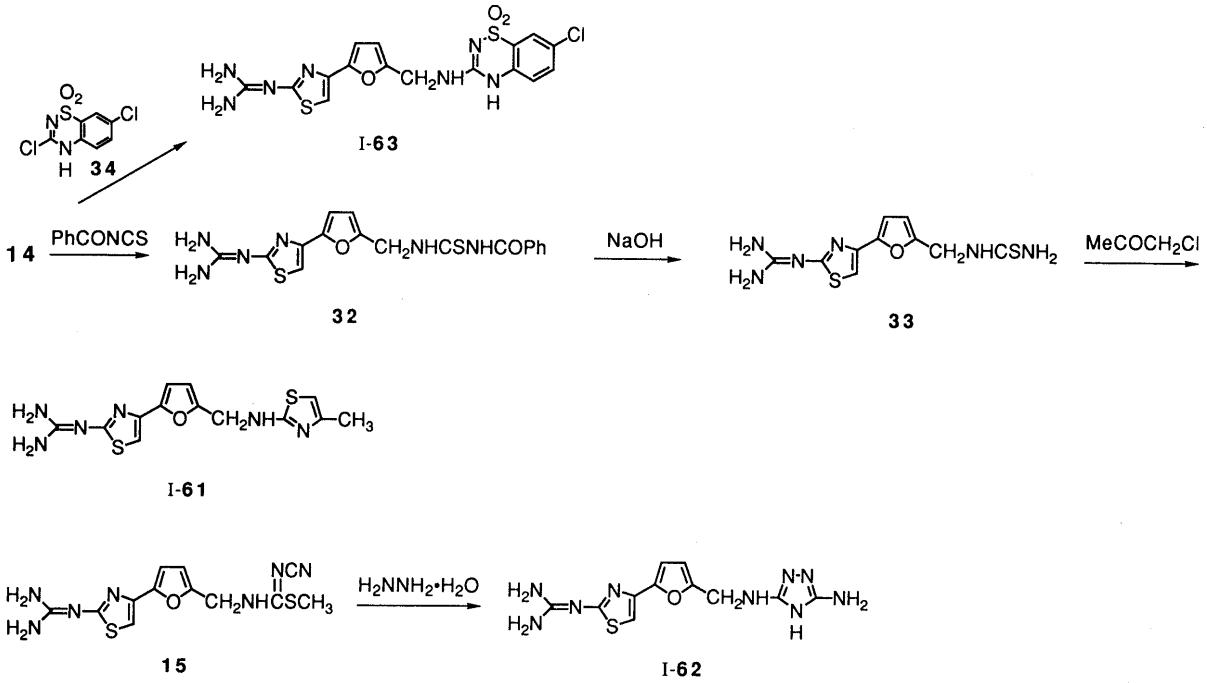


Chart 7

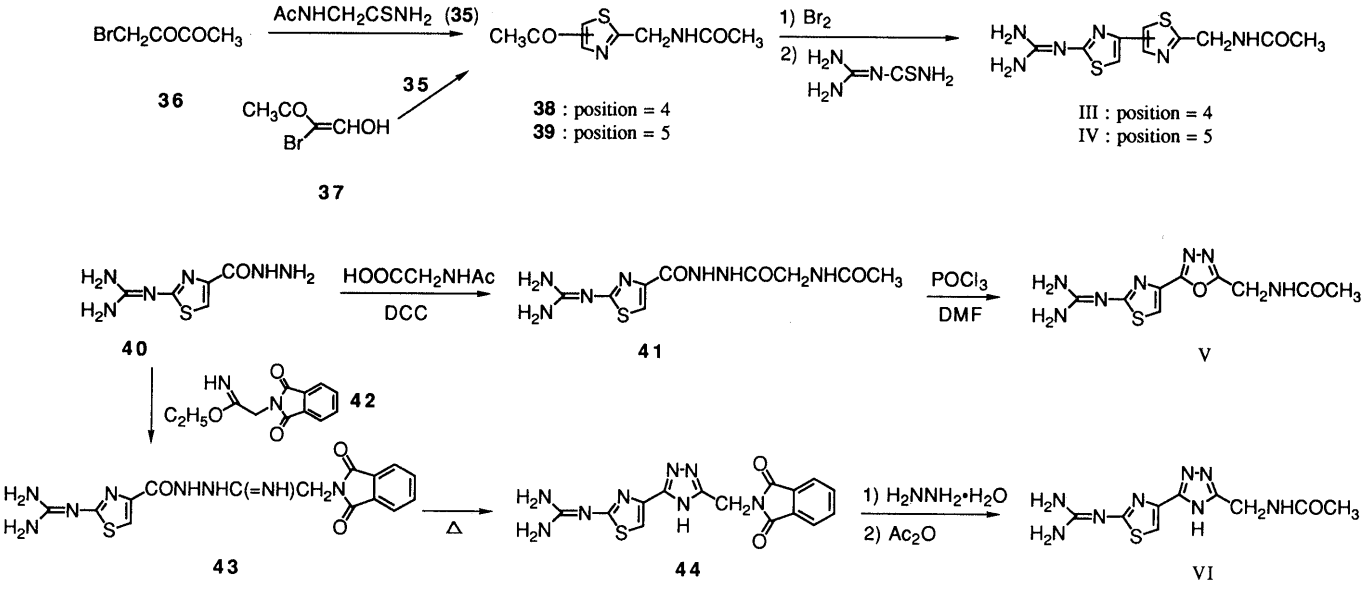


Chart 8

tive (**I-62**).

The derivatives (III—VI) to which were introduced several heteroaryl groups instead of furan rings, were synthesized as depicted in Chart 8. Condensation of the thioamido derivative (**35**) with haloketones (**36** or **37**) gave the corresponding acetylthiazoles (**38** or **39**), which were treated with bromine and subsequently cyclized with amidinothiourea to afford the desired compounds (III or IV), respectively. Thiazolohydrazide derivative (**40**)[14] was coupled with acetylglycine to provide diacylhydrazine (**41**), which on cyclization with phosphorous oxychloride afforded the requisite oxadiazole (V). Reaction of **40** with the imidate **42** gave iminohydrazide (**43**), which on heating cyclized to produce the triazole ring system (**44**). Treatment of **44** with hydrazine, followed by acetylation, afforded the target triazole derivative (VI).

Pharmacological Results and Discussion

The biological results of the guanidinothiazole derivatives (I—VI) are listed in Tables IV—VI. All compounds were evaluated *in vitro* for H_2-antagonist activity using the histamine-stimulated chronotropic response of the guinea pig atrium[15] and *in vivo* for antisecretory activity on histamine-stimulated gastric acid secretion in lumen-perfused anaesthetized rats.[16] Compounds with sufficient potency were also assessed for antisecretory activity on tetragastrin-stimulated gastric acid secretion in conscious Heidenhain pouch dogs.

First, in order to determine a favorable aromatic moiety, the activities of several *N*-thiazolylarylmethylacetamides

TABLE IV. H_2-Receptor Antagonist and Gastric Antisecretory Activities of 2-Guanidinothiazoles

Compd. No.	H_2-Receptor antagonist activity[a] [inhibition (%)] 1×10^{-6} g/ml	Antisecretory activity [inhibition (%)] Rat[b] 1 mg/kg i.v.	Dog[c] 0.32 mg/kg *p.o.*
I-1	85	68	83[d]
I-2	78	75	42
I-3	40	60	
I-4	73	32	
I-5	46	51	
I-6	20	32	
I-7	23	46	
I-8	63	54	
I-9	31	31	
I-10	26	43	
I-11	37	42	
I-12	−27	40	
I-13	−10	−30	
I-14	62	52	
I-15	22	94	
I-16	45	54	
I-17	84	99	92
I-18	93	52	
I-19	73	36	
I-20	85	27	
I-21	57	84	36
I-22	75	68	
I-23	73	99	55
I-24	65	91	41
I-25	57	77	
I-26	23	59	
I-27	30	12	
I-28	56	48	
I-29	78	53	
I-30	91	91	83[d]
I-31	74	19	
I-32	79	85	7
I-33	76	84	
I-34	38	12	
I-35	92	84	
I-36	70	−23	
I-37	68	79	
I-38	28	39	
I-39	84	100	62
I-40	83	100	41
I-41	51	80	30
I-42	72	62	
I-43	64	45	
I-44	78	−22	
I-45	88	100	55[d]
I-46	96	−29	
I-47	72	76	
I-48	78	91	70
I-49	89	87	70
I-50	75	84	
I-51	79	−28	
I-52	47	21	
I-53	60	51	
I-54	72	58	
I-55	57	66	
I-56	98	96	
I-57	91	43	
I-58	94	45	
I-59	47	14	
I-60	−19	−36	
I-61	13	−15	
I-62	25	43	
I-63	25	−58	
II	13	−35	
III	57	44	58[d]
IV	−7	−20	
V	−9	51	
VI	3	37	
Cimetidine	43	53	22[d]
Ranitidine	44	72	41
Roxatidine acetate	76	84	58
Famotidine	87	96	96

a) H_2-Receptor antagonism in isolated guinea pig right atrium. *b*) Inhibition of histamine-stimulated gastric acid secretion in lumen-perfused stomach of the anaesthetized rats ($n=2$). *c*) Inhibitory effect on gastric acid secretion induced by gastrin in the conscious Heidenhain pouch dogs ($n=2$). *d*) 1 mg/kg *p.o.*

TABLE V. Antiulcer Activities of Compounds **I-17**, **I-48** and **I-49** in Rats

Compd. No.	Stress ulcer[a] ED_{50}[d] (mg/kg, *p.o.*)	Ethanol ulcer[b] ED_{50}[d] (mg/kg, *p.o.*)	HCl-Aspirin ulcer[c] ED_{50}[d] (mg/kg, *p.o.*)
I-17	0.66	7.5	5.2
I-48	6.9	22.0	NT
I-49	2.6	21.2	NT
Cimetidine	18.8	>320	>32
Ranitidine	1.5	29.6	>32
Roxatidine acetate	1.6	20.4	>32
Famotidine	0.67	>32	5.2

a) Gastric ulcer induced by water-immersion stress. *b*) Gastric lesion induced by absolute ethanol. *c*) Gastric ulcer induced by HCl-aspirin on pylorus ligated condition. *d*) ED_{50} values were estimated from three or four doses. Ten animals were used per dose. NT = not tested.

TABLE VI. Anti-*Helicobacter Pylori* Activity of Some Derivatives

Compd. No.	MIC (μg/ml; 10 strains)	Range of MICs
I-1	27	25—50
I-2	>100	
I-17	>100	
I-30	62	50—100
I-37	>100	
I-39	>100	
I-45	>100	
I-48	71	25—100
I-49	>100	
III	15	12.5—25
Cimetidine	1130	800—1600
Ranitidine	>1600	
Roxatidine acetate	>1600	
Famotidine	1600	1600

were assessed. Among them, the furyl derivative (**I-1**) revealed fairly good activity. The 2,4-substituted thiazole derivative (III) also showed activity, but the potency was not so strong. The thiophen (II),[17] 2,5-substituted thiazole (IV), oxadiazole (V) and triazole (VI) derivatives resulted in a loss of the H_2-antagonist activity.

Next, the effect of the substitution at the furan ring on **I-1** was examined. As a result, many kinds of substituents, *viz.*, sulfamoylamidine (**I-17**), sulfamoylformamidine (**I-23**

and I-**24**), cyanoguanidine (I-**30**, I-**32** and I-**33**), mesylguanidine (I-**39** and I-**40**), isothiourea (I-**35**), nitroethene (I-**45**), urea (I-**48**—**50**) and thiourea (I-**56**) groups, fitted to express the H_2-antagonist and antisecretory (in rats) activities. Of these derivatives, compounds I-**17**, I-**30**, I-**39**, I-**48** and I-**49** showed potent antisecretory activity in dogs. Although compounds I-**57** and I-**58** consisting of triaryl system also exhibited excellent H_2-antagonist activity, the effect during the *in vivo* test was not satisfactory (Table IV).

Next, the compounds with powerful antisecretory activity in dogs (I-**17**, I-**48** and I-**49**) were evaluated for antiulcer activities on three different conditions. Table V showed a good profile of I-**17**, which possessed higher cytoprotective activity against ethanol-induced gastric lesions than the reference compounds.

Finally, we tested the compounds for antimicrobial activity against *Helicobacter Pylori*, which is accepted as an organism closely associated with gastritis and peptic ulcers.[18] Among the compounds exhibiting potent antisecretory activity in rats, some derivatives having representative amidino function were selected in the screening samples. The results are listed in Table VI. Of the compounds tested, I-**1**. I-**30**, I-**48** and III revealed noticeable activity. In contrast with these derivatives, the activity of the reference compounds was extremely low.

In conclusion, we have demonstrated a successful replacement of the four-membered flexible alkyl chain in the conventional H_2-antagonists with a furfuryl moiety. Among the compounds with potent gastric antisecretory activity, several possessed additional properties: compound I-**17** showed significant activity on cytoprotection and compound I-**48** possessed superior anti-*Helicobacter Pylori* activity in comparison with those of therapeutically used H_2-antagonists. These compounds were selected as candidates for further investigation.

Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were taken with a Hitachi 260-10 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Bruker AC-200P spectrometer using tetramethylsilane as an internal standard.

4-(5-Acetamidomethylfuran-2-yl)-2-guanidinothiazole (I-1) A solution of 2-acetamidomethyl-5-chloroacetylfuran (**11**)[11] (39.9 g, 185 mmol) and amidinothiourea (21.9 g, 185 mmol) in EtOH (400 ml) was refluxed for 2 h with stirring. After removal of the solvent, the residue was dissolved in H_2O (300 ml) and the solution was basified with 20% aqueous K_2CO_3. The resulting precipitate was collected by filtration, washed with H_2O and recrystallized from MeOH–diisopropyl ether (IPE)–tetrahydrofuran (THF) to afford I-**1** (24.1 g, 47%). IR (Nujol); 3430, 3200, 3110, 3060, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.88 (3H, s), 4.26 (2H, d, J=6 Hz), 6.25 (1H, d, J=3 Hz), 6.56 (1H, d, J=3 Hz), 6.73 (1H, s), 6.83 (4H, s), 8.24 (1H, t, J=6 Hz).

4-(5-Aminomethylfuran-2-yl)-2-guanidinothiazole (14) A solution of I-**1** (4.76 g, 17 mmol) in 1 N HCl (51.1 ml, 51 mmol) was refluxed for 8 h with stirring. After the pH of the solution was adjusted to 10, the resulting precipitate was collected by filtration and washed with H_2O to afford **14** (4.03 g, 100%). An analytical sample was obtained by recrystallization from EtOH, mp 200—201 °C. IR (Nujol): 3300 (broad), 1710, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.17 (2H, br s), 4.35 (2H, s), 6.30 (1H, d, J=3 Hz), 6.62 (1H, d, J=3 Hz), 6.78 (1H, s), 7.00 (4H, br s). *Anal.* Calcd for $C_9H_{11}N_5OS$: C, 45.56; H, 4.67; N, 29.51. Found: C, 45.89; H, 4.70; N, 29.38.

2-Guanidino-4-(5-ureidomethylfuran-2-yl)thiazole (I-48) A solution of KOCN (1.0 g, 12 mmol) in H_2O (9 ml) was added dropwise to a solution of **14** (1.5 g, 5.4 mmol) in H_2O (9 ml)–AcOH (4.5 ml) at 35 °C. After being stirred for 2 h at that temperature, the reaction mixture was added to AcOEt–THF–H_2O and the solution was adjusted to pH 9 with 20% aqueous K_2CO_3. The separated organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with AcOEt–MeOH (85 : 15) to give a product which was recrystallized from *N*,*N*-dimethylformamide (DMF)–H_2O to afford I-**48** (0.31 g, 19%). IR (Nujol): 3400, 3320, 3130, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.19 (2H, d, J=5 Hz), 5.53 (2H, s), 6.24 (1H, d, J=3 Hz), 6.36 (1H, t, J=5 Hz), 6.59 (1H, d, J=3 Hz), 6.76 (1H, s), 6.87 (4H, s).

(5-Chloroacetylfuran-2-yl)acetonitrile (12) $AlCl_3$ (34.1 g, 0.26 mol) was added portionwise to a solution of (furan-2-yl)acetonitrile (**10**) (11.4 g, 0.11 mol) and chloroacetyl chloride (12.7 ml, 0.16 mol) in CH_2Cl_2 (170 ml) at 0—5 °C and the mixture was stirred for 1.25 h. The reaction mixture was poured into CH_2Cl_2–ice-H_2O and the organic layer was separated. After washing with H_2O, the solution was added to H_2O and adjusted to pH 8 with 20% aqueous K_2CO_3. The obtained organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to afford **12** (16.4 g, 81%) as an oil. IR (film): 3120, 2210, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.33 (2H, s), 4.83 (2H, s), 6.64 (1H, d, J=4 Hz), 7.55 (1H, d, J=4 Hz).

4-(5-Cyanomethylfuran-2-yl)-2-guanidinothiazole (13) This compound was prepared from **12** in a manner similar to that described for I-**1**. Yield 77%, mp 228—230 °C (MeOH). IR (Nujol): 3450, 3420, 3370, 3110, 2250, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.20 (2H, s), 6.42 (1H, d, J=3 Hz), 6.65 (1H, d, J=3 Hz), 6.83 (1H, s), 6.87 (4H, s). *Anal.* Calcd for $C_{10}H_9N_5OS$: C, 48.57; H, 3.67; N, 28.32. Found: C, 48.58; H, 3.63; N, 28.33.

2-Guanidino-4-[5-(2-imino-2-methoxyethyl)furan-2-yl]thiazole (19) Anhydrous HCl was bubbled into a solution of **13** (19.5 g, 67 mmol) in MeOH (100 ml)–$CHCl_3$ (100 ml) for 4 h at 0—5 °C. After being stirred for 4 h at that temperature, the resulting precipitate was collected by filtration, washed with IPE, and then added to a solution of K_2CO_3 (46 g, 320 mmol) in H_2O (230 ml). The mixture was extracted with AcOEt–THF. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to afford **19** (17.5 g, 94%), mp 156—162 °C. This compound was not recrystallized because of its instability. IR (Nujol): 3420, 3110, 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.60 (3H, s), 3.65 (2H, s), 6.26 (1H, d, J=3 Hz), 6.58 (1H, d, J=3 Hz), 6.73 (1H, s), 6.84 (4H, s), 7.81 (1H, s).

4-[5-{2-Amino-2-(aminosulfonyliminoethyl)}furan-2-yl]-2-guanidinothiazole (I-17) A solution of **19** (14.9 g, 53 mmol) and sulfamide (20.4 g, 212 mmol) in 2-methoxyethanol (75 ml) was stirred at 70 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt (150 ml) and the solution was subjected to silica gel column chromatography eluting with AcOEt–MeOH (9 : 1). The obtained product was washed successively with H_2O (200 ml), AcOEt (100 ml) and MeOH (100 ml) and recrystallized from DMF–AcOEt to afford I-**17** (9.7 g, 53%). IR (Nujol): 3470, 3450, 3400, 3350, 3320, 3230, 1620, 1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.58 (2H, s), 6.28 (1H, d, J=3 Hz), 6.52 (2H, s), 6.56 (1H, d, J=3 Hz), 6.73 (1H, s), 6.81 (4H, s), 7.35 (1H, s), 8.18 (1H, s).

2-Acetamidomethyl-4-acetylthiazole (38) A suspension of 1-bromo-2,3-butanedione (**36**) (47 g, 280 mmol) and *N*-[(thiocarbamoyl)methyl]-acetamide (**35**) (30 g, 230 mmol) in acetone (600 ml) was refluxed for 3 h. The resulting precipitate was collected by filtration to afford **38** (42 g, 93%). An analytical sample was obtained by recrystallization from IPE–MeOH, mp 190—191 °C. IR (Nujol): 3410, 3350, 1690, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.93 (3H, s), 2.55 (3H, s), 4.54 (2H, d, J=6 Hz), 8.44 (1H, s), 8.91 (1H, t, J=6 Hz). *Anal.* Calcd for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; N, 14.13. Found: C, 48.26, H, 5.12; N, 13.99.

4-(2-Acetamidomethylthiazol-4-yl)-2-guanidinothiazole (III) Br_2 (2.2 g, 14 mmol) was added dropwise to a solution of **38** (2.2 g, 11 mmol) in AcOH (20 ml)–H_2O (20 ml) and the mixture was stirred for 4 h at 70 °C. After removal of the solvent, the residue was dissolved in EtOH (50 ml). Amidinothiourea (1.3 g, 11 mmol) was added to the solution and the mixture was refluxed for 4 h. After concentration to dryness, H_2O was added and the solution was basified with 20% aqueous K_2CO_3; then the resulting precipitate was collected by filtration. The filtrate was extracted with AcOEt. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue and the material obtained above were combined and the whole product was chromatographed on alumina eluting with $CHCl_3$–MeOH (10 : 1). Recrystallization from H_2O afforded III (0.43 g, 13%). IR (Nujol): 3250, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.91 (3H, s), 4.45 (2H, d, J=6 Hz), 6.88 (4H, s), 7.02 (1H, s), 7.79 (1H, s), 8.77 (1H, t, J=6 Hz).

2-Acetamidomethyl-5-acetylthiazole (39) This compound was prepared

from 2-bromo-1-hydroxy-3-oxo-1-butene (**37**) in a manner similar to that described for **30**. Yield 30%, mp 100—102 °C (IPE–MeCN). IR (Nujol): 3310, 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.92 (3H, s), 3.55 (3H, s), 4.53 (2H, d, J=6 Hz), 8.50 (1H, s), 8.83 (1H, t, J=6 Hz). *Anal.* Calcd for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; N, 14.13. Found: C, 48.25; H, 5.10; N, 13.94.

4-(2-Acetamidomethylthiazol-5-yl)-2-guanidinothiazole Dihydrobromide (IV) This compound was prepared from **39** in a manner similar to that described for III. Yield 8%, mp 218—219 °C. IR (Nujol): 3280, 3200, 3150, 1675, 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.92 (3H, s), 4.52 (2H, d, J=6 Hz), 7.67 (1H, s), 8.25 (1H, s), 8.27 (4H, s), 8.85 (1H, t, J=6 Hz), 12.11 (1H, br s).

***N*-Acetamidoaceto-*N'*-(2-guanidino-4-thiazolo)hydrazide (41)** A mixture of 2-guanidino-4-thiazolohydrazide (**40**)[14] (10 g, 50 mmol), acetylglycin (5.9 g, 50 mmol) and dicyclohexylcarbodiimide (DCC) (10 g, 50 mmol) in DMF (10 ml) was stirred for 7 h at 70 °C. After removal of the solvent, the residue was added to H_2O (150 ml) and acidified with 6 N HCl. The insoluble material was filtered off and the filtrate was adjusted to pH 8 with 20% aqueous K_2CO_3. The resulting precipitate was collected, washed with H_2O and recrystallized from MeOH to afford **41** (9.5 g, 64%). mp 245—246 °C. IR (Nujol): 3475, 3350, 3300, 3220, 1700, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.87 (3H, s), 3.80 (2H, d, J=6 Hz), 6.79 (4H, s), 7.40 (1H, s), 8.20 (1H, t, J=6 Hz), 10.13 (1H, s), 10.44 (1H, s). *Anal.* Calcd for $C_9H_{13}N_7O_3S \cdot 1/2H_2O$: C, 35.06; H, 4.58; N, 31.80. Found: C, 34.98; H, 4.44; N, 31.61.

2-Acetamidomethyl-5-(2-guanidinothiazol-4-yl)-1,3,4-oxadiazole (V) $POCl_3$ (3.8 g, 25 mmol) was added dropwise to a solution of **41** (2.5 g, 8.4 mmol) in DMF (25 ml) at 0—5 °C and the mixture was stirred for 6 h at that temperature. The reaction mixture was poured into ice-water, adjusted to pH 10 with 20% aqueous K_2CO_3 and extracted with AcOEt–THF. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give a residue which was recrystallized from MeOH–H_2O to afford V (0.67 g, 29%). IR (Nujol): 3490, 3430, 3340, 3220, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.90 (3H, s), 4.53 (2H, d, J=6 Hz), 7.03 (4H, br s), 7.57 (1H, s), 8.65 (1H, t, J=6 Hz).

***N*-(2-Phthalimidoethanimidoyl)-*N'*-(2-guanidino-4-thiazolo)hydrazide (43)** A solution of **40** (2.2 g, 11 mmol) and ethyl 2-phthalimidoethanimidate (**42**) (2.5 g, 11 mmol) in absolute EtOH (50 ml) was refluxed for 5 h. The resulting precipitate was collected by filtration and washed with EtOH to afford **43** (4.0 g, 94%). An analytical sample was obtained by recrystallization from MeOH, mp 195—197 °C. IR (Nujol): 3400, 3300, 3190, 1765, 1690, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.30 (2H, s), 6.37 (2H, br s), 6.74 (4H, br s), 7.23 (1H, s), 7.83—7.94 (4H, m), 9.77 (1H, s). *Anal.* Calcd for $C_{15}H_{14}N_8O_3S$: C, 46.63; H, 3.65; N, 29.00. Found. C, 46.52; H, 3.91; N, 29.27.

2-(2-Guanidinothiazol-4-yl)-5-(2-phthalimido)methyl-1,3,4-triazole (44) Compound **43** (4.1 g, 11 mmol) was heated at 200 °C for 1 h. After cooling, the product was chromatographed on alumina eluting with $CHCl_3$–MeOH (9 : 1) to afford **44** (1.7 g, 44%). An analytical sample was obtained by recrystallization from MeOH, mp 287—289 °C. IR (Nujol): 3430, 3290, 3160, 1765, 1710, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.85 (2H, s), 6.89 (4h, br s), 7.23 (1H, s), 7.83—7.97 (4H, m), 14.08 (1H, br s). *Anal.* Calcd for $C_{15}H_{12}N_8O_2S \cdot H_2O$: C, 46.63; H, 3.83; N, 29.00. Found: C, 46.65; H, 3.77; N, 29.02.

2-Acetamidomethyl-5-(2-guanidinothiazol-4-yl)-1,3,4-triazole Hydrochloride (VI) A solution of **44** (1.7 g, 4.6 mmol) and $H_2NNH_2 \cdot H_2O$ (0.25 g, 5 mmol) in MeOH (15 ml) was stirred for 2 h at room temperature. 2 N HCl (2.5 ml, 5 mmol) was added to the solution and the mixture was stirred for a further 45 h. After evaporation of the solvent, the residue was suspended in H_2O (10 ml) and the insoluble material was filtered off. The filtrate was concentrated to dryness. The residue (1.4 g, 4.5 mmol) was dissolved in pyridine (14 ml) and the mixture was stirred for 20 h at room temperature. After removal of pyridine, the residue was recrystallized from EtOH–H_2O to afford VI (0.54 g, 37%). IR (Nujol): 3325, 3200, 3100, 1690, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.88 (3H, s), 4.34 (2H, d, J=6 Hz), 7.83 (1H, s), 8.46 (6H, br s).

Biological Tests Gastric Acid Secretion in Heidenhain Pouch Dogs Beagle dogs, weighing 8—13 kg, were used for the study on gastric acid secretion. The animals were surgically provided with a vagally denervated Heidenhain pouch. One month later, the dogs were fasted overnight. Gastric acid secretion was stimulated by an intravenous infusion of tetragastrin (10 μg/kg/h). Gastric samples were collected at 15 min intervals. After its volume was almost constant, the test compound suspended in 0.1% methylcellulose (MC) was administered orally. Acid concentration was determined by titrating an aliquot to pH 7 with 0.1 N NaOH using an automatic titrater (Hiranuma RAT-11 Type). Total acid output was calculated by multiplying the total volume of gastric samples by acid concentration, and the percentage change of total acid output was calculated by comparison with the predosing value of the test compound.

Gastric Ulcer Induced by HCl–Aspirin in Pylorus-Ligated Rats[19] Male SD rats, weighing 180 to 210 g, were fasted for 24 h before the experiment. The pylorus was ligated under ether anaesthesia, and a suspension of the test drug in 0.1% MC was administered orally to the group of ten rats. After 10 min, a suspension of aspirin (200 mg/kg) in 0.15 N HCl MC solution (10 ml/kg) was given orally, and the animals were sacrificed 5 h later. The stomachs were isolated and cut open along the greater curvature. The ulcer index was calculated as the sum of the area (mm^2) of each ulcer in the stomach. The inhibitory ratio (%) was obtained by comparing the ulcer index with that of the control group.

Antimicrobial Activity *In vitro* antimicrobial activity 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 d, 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 ager plus 7% lysed horse blood plate containing serial 2-fold dilutions of each drug at 37 °C for 3 d. Incubation was carried out in an atmosphere of 10% CO_2. Minimum inhibitory concentration (MIC) was read after incubation as the lowest drug concentration that inhibited macroscopic colonial growth.

H_2-Antagonism, Gastric Acid Secretion in Lumen-Perfused Rats, Stress Ulcer and Ethanol Ulcer These activities were evaluated by the methods described in literature,[15,16,20,21] and in our previous paper.[6] The ED_{50} values, the dose required for 50% inhibition of the ulcer index, were estimated according to the method of Litchfield and Wilcoxon.[22]

Acknowledgments We are grateful to Drs. K. Yoshida and T. Kamimura for their valuable suggestions, and Mr. H. Yamakuni, Mrs. T. Nakarai and Mrs. Y. Matsumoto for carrying out the biological assays. Thanks are also due to the staff members for our analytical division for elemental analysis and measurement of spectral data.

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