Antiulcer Agents. 4-Substituted 2-Guanidinothiazoles: Reversible, Competitive, and Selective Inhibitors of Gastric H^+,K^+-ATPase

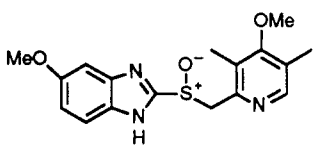
John L. LaMattina, Peter A. McCarthy,* Lawrence A. Reiter, William F. Holt, and Li-An Yeh

Central Research Division, Pfizer Inc., Groton, Connecticut 06340. *Received March 28, 1988*

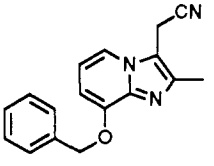
A series of 4-substituted 2-guanidinothiazoles has been found to inhibit the gastric proton-pump enzyme H^+,K^+-ATPase. In general, these compounds were reversible inhibitors of canine gastric H^+,K^+-ATPase, competitive at the K^+ site, and selective relative to canine renal Na^+,K^+-ATPase. Structure–activity relationship (SAR) studies on this series revealed no general replacement for the guanidinothiazole. On the other hand, use of pyrrolyl, phenyl, and indolyl groups as the C-4 substituent yielded active compounds. Extensive studies of substitution patterns on these 4-aryl groups led to more active compounds, but no consistent SAR became apparent. Monosubstitution of the guanidine and substitution of the thiazole at C-5 both often led to increased activity, but combining these changes generated compounds less active than the parents. Despite 100-fold improvement in in vitro inhibitory potency, only a 3-fold increase in gastric antisecretory activity in rats was observed for these agents.

Ulcers are believed to result from an imbalance between the aggressive (acid, pepsin) and defensive forces (bicarbonate, mucous) in the stomach and duodenum. Reduction of acid secretion, especially by antagonism of the H_2 receptor, has proven to be a useful means for promoting the healing of ulcers, particularly those of the duodenal mucosa.[1] Recently, agents have been identified that completely suppress acid secretion by inhibition of the gastric proton pump H^+,K^+-ATPase. Such inhibition leads to a profound and prolonged achlorhydria, which results in ulcer healing rates substantially more rapid than those achievable by H_2 antagonists (2–4 weeks vs 6–8 weeks).

H^+,K^+-ATPase catalyzes the terminal step in gastric acid secretion,[2-7] whereas histamine is but one of three key messengers which stimulate acid secretion (the other two being acetylcholine and gastrin). As a result, inhibition of H^+,K^+-ATPase can provide an intrinsically greater reduction in gastric acid secretion than can H_2 antagonists. Additionally, unlike the H_2 receptor, which is found in tissues throughout the body (e.g. the heart), H^+,K^+-ATPase is located predominantly in the parietal cells of the stomach; thus, H^+,K^+-ATPase inhibitors should have an intrinsic specificity advantage over H_2 antagonists.[2,8] The prototypical H^+,K^+-ATPase inhibitor omeprazole (Astra)[9]



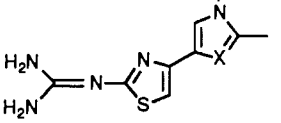
omeprazole



SCH-28080

is remarkably effective and appears to be specific for the target enzyme,[10] but the results of long-term toxicology studies are a concern.[11] Some have suggested that omeprazole's prolonged inhibition of acid secretion, which results from omeprazole's irreversible inhibition of H^+,K^+-ATPase, may lead to potentially serious side effects (e.g. gastric carcinoids), perhaps as a result of elevations in plasma gastrin levels.[11] If such is the case, then a reversible inhibitor of H^+,K^+-ATPase might be preferable since it could provide more rapid ulcer healing than an H_2 antagonist yet avoid the prolonged achlorhydria induced by an irreversible inhibitor. Indeed, limited clinical studies with SCH-28080, a reversible H^+,K^+-ATPase inhibitor, suggest this.[12]

Previous work in our own laboratories identified a novel series of 4-imidazolyl-2-guanidinothiazoles, highlighted by zaltidine (CP-57,361), which are H_2 antagonists.[13] Thereafter, we synthesized numerous 4-heteroaryl-2-guanidinothiazoles. One of these compounds, 4-(2-methyl-1*H*-pyrrol-3-yl)-2-(guanidino)thiazole (1), displayed



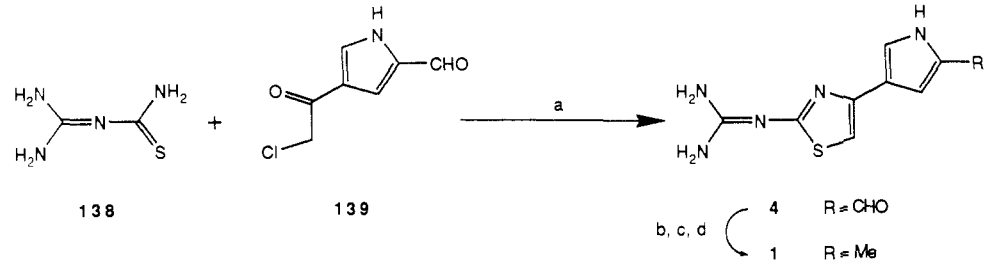
zaltidine X = N
1 X = CH

antisecretory activity in a pylorus-ligated rat model (ED_{50}

(1) Gustavsson, S.; Adam, H.-O.; Loof, L.; Nyberg, A.; Nyren, O. *Lancet* **1983**, *8342*, 124.
(2) Sachs, G.; Chang, H. H.; Rabon, E.; Shackman, R.; Lewin, M.; Saccomani, G. *J. Biol. Chem.* **1976**, *251*, 7690.
(3) Forte, J. G.; Machen, T. F.; Obrink, K. J. *Annu. Rev. Physiol.* **1980**, *42*, 111.
(4) Lind, T.; Cederberg, C.; Eberved, G.; Haglund, U.; Olbe, L. *Gut* **1983**, *24*, 270.
(5) Londong, W.; Londong, V.; Cederberg, C.; Steffen, H. *Gastroenterology* **1983**, *85*, 1373.
(6) Konturek, S. J.; Cieszkowski, M.; Kwiecien, N.; Konturek, J.; Tasler, J.; Bilski, J. *Gastroenterology* **1984**, *86*, 71.
(7) Wallmark, B.; Jaresten, B.-M.; Larsson, H.; Ryberg, B.; Brandstrom, A.; Fellenius, E. *Am. J. Physiol.* **1983**, *245*, G64.
(8) Sonnenberg, A.; Fischer, J. A.; Berglindh, T.; Lewin, W. J. M.; Sachs, G.; Blum, A. L. *Schweiz. Wochenschr. Med.* **1980**, *110*(22), 885.
(9) (a) Borg, K. O.; Olbe, L.; Rune, S. J.; Walan, A. *Scand. J. Gastroenterol.* **1986**, *21* (Suppl. 118), 1. (b) Clissold, S. P.; Campoli-Richards, D. M. *Drugs* **1986**, *32*, 15.
(10) Fellinius, E.; Berglindh, T.; Sachs, G.; Olbe, L.; Elander, B.; Sjostrand, S. E.; Wallmark, B. *Nature (London)* **1981**, *290*, 159.
(11) Ekman, L.; Hansson, E.; Havu, N.; Carlsson, E.; Lundberg, C. *Scand. J. Gastroenterol.* **1985**, *20* (Suppl. 108), 53.
(12) (a) Ene, M. D.; Daneshmend, T. K.; Roberts, C. J. C. *Gastroenterology* **1981**, *80*, 1143. (b) Hillier, K. *Drugs Future* **1982**, *7*, 755. (c) Wallmark, B.; Briving, C.; Fryklund, J.; Munson, K.; Jackson, R.; Mendlein, J.; Rabon, E.; Sachs, G. *J. Biol. Chem.* **1987**, *262*, 2077. (d) Beil, W.; Staar, U.; Sewing, K.-Fr. *Eur. J. Pharmacol.* **1987**, *139*, 349. (e) Scott, C. K.; Sundell, E. *Eur. J. Pharm.* **1985**, *112*, 268. (f) Beil, W.; Hackbarth, I.; Sewing, K.-Fr. *Br. J. Pharmacol.* **1986**, *88*, 19. (g) Kaminski, J. J.; Bristol, J. A.; Puchalski, C.; Lovey, R. G.; Elliott, A. J.; Guzik, H.; Solomon, D. M.; Conn, D. J.; Domalski, M. S.; Wong, S.-C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; Steinberg, M.; McPhail, A. T. *J. Med. Chem.* **1985**, *28*, 876. (h) Kaminski, J. J.; Hilbert, J. M.; Pramanik, B. N.; Solomon, D. M.; Conn, D. J.; Rizvi, R. K.; Elliot, A. J.; Guzik, H.; Lovey, R. G.; Domalski, M. S.; Wong, S.-C.; Puchalski, C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; McPhail, A. T. *J. Med. Chem.* **1987**, *30*, 2031. (i) Kaminski, J. J.; Perkins, D. G.; Frantz, J. D.; Solomon, D. M.; Elliott, A. J.; Chiu, P. J. S.; Long, J. F. *J. Med. Chem.* **1987**, *30*, 2047.
(13) Holt, W. F.; Murphy, W. R.; LaMattina, J. L. *Gastroenterology* **1987**, *92*, 1439.

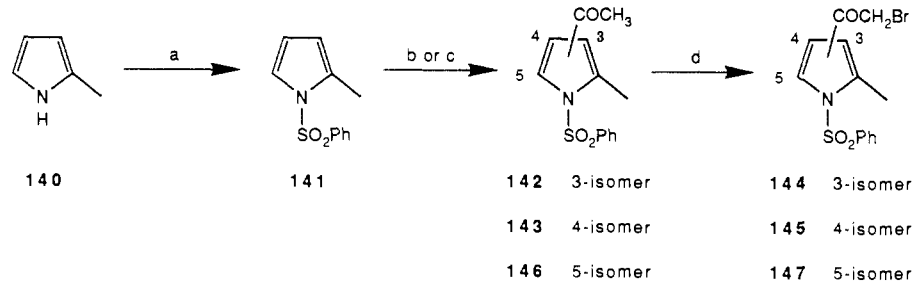
0022-2623/90/1833-0543$02.50/0

Scheme I[a]



[a] (a) EtOH, reflux; (b) NaOH; (c) B_2H_6; (d) HCl(g).

Scheme II[a]



[a] (a) K, $ClSO_2Ph$; (b) Ac_2O, $AlCl_3$; (c) Ac_2O, $BF_3{\cdot}Et_2O$; (d) Br_2.

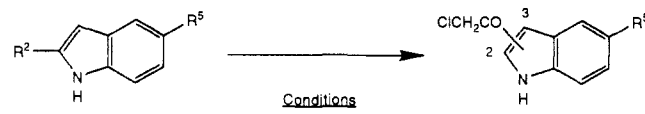
= 26 mg/kg id) comparable to that of cimetidine (11 mg/kg id). Despite this, **1** showed no activity as an H_2 antagonist (isolated guinea pig atria model). This lack of H_2-antagonist activity prompted us to investigate the mechanism of this antisecretory activity. In fact, **1** demonstrated reversible, competitive, and selective inhibition of canine gastric H^+,K^+-ATPase (IC_{50} = 25 μM). Thus, replacement of an imidazole ring with a pyrrole ring causes a remarkable difference in mechanistic profile. This discovery led us to investigate the full potential of 4-substituted 2-guanidinothiazoles as H^+,K^+-ATPase inhibitors.

Chemistry

In general, 4-substituted 2-guanidinothiazoles were obtained by condensation of a guanylthiourea with an α-halo ketone.[14] For example, **1** was prepared by condensation of (diaminomethylene)thiourea (**138**) with 2-chloro-1-(2-formyl-1*H*-pyrrol-4-yl)ethanone (**139**, Scheme I). Subsequent reduction of **4** with diborane afforded the target.[15]

To obtain 2-halo-1-pyrrolylalkanones with a variety of substitution patterns, a number of methods were employed. 2-Chloro-1-(2-formyl-1*H*-pyrrol-4-yl)ethanone (**139**) was synthesized by direct acylation of 2-formyl-1*H*-pyrrole.[16] Targets containing other electron-withdrawing substituents at the 2-position of the pyrrole were also obtained in this manner. N-Sulfonation of pyrroles (Scheme II) allowed access to a number of other substitution patterns.[17] For example, 2-methyl-1-(phenylsulfonyl)pyrrole (**141**) was acylated with aluminum chloride as Lewis acid catalyst to give 3- and 4-acylation in yields of 60% and 24%, respectively. These products were each brominated directly to give **144** and **145**. Use of boron trifluoride etherate as Lewis acid catalyst gave 5-acylation of 2-methyl-1-(phenylsulfonyl)pyrrole. In the same manner as above, **146** was brominated to give **147**.

Scheme III[a]



146	R^2 = H, R^5 = OMe	a	**149** 3-isomer, R^5 = OMe
150	R^2 = H, R^5 = F	b, a, c	**151** 3-isomer, R^5 = F
152	R^2 = CO_2H, R^5 = H	d, e, f	**153** 2-isomer, R^5 = H

[a] (a) $ClCH_2COCl$; (b) MeMgBr; (c) NaOH; (d) $SOCl_2$; (e) CH_2N_2; (f) HCl(g).

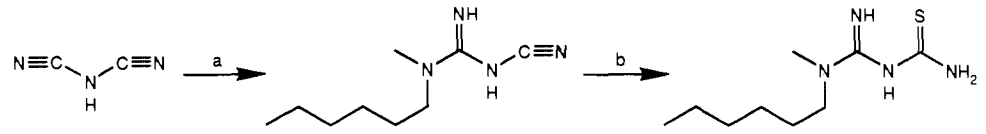
To obtain 2-halo-1-(indol-3-yl)alkanones, two general procedures were used. Indoles with electron-donating substituents were acylated by using Friedel–Crafts type conditions such as those shown for the acylation of 5-methoxy-1*H*-indole (Scheme III, **148** to **149**).[18] Indoles with electron-withdrawing substituents were acylated by using metalation conditions such as those shown for 5-fluoro-1*H*-indole (**150** to **151**).[19] A mixture of 3-acylated and 1,3-diacylated products was often obtained which could be quantitatively converted to the desired 3-acylated product via selective hydrolysis of the 1-acyl group. The 2-halo-1-(indol-2-yl)alkanones were synthesized from the 2-indolylcarboxylic acids via the corresponding diazoketone as is shown for 2-chloro-1-(1*H*-indol-2-yl)ethanone (**153**).[20]

The required α-haloacetophenones were obtained from commercial suppliers or were synthesized from the acetophenones by using literature procedures.[21]

Substituted guanylthioureas were synthesized by a number of procedures. *N*-(*N*-Hexyl-*N*-methylguanyl)-thiourea (Scheme IV, **156**) was synthesized via addition

(14) Lipinski, C. A.; LaMattina, J. L.; Oates, P. J. *J. Med. Chem.* **1986**, *29*, 2154.
(15) Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1968**, *24*, 1145.
(16) Groves, J. T. *Chem. Soc. Rev.* **1972**, *1*, 73.
(17) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.
(18) Bergman, J.; Backvall, J.-E.; Lindstrom, J.-O. *Tetrahedron* **1973**, *29*, 971.
(19) Young, T. E.; Mizianty, M. F. *J. Med. Chem.* **1966**, *9*, 635 and references therein.
(20) (a) Nogrady, T.; Doyle, T. W.; Morris, L. *J. Med. Chem.* **1965**, *8*, 656. (b) *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 119.
(21) (a) King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459. (b) Chatterjea, J. N. *Indian Chem. Soc.* **1955**, *32*, 265.

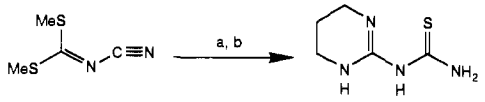
Scheme IV[a]



154 155 156

[a] (a) $CH_3(CH_2)_5NHCH_3$; (b) H_2S.

Scheme V[a]



157 158

[a] (a) $H_2N(CH_2)_3NH_2$; (b) H_2S.

of hexylmethylamine to dicyanamide[22a,b,d] followed by treatment with hydrogen sulfide.[22c,d] Other N-substituted and N,N-disubstituted guanylthioureas were synthesized in a similar manner. As an example of the synthesis of N,N′-cyclic substituted guanylthioureas, *N*-(3,4,5,6-tetrahydropyrimidin-2-yl)thiourea (Scheme V, **158**) was synthesized from dimethyl *N*-cyanodithioiminocarbonate (**157**) and 1,3-propanediamine, followed by treatment with hydrogen sulfide.[23] Acyclic N,N′-disubstituted guanylthioureas were synthesized by using a procedure similar to that shown for the synthesis of *N*-(*N*-hexyl-*N*′-methylguanyl)thiourea (Scheme VI, **161**).[24]

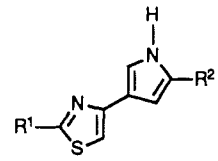
Structure–Activity Relationships

After the initial discovery that **1** was an H^+,K^+-ATPase inhibitor, we sought to establish the kinetic nature of its enzyme inhibition. Wash-out experiments showed **1** to be a reversible inhibitor. A Lineweaver–Burk plot showed that this compound competitively inhibits at the potassium site on H^+,K^+-ATPase. Finally, when tested against canine renal Na^+,K^+-ATPase, **1** displayed an $IC_{50} \gg 100$ μM. Thus, **1** is a reversible, competitive, and selective inhibitor of gastric H^+,K^+ ATPase. Compound **1** was also tested over a wide pH range, but unlike omeprazole, **1** showed no significant variation in its inhibitory activity. In vivo, when administered intraduodenally, **1** blocked acid secretion in a pylorus-ligated rat model with an ED_{50} of 26 mg/kg, which is comparable to what we found with cimetidine (ED_{50} = 11 mg/kg id). Given these data on **1**, we began structure–activity relationships (SAR) studies aimed at finding a compound which was more potent than **1** and which still had a similar profile with regard to enzyme inhibition reversibility, competitiveness, and selectivity.

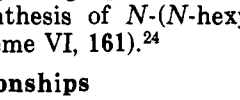
In Vitro Results. SAR studies on this series can be considered in terms of three portions of the molecule—the guanidine, the C-4 substituent on the thiazole, and the thiazole itself—and the interaction between these different moieties.

As shown in Table I, replacement of the guanidine with a methyl group or an amino group led to complete loss of activity (**1** vs **2** and **3**, **4** vs **5** and **6**). Several substituted guanidines were also examined. In the series shown, monosubstitution of the guanidine led to increased potency (**7**, **8**, and **9** vs **1**); however, an additional substituent on the same nitrogen (**10**) or a different nitrogen (**11**) yielded compounds with no potency advantage over the unsubstituted parent. Tying the N,N- or N,N′-substituents into a ring (**12** or **13**, respectively) or adding a third substituent (**14** and **15**) generated compounds with greatly diminished activity. On the basis of these data, we concentrated our efforts on unsubstituted and monosubstituted guanidines.

Table I. Inhibition of Gastric H^+,K^+-ATPase by 4-Pyrrol-3-ylthiazole Derivatives

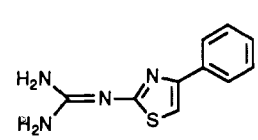


no.	R^1	R^2	activity against gastric H^+,K^+-ATPase: % inhibn at 50 μM	activity against gastric H^+,K^+-ATPase: IC_{50}, μM
1	$(H_2N)_2C{=}N$	CH_3	70	25
2	CH_3	CH_3	0	
3	NH_2	CH_3	17	
4	$(H_2N)_2C{=}N$	CHO	44	
5	CH_3	CHO	5	
6	NH_2	CHO	9	

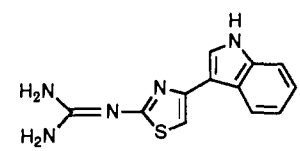


no.	R^3	R^4	R^5	R^2	activity against gastric H^+,K^+-ATPase: % inhibn at 50 μM	activity against gastric H^+,K^+-ATPase: IC_{50}, μM
7	H	$PhCH_2$	H	CH_3	97	11
8	H	*p*-ClPhCH_2	H	CH_3	95	7
9	H	*n*-hexyl	H	CH_3	93	7
10	H	*n*-hexyl	CH_3	CH_3	54	
11	CH_3	*n*-hexyl	H	CH_3	68	
12	H	$-(CH_2)_5-$		CH_3	34	
13	$-(CH_2)_2-$		H	CH_3	25	
14	$-(CH_2)_2-$		CH_3	CH_3	13	
15	$-(CH_2)_3-$		$PhCH_2$	CH_3	19	

The second portion of the molecule to be examined was the substituent at C-4 of the thiazole. Along with pyrrolyl (**1**), phenyl (**48**), and indolyl (**97**) substitution at C-4 of the thiazole led to compounds which are active as H^+,K^+-ATPase inhibitors. Neither simple alkyl groups nor a variety



48 IC_{50} = 40 μM

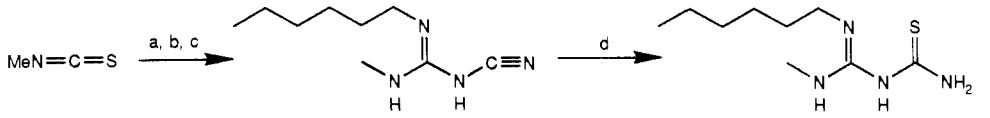


50 IC_{50} = 9 μM

of other heteroaromatic systems situated at C-4 of the thiazole resulted in potent proton-pump inhibitors. Assuming that all of these compounds are acting at the same site, it appears that the C-4 substituent needs to be at least

(22) (a) Curd, F. H. S.; Hendry, J. A.; Kenny, T. S.; Murray, A. G.; Rose, F. L. *J. Chem. Soc.* **1948**, 1630. (b) Redmon, B. C.; Nagy, D. E. U.S. Patent 2 455 807, 7 December, 1948. (c) Cutler, R. A.; Schalit, S. U.S. Patent 4 009 163, 22 February, 1977. (d) Reiter, L. A. U.S. Patent 4 560 690, 24 December, 1985.
(23) Baltizer, C. M.; McCarty, C. G. *J. Org. Chem.* **1973**, *38*, 155.
(24) Papadopoulos, E. P.; Haidar, N. F. *Tetrahedron Lett.* **1968**, 1721.

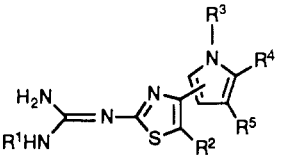
Scheme VI[a]



159 160 161

[a] (a) $CH_3(CH_2)_5NH_2$; (b) CH_3I; (c) H_2NCN; (d) H_2S.

Table II. Inhibition of Gastric H^+,K^+-ATPase by 4-Pyrrolo-2-guanidinothiazoles



no.	X[a]	R^1	R^2	R^3	R^4	R^5	activity against gastric H^+,K^+-ATPase: % inhibn at 50 μM	activity against gastric H^+,K^+-ATPase: IC_{50}, μM
16	4	H	H	H	H	H	68	
1	4	H	H	H	Me	H	70	25
7	4	Bn	H	H	Me	H	97	11
17	4	H	H	H	CH_2NMe_2	H	94	9
4	4	H	H	H	CHO	H	60	29
18	4	H	H	H	$CO(NC_5H_{10})$	H	69	17
19	4	H	H	H	$CH_2(NC_5H_{10})$	H	55	
20	4	H	H	Me	Me	H	74	24
21	4	H	H	Me	CHO	H	44	
22	4	H	H	SO_2Ph	Me	H	92	2
23	4	Bn	H	SO_2Ph	Me	H	69	
24	4	H	Me	H	Me	H	100	1.2
25	4	Ph	Me	H	Me	H	83	9.8
26	4	Bn	Me	H	Me	H	83	7.9
27	4	4-MeBn	Me	H	Me	H	95	2.9
28	4	CH_2CH_2Ph	Me	H	Me	H	87	9.1
29	4	H	Me	H	CHO	H	77	28
30	5	H	H	H	H	H	68	30
31	5	Bn	H	H	H	H	81	9
32	5	H	H	H	Me	H	76	45
33	5	Bn	H	H	Me	H	83	7
34	5	H	H	H	Me	CO_2Et	91	7
35	5	H	H	H	Me	$CONMe_2$	33	
36	5	H	H	H	Me	CH_2NMe_2	87	11
37	5	H	H	Me	Me	H	20	
38	5	H	H	SO_2Ph	Me	H	91	7
39	5	Bn	H	SO_2Ph	Me	H	57	26
40	3	H	H	H	Me		96	7
41	3	Bn	H	H	Me		93	6
42	3	H	H	SO_2Ph	Me		101	2
43	3	Bn	H	SO_2Ph	Me		54	
44	3	H	Me	H	Me		102	1.3
45	3	Bn	Me	H	Me		80	8.8
46	3	H	Me	SO_2Ph	Me		100	4.2
47	3	Bn	Me	SO_2Ph	Me		35	

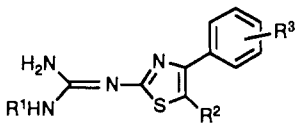
[a] X indicates the position of attachment to the pyrrole ring.

nonbasic. Lack of basicity itself is not enough, however, since some 4-furyl-2-guanidinothiazoles were found to be inactive. These results led us to focus on the pyrrolyl, phenyl, and indolyl groups as C-4 substituents.

In the first of these series, the 4-pyrrolyl-2-guanidinothiazoles (Table II), the position of the nitrogen had only a modest effect on inhibitory activity (**16** vs **30**, **1** vs **32** vs **40**, **7** vs **33** vs **41**) which implies that any hydrogen-bonding capabilities of the pyrrole NH are relatively unimportant for inhibitory activity. As was seen earlier, substitution on the guanidine with a benzyl group improved activity (**7** vs **1**, **31** vs **30**, **33** vs **32**, **41** vs **40**). A variety of substituents on the pyrrole ring were also examined, many of which resulted in moderate improvements in activity. Substitution of the pyrrole nitrogen with a phenylsulfonyl group improved inhibitory activity in all series (**1** vs **22**, **32** vs **38**, **40** vs **42**). However, somewhat disappointing to us, the combination of benzylation of the guanidine with N-phenylsulfonation of the pyrrole nitrogen resulted in compounds which are less active than either parent (i.e. **23** vs **7** and **22**, **39** vs **33** and **38**, **43** vs **41** and **42**). Thus, these single SAR improvements are not additive. Excluding the 5-methyl-4-pyrrolyl-2-guanidinothiazoles to be discussed later, **22** and **42** remain the most active compounds from the 4-pyrrolyl-2-guanidinothiazole series with IC_{50}'s of 2 μM.

The second of these series, the 4-phenyl-2-guanidinothiazoles (Table III), had the least predictable SAR of the

Table III. Inhibition of Gastric H^+,K^+-ATPase by 4-Phenyl-2-guanidinothiazoles

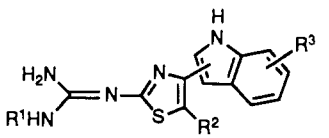


no.	R^1	R^2	R^3	activity against gastric H^+,K^+-ATPase: % inhibn at 50 μM	activity against gastric H^+,K^+-ATPase: IC_{50}, μM
48	H	H	H	52	40
49	Bn	H	H	−1	
50	H	H	2-Cl	71	18
51	H	H	3-Cl	48	53
52	H	H	4-Cl	48	
53	H	H	4-F	61	33
54	Bn	H	2-Cl	99	6
55	Bn	H	3-Cl	80	
56	Bn	H	4-Cl	38	
57	Bn	H	4-F	35	
58	H	H	2-Me	78	20
59	H	H	2-CH_2NMe_2	27	
60	H	H	3-Me	60	32
61	H	H	3-CH_2NMe_2	56	37
62	H	H	4-Me	61	
63	H	H	4-Ph	25	
64	Bn	H	2-Me	111	10
65	Bn	H	3-Me	53	
66	Bn	H	4-Me	16	
67	Bn	H	4-Ph	5	
68	H	H	3-NH_2	45	
69	H	H	3-NMe_2	52	
70	H	H	4-NH_2	63	32
71	H	H	4-NMe_2	75	14
72	Bn	H	4-NH_2	77	5.2
73	H	H	2-OMe	70	27
74	H	H	3-OMe	48	60
75	H	H	4-OMe	54	35
76	Bn	H	2-OMe	99	2.3
77	Bn	H	3-OMe	85	10
78	pentyl	H	3-OMe	25	
79	Bn	H	4-OMe	24	
80	H	H	3,4-$(OMe)_2$	41	
81	Bn	H	3,4-$(OMe)_2$	25	
82	H	H	2-OH	26	
83	H	H	3-OH	69	23
84	H	H	4-OH	75	15
85	Bn	H	2-OH	85	11
86	Bn	H	3-OH	8	
87	Bn	H	4-OH	49	
88	H	H	3,4-$(OH)_2$	100	1.5
89	Bn	H	3,4-$(OH)_2$	111	0.3
90	H	Me	3,4-$(OH)_2$	97	1.6
91	Bn	Me	3,4-$(OH)_2$	103	1.3

C-4 aryl-substituted guanidinothiazoles. The possible substitution patterns were exhaustively studied, yet, with the exception that the ortho-substituted phenyl derivatives were more active than the analogous meta- and para-substituted derivatives (**50** vs **51** and **52**, **58** vs **60** and **62**, **73** vs **74** and **75**), no pattern was apparent with regard to the electronic or steric nature of the substituents. The best compounds from this series were **76** (IC_{50} = 2.3 μM), **88** (IC_{50} = 1.5 μM), **89** (IC_{50} = 0.3 μM), **90** (IC_{50} = 1.6 μM), and **91** (IC_{50} = 1.3 μM).

The third of these series was the 4-indolyl-2-guanidinothiazoles (Table IV). Of the positional isomers tested, the indol-3-yl isomer (**97**), was slightly more active than the indol-2-yl isomer (**92**) as an inhibitor of gastric H^+,K^+-ATPase. Further examination of substituted examples of these isomers show that, with one exception (**95** vs **122**), the indol-3-yl isomers are more potent than the

Table IV. Inhibition of Gastric H^+,K^+-ATPase by 4-Indolyl-2-guanidinothiazoles



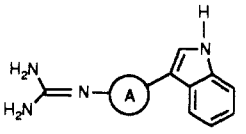
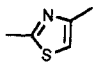
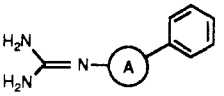
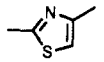
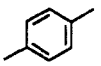
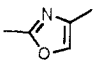
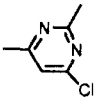
no.	X[a]	R^1	R^2	R^3	activity against gastric H^+,K^+-ATPase: % inhibn at 50 μM	activity against gastric H^+,K^+-ATPase: IC_{50}, μM
92	2	H	H	H	72	14.0
93	2	Bn	H	H	61	16.0
94	2	Bn	H	5-Cl	97	9.1
95	2	H	H	5-F	87	4.0
96	2	Bn	H	5-F	49	
97	3	H	H	H	91	9.0
98	3	Bn	H	H	102	1.5
99	3	H	Me	H	92	7.6
100	3	Bn	Me	H	34	
101	3	H	H	5-OMe	70	19.0
102	3	Bn	H	5-OMe	95	4.3
103	3	H	H	5-OBn	78	1.2
104	3	Bn	H	5-OBn	90	1.8
105	3	H	H	2-Me	85	9.0
106	3	Bn	H	2-Me	102	1.7
107	3	H	Me	2-Me, 5-Cl	103	0.6
108	3	Bn	Me	2-Me, 5-Cl	100	1.1
109	3	Bn	H	4-Me	103	3.3
110	3	H	H	5-Me	76	1.8
111	3	Bn	H	5-Me	104	0.94
112	3	H	H	6-Me	64	
113	3	Bn	H	6-Me	98	1.6
114	3	H	H	7-Me	55[b]	7.6
115	3	Bn	H	7-Me	92	1.0
116	3	H	H	5-Cl	89	1.8
117	3	Bn	H	5-Cl	92	0.7
118	3	H	Me	5-Cl	99	0.59
119	3	Bn	Me	5-Cl	101	0.7
120	3	H	H	5-Br	90[b]	0.96
121	3	Bn	H	5-Br	105	0.7
122	3	H	H	5-F	90	7.4
123	3	Bn	H	5-F	96	2.7
124	3	H	H	5-CO_2Me	86	6.7
125	3	Bn	H	5-CO_2Me	94	3.1
126	3	H	H	5-CN	80	
127	3	Bn	H	5-CN	50	
128	3	Bn	H	5-NHAc	66	23.8

[a] X indicates the position of attachment to the indole ring. [b] Inhibition at 10 μM.

indol-2-yl isomers. As had been seen earlier, substitution of the guanidine generally improved activity. Beyond this, however, the SAR is not clear. On the indole ring, electronic effects of a given substituent appear to be more important than steric effects as evidenced by the similar activity of the positional isomers of the monomethylated derivatives (**106**, **109**, **111**, **113**, and **115**). Despite this, electronically similar substituents result in compounds with significantly different activities (**101** vs **103**, **102** vs **104**). On the whole, the 4-indolyl-2-guanidinothiazole series was the most potent in vitro, with 16 compounds displaying IC_{50}'s less than 2μM.

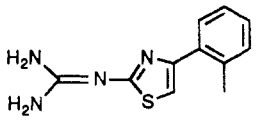
The third portion of the molecule to be investigated was the thiazole moiety (Table V). We hypothesized that the thiazole might serve as a simple spacer between the guanidine and the 4-aryl substituent. However, replacement of the thiazole ring with an ethyl chain led to nearly complete loss of activity (**97** vs **129**). Assuming the spacer group needed to be rigid and planar, **130** was made, but it too was essentially devoid of activity. Concluding that the thiazole nitrogen might have some key binding function

Table V. Inhibition of Gastric H^+,K^+-ATPase by Related Guanidine Derivatives

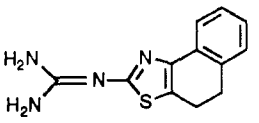
no.	A	activity against gastric H^+,K^+-ATPase: % inhibn at 50 μM	activity against gastric H^+,K^+-ATPase: IC_{50}, μM
			
97		91	9
129	$-CH_2CH_2-$	15	
			
48		56	40
130		16	
131		0	
132		89	6

or that the pK_a of the guanidinothiazole system was of paramount importance, we sought analogues that were structurally more related. Surprisingly, when an oxazole was substituted for a thiazole, activity still was not observed (**131**). In spite of these results, that the thiazole ring is not mandatory for activity was exemplified by **132**, a chloropyrimidine, which was more active than the corresponding thiazole, **48**. Unfortunately, use of the chloropyrimidine group did not prove to be generally successful, and so, we continued to focus on thiazole-containing inhibitors.

Substitution of the thiazole at C-5 sometimes resulted in increased activity. In the pyrrolyl series, this increased activity ranged from 3–10× over the C-5 unsubstituted compounds (Table II, **1** vs **24**, **40** vs **44**). We reasoned that this increase might have resulted from an enforced lack of planarity of the thiazole and its C-4 substituent. Such a hypothesis supported the trend observed in both the pyrrolyl and phenyl series, i.e. ortho substitution of the aryl ring led to improved activity (vide supra). However, that there was more to this effect than simply the orthogonality of the two rings is evident from **59**, which was more potent than its unsubstituted parent (i.e. **48**, IC_{50} = 40 μM), but only equipotent to **137**.



59 IC_{50} = 21 μM



137 IC_{50} = 21 μM

Whatever the reason for this additional activity, methyl substitution at C-5 of the thiazole could only be relied upon to increase activity as long as the guanidine was not substituted. When the guanidine was substituted with a benzyl group, the potency of the resulting compound was inferior to that of its desbenzyl-5-thiazole parent (Table II, **26** vs **24**, **45** vs **44**, **47** vs **46**). A number of modifications to the guanidine substituent failed to improve the situation (**25** and **28** vs **24**), although in one case (**27**), the magnitude of the observed loss in potency was not as great.

The effect of methyl substitution at C-5 of the thiazole was less dramatic in the indolyl series and essentially nonexistent in the phenyl series (Table III, **90** vs **88**, **91** vs **89**). In the indolyl series, addition of a 5-methyl substituent to the thiazole usually led to improved potency (Table IV, **107** vs **105** and **116**, **118** vs **116**), but sometimes this improvement was very slight (**99** vs **97**). Here again, relative to the desbenzyl-5-methylthiazole compounds, benzyl substitution on the guanidine did nothing to improve potency and sometimes decreased it dramatically (**100** vs **99**, **108** vs **107**, and **119** vs **118**). A satisfactory rationalization of this unexpected negative additivity has not been found.

In Vivo Results. The most potent H^+,K^+-ATPase inhibitors from the various series were profiled in vivo using a pylorus-ligated rat model. As mentioned earlier, **1** exhibited an ED_{50} of 26 mg/kg (intraduodenally) in this model (Table VI), and as would be expected, an analogue (**32**) which was slightly less active in vitro was also slightly less active in vivo. Unfortunately, a correlation between in vitro and in vivo activities was not generally observed. Compounds with IC_{50}'s 5–25 times lower than that of **1** demonstrated no potency advantage in vivo (**24**, **41**, **44**).

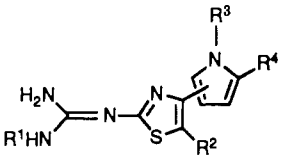
Some of the compounds with the most potent in vitro activity were in the 4-phenyl 2-guanidinothiazoles series, yet these same compounds exhibited little or no in vivo activity. Although 3,4-dihydroxy substitution of the phenyl group yielded compounds (**88** and **89**) which were 20–100-fold more potent in vitro than **1**, these compounds were essentially inactive in vivo. We speculated that poor absorption, rapid clearance, or metabolism might be responsible for this lack of antisecretory activity in rats; consequently, we prepared some simple prodrugs aimed at averting these potential problems. As expected, the diacetoxy derivatives (**133** and **134**) exhibited diminished in vitro activity; but unfortunately, no improvement of in vivo activity was observed. On the other hand, **75** displayed significant in vivo activity, albeit less potent than **1**.

A number of 4-indolyl-2-guanidinothiazoles were also tested in vivo, and the most active of these are shown in Table VI. For the most part, these compounds were less active in vivo than **1** despite their greater than 35-fold in vitro potency advantage. As was seen in the other series, key in vitro SAR points did not translate in vivo (**121** vs **112** vs **102**) and compounds with equivalent in vitro activity gave dramatically different in vivo activity (**121** vs **116** vs **120** vs **119**). The compounds which were designed to have orthogonal indole and thiazole rings (**135** and **136**) did display good in vivo activity. Compound **135** was equipotent with **1**, and **136** was nearly 3 times more potent ($ED_{50} \approx 10$ mg/kg id). The latter compound was advanced to the Heidenhain pouch dog model at 2 mg/kg iv (cimetidine ED_{50} = 0.1 mg/kg iv), but it did not demonstrate antisecretory activity.

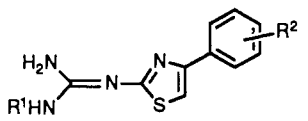
Conclusions

Structure–activity relationship studies of the 4-substituted 2-guanidinothiazole system yielded only a single example wherein the thiazole portion of the molecule could be successfully replaced with another moiety. On the other hand, pyrrolyl, phenyl, and indole groups used as the C-4 substituent all resulted in active compounds. Considerable study of substituents on the pyrrolyl, phenyl, and indolyl groups revealed no consistent trends. Both monoalkylation

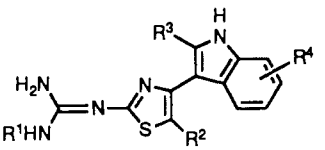
Table VI. Gastric Antisecretory Activity of 4-Substituted 2-Guanidinothiazoles



no.	X[a]	R^1	R^2	R^3	R^4	IC_{50}, μM	% gastric antisecretory activity[b]	dose, mg/kg, id	no. of animals
1	4	H	H	H	Me	25	50 ± 3	26	8
32	5	H	H	H	Me	45	50 ± 4	33	7
24	4	H	Me	H	Me	1	36 ± 6	60	7
41	3	Bn	H	SO_2Ph	Me	6	60 ± 6	30	5
44	3	H	Me	H	Me	1	46 ± 7	60	9



no.	R^1	R^2	IC_{50}, μM	% gastric antisecretory activity[b]	dose, mg/kg, id	no. of animals
88	H	3,4-$(OH)_2$	1.5	−149 ± 9[c]	60	9
89	Bn	3,4-$(OH)_2$	0.3	2.5 ± 2	30	9
133	H	3,4-$(OAc)_2$	27	15 ± 7	30	9
134	Bn	3,4-$(OAc)_2$	>50	−1 ± 11[c]	30	9
75	H	4-OMe	35	87 ± 11	60	9
				26 ± 3	30	8
				27 ± 3	10	8



no.	R^1	R^2	R^3	R^4	IC_{50}, μM	% gastric antisecretory activity[b]	dose, mg/kg, id	no. of animals
121	Bn	H	H	5-Br	0.7	52 ± 6	60	8
112	H	H	H	6-Me	1.6	42 ± 6	60	8
102	Bn	H	H	5-OMe	4.3	48 ± 5	60	9
116	Bn	H	H	5-Cl	0.7	22 ± 11	60	9
120	H	H	H	5-Br	0.96	−43 ± 15[c]	60	8
119	Bn	Me	H	5-Cl	0.7	−59 ± 9[c]	60	8
135	Bn	Me	Me	H	5.3	69 ± 3	60	9
						47 ± 2	30	9
136	H	Me	Me	H	6.2	78 ± 1	60[d]	7
						51 ± 3	10	10

[a] X = position of attachment of the pyrrole ring. [b] Data are means ± SE of 5–10 animals. All drug-treated groups are compared with vehicle-treated groups as control at confidence level $p < 0.05$. Statistics were done by using Student's t test. [c] Negative values indicate that gastric secretion was stimulated relative to controls. [d] Compound was inactive in the Heidenhain pouch dog model when dosed at 2 mg/kg iv.

of the guanidine and alkylation of the thiazole at the C-5 often led to improved in vitro activity, but these improvements were not additive. The optimal compounds for this SAR study were 100-fold more active than the initial lead, **1**. Despite this, only a 3-fold increase in in vivo potency was observed.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on either a Varian XL-300 FT-NMR spectrometer or a Bruker WM-250 FT-NMR spectrometer. Infrared spectra were recorded on a Perkin-Elmer 283B infrared spectrometer. Exact masses were determined using an A.E.I.-MS30 mass spectrometer. Elemental analyses were determined by Pfizer's Central Research Analytical Department. All starting materials were obtained from commercial sources and used as received unless otherwise stated.

Spectral data obtained on all compounds were in good agreement with the assigned structures. A number of the intermediates used are known in the literature and referenced in the Chemistry section; consequently, they are not mentioned in this section.

General Procedure for Synthesizing 4-Aryl-2-guanidinothiazoles. 4-(2-Formyl-1*H*-pyrrol-4-yl)-2-(2-guanidino)thiazole Acetate (4). Reaction of *N*-(diaminomethylene)thiourea (4.8 g, 41 mmol) and 2-chloro-1-(2-formyl-1*H*-pyrrol-4-yl)ethanone (7.0 g, 41 mmol) as previously described[14] provided 3.0 g (30% yield) of the title compound, mp ≥250 °C. Anal. ($C_9H_9N_5OS \cdot C_2H_4O_2$) C, H, S; N calcd, 23.71; found 24.41.

4-(2-Methyl-1*H*-pyrrol-4-yl)-2-(2-guanidino)thiazole Acetate (1). 4-(2-Formyl-1*H*-pyrrol-4-yl)-2-(2-guanidino)thiazole acetate (2.0 g, 6.8 mmol) was converted to its free base, reduced with diborane by using the procedure of Biswas and Jackson,[15] and converted to an acetate salt to give 1.33 g (47% yield) of the title compound, mp 220–222 °C. Anal. ($C_9H_{11}N_5S \cdot C_2H_4O_2$) C, H, N, S.

2-Chloro-1-(2-formyl-1*H*-pyrrol-4-yl)ethanone (139). Anhydrous aluminum chloride (84 g, 630 mmol) was added portionwise over 30 min to a room-temperature solution of 1*H*-pyrrol-2-ylcarboxaldehyde (10 g, 105 mmol) in 1,2-dichloroethane (100 mL) under nitrogen. After stirring for 15 min, chloroacetyl chloride (35.6 g, 315 mmol) was added dropwise over 2 h. After addition was complete, the mixture was stirred at room tem-

Table VII. Physical Characteristics of 4-Substituted 2-Guanidinothiazoles

no.	mp, °C	formula	anal.	no.	mp, °C	formula	anal.
1	235–237	$C_9H_{11}N_5S$	C, H, N	70	>250	$C_{10}H_{11}N_5S\cdot1.75HCl$	C, H, N
2	115–118	$C_9H_{10}N_2S$	C, H, N	71	252–254	$C_{12}H_{15}N_5S\cdot HBr$	C, H, N, Br
3	210	$C_8N_9N_3S\cdot HCl\cdot H_2O$	C, H, N, S	72	>250	$C_{17}H_{17}N_5S\cdot2HCl$	C, H, N
4	>250	$C_9H_9N_5OS\cdot C_2H_4O_2$	C, H, N	73	>250	$C_{11}H_{12}N_4OS\cdot HBr$	H, N; C[a]
5	157–161	$C_9H_8N_2OS$	C, H, N	74	>250	$C_{11}H_{12}N_4OS$	C, H, N
6	165	$C_8H_7N_3OS$	*a*	75	222–225	$C_{11}H_{12}N_4OS\cdot HBr$	*t*
7	115.5–118.5	$C_{16}H_{17}N_5S\cdot C_2H_4O_2\cdot0.5H_2O$	C, H, S; N[b]	76	>250	$C_{18}H_{18}N_4OS\cdot HBr$	C, H, N
8	184–185	$C_{16}H_{16}ClN_5S$	*a*	77	>250	$C_{18}H_{18}N_4OS\cdot HBr$	C, H, N
9	oil	$C_{15}H_{23}N_5S$	*a*	78	185–187	$C_{16}H_{22}N_4OS\cdot HBr$	C, H, N
10	oil	$C_{16}H_{25}N_5S$	*a*	79	238–240	$C_{18}H_{18}N_4OS\cdot HBr$	C, H, N
11	oil	$C_{16}H_{25}N_5S$	*a*	80	222–224	$C_{12}H_{14}N_4O_2S\cdot HCl$	H, N; C[u]
12	foam	$C_{14}H_{19}N_5S$	*a*	81	228–230	$C_{19}H_{20}N_4O_2S\cdot HCl$	C, H, N
13	183–184	$C_{11}H_{13}N_5S\cdot2HCl\cdot H_2O$	C, H, S; N[c]	82	>250	$C_{10}H_{10}N_4OS\cdot HBr$	C, H, N
14	235	$C_{12}H_{15}N_5S\cdot HCl\cdot0.5H_2O$	C, H, N	83	245–246	$C_{10}H_{10}N_4OS\cdot HBr$	C, H, N
15	160–165	$C_{19}H_{21}N_5S\cdot HCl\cdot0.5H_2O$	C, H; N[d]	84	>250	$C_{10}H_{10}N_4OS\cdot HCl$	C, H, N
16	246–247.5	$C_8H_9N_5S\cdot C_2H_4O_2$	C, H, N, S	85	>250	$C_{17}H_{16}N_4OS\cdot HBr$	H, N; C[v]
17	154–156	$C_{11}H_{16}N_6S\cdot1.5C_2H_4O_2$	C, H, N	86	219–220	$C_{17}H_{16}N_4OS\cdot HBr\cdot$ $0.5(CH_3)_2CHOH$	C, H, N
18	>235	$C_{14}H_{18}N_6OS\cdot HCl\cdot0.5H_2O$	C, H, N				
19	175	$C_{14}H_{20}N_6S\cdot C_2H_4O_2\cdot0.5H_2O$	C, H, N	87	189–191	$C_{17}H_{16}N_4OS\cdot HBr$	*a*
20	220–222	$C_{10}H_{13}N_5S\cdot C_2H_4O_2$	C, H, N, S	88	274–278	$C_{10}H_{10}N_4O_2S\cdot HCl$	C, H, N
21	>250	$C_{10}H_{11}N_5OS\cdot C_2H_4O_2$	C, H, N, S	89	205–208	$C_{17}H_{16}N_4O_2S\cdot HCl$	*a*
22	214–216	$C_{15}H_{15}N_5O_2S_2\cdot HCl\cdot H_2O$	C, H, N, S	90	141–143	$C_{11}H_{12}N_4O_2S\cdot HBr$	*a*
23	219–220	$C_{22}H_{21}N_5O_2S_2\cdot HBr$	C, H, N, S	91	202–205	$C_{18}H_{18}N_4O_2S$	*a*
24	215–220	$C_{10}H_{13}N_5S$	*a*	92	309–310 dec	$C_{12}H_{11}N_5S\cdot HBr$	C, H, N
25	165–170 dec	$C_{16}H_{17}N_5S\cdot HCl$	H, N; C[e]	93	294–296	$C_{19}H_{17}N_5S\cdot HBr$	C, H, N
26	205 dec	$C_{17}H_{19}N_5S\cdot HCl\cdot0.5H_2O$	C, H; N[f]	94	293–294	$C_{19}H_{16}ClN_5S\cdot HBr\cdot0.5H_2O$	C, H, N
27	235–240 dec	$C_{18}H_{21}N_5S\cdot HCl\cdot0.5H_2O$	C, H, N	95	281–282	$C_{12}H_{10}FN_5S\cdot HCl\cdot0.25H_2O$	C, H, N
28	125 dec	$C_{18}H_{21}N_5S\cdot HCl\cdot H_2O$	C, H	96	299–300	$C_{19}H_{16}FN_5S\cdot HCl$	C, H, N
29	>240	$C_{10}H_{11}N_5OS\cdot HCl\cdot0.5H_2O$	C, H, N	97	293–295	$C_{12}H_{11}N_5S\cdot HCl$	C, H, N
30	231–233	$C_8H_9N_5S\cdot C_2H_4O_2$	C, H, S; N[g]	98	266–267	$C_{19}H_{17}N_5S\cdot HCl$	C, H, N
31	120–121	$C_{15}H_{15}N_5S\cdot0.5C_2H_4O_2$	C, H, N, S	99	215–217	$C_{13}H_{13}N_5S\cdot0.4H_2O$	C, H, N
32	195–198	$C_9H_{11}N_5S\cdot C_2H_4O_2$	C, H, S; N[h]	100	207–208	$C_{20}H_{19}N_5S\cdot0.25H_2O$	C, H, N
33	113–115	$C_{16}H_{17}N_5S$	*a*	101	259–260	$C_{13}H_{13}N_5OS\cdot HCl$	C, H, N
34	>270	$C_{12}H_{15}N_5O_2S$	*a*	102	255–256	$C_{20}H_{19}N_5OS\cdot HCl$	C, H, N
35	>235	$C_{12}H_{16}N_6OS\cdot C_2H_4O_2\cdot0.5H_2O$	C, H, N	103	243–244	$C_{19}H_{17}N_5OS\cdot HCl$	C, H, N
36	166–166.5	$C_{12}H_{18}N_6S\cdot C_2H_4O_2\cdot H_2O$	H, N; C[i]	104	200–201	$C_{26}H_{23}N_5OS\cdot HCl$	C, H, N
37	231–232	$C_{10}H_{13}N_5S\cdot0.75C_2H_4O_2$	C, H, N, S	105	235–240	$C_{13}H_{13}N_5S\cdot2HCl$	C, H, N
38	203–204	$C_{15}H_{15}N_5O_2S_2\cdot HCl\cdot0.5H_2O$	H, N; C[j]	106	185	$C_{20}H_{16}N_5S\cdot2HCl\cdot H_2O$	C, H, N
39	125–128	$C_{22}H_{21}N_5O_2S_2\cdot HCl\cdot H_2O$	C, H; N[k]	107	240	$C_{14}H_{14}ClN_5S\cdot2HCl$	C, H; N[w]
40	193–195	$C_9H_{11}N_5S\cdot C_2H_4O_2$	C, H, S; N[l]	108	250	$C_{21}H_{20}ClN_5S\cdot2HCl$	C, H, N
41	102–104	$C_{16}H_{17}N_5S\cdot2C_2H_4O_2\cdot0.5H_2O$	C, H, N, S	109	125–126	$C_{20}H_{19}N_5S$	*a*
42	207.5–209	$C_{15}H_{15}N_5O_2S\cdot HCl\cdot0.5H_2O$	C, H, N, S	110	294–295	$C_{13}H_{13}N_5S\cdot HCl$	C, H, N
43	199.5–200.5	$C_{22}H_{21}N_5O_2S_2\cdot HBr$	C, H, N	111	253–254	$C_{20}H_{19}N_5S\cdot HCl\cdot0.5H_2O$	C, H, N
44	>220	$C_{10}H_{13}N_5S\cdot0.5HCl$	H, N; C[m]	112	274–275	$C_{13}H_{13}N_5S\cdot HCl$	C, H, N
45	180 dec	$C_{17}H_{19}N_5S\cdot HCl\cdot0.5H_2O$	*a*	113	257–258	$C_{20}H_{19}N_5S\cdot HCl\cdot0.5H_2O$	C, H, N
46	125–130	$C_{16}H_{17}N_5O_2S_2\cdot HBr\cdot0.5H_2O$	C, H; N[n]	114	288–289	$C_{13}H_{13}N_5S\cdot HCl$	C, H, N
47	110–115	$C_{23}H_{23}N_5O_2S_2\cdot H_2O$	C, N; H[o]	115	284	$C_{20}H_{19}N_5S\cdot HCl\cdot0.5H_2O$	C, H, N
48	145–146	$C_{10}H_{10}N_4S$	C, H, N	116	305–306	$C_{12}H_{10}ClN_5S\cdot HCl$	C, H, N
49	>250	$C_{17}H_{16}N_4S\cdot HBr$	C, H, N	117	267–268	$C_{19}H_{16}ClN_5S\cdot HCl$	H, N; C[x]
50	209–211	$C_{10}H_9ClN_4S\cdot HBr$	C, H, N	118	160–170	$C_{13}H_{12}ClN_5S\cdot0.4CCl_4$	C, H, N
51	224–226	$C_{10}H_9ClN_4S\cdot HBr$	C, H, N	119	166–167	$C_{20}H_{18}ClN_5S\cdot0.2CCl_4$	C, H, N
52	>250	$C_{10}H_9ClN_4S\cdot HBr$	C, H, N	120	297–298	$C_{12}H_{10}BrN_5S\cdot HCl$	C, H, N
53	>250	$C_{10}H_6FN_4S\cdot HCl$	C, H, N	121	260–261	$C_{19}H_{16}BrN_5S\cdot HCl\cdot0.5H_2O$	C, H, N
54	207 dec	$C_{17}H_{15}ClN_4S\cdot HBr$	C, H, N	122	286–287	$C_{12}H_{10}FN_5S\cdot HCl$	C, H, N
55	261–263	$C_{17}H_{15}ClN_4S\cdot HBr$	C, H, N	123	254–255	$C_{19}H_{16}FN_5S\cdot HCl\cdot0.75H_2O$	C, H, N
56	>250	$C_{17}H_{15}ClN_4S$	C, H, N	124	212–214	$C_{14}H_{13}N_5O_2S\cdot HCl\cdot0.25H_2O$	C, H, N
57	>250	$C_{17}H_{15}FN_4S\cdot HCl$	C, H, N	125	255–256	$C_{21}H_{19}N_5O_2S\cdot HCl\cdot H_2O$	C, H, N
58	173–176	$C_{11}H_{12}N_4S\cdot HBr$	C, H, N	126	331–332	$C_{13}H_{10}N_6S\cdot HCl$	C, H, N
59	54–57	$C_{13}H_{17}N_5S$	H; C, N[p]	127	239–241	$C_{20}H_{16}N_6S\cdot HCl\cdot0.5H_2O$	C, H, N
60	236–238	$C_{11}H_{12}N_4S\cdot HBr$	C, H, N	128	166–168	$C_{21}H_{20}N_6OS$	*a*
61	233–235	$C_{13}H_{17}N_5S\cdot2HCl\cdot0.5H_2O$	C, H, N	129	oil	$C_{11}H_{14}N_4\cdot C_2H_4O_2$	*y*
62	>250	$C_{11}H_{12}N_4S\cdot HBr$	C, H, N	130	173–175	$C_{13}H_{13}N_3\cdot C_6H_6O_3S$	*z*
63	>250	$C_{16}H_{14}N_4S\cdot HBr$	H, N; C[q]	131	236–237 dec	$C_{10}H_{10}N_4O$	C, H, N
64	168–171	$C_{18}H_{18}N_4S\cdot HBr$	C, H, N	132	243–245	$C_{11}H_{10}ClN_5\cdot HCl$	C, H, N
65	245–246	$C_{18}H_{18}N_4S\cdot HBr$	C, H, N	133	220 dec	$C_{14}H_{14}N_4O_4S\cdot HCl$	C, H, N
66	254–255	$C_{19}H_{18}N_4S\cdot HBr$	C, H, N	134	215–217	$C_{21}H_{20}N_4O_4S\cdot HCl$	C, H, N
67	114–116	$C_{23}H_{20}N_4S$	C, H, N	135	185–190	$C_{21}H_{21}N_5S\cdot HCl\cdot H_2O$	C, H, N
68	218–223	$C_{10}H_{11}N_5S$	*r*	136	193–195	$C_{14}H_{15}N_5S\cdot HCl\cdot H_2O$	C, H, N
69	255–256	$C_{12}H_{15}N_5S\cdot HBr$	C, H, N, Br	137	283–284	$C_{12}H_{12}N_4S\cdot HBr$	C, H, N

[a] Homogeneous by TLC and high-resolution mass spectra within accepted limits. [b] N: calcd, 18.41; found, 17.85. [c] N: calcd, 20.70; found, 21.10. [d] N: calcd, 17.15; found, 16.56. [e] C: calcd, 55.24; found, 54.76. [f] N: calcd, 18.88; found, 17.15. [g] N: calcd, 26.20; found, 25.64. [h] N: calcd, 24.89; found, 24.06. [i] C: calcd, 46.14; found, 45.57. [j] C: calcd, 44.24; found, 44.82. [k] N: calcd, 13.42; found, 14.00. [l] N: calcd, 24.89; found, 24.35. [m] C: calcd, 47.37; found, 46.88. [n] N: calcd, 14.48; found, 13.89. [o] H: calcd, 5.21; found, 4.69. [p] C: calcd, 56.70; found, 53.05. N: calcd, 25.53; found, 22.18. [q] C: calcd, 51.20; found, 51.77. [r] Eur. Patent Appl. 83,200,388.3. [s] C: calcd, 52.44; found, 51.64. [t] *Chem. Ber.* **1962**, *95*, 893. [u] C: calcd, 45.70; found, 45.27. [v] C: calcd, 50.37; found, 49.84. [w] N: calcd, 17.83; found, 16.80. [x] C: calcd, 54.55; found, 53.56. [y] *Collect. Czech. Chem. Commun.* **1975**, *40*, 3904. [z] *J. Chem. Soc.* **1951**, 2342.

perature for 16 h. The mixture was poured onto crushed ice and the resulting precipitate was collected, washed well with water, and dried in vacuo. Separation of the organic layer from the aqueous filtrate, followed by drying over anhydrous sodium sulfate, filtering, and evaporation, afforded a second crop of product identical with the first by TLC. Recrystallization from acetone (decolorization with charcoal) afforded 16.8 g (94% yield) of the product, mp 178–179 °C. Anal. ($C_7H_6ClNO_2$) C, H, N.

2-Methyl-1-(phenylsulfonyl)pyrrole (141). 2-Methyl-1*H*-pyrrole (9.4 g, 97 mmol) was converted to its potassium salt and phenylsulfonated according to a literature procedure[25] to give 11.5 g (67% yield) of the title compound, mp 37.5–39.5 °C. Physical properties were in agreement with literature reports.[25]

2-Bromo-1-[2-methyl-1-(phenylsulfonyl)pyrrol-4-yl]-ethanone (145). A solution of 1-[2-methyl-1-(phenylsulfonyl)-pyrrol-4-yl]ethanone[17] (13.3 g, 50 mmol) in 320 mL of chloroform was stirred at −10 °C and a solution of 2.56 mL (8.0 g, 50 mmol) of bromine in 40 mL of chloroform was added dropwise over 6 h. After the addition was completed, the mixture was stirred at −10 °C for 0.5 h and then allowed to warm to room temperature. The mixture was concentrated, and the residue was chromatographed over silica gel using 1:1:0.1 hexane/toluene/ethyl acetate as eluent to give 10.0 g (59% yield) of the title compound, mp 86–88 °C. Anal. ($C_{13}H_{12}BrNO_3S$) C, H, N.

The following compounds were also synthesized by using this procedure. 144: mp 108.5–110.0 °C. Anal. ($C_{13}H_{12}BrNO_3S$) C, H, N. 147: mp 82.5–83.5 °C. Anal. ($C_{13}H_{12}BrNO_3S$) C, H, N.

2-Chloro-1-(5-methoxy-1*H*-indol-3-yl)ethanone (149). With use of the procedure of Bergman et al.,[18] 5-methoxy-1*H*-indole (12.00 g, 81.5 mmol) was acylated to give 7.02 g (39% yield) of the title compound, mp 267–268 °C (lit.[18] mp 271 °C). Spectral data was identical with literature reports.[18]

2-Chloro-1-(5-fluoro-1*H*-indol-3-yl)ethanone (151). To a stirred, 0 °C solution of 5-fluoro-1*H*-indole (5.00 g, 37.0 mmol) in dry ether (65 mL) was added methylmagnesium bromide (11.7 mL of a 3.18 M ether solution, 37.2 mmol). After stirring at 0 °C for 1 h, chloroacetyl chloride (4.21 g, 37.3 mmol) was added rapidly. The reaction was stirred at 0 °C for 30 min and 10% aqueous ammonium chloride (75 mL) was added. After stirring for 15 min at room temperature, the mixture was filtered. The collected solid was washed with ether (30 mL) and dried to give 2.24 g of a mixture of mono- and diacylated products. This material was dissolved in methanol (350 mL) and treated with potassium carbonate (1.10 g, 8 mmol, dissolved in 15 mL of water) for 16 h at room temperature. Water (500 mL) was added to this reaction and the resulting precipitate was removed by filtration, washed with water (100 mL), and dried to give 1.45 g (19% yield) of the title compound: mp 236–237 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 4.82 (s, 2 H), 7.05 (ddd, J = 1, 4, and 5 Hz, 1 H), 7.47 (dd, J = 2 and 4 Hz, 1 H), 7.77 (dd, J = 1 and 5 Hz, 1 H), 8.44 (s, 1 H), 12.26 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ (ppm) 46.2, 105.8, 106.2, 111.0, 111.5, 113.5, 113.6, 125.8, 126.0, 133.1, 136.0, 156.8, 160.6, 186.1; IR (KBr) 3181, 1587, 1401 cm^{-1}; mass spectrum, m/e (relative intensity) M$^+$ 210.9 (21), 161.9 (100), 148 (16), 133.9 (18), 106.9 (18).

***N*-(3,4,5,6-Tetrahydropyrimidin-2-yl)thiourea (158).** A 5 °C mixture of *N*-(3,4,5,6-tetrahydropyrimidin-2-yl)cyanamide (2.1 g, 17 mmol),[23] diethylamine (0.45 mL), and methanol (45 mL) was saturated with hydrogen sulfide (bubbled at moderate rate for 45 min). The mixture was transferred to a steel bomb. The bomb was sealed and heated at 80 °C (external) for 20 h. The bomb was cooled, opened, and purged with nitrogen gas. Concentration of the mixture gave a solid, which, upon recrystallization from *n*-propanol, afforded 1.2 g (44% yield) of the title compound, mp 145–147 °C. This material was used without any further purification.

***N*-Cyano-*N'*-hexyl-*N''*-methylguanidine (160).** A solution of methyl isothiocyanate (7.31 g, 0.10 mol) in acetone (25 mL) was added to a solution of hexylamine (10.12 g, 0.10 mol) in acetone (50 mL). A slight exotherm ensued. After stirring at room temperature overnight, the acetone was removed in vacuo and the residue was triturated with hexane. The resulting solid was collected, washed with hexane, and dried, giving 15.23 g (87%) of *N*-hexyl-*N'*-methylthiourea as an off-white solid: mass spectrum, m/e (relative intensity) M$^+$, 174 (100), 145 (9.6), 141 (34.2), 131 (14.2), 117 (9.6), 104 (22.9), 74 (40.9), 71 (18.1), 57 (61.1); ^{1}H NMR (acetone-d_6) δ 0.9–1.0 (3 H, m), 1.2–1.8 (8 H, m), 2.92 (3 H, d, J = 7.5 Hz), 3.3 (2 H, br q), 6.72 (1 H, br s).

A portion of the above thiourea (8.02 g, 46.0 mmol) was dissolved in THF (150 mL) and treated with methyl iodide (6.86 g, 48.3 mmol). After stirring at room temperature for 6 h, the solvent was removed in vacuo to give 16.01 g (>100% of a brown oil, which was used without purification: mass spectrum, m/e (relative intensity) M$^+$ + 1, 189 (1.6), M$^+$, 188 (1.2), 174 (76.6), 173 (22.3), 142 (100), 143 (47.0), 127 (55.5), 104 (15.4), 74 (21.3), 57 (50.7).

The crude isothiourea (≤46.0 mmol), cyanamide (4.35 g, 104.0 mmol), and sodium acetate (3.77 g, 46.0 mmol) were combined in ethanol (150 mL) and heated under reflux for 48 h. Additional cyanamide (1.00 g, 23.7 mmol) was added and the mixture was heated under reflux for another 24 h. The reaction mixture was concentrated in vacuo and the residual oil was dissolved in chloroform (100 mL). This solution was washed with water (3 × 50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give an oil. This was flash chromatographed (5:95 methanol/chloroform), giving 7.26 g (87%) of the title compound as a yellow oil: mass spectrum, m/e (relative intensity) M$^+$ + 1, 183 (100), 167 (8.8), 153 (16.4), 139 (17.4), 126 (24.1), 125 (75.8), 112 (60.7), 111 (10.8), 99 (21.1), 87 (12.3), 82 (48.6).

***N*-(*N*-Hexyl-*N'*-methylguanyl)thiourea (161).** *N*-Cyano-*N'*-hexyl-*N''*-methylguanidine was treated with hydrogen sulfide according to literature preparations[22c,d] to give a 46% yield of the title compound as a light yellow oil after flash chromatography (2:98 methanol/chloroform): mass spectrum, m/e (relative intensity) M$^+$ + 1, 217 (83.8), M$^+$, 216 (100), 183 (79.7), 127 (13.0), 116 (14.3), 113 (22.9), 99 (34.8), 84 (16.3), 77 (11.9), 60 (21.1), 57 (68.1); ^{1}H NMR ($CDCl_3$) δ 0.8–1.0 (3 H, m), 1.1–1.7 (8 H, m), 2.80 (3 H, d, J = 7.5 Hz), 3.17 (2 H, br q), 6.37 (1 H, br s).

Assay of H$^+$,K$^+$-ATPase Inhibition. H$^+$,K$^+$-ATPase was isolated from canine gastric mucosa. The enzyme activity was assayed according to Beil et al.,[25] with slight modifications. The enzyme (1–2 μg) was preincubated at 37 °C for 45 min with a medium containing 2 × 10^{-3} M $MgCl_2$, 5 × 10^{-2} M Tris–Cl buffer (pH 7.5) with or without 1 × 10^{-2} M KCl, and the test drug in a final volume of 590 μL. The reaction was started by the addition of 0.010 mmol of ATP (final concentration 3 × 10^{-3} M). The reaction was terminated by adding trichloroacetic acid to a concentration of 4.2%. Liberated inorganic phosphate was determined spectrophotometrically with Fiske and Subarrow Reducer available from Sigma Chemical Co. Data on reference standards, omeprazole and SCH 28080, illustrate the confidence limits for this screen. At pH 7.0, omeprazole gave 90% ± 12% inhibition at 50 μM (n = 8) and 64% ± 16% at 10 μM (n = 8). At pH = 2.0, omeprazole gave 99% ± 6% at 50 μM (n = 4), 93% ± 4% at 10 μM (n = 6), 91% ± 3% at 5 μM (n = 9), and 50% ± 20% at 1 μM (n = 11) for an IC_{50} of 0.98 μM ± 0.47. At pH 7.5, SCH 28080 gave 45% ± 11.3% inhibition at 0.5 μM (n = 330). At pH 2.0, SCH 28080 gave 43% ± 13% inhibition at 0.5 μM (n = 56). Statistics were done with Student's t test.

Gastric Acid Antisecretory Activity in the Pylorus-Ligated Rat Model. The gastric acid antisecretory activity of compounds was determined in conscious pylorus-ligated rats. The pylorus of rats was ligated under ether anesthesia with silk thread and the drug or vehicle was injected into the duodenum. The rats were allowed to regain consciousness, housed in show box cages for 2 h after surgery, and then sacrificed by ip injection of sodium pentabarbital (1 mg/mL). A hemostat clamp was placed between the esophagus and stomach, and the stomach was gently cut free. The stomach contents were funneled into tubes and spun in a Sorvall RT6000 at 3000 rpm for 15 min at room temperature. A Radiometer Titrater (endpoint = pH 7.0) was used to determine pH and uEq of acid output/h per 100 g of rat body weight. Gastric acid antisecretory effects of drug were calculated by comparing uEq of acid output/h per 100 g of rat body weight with that of the vehicle-treated animals. Data are presented as means ± SE of 5–10 animals. All drug-treated groups are compared with vehicle-treated groups as control at a confidence level of $p < 0.05$. Statistics were done with Student's t test.

Gastric Acid Antisecretory Activity in the Heidenhain Pouch Dog Model. The gastric acid antisecretory activity of

(25) Beil, R. *Br. J. Pharmacol.* 1984, *82*, 651.

compounds was determined in overnight-fasted, conscious Heidenhain pouch dogs. Pentagastrin (Pentavolon-Ayerst) was used to stimulate acid output by continuous infusion into a superficial leg vein at doses earlier determined to stimulate near maximal acid output from the gastric pouch. Gastric juice was collected at 30-min intervals following the start of a pentagastrin infusion and measured to the nearest 0.1 mL. Ten collections were taken for each dog during an experiment. Acid concentration was determined by titrating 1.0 mL of gastric juice to pH 7.4 with 0.1 N sodium hydroxide with an Autoburette and a glass electrode pH meter (Radiometer).

Drug or vehicle was given intravenously or orally 90 min following the start of the pentagastrin infusion at a dose of 2 mg/kg or less. Gastric acid antisecretory effects were calculated by comparing the lowest acid output after drug administration with the mean acid output immediately before drug.

Acknowledgment. The expert synthetic chemical assistance of C. J. Mularski, D. E. Muse, L. T. Wint, and M. P. Zawistoski is gratefully acknowledged. J. P. Hakkinen's important contribution to the generation of the biological data is gratefully acknowledged as is the expert biological technical assistance of H. R. Bolen, F. W. Bangerter, P. G. Cosgrove, D. Hessinger, and J. T. MacAndrew.

Registry No. 1, 115027-84-4; 1·$C_2H_4O_2$, 123311-07-9; 2, 123309-49-9; 3, 123309-50-2; 3·HCl, 123310-52-1; 4, 123309-51-3; 4·$C_2H_4O_2$, 123310-53-2; 5, 123309-52-4; 6, 123309-53-5; 7, 115027-85-5; 7·$C_2H_4O_2$, 115027-86-6; 8, 123309-54-6; 9, 123309-55-7; 10, 123309-56-8; 11, 123309-57-9; 12, 123309-58-0; 13, 123309-59-1; 13·2HCl, 123310-54-3; 14, 123309-60-4; 14·HCl, 123310-55-4; 15, 123309-61-5; 15·HCl, 123310-56-5; 16, 115027-94-6; 16·$C_2H_4O_2$, 115027-95-7; 17, 115027-68-4; 17·$C_2H_4O_2$, 123310-57-6; 18, 123309-62-6; 18·HCl, 115027-61-7; 19, 115027-72-0; 19·$C_2H_4O_2$, 115027-73-1; 20, 115027-74-2; 20·$C_2H_4O_2$, 115027-75-3; 21, 115027-62-8; 21·$C_2H_4O_2$, 115027-63-9; 22, 115027-77-5; 22·HCl, 115027-76-4; 23, 123309-63-7; 23·HBr, 115027-78-6; 24, 123309-64-8; 25, 123309-65-9; 25·HCl, 115027-49-1; 26, 123309-66-0; 26·HCl, 115027-51-5; 27, 123309-67-1; 27·HCl, 115027-50-4; 28, 123309-68-2; 28·HCl, 115027-52-6; 29, 123309-69-3; 29·HCl, 115027-47-9; 30, 115027-66-2; 30·$C_2H_4O_2$, 115027-67-3; 31, 115027-64-0; 31·$^1/_2C_2H_4O_2$, 123310-58-7; 32, 115027-91-3; 32·$C_2H_4O_2$, 115027-92-4; 33, 115027-93-5; 34, 123309-70-6; 35, 115027-59-3; 35·$C_2H_4O_2$, 115027-60-6; 36, 115027-70-8; 36·$C_2H_4O_2$, 123330-27-8; 37, 123309-71-7; 37·$2C_2H_4O_2$, 123310-59-8; 38, 123309-72-8; 38·HCl, 115027-81-1; 39, 123309-73-9; 39·HCl, 115027-82-2; 40, 115027-87-7; 40·$C_2H_4O_2$, 115027-88-8; 41, 115027-89-9; 41·$2C_2H_4O_2$, 115027-90-2; 42, 123309-74-0; 42·HCl, 123330-28-9; 43, 123309-75-1; 43·HBr, 123310-60-1; 44, 123309-76-2; 44·$^1/_2$HCl, 123310-61-2; 45, 123309-77-3; 45·HCl, 123310-62-3; 46, 123309-78-4; 46·HBr, 123310-63-4; 47, 123309-79-5; 48, 2507-81-5; 49, 123309-80-8; 49·HBr, 123310-64-5; 50, 123309-81-9; 50·HBr, 123310-65-6; 51, 123309-82-0; 51·HBr, 123310-66-7; 52, 7120-02-7; 52·HBr, 123310-67-8; 53, 2438-34-8; 53·HCl, 123310-68-9; 54, 123309-83-1; 54·HBr, 123310-69-0; 55, 123309-84-2; 55·HBr, 123310-70-3; 56, 123309-85-3; 57, 123309-86-4; 57·HCl, 123310-71-4; 58, 123309-87-5; 58·HBr, 96996-07-5; 59, 123309-88-6; 60, 123309-89-7; 60·HBr, 123310-72-5; 61, 123309-90-0; 61·2HCl, 123310-73-6; 62, 7120-04-9; 62·HBr, 123310-74-7; 63, 123309-91-1; 63·HBr, 123310-75-8; 64, 123309-92-2; 64·HBr, 123310-76-9; 65, 123309-93-3; 65·HBr, 123310-77-0; 66, 24644-41-5; 66·HBr, 123310-78-1; 67, 123309-94-4; 68, 72801-60-6; 69, 112598-38-6; 69·HBr, 112598-39-7; 70, 83831-31-6; 70·2HCl, 107880-80-8; 71, 123309-95-5; 71·HBr, 123310-79-2; 72, 123309-96-6; 72·2HCl, 123310-80-5; 73, 123309-97-7; 73·HBr, 123310-81-6; 74, 123309-98-8; 75, 91089-11-1; 75·HBr, 96996-05-3; 76, 123309-99-9; 76·HBr, 123310-82-7; 77, 123310-00-9; 77·HBr, 123310-83-8; 78, 123310-01-0; 78·HBr, 123310-84-9; 79, 123310-02-1; 79·HBr, 123310-85-0; 80, 123310-03-2; 80·HCl, 123310-86-1; 81, 123310-04-3; 81·HCl, 123310-87-2; 82, 123310-05-4; 82·HBr, 96996-13-3; 83, 123310-06-5; 83·HBr, 96996-11-1; 84, 2507-84-8; 84·HCl, 123310-88-3; 85, 123310-07-6; 85·HBr, 123310-89-4; 86, 123310-08-7; 86·HBr, 123310-90-7; 87, 123310-09-8; 87·HBr, 123310-91-8; 88, 123310-10-1; 88·HCl, 123310-92-9; 89, 123310-11-2; 89·HCl, 123310-93-0; 90, 123310-12-3; 90·HBr, 123310-94-1; 91, 123310-13-4; 92, 123310-14-5; 92·HBr, 115027-42-4; 93, 123310-15-6; 93·HBr, 115027-43-5; 94, 123310-16-7; 94·HBr, 115027-44-6; 95, 123310-17-8; 95·HCl, 115027-46-8; 96, 123310-18-9; 96·HCl, 115027-45-7; 97, 115027-97-9; 97·HCl, 65040-42-8; 98, 123310-95-2; 98·HCl, 115027-96-8; 99, 115027-55-9; 100, 115027-56-0; 101, 123310-19-0; 101·HCl, 115027-99-1; 102, 123310-20-3; 102·HCl, 115027-98-0; 103, 123310-21-4; 103·HCl, 115028-02-9; 104, 123310-22-5; 104·HCl, 115028-03-0; 105, 123310-23-6; 105·2HCl, 115027-31-1; 106, 123310-24-7; 106·2HCl, 123310-96-3; 107, 123310-25-8; 107·2HCl, 123310-97-4; 108, 123310-26-9; 108·2HCl, 123310-98-5; 109, 115028-04-1; 110, 123310-27-0; 110·HCl, 115028-05-2; 111, 123310-28-1; 111·HCl, 115028-06-3; 112, 123310-29-2; 112·HCl, 115028-07-4; 113, 123310-30-5; 113·HCl, 115028-08-5; 114, 123310-31-6; 114·HCl, 115028-09-6; 115, 123310-32-7; 115·HCl, 115027-30-0; 116, 123310-33-8; 116·HCl, 115028-00-7; 117, 123310-34-9; 117·HCl, 115028-01-8; 118, 115027-54-8; 119, 115027-10-6; 120, 123310-35-0; 120·HCl, 115027-33-3; 121, 123310-36-1; 121·HCl, 115027-34-4; 122, 123310-37-2; 122·HCl, 115027-35-5; 123, 123310-38-3; 123·HCl, 115027-36-6; 124, 123310-39-4; 124·HCl, 115027-37-7; 125, 123310-40-7; 125·HCl, 115027-38-8; 126, 123330-26-7; 126·HCl, 115027-39-9; 127, 123310-41-8; 127·HCl, 115027-40-2; 128, 115027-41-3; 129, 3858-85-3; 129·$C_2H_4O_2$, 123310-99-6; 130, 123310-42-9; 130·$C_6H_6O_3S$, 123311-00-2; 131, 123310-43-0; 132, 123310-44-1; 132·HCl, 123311-01-3; 133, 123310-45-2; 133·HCl, 123311-02-4; 134, 123310-46-3; 134·HCl, 123311-03-5; 135, 123310-47-4; 135·HCl, 123311-04-6; 136, 123310-48-5; 136·HCl, 123311-05-7; 137, 123310-49-6; 137·HBr, 123311-06-8; 139, 115027-23-1; 141, 115027-28-6; 142, 115027-29-7; 143, 115027-11-7; 144, 115027-14-0; 145, 115027-13-9; 146, 115027-12-8; 147, 115027-15-1; 149, 30030-91-2; 150, 399-52-0; 151, 115027-06-0; 152, 1477-50-5; 153, 36709-95-2; 154, 504-66-5; 155, 101190-73-2; 156, 101857-92-5; 158, 88964-74-3; 159, 556-61-6; 160, 72751-64-5; 161, 123310-51-0; $CH_3(CH_2)_5NHCH_3$, 35161-70-7; $ClCH_2COCl$, 79-04-9; $CH_3(CH_2)_5NH_2$, 111-26-2; H^+,K^+-ATPase, 9000-83-3; H_2NCN, 420-04-2; $CH_3(CH_2)_5NHC(SMe)$=NMe·HI, 93484-22-1; pyrrol-2-ylcarboxaldehyde, 1003-29-8; (3,4,5,6-tetrahydropyrimidin-1-yl)cyanamide, 36982-81-7; *N*-hexyl-*N'*-methylthiourea, 53393-06-9.

Hypolipidemic Activity of Rifamycin Derivatives

Peter Traxler,* Wilhelm Kump, Klaus Mueller, and Werner Tosch

Pharmaceuticals Research Laboratories, Ciba-Geigy, Ltd., CH-4002 Basle, Switzerland. *Received March 2, 1989*

Series of 3-piperidinyl- and 3-piperazinylrifamycins and to a certain extent 3-hydrazonorifamycins all bearing lipophilic side chains were found to exert potent hypolipidemic activity in lowering both serum cholesterol and LDL-cholesterol in rats. Starting from 3-[*N'*-(2,4,6-trimethylbenzyl)-*N*-piperazinyl]rifamycin SV (compound **25**), a series of derivatives were synthesized with the aim of dissociating the hypolipidemic from the antibacterial activity, leading to the 8-*O*,*N*-dipivaloyl derivative of **25** (compound **48**), which is devoid of any antibacterial activity but shows about 50–60% reduction of LDL-cholesterol and 20–30% reduction of serum cholesterol at a dose of 10 mg/kg. Compound **48** was selected for further pharmacological evaluation.

The rifamycins, which were first isolated toward the end of the 1950s from cultures of the microorganism *Nocardia mediterranei*, are antibiotics active in vitro against Gram-positive and Gram-negative bacteria.[1] They are

0022-2623/90/1833-0552$02.50/0