Bioisosteric Prototype Design of Biaryl Imidazolyl and Triazolyl Competitive Histamine H_2-Receptor Antagonists

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The structural relationship of the competitive histamine H_2-receptor antagonist 3-amino-5-(2-amino-4-pyridyl)-1,2,4-triazole (1) to the agonist histamine and to antagonists of the cimetidine type was explored by the design and synthesis of four series of bioisosterically designed prototypes. Biological data from these series was best interpreted as indicating a similarity between the imidazole moiety of histamine and cimetidine and the 2-amino-4-pyridyl moiety of 1. On the basis of this data, sequential replacement of 2-amino-4-pyridyl by 2-[(dimethylamino)methyl]-5-furyl and 2-guanidino-4-triazolyl moieties led to a structurally more potent series of biaryl histamine H_2-receptor antagonists. The best of these, 2-methyl-4-(2-guanidino-4-thiazolyl)imidazole (**29**, CP-57,361-1) was 120 times more potent as a histamine H_2-receptor antagonist than 1.

Previous work from these laboratories described the structure–activity relationship (SAR) in a series of biaryl pyridyltriazole and imidazole histamine H_2-receptor antagonists with particular focus on pseudosymmetrical properties, bioisosterism, and a quantitative structure–activity relationship (QSAR) study relating increased gastric acid antisecretory activity to reduced lipophilicity.[1] In this paper we describe the reasoning process and data that allowed us to solve a common and difficult medicinal chemistry problem—namely, the generation of a new, more active lead series from an existing lead series whose activity has already been optimized by application of QSAR principles.

The solution to this type of problem often involves a major structural change of the type not usually found by the sequence of small progressive changes frequently derived from a QSAR analysis. Our solution to obtaining a new lead series with markedly enhanced histamine H_2-receptor antagonist and gastric acid antisecretory activities relied on series of bioisosteric prototypes designed to explore the structural relationship of the pseudosymmetrical biaryl pyridyltriazoles and imidazoles to structurally divergent histamine H_2-receptor agonists and antagonists (Figure 1).

Chemistry

New 4-substituted pyridines **3–5**, **7**, and **9** (Table I) were prepared by a variety of short, simple reaction sequences as described in the Experimental Section.

Derivatives in Table II, with the exception of **12**, whose synthesis has previously been published,[2] were prepared by reaction of precursor primary amines with methyl isothiocyanate to produce thioureas **13–16**, **21**, and **22** or in two steps by reaction with dimethyl cyanodithioimidocarbonate followed by reaction with methylamine to produce cyanoguanidines **17–20** and **23**. The amine precursor of triazole **11** (Table II) was prepared by a sequence starting with ethyl 2-cyanoisonicotinate (Scheme I) while that for triazoles **13** and **17** (Table II) was prepared by a sequence starting with 2-chloroisonicotinonitrile and hydantoic acid hydrazide (Scheme II). The amine precursors for triazole thioureas and cyanoguanidines **14–16** and **18–20** having two to four carbons in the alkyl chain separating the triazole and the alkyl chain primary amine terminus were prepared by reacting 2-(ethylamino)isonicotinic acid hydrazide with the imino ethers formed from ω-phthalimidoalkyl nitriles followed by deblocking with hydrazine hydrate (Scheme III).

These same imino ethers were used in the syntheses of imidazoles **21–23** (Scheme IV). Thus, condensation of these with 2-[2-(ethylamino)-4-pyridyl]-2,2-diethoxyethylamine,[3] followed by deprotection with hydrazine, afforded the requisite imidazole alkylamines. Conversion of these intermediates to **21–23** was achieved exactly as delineated for the analogous triazoles.

[[(Dimethylamino)methyl]furyl]triazole **24** (Table III) and the amine precursor to **25** (Table III) were prepared from 5-[(dimethylamino)methyl]-2-furoic acid hydrazide as depicted in Scheme V.

(Guanidinothiazolyl)triazoles **26** and **27** (Table IV) were prepared by triazole ring formation from precursor 2-guanidino-4-thiazolecarboxylic acid hydrazides as previously described (Scheme VI).[4] The sequence used to prepare (guanidinothiazolyl)imidazoles (**28–30**) involves an inversion in the order of formation of the aromatic rings from **26** and **27** in that the thiazole ring is formed after the imidazole ring is closed by a sequence involving reaction of amidinothiourea with precursor imidazolyl α-bromo ketones (Scheme VI).[4] A variety of routes to 4-acetylimidazole starting materials required for this sequence have been described.[5,6,7]

Results and Discussion

SAR Study Approach. The (aminopyridyl)aminotriazole histamine H_2-receptor antagonist 1 (Table I) has a pseudosymmetric structure,[2] and from simple inspection of the chemical structure it is not clear whether the triazole moiety in a receptor binding sense corresponds to the imidazole/triazole moieties of known histamine H_2-receptor agonists and antagonists such as histamine and cimetidine. Alternatively the aminopyridine might be more related to the heterocyclic "heads" of known agonists and antagonists and the aminotriazole might function as an ethylamine surrogate, possibly in a manner somewhat related to the side-chain guanidine moiety in the weak partial agonist guanidino histamine. By preparation of key prototype compounds, we attempted to discern the relationship of our biaryl antagonists to known agonists and antagonists, since we anticipated that insight in this area could lead to marked activity increases.

The histamine H_2-receptor antagonist literature is particularly rich in examples of the interchange of a structural moiety from one series to another, although with a considerable variation in the degree to which desirable SAR features are additive.[8] The cause of this variation

(1) Lipinski, C. A.; LaMattina, J. L.; Hohnke, L. A. *J. Med. Chem.* **1985**, *28*, 1628–1636.
(2) Lipinski, C. A. *J. Med. Chem.* **1983**, *26*, 1–6.
(3) LaMattina, J. L.; Suleske, R. T. *Org. Synth.* **1985**, *64*, 19–24.
(4) LaMattina, J. L.; Lipinski, C. A. U.S. Patent 4 374 843, 1983.
(5) LaMattina, J. L.; Mularski, C. J. *Tetrahedron Lett.* **1984**, *25*, 2957–2961.
(6) Lipinski, C. A.; Blizniak, T. E.; Craig, R. H. *J. Org. Chem.* **1984**, *49*, 566–570.
(7) Reiter, L. A. *J. Org. Chem.* **1984**, *49*, 3494–3498.
(8) Yanagisawa, I.; Mirata, Y.; Ishii, Y. *J. Med. Chem.* **1984**, *27*, 849–857 and references therein.

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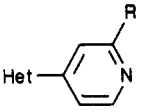
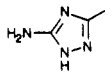
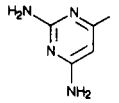
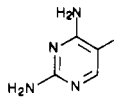
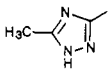
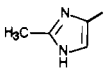
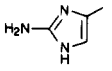
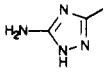
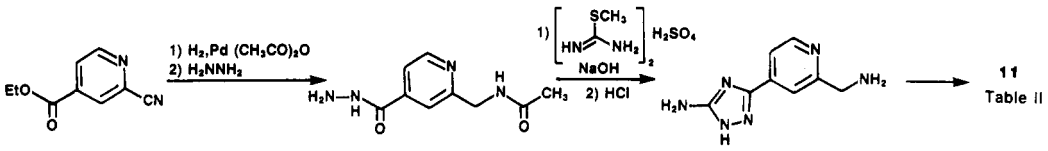
Table I. Prototype Probes: 4-Substituted Pyridines



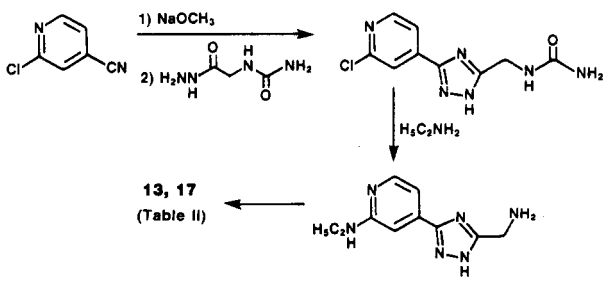
no.	Het	R	mp, °C	mol formula[a]	H_2-receptor antagonist act. (guinea pig atrium):[b] K_B, 10^{-6} M (±SD)	Schild plot slope[c]
1		NH_2	246–247	$C_7H_8N_6 \cdot H_2O$[d]	2.22 (±0.18)	0.91
2		H	228–230	$C_9H_9N_5$[e]	not active[f]	
3		H	338	$C_9H_9N_5$	not active[g]	
4		H	188–190	$C_9H_9N_3$	not active[f]	
5		H	234–236	$C_{10}H_8N_2O$	not active[f]	
6		H	207–209	$C_8H_8N_4$[h]	12.3 (±4.3)	0.81
7		H	152–153	$C_9H_9N_3$	36.2 (±10.6)	0.99
8		H	189–191	$C_8H_7N_3$[i]	194 (±80)	1.24
9		H	225 dec	$C_8H_8N_4 \cdot 2H_2O$	23.6 (±6.2)	1.09
10		H	279–281	$C_7H_7N_5$[d]	41.9 (±28.8)	1.22

[a] All compounds were analyzed for C, H, and N. [b] The dissociation constant (K_B) was calculated from the equation $K_B = B/(DR - 1)$, where DR is the respective ratio of concentrations of histamine needed to produce half maximal responses in the presence and absence of different concentrations (B) of antagonists. [c] Slope of the plot of log (DR − 1) on log B. [d] Reference 1. [e] Tani, H.; Nakamura, K.; Yokoo, N.; Kyotani, Y.; Akaishi, K. Japanese Patent 49/35633, 1974; *Chem. Abstr.* **1970**, *83*, 10127Z. [f] Highest dose tested 1×10^{-3} M. [g] Highest dose tested 2×10^{-4} M, increase in rate of contraction. [h] Uda, M.; Hisazumi, Y.; Sato, K.; Kubota, S. *Chem. Pharm. Bull.* **1976**, *24*, 3103–3108. [i] Schunack, W. *Arch. Pharm. (Weinheim, Ger.)* **1973**, *306*, 934–942.

Scheme I



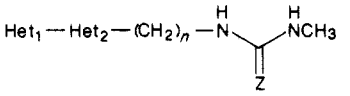
Scheme II

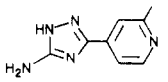
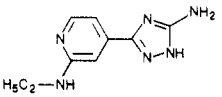
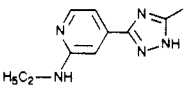
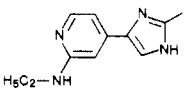


in SAR additivity among histamine H_2-receptor antagonists is not known, but the phenomenon is a commonly encountered problem. Because we were studying pseudosymmetric compounds, we focused on one of the few examples of binding of small pseudosymmetric substrates to a receptor protein. The X-ray literature[9] on binding of small inhibitors to thermolysin suggested to us that a remote parallel could be drawn to histamine H_2-antagonist SAR, and that the variability in SAR among some histamine H_2-receptor antagonists was possibly due to small structural changes in chemically similar series inducing marked changes in receptor binding and thus nonadditivity of SAR. We expected this problem to be particularly troublesome in the case of inhibitors having a pseudosymmetrical structure, and we anticipated that relating our biaryl series to other agonist/antagonist series might prove difficult. Thus a major focus of our chemistry was the preparation of multiple series of bioisosterically designed prototypes.[2]

(9) Holmes, M. A.; Mathews, B. W. *Biochemistry* **1981**, *20*, 6912–6920.

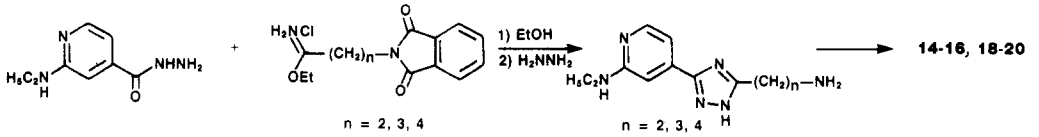
Table II. Prototype Probes: Thioamides and Cyanoguanidines



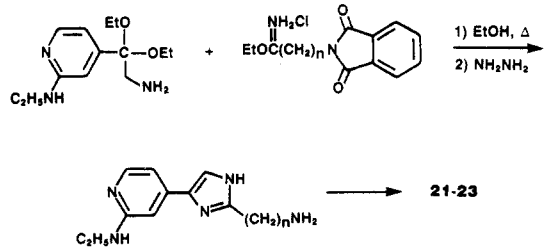
no.	Het_1–Het_2	n	Z	mp, °C	mol formula[a]	H_2-receptor antagonist act. (guinea pig atrium):[b] K_B, 10^{-6} M (±SD)	Schild plot slope[c]	acid antisecretory act.:[d] max % inhibn in dogs at (dose) iv
11		1	S	225–227	$C_{10}H_{13}N_7S$[e]	15.1 (±3.1)	0.87	19 (10)
12				275–278	$C_9H_{12}N_6 \cdot 2HCl \cdot H_2O$[f]	0.235 (±0.056)	1.00 (±0.10)	ED_{50} = 0.87 (r = 0.97, n = 2)
13		1	S	230–232	$C_{12}H_{17}N_7S \cdot HCl$[g]	2.33 (±0.32)	0.93	48 (10)
14	*l*	2	S	189–191	$C_{13}H_{19}N_7S$[h]	0.69 (±0.36)	1.16	59 (1)
15	*l*	3	S	107–110	$C_{14}H_{21}N_7S \cdot H_2O$[h]	3.84 (±1.18)	0.93	20 (1)
16	*l*	4	S	159–161	$C_{15}H_{23}N_7S$[h]	2.51 (±0.62)	1.15	27 (5)
17	*l*	1	NCN	279–280 dec	$C_{13}H_{17}N_9$[g]	0.68 (±0.34)	0.97	0 (10)
18	*l*	2	NCN	244–246	$C_{14}H_{19}N_9$[h]	1.24 (±0.36)	0.77	0 (7)
19	*l*	3	NCN	238–239	$C_{15}H_{21}N_9 \cdot {}^1/_2H_2O$[h]	not active[i]		
20	*l*	4	NCN	169–172	$C_{16}H_{23}N_9 \cdot {}^1/_4H_2O$[h]	3.16 (±0.44)	1.12	16 (10)
21		1	S	185–187	$C_{13}H_{18}N_6S$[j]	1.14 (±0.21)	1.03	54 (5)
22	*m*	2	S	183–185	$C_{14}H_{20}N_6S \cdot 2HCL \cdot {}^3/_2H_2O$[j]	0.55 (±0.15)	1.24	47 (5)
23	*m*	1	NCN	242–243	$C_{14}H_{18}N_8$[j]	0.46 (±0.21)	1.05	32 (5)
cimetidine[k]						0.63 (±0.36)	0.87 (±0.31) (n = 11)	ED_{50} = 1.02 (r = 0.97, n = 22)

[a] Footnote *a*, Table I. [b] Footnote *b*, Table I. [c] Footnote *c*, Table I. [d] Maximum percent inhibition of acid output in single experiments in pentagastrin-stimulated Heidenhain pouch dogs at a dose in milligrams per kilogram, given intravenously. [e] Prepared as in Scheme I. [f] Reference 1. [g] Prepared as in Scheme II. [h] Prepared as in Scheme III. [i] Highest dose tested 1×10^{-5} M. [j] Prepared as in Scheme IV. [k] Data based on comparative testing of compounds **1**, **12**, and cimetidine. Lipinski, C. A. *J. Med. Chem.* **1983**, *26*, 1–6. [l] Het_1–Het_2 same as in compound **13**. [m] Het_1–Het_2 same as in compound **21**.

Scheme III



Scheme IV



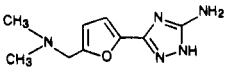
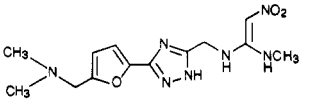
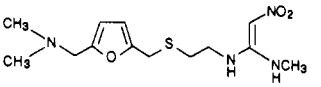
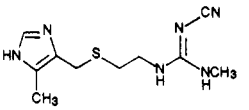
Our first three series of prototypes were prepared on the hypothesis that the triazole moiety was related to the imidazole rings of histamine and cimetidine and that the aminopyridine as in **1** and *N*-ethyl homologue **12** was a histamine side chain surrogate. To probe this hypothesis, we initially prepared the 6- and 5-(4-pyridyl)-2,4-diaminopyrimidines **2** and **3** (Table I) with the hope that the diaminopyrimidine (which has bidentate hydrogen bonding ability and is likely to exist in significant proportion in both neutral and protonated forms at physiological pH) might be an aminotriazole surrogate.[10]

A second series of prototypes (**4–10**) were prepared in which the aminotriazole ring was replaced by heterocyclic moieties that are found in cimetidine and related histamine H_2-receptor antagonists.

In a third prototype class, we directly probed the possibility that the aminopyridine was a histamine side chain surrogate, and in a manner related to the logic used to discover metiamide/cimetidine,[11] we prepared the prototype **11** (Table II). This compound is related to metiamide in that a 4-pyridyl-2-methylene moiety acts as a four-atom

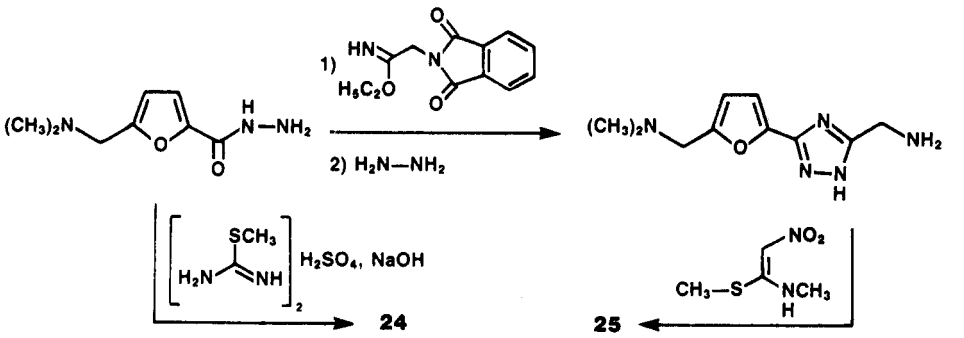
(10) Unpublished observations, Pfizer, Sandwich, UK. SK&F 11,197, 2,6-diamino-4-[(dimethylamino)ethoxy]pyridine, is comparable to histamine as an H_2-receptor agonist.
(11) Ganellin, R. *J. Med. Chem.* **1981**, *24*, 913–920.

Table III. Pyridine to Furan Transition

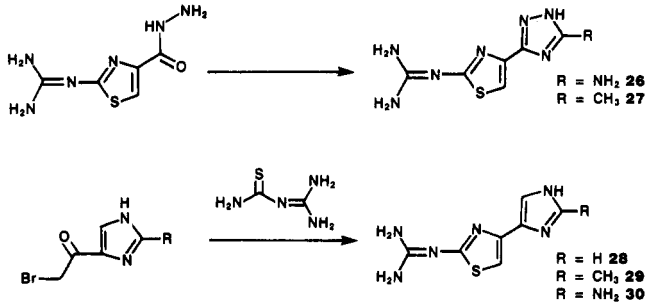
compound	structure	mp, °C	mol formula[a]	H_2-receptor antagonist act. (guinea pig atrium):[b] K_B, 10^{-6} M (±SD)	Schild plot slope[c]
24		220–222	$C_9H_{13}N_5O$[d]	6.40 (±3.38)	1.17
25		200–203	$C_{13}H_{19}N_7O_3$[d]	21.5 (±7.3)	0.77
ranitidine				0.166 (±0.075)[e]	0.90
cimetidine				0.63 (±0.36)[e,f]	0.87 (±0.31) (n = 11)

[a] Footnote *a*, Table I. [b] Footnote *b*, Table I. [c] Footnote *c*, Table I. [d] Prepared as in Scheme V. [e] Data based on comparative testing of ranitidine, cimetidine, and **29**, Table IV. [f] Footnote *k*, Table II.

Scheme V



Scheme VI



side-chain spacer between the aminotriazole ring and a thiourea group.

We considered also the alternate hypothesis, namely, that the pyridine might be more related to the imidazole moieties in histamine and cimetidine. Accordingly we prepared derivatives having a pyridine separated from a thiourea or cyanoguanidine by an atom sequence incorporating an imidazole or triazole plus an alkyl chain spacer. These derivatives include thioureas **13–16** (Table II) and corresponding cyanoguanidine derivatives **17–20** as well as the imidazole analogues **21–23** of triazole thioureas **13** and **14** and cyanoguanidine **17**. In these series, derivatives **13**, **21** and **17**, **23** correspond most closely to the structures of metiamide and cimetidine if the disubstituted triazole or imidazole ring is viewed as a three-atom spacer group.

Biological Results

Our first three series of prototypes tested the hypothesis that the triazole moiety was related to the imidazole rings of histamine and cimetidine and that the aminopyridine

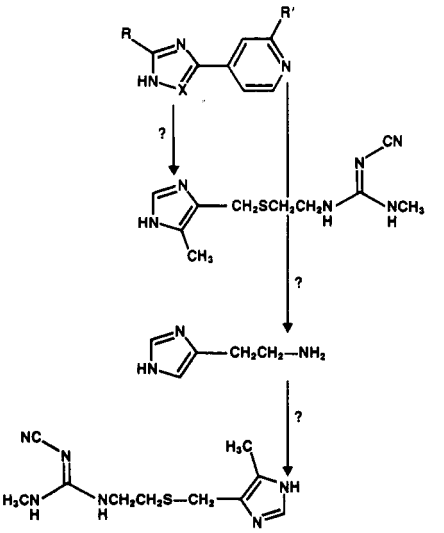


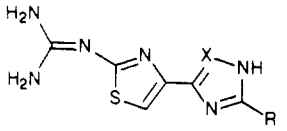
Figure 1.

was a histamine side chain surrogate.

Derivatives **2** and **3**, which tested the idea that 2,4-diaminopyrimidine appended to a 4-substituted pyridine might be an aminotriazole surrogate, were inactive. This suggests that the 2,4-diaminopyrimidine moiety, which is acceptable as a component of a histamine H_2-receptor agonist structure,[10] cannot function in this series as a triazole/imidazole replacement.

Derivatives **4–10** tested the idea that the aminotriazole was related to the imidazole of cimetidine. Thus, the aminotriazole ring was replaced by heterocyclic moieties that are found in cimetidine and related histamine H_2-receptor antagonists. The 5-(4-pyridyl)-4-methylimidazole

Table IV. Heteroarylguanidinothiazoles



no.	X	R	mp, °C	mol formula[a]	H_2-receptor antagonist act. (guinea pig atrium):[b] K_B, 10^{-6} M (±SD)	Schild plot slope[c]	acid antisecretory act.:[d] max % inhibn in dogs at (dose) iv
26	N	NH_2	193–195	$C_6H_8N_8S$[e]	0.128 (±0.042)	0.88	58 (1)
27	N	CH_3	272–274	$C_7H_9N_7S \cdot {}^1/_2H_2O$[e]	0.180 (±0.108)	0.98	50 (1)
28	CH	H	225 dec	$C_7H_8N_6S \cdot HBr \cdot H_2O$[e]	0.101 (±0.10)	1.11	95 (1)
29	CH	CH_3	330–332	$C_8H_{10}N_6S \cdot 2HCl$[e]	0.018 (±0.0096)	0.84	90 (0.5)[f]
30	CH	NH_2	267 dec	$C_7H_9H_7S$[e]	0.013 (±0.007)	1.19	96 (1)

[a] Reference *a*, Table I. [b] Reference *b*, Table I. [c] Reference *c*, Table I. [d] Reference *d*, Table II. [e] Prepared as in Scheme VI. [f] Data based on comparative testing of **29** (CP-57,361-1), ED_{50} = 0.27 mg/kg, given orally (r = 0.97, n = 16), and cimetidine, ED_{50} = 1.32 mg/kg, given orally (r = 0.94, n = 10) in pentagastrin-stimulated Heidenhain pouch dogs.

4 (Table I) having a cimetidine methylimidazole moiety and the 2-(4-pyridyl)-3-hydroxypyridine **5** (Table I) having the pyridine moiety found in a related histamine H_2-antagonist series[12] were prepared but, like previous derivatives **2** and **3**, proved inactive. Activity was, however, found in derivatives **6–10** (Table I), indicating that 3-methyltriazolyl, 2-methylimidazolyl, unsubstituted imidazolyl, and 2-aminoimidazolyl moieties as well as the 3-aminotriazolyl moiety as in **1** and **10** all led to activity when appended to a 4-pyridyl group. We concluded that results from these two series were ambiguous and did not definitively support or reject our initial hypothesis that the triazole moiety in **1** was related to the imidazole rings of histamine and cimetidine.

In a third prototype class, derivative **11** tested the idea that the aminopyridine was a histamine side chain surrogate. On testing, **11** (Table II), which is related to metiamide in that the 4-substituted pyridine acts as part of a side-chain spacer, proved weakly active. We concluded that this was also an ambiguous result since the level of activity was low and less than that found for **1** or **12**.

The alternate hypothesis, namely, that the pyridine might be more related to the imidazole moieties in histamine and cimetidine, was tested by derivatives having a pyridine separated from a thiourea or cyanoguanidine by an atom sequence incorporating an imidazole or triazole plus an alkyl chain spacer.

Triazolyl and imidazolyl thioureas **13** and **21** and cyanoguanidines **17** and **23** (Table II), which are most closely related to the structures of metiamide and cimetidine, have appreciable histamine H_2-receptor antagonist activity, and the best members in Table II are comparable to these agents with respect to in vitro activity but are slightly less active than the biaryl aminopyridyl aminotriazole **12**. Unlike the cases of metiamide, cimetidine, and **12**, the level of acid antisecretory activity is in general reduced. The best antisecretory activity is found in triazole thiourea **14**, which could be viewed as being related to the higher homologue of metiamide. Derivatives with one and two methylene spacer units are more active than those with three or four, suggesting that these compounds are not metiamide- or cimetidine-like compounds in which an imidazole has simply been replaced by a pyridyltriazole or pyridylimidazole. The pattern of better in vitro activity for both thiourea and cyanoguanidine derivatives having two methylene spacers over those with three and four supports the bioisosterism of thiourea and cyanoguanidine moieties,[13] although there are some puzzling deviations. In particular, we noted the inactivity of cyanoguanidine **19** relative to the related thiourea **15** and the good antisecretory activity of thiourea **14** as opposed to the inactivity of related cyanoguanidine **18**. Imidazoles **21–23** have in vitro and in vivo activities similar to those of related triazoles **13**, **14**, and **17**, supporting the bioisosterism in this series of imidazole and triazole moieties.

In summary, we conclude that an exact parallel cannot be drawn between thioamide and cyanoguanidine SAR in this series and that previously reported for metiamide and cimetidine.[11] We were struck, however, by one major point. Derivatives **13–23**, with the exception of the inactive **19**, were all more active at the histamine H_2 receptor than derivative **11**. This suggested to us that, since this series had been prepared on the hypothesis of a similarity between pyridine and imidazole moieties, we should further pursue the hypothesis that the pyridine moiety might be more related to the imidazole moieties in histamine and cimetidine even though an exact parallel was not evident between SAR in the two series.

A comparison of the structures of cimetidine and ranitidine suggests that the [(dimethylamino)methyl]furan as found in ranitidine may be an imidazole bioisostere, although SAR differences between the two series have been noted.[11,12] Since we wanted to explore the hypothesis that the pyridine is in some manner imidazole-like, we decided to replace a 4-substituted pyridyl moiety with a 5-[(dimethylamino)methyl]furan moiety. We thus prepared furan prototype **24** (Table III) in which the 2-furyl moiety is appended to an aminotriazole moiety. To our delight this prototype as well as the more ranitidine-like derivative **25** (Table III) proved weakly active. This result encouraged us further, and so we next prepared the guanidinothiazole derivative **26** (Figure 2 and Table IV) on the basis of the bioisosteric similarity of the [(dimethylamino)methyl]furan moiety as in ranitidine and the 4-substituted 2-guanidinothiazole moiety as in the histamine H_2-receptor antagonist tiotidine.[14] When tested, compound **26** displayed a marked improvement in activity both in vitro and in vivo over furan derivative **24** and, more importantly, over all members of previously prepared pyridine derivatives. Thus, the sequence of prototypes depicted in Tables I–III led to the bioisosteric prototype sequence depicted in Figure 2 and an 1800 times increase in histamine H_2-

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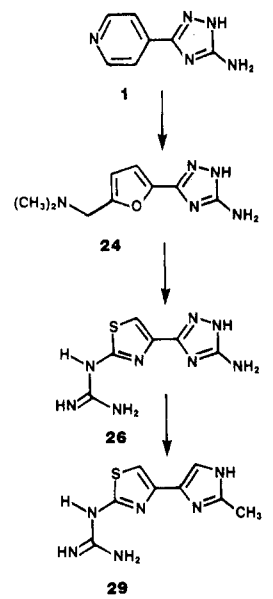

Figure 2. Sequence of bioisosteric replacement.

receptor antagonist activity.

At this point we used the information gained earlier from preparation of prototypes **6–10** (Table I), namely, that 3-methyltriazole, unsubstituted and 2-methylimidazole, and 2-aminoimidazole might function as aminotriazole bioisosteres. These moieties appended to a 2-guanidino-4-thiazolyl moiety were prepared (**27–30**) (Table IV). When tested it was clear that all these derivatives were very active and in particular that imidazoles **28–30** were more active both in vitro and in vivo than corresponding triazoles **26** and **27**. This is in contrast to the better activity of triazoles over imidazoles in a previous biaryl histamine H_2-receptor antagonist series.[1] In particular methylimidazole **29** displayed excellent competitive histamine H_2-receptor antagonist activity and marked gastric acid antisecretory activity combined with a long half-life in dogs.[16] This derivative (CP 57,361-1) is among the most potent competitive histamine H_2-receptor antagonists reported to date.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Analytical Department of Pfizer Inc., and analytical values were within ±0.4% of theoretical values unless otherwise noted. NMR and/or mass spectra were obtained on all compounds and were consistent with structures and assignments.

2,4-Diamino-5-(4-pyridyl)pyrimidine (3). To 20 mL of dimethylformamide dimethyl acetal was added 9.2 g (78 mmol) of 4-pyridylacetonitrile. An exotherm ensued and 24 mL of methanol was added. After 1 h at ambient temperature, the reaction mixture was concentrated in vacuo to a dark red solid. Reconcentration in vacuo of a methanol–ethyl acetate solution of this solid followed by a slurry in diethyl ether containing a small quantity of ethyl acetate gave 7.18 g (53%) of 3-(dimethylamino)-2-(4-pyridyl)acrylonitrile, mp 148–150 °C. Anal. ($C_{10}H_{11}N_3$) C, H, N.

To an ethanolic solution of sodium ethoxide (prepared by dissolving 494.9 mg (21.53 mmol) of sodium in 30 mL of ethanol) was added 1.714 g (17.94 mmol) of guanidine hydrochloride. The sodium chloride precipitate was removed by filtration, and to the clear mother liquor was added 3.006 g (17.36 mmol) of 3-(dimethylamino)-2-(4-pyridyl)acrylonitrile, and the reaction was heated at reflux. A precipitate soon began to form. After 2 h at reflux, the reaction was filtered while still hot to give 2.276 g (70%) of 2,4-diamino-5-(4-pyridyl)pyrimidine as a pale yellow solid, mp (by differential thermal analysis) 338 °C. Anal. ($C_9H_9N_5$) C, H, N.

4-(4-Pyridyl)-5-methylimidazole (4). Potassium (1.37 g, 35 mmol) was dissolved in 30 mL of absolute ethanol under a nitrogen atmosphere. To this solution was added a warm solution of 9.13 g (30 mmol) of 1-(4-pyridyl)propanone oxime tosylate[16] in 80 mL of absolute ethanol, and a precipitate immediately formed. After the mixture was stirred at room temperature under nitrogen for 1 h, 400 mL of ether was added and the precipitate was removed by filtration. The organic filtrate was extracted three times with a total of 100 mL of 2 N hydrochloric acid. The combined acid extracts were concentrated under reduced pressure, with care to keep the temperature below 40 °C. The resulting crude 2-amino-1-(4-pyridyl)propanone dihydrochloride was dissolved in 30 mL of water, and 3.10 g (30 mmol) of potassium thiocyanate was added. The mixture was heated on a steam bath for 1 h and then cooled in an ice bath. The resulting precipitate was collected and then treated with 40 mL of saturated sodium bicarbonate solution. The pale yellow solid was collected, washed well with water, and dried in vacuo to afford 3.92 g of 4-(4-pyridyl)-5-methyl-2-mercaptoimidazole, mp >270 °C. This material was slowly added to a hot solution of 30 mL of concentrated nitric acid in 120 mL of water. After addition was complete, the mixture was heated on a steam bath for 1 h. The mixture was cooled and then neutralized with solid sodium bicarbonate. The resulting precipitate was collected, washed well with water, and dried in vacuo. Recrystallization from water afforded 2.36 g (49%) of **4**, mp 196–198 °C. Anal. ($C_9H_9N_3$) H, N; C: calcd, 67.90; found, 67.20.

3-Hydroxy-2-(4-pyridyl)pyridine (5). A 0.48 M solution of *n*-butyllithium in hexane was concentrated in a nitrogen stream to a volume of 75 mL and was diluted with 454 g of diethyl ether. To this was added 36 mL (0.5 mol) of furan at a rate so as to maintain reflux. After an additional 3 h at reflux, the resulting yellow suspension was cooled to 23 °C and 50 g (0.48 mol) of 4-cyanopyridine was added as a solid over 15 min. Reflux occurred spontaneously, and a color change to red was observed. After 1.5 h of stirring, the dark brown reaction was poured onto ice and the pH was brought to 5.0 with concentrated hydrochloric acid. After being stirred for 1 h, the reaction mixture was successively extracted with 500 mL of diethyl ether followed by 3 × 500 mL of ethyl acetate. The combined organics were dried over anhydrous magnesium sulfate and concentrated in vacuo to a crude solid, which after sublimation at 23 °C (0.05 mmHg) gave 14.65 g (17.6%) of 2-furyl 4-pyridyl ketone, mp 79–81 °C.

To a solution of 30 mL of 28% ammonium hydroxide and 30 mL of methanol was added 3.46 g (0.02 mol) of 2-furyl 4-pyridyl ketone. Following heating at 155 °C in a pressure vessel for 3 h, the reaction contents were concentrated in vacuo and triturated with diethyl ether to give a crude solid, which was recrystallized from ethyl acetate–ethanol. The mother liquors were concentrated in vacuo to give 3-hydroxy-2-(4-pyridyl)pyridine as a light tan solid (1.12 g, 32%), mp 234–236 °C. The product was identified as the 3-hydroxy-2-(4-pyridyl)pyridine rather than the 2-pyrrolyl 4-pyridyl ketone product on the basis of the ^{13}C NMR spectrum, which did not show a low-field carbonyl resonance. ^{13}C NMR (Me_2SO-d_6): δ 123.0, 124.2, 125.0, 140.6, 140.9, 145.0, 149.4, 152.7. Anal. ($C_{10}H_8N_2O$) C, H, N.

4-(4-Pyridyl)-2-methylimidazole (7). 2,2-Diethoxy-2-(4-pyridyl)ethylamine[3] (6.3 g, 30 mmol) was dissolved in 100 mL of absolute ethanol, 3.7 g (30 mmol) of ethylacetimidate hydrochloride was added, and the mixture was heated at reflux for 2 h. The mixture was concentrated, and the residue was treated with 25 mL of concentrated hydrochloric acid and heated on a steam bath for 1 h. The mixture was again concentrated, the residue was dissolved in 30 mL of water, and the solution was made basic with potassium carbonate. The resulting precipitate was collected, washed well with water, and dried in vacuo. Recrystallization from acetone afforded 2.59 g (54%) of **7**, mp 152–153 °C. Anal. ($C_9H_9N_3$) C, H, N.

2-Amino-4-(4-pyridyl)imidazole (9). A mixture of 2-amino-1-(4-pyridyl)ethanone dihydrochloride[16] (4.4 g, 21 mmol),

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cyanamide (2.5 g, 60 mmol), and 25 mL of water was brought to pH 4.5 with 2 N sodium hydroxide solution and heated on a steam bath for 1 h. The mixture was cooled in an ice bath and made basic with concentrated ammonium hydroxide. The resulting precipitate was collected, washed well with water, and dried in vacuo. Recrystallization from absolute ethanol afforded 1.7 g (50%) of **9**, mp 225 °C dec.

Scheme I. *N*-[[4-(3-Amino-1,2,4-triazol-5-yl)-2-pyridyl]methyl]-*N'*-methylthiourea (11). A solution of 6.70 g (38.0 mmol) of ethyl 2-cyanoisonicotinate in 60 mL of acetic anhydride was hydrogenated (50 °C (47 psi)) over 1.06 g of palladium on carbon for 1.5 h. The mixture was filtered and concentrated in vacuo to give 8.0 g (95%) of ethyl 2-(acetylamino)isonicotinate as a brown oil.

This material was dissolved in 100 mL of ethanol and was heated for 5 h with 5.2 mL (107 mmol) of hydrazine hydrate. After remaining at 23 °C for 60 h, the orange reaction mixture was concentrated in vacuo to afford 7.5 g of 2-(acetylamino)isonicotinic acid hydrazide as an orange oil.

This material was added to a mixture of 10.0 g (71.9 mmol) of 5-methyl-2-thiopseudourea hemisulfate and 1.5 g (37.5 mmol) of sodium hydroxide in 80 mL of water. As the slurry was stirred at 23 °C, solution occurred. After 1 h the remaining solid was removed by filtration, and the clear orange solution was kept at 23 °C for an additional 20 h and then was concentrated in vacuo to an oily solid. Slurrying with ethanol removed inorganic salts, and the mother liquors were concentrated in vacuo to give 9.9 g of 2-(acetylamino)isonicotinic acid 2-amidinohydrazide as a yellow foam.

The foam (9.9 g, 34.58 mmol) was heated at 210 °C for 30 min. The foam melted and gas evolution was observed. On cooling to 23 °C the residue solidified. Chromatography on silica gel with 9:1 ethyl acetate–methanol as eluent gave 2.66 g of 2-[(acetylamino)methyl]-4-(3-amino-1,2,4-triazol-5-yl)pyridine, mp 215–218 °C. Anal. ($C_{10}H_{12}N_6O$) C, H, N.

A solution of 300 mg (1.2 mmol) of 2-[(acetylamino)methyl]-4-(3-amino-1,2,4-triazol-5-yl)pyridine in 30 mL of concentrated hydrochloric acid was heated at reflux for 30 min. After standing for 20 h at 23 °C, the cloudy solution was concentrated in vacuo to a crude yellow solid, which was triturated with ethyl acetate–methanol to remove insoluble material, and then the concentrated mother liquor residue was triturated again with ethyl acetate–methanol to give 111.8 mg of 2-(aminomethyl)-4-(3-amino-1,2,4-triazol-5-yl)pyridine dihydrochloride, mp 198–200 °C dec. MS, calcd for $C_8H_{10}N_6$ 109.0904, found 109.0934. Anal. ($C_8H_{10}N_6$·2HCl) C, H; N: calcd, 31.94; found, 30.97.

The crude product obtained from hydrolysis of 2.0 g (7.99 mmol) of 2-[(acetylamino)methyl]-4-(3-amino-1,2,4-triazol-5-yl)pyridine in 80 mL of concentrated hydrochloric acid was combined with 585 mg (8.0 mmol) of methyl isothiocyanate in 15 mL of water. Upon heating to reflux, the initial slurry changed to a clear yellow solution, which gradually turned greenish, and a precipitate began to form. After 1.5 h of reflux, the reaction mixture was cooled to 23 °C and stirred for 20 h. Filtration gave, after drying, 1.41 g (67%) of *N*-[[4-(3-amino-1,2,4-triazol-5-yl)-2-pyridyl]methyl]-*N'*-methylthiourea, mp 225–227 °C. MS calcd for $C_{10}H_{13}N_7S$ 263.0953, found 263.0968. Anal. ($C_{10}H_7N_7S$) C, H; N: calcd, 37.23; found, 36.53.

Scheme II. *N*-Methyl-*N'*-[[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]methyl]thiourea Hydrochloride (13). To 100 mL of sodium methoxide in methanol (from 150 mg (6.5 mmol) of sodium) was added 6.9 g (50 mmol) of 2-chloroisonicotinonitrile, and the reaction mixture was stirred at 23 °C for 1.5 h. Hydantoic acid hydrazide (6.6 g, 50 mmol) was added, and the reaction mixture was heated at reflux for 60 h. The resultant solid was collected by filtration and dried to give 7.6 g (53%) of *N*-(2-chloroisonicotinimidoyl)-*N'*-[(ureidomethyl)carbonyl]hydrazine hydrate, mp 196–197 °C (with effervescence).

N-(2-Chloroisonicotinimidoyl)-*N'*-[(ureidomethyl)carbonyl]-hydrazine hydrate (7.5 g, 25.98 mmol) was combined with 150 mL of 70% aqueous ethylamine and heated at 170 °C in a pressure vessel for 96 h. The reaction contents were cooled and concentrated in vacuo to an oily solid. Trituration with isopropyl alcohol gave a gray-white solid, which was treated with activated charcoal and recrystallized from isopropyl alcohol–methanol to give 0.87 g (13%) of 3-(aminomethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole hydrochloride, mp 220–223 °C. Anal. ($C_{10}H_{14}N_6$·HCl) N; C: calcd, 47.14; found, 47.63. H: calcd, 5.93; found, 5.28.

3-(Aminomethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole hydrochloride (500 mg, 1.96 mmol) was combined with 0.2 mL (2.92 mmol) of methyl isothiocyanate in 7 mL of water and heated at reflux for 3 h. The reaction mixture was concentrated in vacuo to a glassy solid, which was recrystallized from ethyl acetate–methanol to give 390 mg (59%) of *N*-methyl-*N'*-[[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]methyl]thiourea hydrochloride, mp (by differential thermal analysis) endotherm 232 °C. MS calcd for $C_{12}H_{17}N_7S$ 291.1266, found 291.1272. Anal. ($C_{12}H_{17}N_7S$·HCl) C, H, N.

***N*-Cyano-*N'*-[[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]methyl]-*N'*-methylguanidine (17).** 3-(Aminomethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole hydrochloride (2.0 g, 6.9 mmol) was combined with 949 mg (6.9 mmol) of anhydrous potassium carbonate in 20 mL of ethanol and 10 mL of water and the mixture was heated to 50 °C with a slow gas evolution. After 2 h all the potassium carbonate had dissolved. The reaction mixture was concentrated to a semisolid, which was triturated with water, and the resultant solid was collected by filtration and recrystallized from isopropyl alcohol–water to give, after drying, *N*-cyano-*N'*-[[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]-methyl]-*S*-methylisothiourea, mp 214–216 °C.

N-Cyano-*N'*-[[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]-methyl]-*S*-methylisothiourea (1.132 g, 3.2 mmol) was combined with 25 mL of 40% aqueous methylamine at 50 °C for 3 h. The reaction mixture was concentrated in vacuo to a solid, which was recrystallized from dimethylformamide–water to give 400 mg (42%) of *N*-cyano-*N'*-[[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]methyl]-*N'*-methylguanidine, mp 279–280 °C dec. MS calcd for $C_{13}H_{17}N_9$ 299.1607, found 299.1626. Anal. ($C_{13}H_{17}N_9$) C, H; N: calcd, 42.11; found, 41.65.

Scheme III. *N*-[2-[3-[2-(Ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]ethyl]-*N'*-methylthiourea (14). Ethyl 3-phthalimidopropionimidate hydrochloride (18.7 g, 66.1 mmol), prepared from 14.0 g (70 mmol) of 3-phthalimidopropionitrile, was combined with 66.2 mmol of sodium ethoxide (from 1.52 g of sodium) in 225 mL of ethanol. The slurry was stirred for 15 min and then filtered. To the clear filtrate was added 12.5 g (69.3 mmol) of 2-(ethylamino)isonicotinic acid hydrazide, and the reaction mixture was heated at reflux for 16 h and filtered while still warm. The precipitate was slurried in water, collected by filtration, and dried to give 12.4 g (52%) of 3-(2-phthalimidoethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole, mp 254–256 °C.

This product (11.85 g, 32.7 mmol) was combined with 2.4 mL (49.05 mmol) of hydrazine hydrate in 200 mL of ethanol and warmed on the steam bath for 2 h. The reaction mixture changed from a slurry to near solution and back to a slurry during this period. The reaction mixture was cooled and filtered, and the filtrate was concentrated in vacuo to a crude solid. This was slurried in water, and hydrochloric acid was added until the pH was stable at 3. The slurry was filtered, and the filtrate was concentrated in vacuo to a yellow solid, which was recrystallized from methanol to give 3.46 g (34.7%) of 3-(2-aminoethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole dihydrochloride, mp 260–261 °C dec. Anal. ($C_{11}H_{16}N_6$·2HCl) C, H, N.

3-(2-Aminoethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole dihydrochloride (0.806 g, 2.6 mmol) was combined with 0.22 g (3.0 mmol) of methyl isothiocyanate in 30 mL of water and was heated at reflux for 18 h. On cooling, a solid formed and was collected by filtration and recrystallized from water to give 0.3 g (39%) of *N*-[2-[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]ethyl]-*N'*-methylthiourea, mp 189–191 °C. Anal. ($C_{13}H_{19}N_7S$) C, H, N.

***N*-Cyano-*N'*-[2-[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]ethyl]-*N'*-methylguanidine (18).** A mixture of 829 mg (6.0 mmol) of anhydrous potassium carbonate and 1.83 g (6.0 mmol) of 3-(2-aminoethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole dihydrochloride in 55 mL of 70% aqueous ethanol was stirred for 20 min at 23 °C. Dimethyl cyanodithiocarbonate (0.973 g, 6.6 mmol) was added, and the reaction mixture was stirred at 23 °C for 36 h at which point a precipitate began to form. After a total reaction time of 48 h, the precipitate was collected by filtration to give, after drying, 1.24 g (63%) of *N*-cyano-*N'*-[2-[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]ethyl]-*S*-methyl-

isothiourea, mp 165–166 °C dec. Anal. ($C_{14}H_{18}N_8S$) C, H, N.

N-Cyano-*N'*-[2-[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]ethyl]-*S*-methylisothiourea (1.03 g, 3.1 mmol) was combined with 30 mL of 40% aqueous methylamine for 4 h at 23 °C. Concentration in vacuo gave a crude solid, which was recrystallized from dimethylformamide–water to give 557 mg (57%) of *N*-cyano-*N'*-[2-[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]-ethyl]-*N'*-methylguanidine, mp 244–246 °C. Anal. ($C_{14}H_{19}N_9$) C, H, N.

Scheme IV. 2-(Aminomethyl)-4-[2-(ethylamino)-4-pyridyl]imidazole (Precursor to 21 and 23). A mixture of 2-[2-(ethylamino)-4-pyridyl]-2,2-diethoxyethylamine[17] (14.1 g, 56 mmol), ethyl α-phthalimidoacetimidate hydrochloride (15 g, 56 mmol), and 20 mL of absolute ethanol was heated at reflux for 4 h, after which time another 3 g of the imidate was added and heating continued for 2 h. The mixture was concentrated, and the residue was taken up into 100 mL of 6 N hydrochloric acid. The mixture was heated on a steam bath for 1.5 h, cooled, and made basic with sodium carbonate. The aqueous mixture was extracted three times with a total of 300 mL of chloroform. The combined extracts were dried over sodium sulfate, filtered, and evaporated. The oil residue was chromatographed over 300 g of silica gel with use of 19:1 chloroform–methanol as eluent to give 4.5 g of 4-[2-(ethylamino)-4-pyridyl]-2-(phthalimidomethyl)-imidazole. This material could be further purified from acetonitrile to afford 3.2 g (17%) of a pale yellow solid, mp 125–128 °C. This material was dissolved in 25 mL of absolute ethanol, 0.6 g of hydrazine hydrate was added, and the mixture was heated at reflux for 20 h. The mixture was cooled, the insolubles were removed by filtration, and the filtrate was concentrated, leaving a foam. Recrystallization from acetonitrile afforded 1.62 g (81%) of the title compound as a white solid, mp 151–154 °C. Anal. ($C_{11}H_{15}N_5$) C, H, N. With use of the procedures described for the analogous triazoles, this amine was converted to **21** and **23**. In addition, this general procedure was also used to prepare 2-(2-aminoethyl)-4-[2-(ethylamino)-4-pyridyl]imidazole, the precursor to **22**.

Scheme V. 3-Amino-5-[5-[(dimethylamino)methyl]-2-furyl]-1,2,4-triazole (24). Ethyl 2-furoate (210 g, 1.5 mol), 45 g (1.5 mol) of paraformaldehyde, 405.5 g (1.5 mol) of ferric chloride hexahydrate, and 213 g (1.5 mol) of sodium sulfate were finely ground in a mortar and pestle and were slurried in 500 mL of chloroform with an efficient mechanical stirrer for 1 h. Hydrogen chloride gas was slowly introduced into the well-stirred reaction mixture over 2 h. The temperature rose to 50 °C and then declined. The temperature was kept at 58 °C for an additional 1.5 h while addition of hydrogen chloride continued. The black chloroform solution was decanted from the gummy inorganic residue, which was repeatedly stirred with small portions of chloroform. The combined chloroform extracts were washed with 2 × 500 mL of water, 250 mL of saturated sodium bicarbonate, and 250 mL of brine and were dried over anhydrous magnesium sulfate and concentrated in vacuo to a black oil. Attempted distillation at 0.5 mmHg gave 22.0 g of pale yellow oil containing crude product and ethyl furoate before the pot residue polymerized.

Crude 5-(chloromethyl)-2-furoic acid ethyl ester (22.0 g) was dissolved in 150 mL of ethanol, and dimethylamine gas was bubbled in while the reaction mixture was warmed at 45 °C for 1 h. The reaction mixture was concentrated in vacuo to an oil, which was taken up in 1 N hydrochloric acid and was extracted with chloroform. The aqueous pH was brought to 7 and was extracted with chloroform and then was brought to 11 and then extracted with chloroform. The latter chloroform extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to give crude ethyl 5-[(dimethylamino)methyl]-2-furoate (21.2 g) as an orange oil.

Crude ethyl 5-[(dimethylamino)methyl]-2-furoate (19.7 g, 0.1 mol) was combined with 5.35 mL (0.11 mol) of hydrazine hydrate in 100 mL of ethanol and heated at reflux for 1 h. An additional 5.35 mL of hydrazine hydrate was added, and refluxing was continued for 20 h. The reaction mixture was concentrated in vacuo to a wet solid, which on trituration with ethyl acetate gave 5.5 g (30%) of 5-[(dimethylamino)methyl]-2-furoic acid hydrazide, mp 122–124 °C. Anal. ($C_8H_{13}N_3O_2$) C, H, N.

5-[(Dimethylamino)methyl]-2-furoic acid hydrazide (5.49 g, 30 mmol) was combined with 1.2 g (30 mmol) of sodium hydroxide and 4.17 g (30 mmol) of *S*-methylisothiouronium hemisulfate in 100 mL of water and was stirred for 20 h at 23 °C. During this time a precipitate formed. The reaction mixture was stirred at 23 °C for an additional 48 h, and 1.0 g of additional *S*-methylisothiouronium hemisulfate was added. After an additional 24 h at 23 °C, the precipitate was collected by filtration and dried to give 4.0 g of material. This material (3.0 g) was thermally cyclized by warming to 225 °C for 30 min. On cooling, the solidified melt was triturated with water, and the resultant solid was collected by filtration, dried, and chromatographed on silica gel with use of a 5% to 20% methanol–chloroform gradient as eluent to give 911 mg of 3-amino-5-[5-[(dimethylamino)methyl]-2-furyl]-1,2,4-triazole, mp 220–222 °C. MS Calcd for $C_9H_{13}N_5O$ 207.1120, found 207.1106. Anal. ($C_9H_{13}N_5O$) H, N; C: calcd, 52.16; found, 51.67.

***N*-[[3-[5-[(Dimethylamino)methyl]-2-furyl]-1,2,4-triazol-5-yl]methyl]-*N'*-methyl-2-nitro-1,1-ethanediamine (25).** To an ethanolic solution of sodium ethoxide (prepared by dissolving 2.01 g (87.5 mmol) of sodium in 100 mL of ethanol) was added 23.5 g (87.5 mmol) of ethyl 2-phthalimidoethanimidate hydrochloride (prepared from 18.6 g (100 mmol) of 2-phthalimidoacetonitrile) in 50 mL of ethanol. The reaction mixture was heated at reflux for 2 h and concentrated in vacuo to a crude solid, which was triturated with 300 mL of ethyl acetate. The solid was collected by filtration and dried to give 51.6 g of solid. This was taken up in 500 mL of chloroform and filtered to remove sodium chloride. The mother liquors were concentrated in vacuo to a soft solid, which was triturated with diethyl ether and dried to give 15.8 g (64%) of crude *N*-(2-phthalimidoethanimidoyl)-*N'*-[5-[(dimethylamino)methyl]-2-furyl]hydrazine hemihydrate. Recrystallization from isopropyl alcohol gave 10.2 g, mp (by differential thermal analysis) endotherms 112 °C, 185 °C, 197 °C. Anal. ($C_{18}H_{19}N_5O_4 \cdot {}^1/_2H_2O$) C, H, N.

N-(2-Phthalimidoethanimidoyl)-*N'*-[5-[(dimethylamino)-methyl]-2-furyl]hydrazine hemihydrate (10.0 g, 27 mmol) was warmed neat in an oil bath at 195 °C for 10 min. After bubbling stopped, the reaction mixture was cooled and the solidified melt was taken up in methanol and treated with activated charcoal and was concentrated in vacuo to a viscous gum, which on trituration with ether isopropyl alcohol gave a tan solid. This was collected by filtration and was slurried in diethyl ether containing a small quantity of ethanol, and the resulting solid, which gummed readily in air, was collected by filtration under nitrogen to give crude 3-(phthalimidomethyl)-5-[5-[(dimethylamino)methyl]-2-furyl]-1,2,4-triazole, mp 138–141 °C. An analytical sample was prepared by chromatography on silica gel with use of 9:1 chloroform–methanol as eluent followed by crystallization from isopropyl alcohol to give pure 3-(phthalimidomethyl)-5-[5-[(dimethylamino)methyl]-2-furyl]-1,2,4-triazole, mp 167–168 °C. Anal. ($C_{18}H_{17}N_5O_3$) C, H, N.

3-(Phthalimidomethyl)-5-[5-[(dimethylamino)methyl]-2-furyl]-1,2,4-triazole (5.5 g, 15.65 mmol) was combined with 1.52 mL (31.3 mmol) of hydrazine hydrate in 70 mL of ethanol and stirred at 23 °C for 30 min and then was heated at reflux for 1.5 h during which time a precipitate formed. After the mixture was allowed to stand at 23 °C for 18 h, the solid was removed by filtration and the mother liquors were concentrated in vacuo to a red gum, which was taken up in 70 mL of 1 N hydrochloric acid and filtered. The aqueous solution was extracted with 2 × 30 mL of chloroform, and then the aqueous solution was concentrated in vacuo to a solid foam. Sequential solution in methanol, ethanol, and ethanol–isopropyl alcohol followed each time by concentration in vacuo gave a crude solid, which was dissolved in refluxing ethanol containing a small amount of methanol. Filtration from undissolved tarry material and concentration in vacuo gave a tan solid, which on trituration with diethyl ether–ethanol gave a hygroscopic crystalline light tan solid. Drying under a high vacuum at 80 °C gave 4.0 g (87%) of 3-(aminomethyl)-5-[5-[(dimethylamino)-methyl]-2-furyl]-1,2,4-triazole dihydrochloride, mp 170–180 °C.

3-(Aminomethyl)-5-[5-[(dimethylamino)methyl]-2-furyl]-1,2,4-triazole dihydrochloride (4.0 g, 13.6 mmol) was combined

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with 2.015 g (13.6 mmol) of *N*-methyl-1-(methylthio)-2-nitroethenamine and 1.88 g (13.6 mmol) of anhydrous potassium carbonate in 100 mL of 80% aqueous ethanol and was heated at reflux for 19 h. The reaction mixture was concentrated in vacuo to a gummy solid and was taken up in methanol and concentrated in vacuo to remove water. The residue was dissolved in methanol, filtered, and concentrated to give 5.6 g of solid foam. Chromatography on silica gel with use of 9:1 chloroform–methanol as eluent gave 485 mg (11%) of crude *N*-[[3-[5-[(dimethylamino)-methyl]-2-furyl]-1,2,4-triazol-5-yl]methyl]-*N'*-methyl-2-nitro-1,1-ethenediamine, mp 185–190 °C. An analytical sample was recrystallized from methanol–isopropyl alcohol, mp 200–203 °C. Anal. ($C_{13}H_{19}N_7O_3$) C, H, N.

Scheme VI. 2-Guanidino-4-(3-amino-1,2,4-triazol-5-yl)-thiazole (26). 2-Amidinothiourea (111.2 g, 0.94 mol) was dissolved in 1 L of refluxing ethanol. To the refluxing solution was rapidly added over a 10-min period 200 g (1.02 mol) of ethyl bromopyruvate. After 2 h of refluxing, an additional 20 g (0.1 mol) of ethyl bromopyruvate was added, and refluxing was continued for an additional 2 h. The reaction mixture was cooled to 10 °C, and concentrated ammonium hydroxide solution was added to raise the pH to 10. A solid formed and was collected by filtration, washed twice with ether, and dried in vacuo to give 176.4 g (88%) of 2-guanidino-4-thiazolecarboxylic acid ethyl ester, mp 229–230 °C dec. Anal. ($C_7H_{10}N_4O_2S$) C, H, N.

2-Guanidino-4-thiazolecarboxylic acid ethyl ester (16.7 g, 0.0779 mol) was combined with 25 mL (0.514 mol) of hydrazine hydrate in 200 mL of absolute ethanol. The slurry was heated to reflux. After 1.5 h of refluxing, a solid began to form from the clear solution. After 2 h of refluxing, the reaction slurry was cooled, and the resulting solid was collected by filtration and washed with isopropyl alcohol and ether to give 12.8 g (82%) of 2-guanidino-4-thiazolecarboxylic acid hydrazide, mp 247 °C dec. Anal. ($C_5H_8N_6OS$) C, H, N.

2-Guanidino-4-thiazolecarboxylic acid hydrazide (17.9 g, 0.089 mol) was combined with 24.9 g of 2-methyl-2-thiopseudourea sulfate (0.089 mol) and heated rapidly to reflux in 125 mL of dimethyl sulfoxide. The reactants dissolved, and within 5 min of refluxing a heavy precipitate formed. Refluxing was continued for a total of 30 min. The reaction mixture was cooled, and the resulting heavy precipitate was isolated by filtration and washed with a small portion of dimethyl sulfoxide followed by washing with isopropyl alcohol and ether. The resulting solid was dried in vacuo to give 34.6 g of 2-guanidino-4-thiazolecarboxylic acid 2-amidinohydrazide hemisulfate.

2-Guanidino-4-thiazolecarboxylic acid 2-amidinohydrazide hemisulfate (29.1 g, 0.1 mol) was heated to boiling with 250 mL of concentrated ammonium hydroxide. Additional ammonium hydroxide was added to replace the volume lost due to loss of ammonia. After 8 h of heating, boiling was continued until the pH was below 8.0, and the mixture was allowed to cool. The resulting solid was collected by filtration, washed with a small portion of water, decolorized with charcoal, recrystallized from water, and dried in vacuo to give 10.8 g (48%) of 2-guanidino-4-(3-amino-1,2,4-triazol-5-yl)thiazole, mp 173–175 °C. Anal. ($C_6H_8N_8S$) C, H, N.

2-Guanidino-4-(4-imidazolyl)thiazole Hydrobromide Hydrate (28). A solution of 0.50 g (4.5 mmol) of 4-acetylimidazole[18] in 10 mL of methanol was stirred at room temperature, and 10 drops of 48% hydrogen bromide was added. After the mixture was stirred at room temperature for 15 min, 50 mL of absolute ether was added, and the resulting precipitate was collected by filtration and dried to give 0.54 g of the hydrobromide salt, mp 214 °C dec. This was dissolved in 10 mL of 48% hydrogen bromide and warmed to 60 °C, and 0.15 mL (3.0 mmol) of bromine was added. After stirring at 60 °C for 1 h, the mixture was concentrated and the residue triturated with a mixture of isopropyl alcohol/ether. The white crystalline precipitate was filtered, washed with ether, and dried to give 0.42 g (35%) of 2-bromo-1-(4-imidazolyl)ethanone hydrobromide, mp 188–192 °C.

A mixture of 0.38 g (1.4 mmol) of 2-bromo-1-(4-imidazolyl)-ethanone hydrobromide in 10 mL of acetone was warmed until homogeneous, then 0.17 g (1.4 mmol) of amidinothiourea was added, and the mixture was heated at reflux for 0.5 h. The mixture was cooled, and the white precipitate was collected, washed with ether, and dried, thereby affording 0.24 g (60%) of **28**, mp 225 °C dec.

With use of this same procedure,[7] 5-acetyl-2-aminoimidazole[5] was converted into **30**.

2-Methyl-4-(2-guanidino-4-thiazolyl)imidazole (29). 1-(2-Methyl-4-imidazolyl)ethanone (2.40 g, 19.3 mmol) was dissolved in 30 mL of 48% hydrogen bromide. To the stirred solution at 25 °C was added over a 5-min period 3.36 g (21 mmol) of bromine dissolved in 5 mL of 48% hydrogen bromide. The reaction mixture was heated at 70 °C for 2.5 h and then concentrated in vacuo to a dark oil. A mixture of isopropyl alcohol/diethyl ether was added, and trituration of the oil gave a solid. This was collected by filtration and washed with diethyl ether to give 2.8 g (51%) of 1-(2-methyl-4-imidazolyl)-2-bromoethanone hydrobromide, mp 181 °C.

1-(2-Methyl-4-imidazolyl)-2-bromoethanone hydrobromide (2.8 g, 9.86 mmol) was dissolved in 10 mL of water. Saturated sodium bicarbonate solution was added until the pH was 10, and the resultant solid was collected by filtration and washed with 15 mL of water. The dried free base was heated at reflux in 50 mL of acetone. To the refluxing clear acetone solution was added 1.2 g (9.86 mmol) of amidinothiourea. Solution occurred immediately, and within 1 min a solid began to form. After 1 h of refluxing, the slurry was cooled and the solid was collected by filtration and washed with acetone followed by diethyl ether to give 2.37 g (79%) of 2-guanidino-4-(2-methyl-4-imidazolyl)thiazole hydrobromide, mp 158 °C dec. Anal. ($C_8H_{10}N_6S$·HBr) C, H, N. The free base isolated as a precipitate from a pH 9 aqueous solution of the dihydrobromide salt was converted to the dihydrochloride with concentrated hydrochloric acid, mp by differential thermal analysis 332 °C. Anal. ($C_8H_{10}N_6S$·2HCl) C, H, N.

Histamine H_2-Antagonist Activity. The procedure is a modification of that described by Black.[19] Guinea pigs were killed rapidly with a blow to the head, the hearts were removed, and the right atria were dissected free. Atria were suspended, isometrically, in a temperature-controlled (32 ± 2 °C) tissue bath (10 mL) containing oxygenated (95% O_2/5% CO_2) Krebs–Henseleit buffer (pH 7.4) and allowed to stabilize for approximately 1 h, during which time the tissue bath was flushed several times. Individual atrial contractions were followed with a force-displacement transducer connected to a cardiotachometer and Grass polygraph recorder. After a dose–response curve to histamine was obtained, the bath containing each atrium was flushed several times with fresh buffer, and the atria were reequilibrated to basal rates. Following the return to basal rate, test compounds were added at selected final concentrations, and the histamine dose–response curve was again determined in the presence of antagonist. Dose ratios (DR) were calculated as the ratio of histamine concentrations required to produce one-half of maximal stimulation in the presence and absence of antagonist concentration, *B*. The arithmetic means plus or minus standard deviation of the Schild plots in *n* atria of log (DR−1) vs. log *B* were not significantly different from unity. Compounds **1–25**, like cimetidine, equilibrated rapidly with the atria within a 3-min time period. Compounds **26–30** were tested with use of 30-min equilibration times since previous work had shown that 3-min equilibration times with some derivatives led to non-unit Schild plot slopes due to insufficient time for drug equilibration.[2]

Gastric Acid Antisecretory Activity. Compounds were tested for their ability to inhibit gastric acid secretion in fasted unanesthetized Heidenhain pouch dogs. Animals were first administered pentagastrin in order to stimulate acid output by continuous infusion of drug into a superficial leg vein at doses earlier determined to stimulate near-maximal acid output from the gastric pouch. Gastric juice was then collected at 30-min intervals following the start of a pentagastrin infusion, and volume was measured to the nearest one-tenth of a milliliter (0.1 mL). Ten collections were taken for each dog during an experiment. Acid concentration was determined by titrating 0.1 mL of gastric

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juice to a pH value of 7.4 with 0.1 N aqueous sodium hydroxide, with use of an Autoburette and a glass electrode pH meter (Radiometer). Animals were administered the test compounds at a specified dose in milligrams per kilogram, or the control vehicle alone, via the intravenous route of administration, at 90 min following the start of the pentagastrin infusion. Gastric antisecretory effects were calculated by comparing the lowest acid output after drug administration with the mean acid output immediately prior to drug administration. The results obtained in this manner were expressed in terms of percent inhibition. The doses required for 50% inhibition (ID_{50}) for **12**, **29**, and cimetidine were calculated from the linear regression of log dose on percent inhibition in *n* dogs. The mean percent inhibition in pentagastrin-stimulated dogs given 1 mg/kg iv of cimetidine was 46% ± 11%.

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Registry No. **1**, 77314-75-1; **2**, 53345-17-8; **3**, 103851-71-4; **4**, 103851-72-5; **5**, 103851-73-6; **6**, 57980-40-2; **7**, 98087-94-6; **8**, 51746-87-3; **9**, 103851-74-7; **10**, 3652-17-3; **11**, 103851-75-8; **12**, 77314-77-3; **12**·2HCl, 83417-28-1; **13**, 103851-76-9; **13**·HCl, 86649-51-6; **14**, 103851-77-0; **15**, 103851-78-1; **16**, 103851-79-2; **17**, 103851-80-5; **18**, 86649-50-5; **19**, 103851-81-6; **20**, 103851-82-7; **21**, 103851-83-8; **22**, 103851-84-9; **22**·2HCl, 103851-88-3; **23**, 103851-85-0; **24**, 103851-86-1; **25**, 103851-87-2; **26**, 82982-30-7; **27**, 82982-32-9; **28**, 82982-50-1; **28**·HBr, 82982-49-8; **29**, 85604-00-8; **29**·2HCl, 90274-23-0; **30**, 82982-39-6; $(CH_3)_2NCH(OCH_3)_2$, 4637-24-5; 4-pyridylacetonitrile, 13121-99-8; 3-(dimethylamino)-2-(4-pyridyl)acrylonitrile, 103851-89-4; 1-(4-pyridyl)propanone oxime tosylate, 74209-53-3; 2-amino-1-(4-pyridyl)propanone dihydrochloride, 98377-52-7; 4-(4-pyridyl)-5-methyl-2-mercaptoimidazole, 103851-90-7; furan, 110-00-9; 4-cyanopyridine, 100-48-1; 2-furyl 4-pyridyl ketone, 103851-91-8; 2,2-diethoxy-2-(4-pyridyl)ethylamine, 74209-44-2; ethylacetimidate hydrochloride, 2208-07-3; 2-amino-1-(4-pyridyl)ethanone dihydrochloride, 51746-83-9; cyanamide, 420-04-2; ethyl 2-cyanoisonicotinate, 58481-14-4; ethyl 2-[(acetylamino)methyl]isonicotinate, 58481-15-5; 2-[(acetylamino)methyl]isonicotinic acid hydrazide, 58481-03-1; *S*-methyl-2-thiopseudourea hemisulfate, 867-44-7; 2-[(acetylamino)methyl]isonicotinic acid 2-amidinohydrazide, 103851-92-9; 2-[(acetylamino)methyl]-4-(3-amino-1,2,4-triazol-5-yl)pyridine, 103851-93-0; 2-(aminomethyl)-4-(3-amino-1,2,4-triazol-5-yl)pyridine dihydrochloride, 103851-94-1; methyl isothiocyanate, 556-61-6; 2-chloroisonicotinonitrile, 33252-30-1; hydantoic acid hydrazide, 64616-77-9; *N*-(2-chloroisonicotinimidoyl)-N^1-[(ureidomethyl)carbonyl]hydrazine, 103851-95-2; ethylamine, 75-04-7; 3-(aminomethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole hydrochloride, 86649-64-1; *N*-cyano-N^1-[[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazolyl]-5-methyl]-*S*-methylisothiourea, 103851-96-3; methylamine, 74-89-5; ethyl 3-phthalimidopropionimidate hydrochloride, 22193-18-6; 2-(ethylamino)isonicotinic acid hydrazide, 77314-47-7; 3-(2-phthalimidoethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole, 86649-20-9; 3-(2-aminoethyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole dihydrochloride, 86649-21-0; dimethyl cyanodithioimidocarbonate, 71431-34-0; *N*-cyano-N^1-[2-[3-[2-(ethylamino)-4-pyridyl]-1,2,4-triazol-5-yl]ethyl]-*S*-methylisothiourea, 86649-62-9; 2-[2-(ethylamino)-4-pyridyl]-2,2-diethoxyethylamine, 80882-63-9; ethyl-α-phthalimidoacetimidate hydrochloride, 3644-69-7; 4-[2-(ethylamino)-4-pyridyl]-2-(phthalimidomethyl)imidazole, 103851-97-4; 2-(aminomethyl)-4-[2-(ethylamino)-4-pyridyl]imidazole, 103851-98-5; 2-(aminoethyl)-4-[2-(ethylamino)-4-pyridyl]imidazole, 103851-99-6; ethyl 2-furoate, 614-99-3; 5-(chloromethyl)-2-furoic acid ethyl ester, 2528-00-9; ethylamine, 75-04-7; ethyl 5-[(dimethylamino)methyl]-2-furoate, 100132-45-4; 5-[(dimethylamino)methyl]-2-furoic acid hydrazide, 103852-00-2; *N*-(2-phthalimidoethanimidoyl)-N^1-[[(5-dimethylamino)methyl]-2-furyl]hydrazine, 103852-01-3; 3-(phthalimidomethyl)-5-[(5-dimethylamino)-methyl-2-furyl]-1,2,4-triazole, 103852-02-4; 3-(aminomethyl)-5-[[(5-dimethylamino)methyl]-2-furyl]-1,2,4-triazole dihydrochloride, 103852-03-5; *N*-methyl-1-(methylthio)-2-nitroethenamine, 61832-41-5; 2-amidinothiourea, 26365-08-2; ethyl bromopyruvate, 70-23-5; 2-guanidino-4-thiazolecarboxylic acid ethyl ester, 82982-26-1; 2-guanidino-4-thiazolecarboxylic acid hydrazide, 82982-27-2; 2-guanidino-4-thiazolecarboxylic acid 2-amidinohydrazine hemisulfate, 103852-05-7; 4-acetylimidazole, 61985-25-9; 4-acetylimidazole hydrobromide, 82982-68-1; 2-bromo-1-(4-imidazolyl)ethanone hydrobromide, 82982-48-7; amidinothiourea, 2114-02-5; 5-acetyl-2-aminoimidazole, 67560-27-4; 1-(2-methyl-4-imidazolyl)ethanone, 78210-66-9; 1-(2-methyl-4-imidazolyl)-2-bromoethanone hydrobromide, 82982-52-3; 1-(2-methyl-4-imidazolyl)-2-bromoethanone, 92049-88-2; ethyl 4-phthalimidobutimidate hydrochloride, 97961-52-9; ethyl 5-phthalimidopentimidate hydrochloride, 86649-65-2; 3-(3-aminopropyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole, 103852-06-8; 3-(4-aminobutyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole, 103852-07-9; 4-[2-(ethylamino)-4-pyridyl]-2-(phthalimidoethyl)imidazole, 103852-08-0; 3-(3-phthalimidopropyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole, 103852-09-1; 3-(4-phthalimidobutyl)-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole, 86649-66-3.