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Anti-*Helicobacter pylori* agents. 2. Structure activity relationships in a new series of 2-alkylguanidino-4-furylthiazoles

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Abstract

SAR for antimicrobial activity against *H. pylori* was investigated in a new series of 2-alkylguanidino-4-furylthiazoles. Of the compounds obtained, cyclohexylmethyl and ethoxyethyl derivatives were identified as a novel class of anti-*H. pylori* agents which possessed potent and selective antimicrobial activity against *H. pylori*. These compounds also showed gastric antisecretory activity.

Keywords: Antimicrobial compds; Gastrointestinal activity

It has been recognized that eradication of *Helicobacter pylori* (*H. pylori*) is the most rational approach to prevent the recurrence of idiopathic digestive ulcers [1–14]. Aiming to obtain novel and potent anti-*H. pylori* agents, we have previously attempted some chemical modifications of a lead compound (**1**), which was originally obtained as a novel class of histamine H2 receptor antagonist (H2 antagonist) and showed significant anti-*H. pylori* activity compared with the clinical useful H2 antagonists [15,16]. From those results, it was found that the guanidino moiety is essential for anti-*H. pylori* activity and introduction of a linear alkyl substituent to the guanidino moiety increases the activity.

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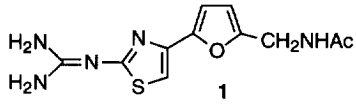
Continuing this line of research on **1** to obtain potent anti-*H. pylori* agents, therefore, we have introduced various kinds of alkyl substituents, i. e., cyclic alkyls, unsaturated alkyls, and heteroatom-containing alkyls, to the guanidino moiety. This paper describes the synthesis and the pharmacological evaluation of this new series of 2-alkylguanidino-4-furylthiazoles.

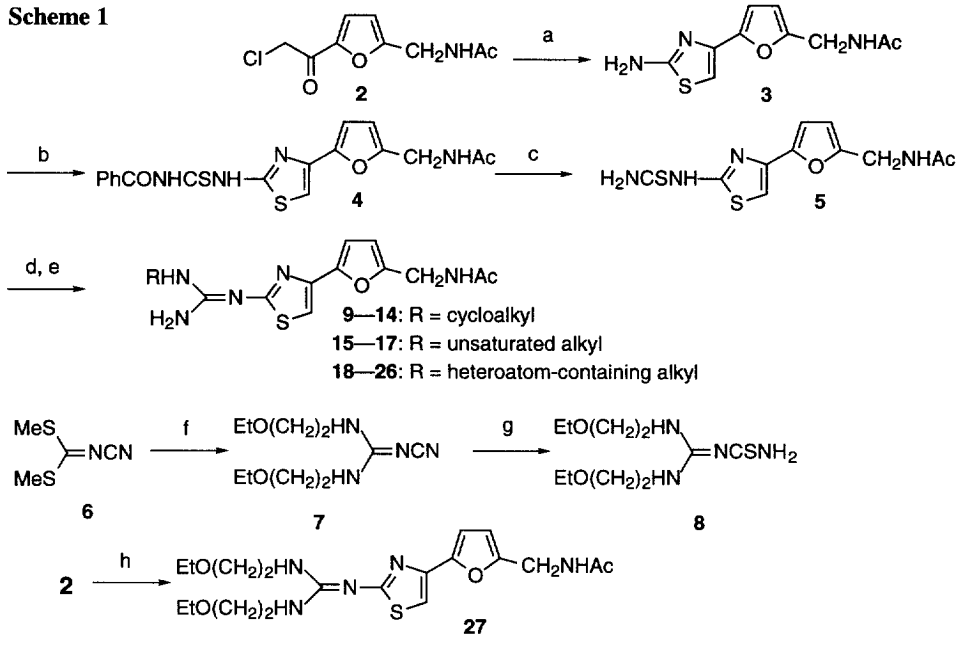


1

Chemistry

The syntheses of the target compounds are depicted in Scheme 1. According to the method described in the previous paper [16], the desired monosubstituted guanidino derivatives (**9–26**) were prepared by treatment of thiourea derivative (**5**) with methyl iodide followed by reaction with the appropriate amines. Diethoxyethylguanidino derivative (**27**) was obtained by cyclization of chloroacetylfuran derivative (**2**) with (*N*, *N'*-diethoxyethyl-amidino)thiourea (**8**), which was prepared by a two-step procedure from dimethyl *N*-cyanodithioiminocarbonate (**6**).[1)]

Scheme 1



2 **3** **4** **5** **6** **7** **8** **27**

Reagents: (a) H_2NCSNH_2 / EtOH (b) PhCONCS / Me_2CO (c) NaOH / MeOH – H_2O (d) MeI / MeOH (e) RNH_2 /EtOH (f) $EtO(CH_2)_2NH_2$ / DMF (g) 4N HCl / $MeCSNH_2$ (h) **8** / EtOH

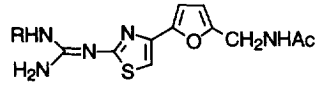
[1] **1-Cyano-2,3-di(2-ethoxyethyl)guanidine** (**7**) A solution of *S*, *S'*-dimethyl-*N*-cyanodithioimino-carbonate (**6**) (8.9 g, 60 mmol) and 2-ethoxyethylamine (22 g, 240 mmol) in *N*, *N*-dimethylformamide (80 mL) was refluxed for 7 h. After removal of the solvent, the residue was added to water and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and concentrated to dryness to give **7** (6.8 g, 60%). mp 83–84 °C. IR: (Nujol) 3320, 3280, 2160, 1690 cm^{-1}; ^1H NMR: (DMSO-d_6, δ) 1.11 (6H, t, J = 7 Hz), 3.20–3.51 (12H, m), 6.96 (2H, t, J = 5 Hz). MS: m/z 229 (M^++1).

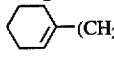
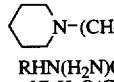
***N*-[*N*, *N'*-Di(2-ethoxyethyl)amidino]thiourea** (**8**) A mixture of **7** (9.1 g, 40 mmol) and thioacetamide (3.0 g, 400 mmol) in 4N HCl (45 mL) was stirred for 3h at room temperature. After concentration to a half volume, the mixture was adjusted to pH 11 with 28% NH_4OH and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated to dryness to give a residue, which was washed with Et_2O to give **8** (9.1 g, 87%). mp 56–58 °C. IR: (Nujol) 3260, 3140, 1615, 1560 cm^{-1}; ^1H NMR: (DMSO-d_6, δ) 1.11 (6H, t, J = 7 Hz), 3.20–3.50 (12H, m), 7.09 (2H, s). MS: m/z 263 (M^++1).

Results and Discussion

Initially, all compounds obtained were tested for antimicrobial activity against *H. pylori* and the results are summarized in Table 1. In the cyclo-alkyl series (**9–14**), the cyclopentylmethyl (**10**), cyclohexylmethyl (**12**) and cyclohexylethyl (**13**) derivatives showed excellent activity. Both shortening (**11**) and lengthening (**14**) the alkylene spacer between the cyclohexyl and guanidino parts decreased the activity. Concerning the ring size, though the effect of expansion has not yet been investigated, a smaller ring (**9**) was not tolerated at all. An unsaturated analog (**16**) for **13** maintained the activity. The activity of allyl derivative (**15**) was also equal to that of the appropriate alkyl analog (n-propyl derivative, MIC = 1.67 μg/ml) [15]. Thus, unsaturation was not crucial for the activity. On the other hand, introduction of a propargyl group (**17**) considerably reduced the activity. Compound **18** showed much reduced activity. These data seem to indicate that substitution containing an active proton could not be accommodated. Compounds with an oxygen- or a sulfur-containing alkyl chain (**19–25**) showed good or marginal activity, and when the chain length was 5 or 6, optimal activity was provided (**20**, **21** and **23**). These types of derivatives were, however, 6–7 fold less potent than the corresponding alkyl analogs, e. g., n-butyl or n-hexyl derivatives (MIC = 0.21 μg/ml and 0.11 μg/ml, respectively) [15]. Compound **26**, a nitrogen-incorporating analog of **13**, was 400 fold less active than **13**. Disubstituted derivative (**27**) resulted in an over 100 fold reduction in potency as compared to the corresponding monosubstituted analog (**20**). From these SARs in anti-*H. pylori* activity, it is clarified that (a) the length of the substituent is important (b) incorporation of polarity into the substituent is disadvantageous and (c) the number of substituents on the guanidino moiety is crucial.

Table 1. Antimicrobial Activity Against *Helicobacter pylori*

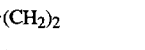


compd[a]	R	MIC (μg/ml)[c] mean	MIC (μg/ml)[c] range	mp (°C)
1[b]	H	27	25–50	
9	c-$C_3H_5CH_2$	1.46	0.39–3.13	185–186
10	c-$C_5H_9CH_2$	0.06	0.0125–0.2	168–169
11	c-C_6H_{11}	1.06	0.78–1.56	154–155
12	c-$C_6H_{11}CH_2$	0.056	0.025–0.1	183–184
13	c-$C_6H_{11}(CH_2)_2$	0.069	0.025–0.1	129–130
14	c-$C_6H_{11}(CH_2)_3$	0.129	0.05–0.2	220–221
15	CH_2=$CHCH_2$	1.45	0.78–1.56	160–161
16		0.052	0.0125–0.1	168–169
17	CH≡CCH_2	8.2	3.13–12.5	209–210 (hydrochloride)
18	$HO(CH_2)_2$	34	25–50	181–182
19	$CH_3O(CH_2)_2$	1.45	0.78–1.56	137–138
20	$C_2H_5O(CH_2)_2$	0.42	0.2–0.78	144–145
21	n-$C_3H_7O(CH_2)_2$	0.66	0.1–1.56	142–143
22	n-$C_4H_9O(CH_2)_2$	1.43	0.39–3.13	178–179 (oxalate)
23	$C_2H_5O(CH_2)_3$	0.63	0.2–1.56	155–156
24	$C_2H_5O(CH_2)_4$	1.10	0.2–1.56	135–136 (oxalate)
25	$CH_3S(CH_2)_2$	1.67	0.39–3.13	138–139
26		27	12.5–50	125–128 (oxalate)
27	RHN(H_2N)C=N- : $[C_2H_5O(CH_2)_2HN]_2C$=N-	81	25–100	95–97

[a] Elemental analyses for C, H, and N in all compounds were within ±0.4% of the theoretical values. [b] Ref 15. [c] Minimum inhibitory concentration (MIC) was determined as the lowest drug concentration that inhibited macroscopic colony growth. Mean MIC and range of MIC's were obtained from the results of 10 different strains.

Next, the compounds with high anti-*H. pylori* activity (MIC<1μg/ml) were evaluated for gastric antisecretory and H2 antagonist activities and the results are presented in Table 2. Of these, compound **20** showed similar activities to those of the lead compound (**1**) and higher activities than those of the referenced H2 antagonist, cimetidine. Compound **12**, showing 10-fold potent anti-*H. pylori* activity than **20**, also possessed antisecretory activity which were comparable to that of cimetidine.

Table 2. Pharmacological Activities of Some Derivatives

compd	R	inhibition, %		
		gastric secretion		H_2-antagonism,[c]
		rat,[a] 1 mg/kg iv	dog,[b] 1 mg/kg po	$1X10^{-6}$ g/mL
1	H	68	83	85
10	c-$C_5H_9CH_2$	51		55
12	c-$C_6H_{11}CH_2$	60	38	33
13	c-$C_6H_{11}(CH_2)_2$	32		23
14	c-$C_6H_{11}(CH_2)_3$	68	35	47
16	 $-(CH_2)_2$	50		89
20	$C_2H_5O(CH_2)_2$	64	71	85
21	n-$C_3H_7O(CH_2)_2$	30		67
23	$C_2H_5O(CH_2)_3$	24		75
	cimetidine	53	22	43

[a] Inhibition of histamine-stimulated gastric acid secretion in lumen-perfused stomach of the anaesthetized rats (n = 2). [b] Inhibitory effect on gastric acid secretion induced by gastrin in the conscious Heidenhain pouch dogs (n = 2). [c] Inhibition of the histamine-stimulated chronotoropic response in the isolated guinea pig right atrium.

Finally, we have assessed the specificity of antimicrobial activity for *H. pylori* (Table 3). The therapeutically useful drugs for the treatment of *H. pylori* eradication, bismuth salicylate, metronidazole and amoxicillin, showed susceptibility for a variety of organisms. On the other hand, the antimicrobial activities of the representative compounds (**12** and **20**) were specific for *H. pylori*.

In conclusion, we have obtained some potent anti-*H. pylori* agents in a series of 2-alkylguanidino-4-furylthiazoles. Among them, ethoxyethyl derivative (**20**) possessed good antimicrobial and antisecretory activities. Cyclohexylmethyl derivative (**12**) demonstrated more potent antimicrobial activity than **20**. The antimicrobial activities of these compounds were selective for *H. pylori*.

Acknowledgement

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Table 3. Antimicrobial Activity of **12**, **20** and the Reference Compounds against Various Organisms

	MIC; μg/ml (range)				
organisms (n)	**12**	**20**	bismuth salicylate	metronidazole	amoxicillin
H. pylori (10)	0.056 (0.025–0.1)	0.42 (0.2–0.78)	8.7	5.4 (1.56–25)	0.021 (0.0063–0.1)
C. jejuni (8)	30 (25–50)	>100	7.4 (6.25–12.5)	30 (0.78–100)	2.2 (0.39–6.25)
C. difficile (4)	>100	>100	50	0.2 (0.1–0.39)	0.28 (0.1–0.78)
C. perfrigens (6)	>100	>100	>100	1.75 (0.78–3.13)	0.027 (0.025–0.05)
B. fragilis (10)	>100	>100	50	0.59 (0.39–0.78)	2.1 (0.2–12.5)
N. gonorrhoeas (10)	>100	>100	4.7 (3.13–6.25)	>100	7.7 (0.39–100)
N. meningitidis (10)	>100	>100	12.5 (3.13–100)	>100	0.056 (0.05–0.1)

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