of 8-substituted AT inhibitors, these derivatives may be useful for depot administration.

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Cyanoguanidine-Thiourea Equivalence in the Development of the Histamine H_2-Receptor Antagonist, Cimetidine

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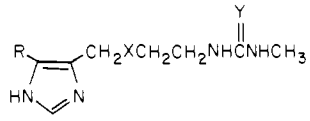
In the histamine H_2-receptor antagonist metiamide (**2a**) isosteric replacement of thione sulfur (=S) by carbonyl oxygen (=O) or imino nitrogen (=NH) affords the urea **2c** and guanidine **2d** which are antagonists of decreased potency. The guanidine is very basic and at physiological pH is completely protonated. However, introduction of strongly electronegative substituents into the guanidine group reduces basicity and gives potent H_2-receptor antagonists, viz. the cyanoguanidine **2b** (cimetidine, "Tagamet") and nitroguanidine **2e**. A correspondence between the activity of thioureas and cyanoguanidines is demonstrated for a series of structures **1–4**. The close correspondence between cyanoguanidine and thiourea in many physicochemical properties and the pharmacological equivalence of these groups in H_2-receptor antagonists leads to the description of cyanoguanidine and thiourea as bioisosteres. Acid hydrolysis of the cyanoguanidine **2b** yields the carbamoylguanidine **2f** at ambient temperatures and the guanidine **2d** at elevated temperatures. Cimetidine is slightly more active than metiamide in vivo as an inhibitor of histamine-stimulated gastric acid secretion and has clinical use in the treatment of peptic ulcer and associated gastrointestinal disorders.

The discovery of the selective antagonist burimamide (**1a**, Table I) permitted the characterization of histamine H_2-receptors and furnished a class of drug with a completely novel pharmacological action.[1] Chemical modification of burimamide led to the orally active antagonist metiamide[2,3] (**2a**) which proved sufficiently active to allow the exploration of the therapeutic potential of this new type of drug. Clinical studies established that metiamide is a highly effective inhibitor of gastric acid secretion and that it gave marked symptomatic relief to patients with peptic ulcer;[4] healing of recalcitrant multiple ulcers following treatment with metiamide was also reported.[5,6] To explore further the structural requirements for H_2-receptor antagonism, we have investigated the effect of replacing the thiourea group of metiamide. A factor that has emphasized the importance of this investigation has been the finding of kidney damage and agranulocytosis in high-dosage chronic toxicity tests with metiamide[7,8] and the possibility that these effects are attributable to the presence of a thiourea group in the drug molecule. As part of this study we have investigated the isosteric replacement of the thiourea sulfur atom of metiamide.

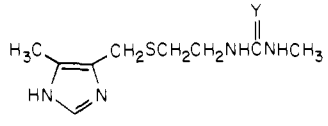
Carbonyl oxygen (=O) and imino nitrogen (=NH) are well precedented[9] as isosteres of thione sulfur (=S) (e.g., in the barbiturates) and, initially, these isosteric replacements were considered for metiamide. The urea **2c**

Table I. Structures and H_2-Receptor Antagonist Activities

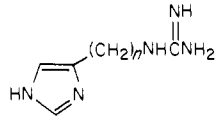


Compd	R	X	Y	Mp, °C	Crystn solvent	Mol formula[a]	H_2-Receptor antagonist act.,[b] K_B (95% limits) × 10^{-6} M: Atrium	Uterus
1a	H	CH_2	S	128-129	H_2O	$C_9H_{16}N_4S$	7.8 (6.4-9.6)	6.6 (4.9-8.3)
1b	H	CH_2	NCN	147-148	H_2O	$C_{10}H_{16}N_6$	8.3 (2.0-59)	7.1 (2.9-23)
2a	CH_3	S	S	152-154	H_2O	$C_9H_{16}N_4S_2$	0.92 (0.74-1.15)	0.75 (0.40-1.36)
2b	CH_3	S	NCN	141-143	H_2O	$C_{10}H_{16}N_6S$	0.79 (0.68-0.92)	0.81 (0.54-1.2)
2c	CH_3	S	O	158-159	*i*-PrOH-MeCN	$C_9H_{16}N_4OS$	22 (8.9-65)[d]	7.1 (1.6-30)
2d	CH_3	S	NH	205-206	EtOH-Et_2O	$C_9H_{17}N_5S \cdot 2HCl$	16 (8.1-32)	5.5 (2.8-13)
2e	CH_3	S	NNO_2	112-114	*c*	$C_9H_{16}N_6O_2S$	1.4 (0.78-2.8)[e]	1.4 (0.72-3.2)
2f	CH_3	S	$NCONH_2$	186-187	EtOH	$C_{10}H_{18}N_6OS \cdot 2HCl$	7.1 (4.0-14)	6.9 (4.1-12)
3a	H	S	S	98-99	Me_2CO	$C_8H_{14}N_4S_2$	3.2 (2.5-4.5)[f]	3.2 (2.5-4.5)[g]
3b	H	S	NCN	138-140	MeCN	$C_9H_{14}N_6S$	1.4 (0.78-2.7)	1.6 (0.83-3.2)
4a	CH_3	CH_2	S	110-112	MeCN	$C_{10}H_{18}N_4S$	8.9 (5.6-15)	10.7 (4.5-31)
4b	CH_3	CH_2	NCN	152-154	MeCN	$C_{11}H_{18}N_6$	8.1 (2.3-69)	4.9 (2.4-12)

[a] All compounds were analyzed for C, H, N, and Cl or S (if present). [b] The dissociation constant (K_B) was calculated from the equation $K_B = B/(x-1)$, where x 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 and $-\log K_B = pA_2$. Slopes of plots of $\log(x-1)$ on $\log B$ for these determinations are not significantly different from unity within 95% limits. Differences from unity are indicated. [c] Crystallized under Et_2O-MeCOEt. [d] Slope 0.70 ± 0.12. [e] Slope 0.71 ± 0.16. [f] Slope 0.82 ± 0.08. [g] Slope 1.27 ± 0.16.



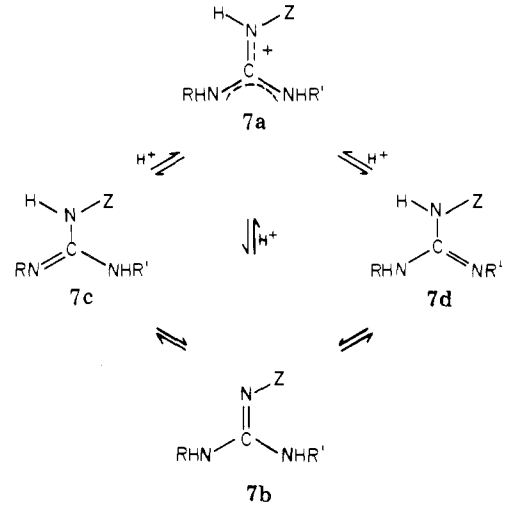
metiamide (Y = S, 2a)
cimetidine (Y = NCN, 2b)



5, $n = 2$
6, $n = 3$

and guanidine **2d** were synthesized and demonstrated to be H_2-receptor antagonists. However, potency was reduced relative to metiamide when tested on guinea-pig atrium and rat uterus preparations[1,2] (Table I). Carbonyl oxygen and imino nitrogen may therefore be described as partial bioisosteres[10] of thione sulfur in histamine H_2-receptor antagonists. The activity of the guanidine **2d** was of particular interest. Imidazolylalkylguanidines **5** and **6** had furnished the earliest examples of H_2-receptor antagonists, but these were weakly active and behaved as partial agonists at histamine H_2-receptors.[11,12] Interestingly, the guanidine **2d** differs from the shorter alkylene chain guanidines since it is not a partial agonist but is an H_2-receptor antagonist of greater potency than either **5** or **6**. Although **2d** is less active than metiamide, it served as a suitable structure for molecular modification to compounds of potentially increased potency. The presence of the third nitrogen atom provides a site for introducing further substituents while retaining the side chain and terminal *N*-methyl substituent that are present in metiamide. Thus groups can be incorporated to modify the physicochemical properties of the guanidine moiety. Guanidine and thiourea differ markedly in their ionization behavior. Whereas thiourea is essentially neutral ($pK_a = -1.2$),[13] guanidine is one of the strongest organic bases known ($pK_a = 13.6$)[14] and the disubstituted guanidine group of **2d** would exist almost exclusively as a charged monocationic species under any physiological conditions that might be envisaged. However, guanidine basicity may be reduced by introducing a further substituent Z onto the third nitrogen atom. As illustrated in Scheme I, a trisubstituted guanidinium cation (**7a**) exists in equilibrium with three conjugate bases (**7b–d**) since proton dissociation can occur from each of the three nitrogen atoms. If the substituent Z is electronegative, basicity is reduced and the neutral guanidine species is stabilized.

Scheme I. Guanidine Species Equilibria



The quantitative effect of electron-withdrawing substituents on the ionization of guanidinium cations (**7a**, R = R_1 = H) has been studied by Charton[15] using the Hammett equation.

$$pK_{a,Z} = pK_{a,H} + \rho\sigma_Z$$

Charton obtained an excellent correlation between guanidinium pK_a and Taft's[16] σ_I values (Figure 1). Although Liler[17] has since argued that a correlation with σ_m would be better justified on theoretical grounds, Charton's data strongly support a correlation with σ_I and indicate that the influence of the substituent is largely inductive. The very high ρ value (−24) for the σ_I correlation reflects the high sensitivity of guanidinium cation dissociation to substituent effects; this can be attributed to the substituent being attached directly to the nitrogen atom bearing the dissociable proton. Electron-withdrawing substituents (Z) would be expected to favor the imino tautomer **7b** compared with the amino tautomers **7c** and **7d** since the proton on the adjacent nitrogen atom in the cation **7a** would be

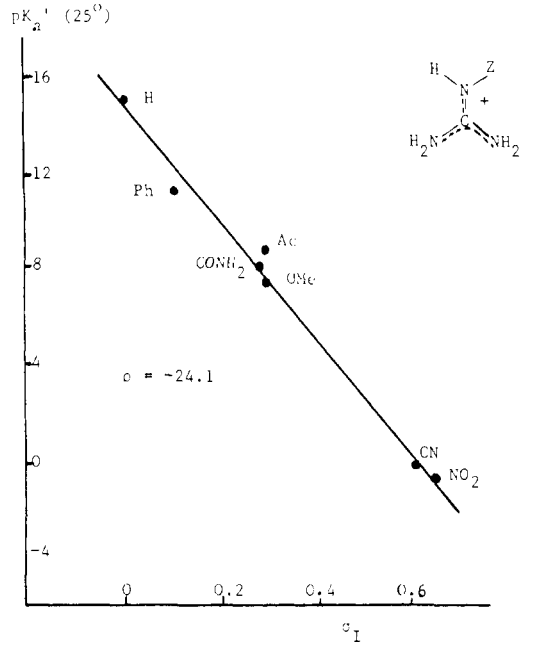


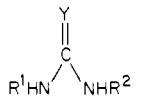
Figure 1. Apparent pK_a values at 25 °C of N-substituted guanidinium cations vs. σ_I substituent constants. Data from Charton.[15] The line corresponds to the equation pK_a' = 14.20 − 24.1 σ_I.

more acidic than the protons on the more distant terminal nitrogen atoms.[15]

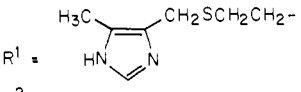
The groups cyano and nitro are sufficiently electron attracting to reduce guanidinium pK_a by 14 units; indeed the ionization constants of cyanoguanidine (pK_a = −0.4)[18] and nitroguanidine (pK_a = −0.9)[19] approach that of thiourea (−1.2). Such considerations of guanidine structure and basicity prompted the synthesis of the nitroguanidine **2e** and cyanoguanidine **2b** analogues of metiamide as potential histamine H_2-receptor antagonists. Compounds were tested by their ability to inhibit the effects of histamine on guinea-pig atrium and rat uterus in vitro. The cyanoguanidine **2b** and most of the compounds in Table I met the criteria for surmountable and competitive antagonism at histamine H_2-receptors. The effectiveness of each compound was compared by estimating the apparent dissociation constant K_B (with 95% confidence limits) for the drug–receptor complex as described.[1,2] From the results (Table I) it is clear that the introduction of either the nitro or the cyano group into the guanidine **2d** results in a marked increase in H_2-receptor antagonist activity; the cyanoguanidine **2b** is as active as the thiourea **2a**. Furthermore, it was found that in the series of imidazole derivatives in which the thioureas, burimamide (**1a**), metiamide (**2a**), thiaburimamide (**3a**), and methylburimamide (**4a**) span a range of antagonist potency of at least one order of magnitude, the corresponding cyanoguanidines **1b**–**4b** were antagonists with potencies very similar to those of analogous thioureas (Table I).

Cyanoguanidine–Thiourea Equivalence. In Table II, cyanoguanidine and thiourea are compared with respect to several physicochemical properties. In addition to being weakly basic, cyanoguanidine and thiourea are also weakly acidic and both are therefore neutral and weakly amphoteric compounds. For cyanoguanidine, the overwhelming predominance of the cyanoimino tautomer **7b** (Z = NCN, R = R^1 = H) has been shown by UV spectroscopy for aqueous solutions[20] and by NMR for solutions in dipolar aprotic solvents.[21] The cyanoimino tautomer is the only form of cyanoguanidine that has been found in crystal structure determinations by x-ray diffraction[22]

Table II. Comparison of Physicochemical Properties of Cyanoguanidines and Thioureas[a]



R^1 = R^2 = H	Y = S, thiourea	Y = N–CN, cyanoguanidine
Geometry		
C–N bond length (Å)	1.34[a]	1.34,[b] 1.32[c]
N–C–N bond angle (deg)	119[a]	124,[b] 120[c]
Acidity (pK_a)		
Proton gained at 25 °C	−1.2[d]	−0.4[e]
Proton lost at 25 °C	15[f]	14[g]
Hydrophobicity		
Partition, P = C_{Oct}/C_{H_2O} at 37 °C	0.09[h]	0.07[h]
Dipole moment, μ(dioxane) (D)	4.89[i]	8.16[j]
R^1 = R^2 = CH$_3$		
Partition, P (Oct–H$_2$O) at 37 °C	0.58[h]	0.40[h]
$\Delta G^{\ddagger}$ for interconv between conformers (kcal mol^{-1})	11.8[k]	12.4[l]

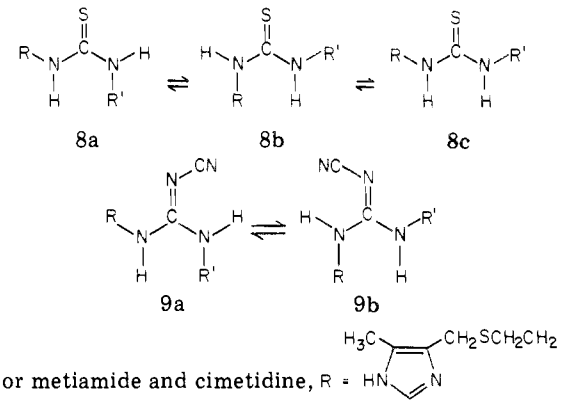


R^2 = CH$_3$	metiamide	cimetidine
Partition, P (Oct–H$_2$O at pH 9.2)	3.2[h]	2.5[h]
Solubility in H$_2$O (37 °C)		
w/v, %	0.32[h]	1.14[h]
Molar, M	0.013	0.045

[a] Reference 41. [b] Reference 22. [c] Reference 23. [d] Reference 13. [e] Reference 18. [f] Reference 42. [g] Reference 43. [h] Reference 30. [i] Reference 25. [j] Reference 26. [k] Reference 27. [l] Reference 28.

and neutron diffraction[23] methods. Thus the cyanoimino (=NCN) functionality has a similar effect to thione sulfur (=S) in reducing the electron density of the amino groups in 1,1-diaminomethylene [$(H_2N)_2C$=] and renders cyanoguanidine neutral analogously to thiourea. Cyanoguanidine is also similar to thiourea in its geometry since both are planar structures with almost identical C–N bond lengths and bond angles (Table II). The experimental bond lengths in cyanoguanidine[22] (and also *N''*-cyano-*N,N'*-dimethylguanidine)[24] are indicative of considerable delocalization of π electrons extending over all six carbon and nitrogen atoms. Both thiourea[25] and cyanoguanidine[26] (Table II) have high dipole moments that have been attributed to considerable resonance contributions from dipolar canonical structures. Another property common to thioureas and cyanoguanidines is conformational isomerism resulting from restricted C–N bond rotation. Free energies of activation $\Delta G^{\ddagger}$ for the interconversion between isomers are similar (11.8 kcal/mol for *N,N'*-dimethylthiourea[27] and 12.4 kcal/mol for the corresponding cyanoguanidine[28]). There is, however, an important difference between the two types of structure, since *N,N'*-disubstituted thioureas (**8**, Scheme II) assume *Z,Z* (**8c**) and two *E,Z* stable configurations (**8a,b**; *E,Z* nomenclature defined by Blackwood et al.[29]) whereas cyanoguanidines (**9**, Scheme II) assume only the two staggered *E,Z* forms (**9a,b**). Internal steric interactions between the substituents and the CN group disfavor the other possible forms. Cyanoguanidine and thiourea are similar in their hydrophilicity and hydrogen-bonding properties; they have comparably low octanol–water partition coefficients (P) and are both reasonably soluble in water. Thus there is

Scheme II. Planar Conformations of N,N'-Disubstituted Thioureas and Cyanoguanidines in Solution[a]



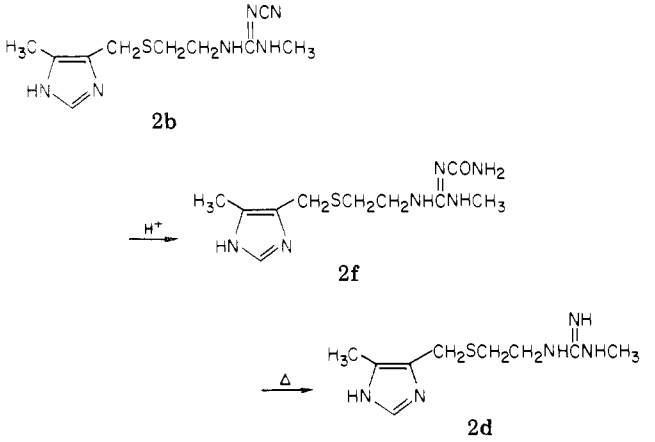
[a] For metiamide and cimetidine, R = H_3C, $CH_2SCH_2CH_2$, HN, N; R' = CH_3.

a close similarity in many physicochemical properties of thioureido and cyanoguanidino groups and since there is a corresponding parallelism between these groups with respect to histamine H_2-receptor antagonist activity, cyanoguanidine and thiourea may be classed as true bioisosteres.[9,10] Similarly, the partial bioisosterism of urea and thiourea in H_2-receptor antagonists is likely to reflect the similarity of many physicochemical properties of urea and thiourea; quantitative differences in antagonist potency between the urea **2c** and metiamide could be related to partition differences between urea (P_{Oct-H_2O} = 0.02)[30] and thiourea (P = 0.09).

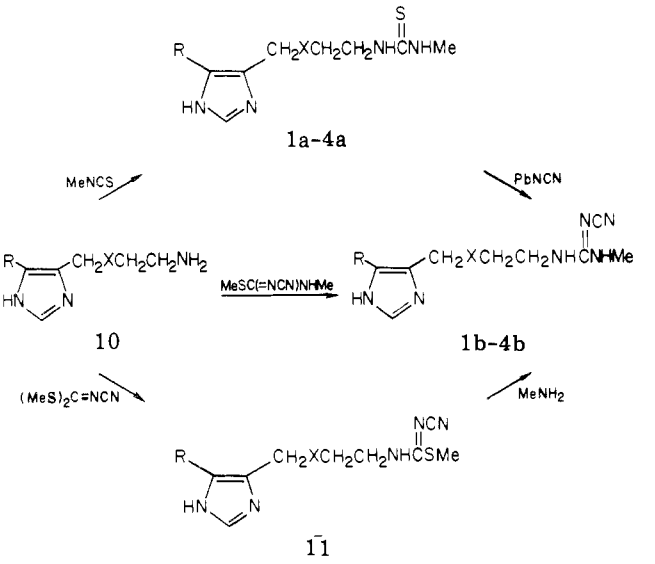
It is also apparent that although cyanoguanidine and thiourea are similar in many of their physicochemical properties, they differ sufficiently in chemical reactivity, e.g., in oxidative and hydrolytic behavior for differences to be expected in the rates and products of biotransformation of drug molecules containing these groups.

Cimetidine. The cyanoguanidine analogue of metiamide, *N''*-cyano-*N*-methyl-*N'*-[2-[(5-methylimidazol-4-yl)methylthio]ethyl]guanidine (**2b**), has the WHO recommended international nonproprietary name, cimetidine ("Tagamet"). Many of the physicochemical properties of cimetidine and metiamide are similar and reflect the characteristics of cyanoguanidine and thiourea (Table II). They are polar molecules with similar octanol–water partition coefficients. Cimetidine is slightly more water soluble than metiamide and the solubility of both is greatly increased by the addition of dilute acid to protonate the imidazole ring. The ring pK_a (6.80) is identical in the two compounds[31] which should therefore have similar species composition of the disubstituted imidazole ring. Metiamide and cimetidine possess the conformational properties expected for *N,N'*-disubstituted thioureas and cyanoguanidines (Scheme II). NMR studies have demonstrated that, in solution, metiamide assumes three stable configurations of the thiourea group [Z,Z (**8c**) and two E,Z forms (**8a,b**)] whereas cimetidine assumes only the two staggered (*E,Z*) configurations (**9a,b**) of the cyanoguanidine group.[32] In the presence of excess dilute hydrochloric acid, cimetidine is slowly hydrolyzed to the guanylurea (**2f**, Scheme III), conversion being complete after 5 days at 20 °C. **2f** is also an H_2-receptor antagonist but it is less active than cimetidine and more comparable with the guanidine **2d** in antagonist potency (Table I). Acid hydrolysis at elevated temperatures yields the guanidine **2d** (Scheme III), complete conversion occurring after 2 h at 100 °C in concentrated hydrochloric acid. Neither of these acid decomposition products is formed to a significant extent in the metabolism of cimetidine. Cimetidine, like metiamide, is excreted largely unchanged, together with small amounts of the thioether sulfoxide.[33] Cimetidine has not shown the toxicological effects seen with metiamide at high doses. It is slightly more active than metiamide as an inhibitor of gastric acid secretion in animals[34] and man.[35] Extensive clinical studies have been conducted with cimetidine and its therapeutic effectiveness has been demonstrated in the treatment of peptic ulcer and associated gastrointestinal disorders.[36-40]

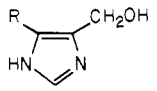
Scheme III



Scheme IV



Synthesis. *N*-Methylthioureas **1a–4a** and the urea **2c** were made from intermediate amines **10** and methyl isothiocyanate or methyl isocyanate. *N'*-Cyano-*N*-methylguanidines **1b–4b** were synthesized (Scheme IV) from amines **10** and *N*-cyano-*N',S*-dimethylisothiourea[44] (method 1); from **10** and dimethylcyanodithioimidocarbonate[45] followed by treatment of the intermediate isothiourea **11** with methylamine (method 2); and from corresponding thioureas and lead cyanamide (method 3). The nitroguanidine **2e** was prepared analogously to method 1 (above) from the amine **10** (X = S; R = CH_3) and *N,S*-dimethyl-*N'*-nitroisothiourea. Intermediate imidazolylmethylthioethylamines **10** (X = S) were synthesized from carbinols **12** by acid-catalyzed condensation with cysteamine hydrochloride. 4-(4-Aminobutyl)-5-methylimidazole **10** (X = CH_2; R = CH_3) was synthesized from *N,N'*-dibenzoyllysine[46] by a Dakin–West[47] rearrangement followed by cyclization (see the Experimental Section).



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Experimental Section[48]

NMR spectra were recorded on a Varian A-60A instrument using Me_4Si as internal standard. Microanalyses for elements indicated are within 0.4% of theoretical values. Melting points, recrystallization solvents, and analytical data of final products are included in Table I.

***N*-Methyl-*N'*-[4-(imidazol-4-yl)butyl]thiourea (1a).** Methyl isothiocyanate (15.3 g, 0.21 mol) was added to a solution of 4-(4-aminobutyl)imidazole[49] (26.9 g, 0.19 mol) in EtOH (250 mL) and heated under reflux for 0.5 h. Concentration, followed by trituration of the residue with warm *i*-PrOAc and recrystallization from H_2O, afforded 1a (28.1 g, 68%).

***N*-Methyl-*N'*-[2-(imidazol-4-yl)methylthioethyl]thiourea (3a).** (i) A solution of 4-hydroxymethylimidazole hydrochloride[50] (67.0 g, 0.5 mol) and cysteamine hydrochloride (56.8 g, 0.5 mol) in aqueous HBr (1 L, 48%) was heated under reflux for 18 h. After cooling the solution was evaporated to dryness and the residual solid was washed with EtOH–Et_2O and recrystallized from EtOH to give 4-[(2-aminoethyl)thiomethyl]imidazole dihydrobromide (156 g, 98%): mp 178–179 °C. Anal. ($C_6H_{13}Br_2N_3S$) C, H, N, Br, S.

(ii) A solution of the amine dihydrobromide (10.0 g, 0.031 mol) in H_2O was basified to pH 11 with K_2CO_3 (8.7 g) in H_2O. Evaporation to dryness and extraction with *i*-PrOH afforded the amine base which was freed from inorganic material by further extraction with *i*-PrOH. Methyl isothiocyanate (2.3 g, 0.032 mol) was added to the amine in *i*-PrOH (70 mL) and the mixture was heated under reflux for 1.5 h. After concentration, the residue was dissolved in acetone, clarified by filtration, and concentrated to give 3a (4.1 g, 60%).

***N*-Methyl-*N'*-[2-(5-methylimidazol-4-yl)methylthioethyl]thiourea (Metiamide, 2a).** (i) The reaction of 4-hydroxymethyl-5-methylimidazole hydrochloride[51] with cysteamine hydrochloride and HBr by the method described for 3a afforded 4-[(2-aminoethyl)thiomethyl]-5-methylimidazole dihydrobromide (80–90%): mp 210–212 °C. Anal. ($C_7H_{15}Br_2N_3S$) C, H, N, Br, S.

(ii) Reaction of the amine with methyl isothiocyanate in H_2O or EtOH afforded the thiourea 2a in 80–90% yield.

***N*-Methyl-*N'*-[4-(5-methylimidazol-4-yl)butyl]thiourea (4a).** (i) *N*,*N'*-Dibenzoyllysine[46] (140.4 g, 0.36 mol) dissolved in dioxane (350 mL) was added over 45 min to dicyclohexylcarbodiimide (88.0 g, 0.43 mol) in dioxane (193 mL). After stirring for 2 h the mixture was set aside overnight, filtered from dicyclohexylurea (88.1 g), concentrated to half-volume, and added to H_2O. The precipitate was collected and recrystallized from dimethoxymethane to give 4-(4-benzamidobutyl)-2-phenyl-5-oxazolone (104 g, 86%): mp 118–122 °C. Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

(ii) A mixture of the oxazolone (1.69 g, 0.005 mol), 4-dimethylaminopyridine (0.025 g), acetic anhydride (1 mL), and triethylamine (1 mL) was stirred until solution was obtained (1 h). Acetic acid (7.5 mL) was added and the solution was set aside overnight and evaporated to dryness. The residue was dissolved in $CHCl_3$ and washed with dilute NaOH and dilute HCl and then dried over $MgSO_4$. Concentration gave the crude product which could be purified by dry-column chromatography on alumina with ethyl acetate as solvent to give 3,7-dibenzamidoheptan-2-one (0.60 g, 34%): NMR δ (60 MHz, Me_2SO-d_6) 8.5 (t, NH), $\simeq$8.3 (br s, NH), $\simeq$7.8, 7.4 (m, C_6H_5), 4.4 (m, CH), 3.2 (m, NCH_2), 2.1 (s, CH_3), 1.5 [m, $(CH_2)_3$].

(iii) Crude 3,7-dibenzamidoheptan-2-one (123 g, 0.35 mol) was hydrolyzed with HCl for 18 h to give 3,7-diaminoheptan-2-one dihydrochloride (49 g, 65%): mp 160–166 °C (MeCN); NMR δ (60 MHz, D_2O) 4.3 (t, CH), 3.1 (t, NCH_2), 2.35 (s, CH_3), 1.7 [m, $(CH_2)_3$].

(iv) A solution of the amino ketone dihydrochloride (21.7 g, 0.10 mol) and potassium thiocyanate (19.40 g, 0.20 mol) in H_2O was heated under reflux for 7 h and then evaporated to dryness. The residue was extracted with hot AcOH, and the filtered extracts were allowed to cool. The product obtained was recrystallized from AcOH to give 4-(4-aminobutyl)-5-methylimidazole-2-thione hydrochloride (14.1 g, 64%): mp 279–280 °C. Anal. ($C_8H_{16}N_3SCl$) C, H, N, S.

(v) The imidazolethione (14.1 g, 0.064 mol) in absolute EtOH (250 mL) was desulfurized with Raney nickel (approximately 25 g) for 30 min. Filtration followed by concentration under reduced pressure and treatment of the residue with HCl gave 4-(4-aminobutyl)-5-methylimidazole dihydrochloride (8.2 g, 57%): mp 206–208 °C (AcOH). Anal. ($C_8H_{17}Cl_2N_3$) C, H, N, Cl.

(vi) A solution of the amine [obtained from the dihydrochloride (9.60 g, 0.049 mol) by basification with K_2CO_3] and methyl isothiocyanate (4.0 g, 0.055 mol) in EtOH (100 mL) containing a few drops of H_2O was heated under reflux for 30 min. Filtration, followed by evaporation under reduced pressure and recrystallization of the residue from MeCN, gave 4d (6.9 g, 62%): mp 110–112 °C.

***N''*-Cyano-*N*-methyl-*N'*-[2-[(5-methylimidazol-4-yl)methylthio]ethyl]guanidine (Cimetidine, 2b). Method 1.** A solution of 4-[(2-aminoethyl)thiomethyl]-5-methylimidazole (34.0 g, 0.20 mol) and *N*-cyano-*N'*,*S*-dimethylisothiourea[44] (22.4 g, 0.17 mol) in acetonitrile (1 L) was heated under reflux for 48 h. Following concentration, the residue was chromatographed (SiO_2–CH_3CN) and the product obtained was recrystallized from CH_3CN to yield 2b (8.7 g, 20%): mp 141–142 °C.

Method 2. 4-[(2-Aminoethyl)thiomethyl]-5-methylimidazole (23.4 g, 0.14 mol) in EtOH (200 mL) was added slowly with stirring to a solution of dimethylcyanodithioimidocarbonate[45] (20.0 g, 0.14 mol) in EtOH at room temperature. The mixture was set aside overnight and filtered to afford *N*-cyano-*N'*-[2-(5-methylimidazol-4-yl)methylthioethyl]-*S*-methylisothiourea in two crops (total 25.0 g, 73%): mp 148–150 °C. Anal. ($C_{10}H_{14}N_5S_2$) C, H, N, S. A solution of $MeNH_2$ in EtOH (33%, 75 mL) was added to a solution of the isothiourea (10.1 g, 0.038 mol) in EtOH (30 mL) and the mixture was set aside at room temperature for 2.5 h. Concentration and recrystallization afforded 2b (8.6 g, 90%): mp 141–143 °C (H_2O).

***N''*-Cyano-*N*-methyl-*N'*-[4-(imidazol-4-yl)butyl]guanidine (1b). Method 3.** Lead cyanamide (30.0 g, 0.12 mol) was added to a solution of 1a (30.0 g, 0.12 mol) in CH_3CN (500 mL) and DMF (50 mL). The suspension was stirred under reflux for 48 h, with fresh lead cyanamide (15 g) being added during this period. Following filtration and concentration the product was chromatographed (SiO_2–*i*-PrOH) affording 1b (9.4 g, 43%).

***N''*-Cyano-*N*-methyl-*N'*-[2-(imidazol-4-yl)methylthioethyl]guanidine (3b).** Reaction of the thiourea 3a (11.5 g, 0.05 mol) with lead cyanamide (24.7 g, 0.10 mol) according to method 3, followed by chromatographic purification (SiO_2, EtOAc–*i*-PrOH), afforded 3b (3.7 g, 31%).

***N''*-Cyano-*N*-methyl-*N'*-[4-(5-methylimidazol-4-yl)butyl]guanidine (4b).** The reaction of 4-(4-aminobutyl)-5-methylimidazole (from the dihydrochloride, 2.71 g, 0.012 mol) with dimethyl cyanodithioimidocarbonate (1.75 g, 0.013 mol), according to method 2, afforded the isothiourea 11 (R = CH_3; X = CH_2) (2.27 g, 79%) which was treated directly with $MeNH_2$ to yield 4b (1.35 g, 60%).

***N*-Methyl-*N'*-[2-(5-methylimidazol-4-yl)methylthioethyl]urea (2c).** A solution of 4-[(2-aminoethyl)thiomethyl]-5-methylimidazole (5.1 g, 0.030 mol) and methyl isocyanate (2.0 g, 0.036 mol) in acetonitrile was heated for 18 h at 100 °C in a pressure vessel to give 2c (4.0 g, 63%).

***N*-Methyl-*N'*-[2-(5-methylimidazol-4-yl)methylthioethyl]guanidine Dihydrochloride (2d).** A solution of 2b (20.0 g, 0.08 mol) in concentrated HCl (200 mL) was heated under reflux for 10 h. Evaporation and recrystallization afforded 2d (17.5 g, 73%).

***N*-Methyl-*N'*-[2-(5-methylimidazol-4-yl)methylthioethyl]-*N''*-nitroguanidine (2e).** (i) *N*,*S*-Dimethylisothiourea methosulfate (10.8 g, from *N*-methylthiourea and dimethyl sulfate) was added over 0.5 h to a stirred mixture of fuming HNO_3 (15 mL) and concentrated H_2SO_4 (45 mL) at −20 °C. After addition, the mixture was stirred for 5 min and poured over crushed ice (500 mL) with stirring. Following filtration and washing with H_2O, the product was recrystallized from water to afford *N*,*S*-dimethyl-*N'*-nitroisothiourea: mp 149.5–150 °C; NMR δ (60 MHz,

Me_2SO-d_6) 2.5 (s, SCH_3), 2.9 (d, NCH_3, J = 5 Hz), 9.0 (br s, NH). Anal. ($C_3H_7N_3O_2S$) C, H, N, S.

(ii) A solution of the isothiourea (1.6 g, 0.11 mol) in warm MeOH (20 mL) was added to a solution of 4-methyl-5-[(2-aminoethyl)thiomethyl]imidazole (1.72 g, 0.10 mol) in warm MeOH (5 mL). The reaction mixture was maintained at 60 °C for 30 min and at 50 °C for 2 h. Following evaporation to dryness the resultant oil was chromatographed (SiO_2–Me_2CO). The product crystallized under Et_2O–MeCOEt to give **2e** (1.2 g, 44%).

***N'*-Carbamyl-*N*-methyl-*N'*-[2-(5-methylimidazol-4-yl)-methylthioethyl]guanidine Dihydrochloride (2f).** A solution of **2b** (2.0 g, 0.008 mol) in 1 N HCl (24 mL) was set aside at room temperature for 5 days. Following concentration, the residue crystallized under *i*-PrOH yielding **2f** (1.92 g, 71%, mp 184–187 °C). An analytically pure sample was obtained by recrystallization from EtOH.

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