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<sub>2</sub>-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 gastrionated for the secretion and has clinical use in the treatment of peptic ulcer and associated gastrionated for the secretion and has clinical use in the treatment of peptic ulcer and associated gastrionated gastric acid secretion and has clinical use in the treatment of peptic ulcer and associated gastrionated for the secretion and has clinical use in the treatment of peptic ulcer and associated gastrionated for the secretion and has clinical use in the treatment of peptic ulcer and associated gastrionated for the secretion and has clinical use in the treatment of peptic ulcer and associated gastrionated for the secretion and has clinical use in the treatment of peptic ulcer and associated gastrionated for the secretion anteget the performance and the performance anteget the performance ant

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.<sup>1</sup> Chemical modification of burimamide led to the orally active antagonist metiamide<sup>2.3</sup> (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;<sup>4</sup> healing of recalcitrant multiple ulcers following treatment with metiamide was also reported.<sup>5,6</sup> 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 highdosage chronic toxicity tests with metiamide<sup>7,8</sup> 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 (=0) and imino nitrogen (=NH) are well precedented<sup>9</sup> as isosteres of thione sulfur (=S) (e.g., in the barbiturates) and, initially, these isosteric replacements were considered for metiamide. The urea 2c

					R CH <sub>2</sub> XCH <sub>2</sub> C HN N	H₂NHĊNHCH₃	${f H_2} ext{-Receptor antagonist act.,}^b \ K_B \ (95\% \ limits) \  imes \ 10^{-6} \ { m M}$	
Compd	R	Х	Y	Mp, $^{\circ}C$	Crystn solvent	Mol formula <sup>a</sup>	Atrium	Uterus
1a 1b 2a 2b 2c 2d 2e 2f 3a 3b 4a	H H CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> H H CH <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> S S S S S S S CH <sub>2</sub>	S NCN S NCN O NH NNO <sub>2</sub> NCONH <sub>2</sub> S NCN S	$\begin{array}{c} 128-129\\ 147-148\\ 152-154\\ 141-143\\ 158-159\\ 205-206\\ 112-114\\ 186-187\\ 98-99\\ 138-140\\ 110-112 \end{array}$	H <sub>2</sub> O H <sub>2</sub> O H <sub>2</sub> O <i>i</i> -PrOH-MeCN EtOH-Et <sub>2</sub> O <i>c</i> EtOH Me <sub>2</sub> CO MeCN MeCN	$\begin{array}{c} C_{9} H_{16} N_{4} S \\ C_{10} H_{16} N_{6} \\ C_{9} H_{16} N_{4} S_{2} \\ C_{10} H_{16} N_{6} S \\ C_{9} H_{16} N_{4} S_{5} \\ C_{9} H_{16} N_{4} OS \\ C_{9} H_{16} N_{5} S 2 HCl \\ C_{9} H_{16} N_{6} O_{5} S \\ C_{10} H_{18} N_{6} OS \cdot 2 HCl \\ C_{8} H_{14} N_{4} S_{2} \\ C_{9} H_{14} N_{6} S \\ C_{10} H_{14} N_{5} S \\ \end{array}$	7.8 $(6.4-9.6)$ 8.3 $(2.0-59)$ 0.92 $(0.74-1.15)$ 0.79 $(0.68-0.92)$ 22 $(8.9-65)^d$ 16 $(8.1-32)$ 1.4 $(0.78-2.8)^e$ 7.1 $(4.0-14)$ 3.2 $(2.5-4.5)^f$ 1.4 $(0.78-2.7)$ 8.9 $(5.6-15)$	$\begin{array}{c} 6.6 \ (4.9-8.3) \\ 7.1 \ (2.9-23) \\ 0.75 \ (0.40-1.36) \\ 0.81 \ (0.54-1.2) \\ 7.1 \ (1.6-30) \\ 5.5 \ (2.8-13) \\ 1.4 \ (0.72-3.2) \\ 6.9 \ (4.1-12) \\ 3.2 \ (2.5-4.5)^g \\ 1.6 \ (0.83-3.2) \\ 10.7 \ (4.5-31) \end{array}$

Y II

<sup>a</sup> All compounds were analyzed for C, H, N, and Cl or S (if present). <sup>b</sup> 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 halfmaximal 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. <sup>c</sup> Crystallized under Et<sub>2</sub>O-MeCOEt. <sup>d</sup> Slope 0.70 ± 0.12. <sup>e</sup> Slope 0.71 ± 0.16. <sup>f</sup> Slope 0.82 ± 0.08. <sup>g</sup> Slope 1.27 ± 0.16.



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<sup>1,2</sup> (Table I). Carbonyl oxygen and imino nitrogen may therefore be described as partial bioisosteres<sup>10</sup> of thione sulfur in histamine H<sub>2</sub>-receptor antagonists. The activity of the guanidine 2d was of particular interest. Imidazolylalkylguanidines 5 and 6 had furnished the earliest examples of H<sub>2</sub>-receptor antagonists, but these were weakly active and behaved as partial agonists at histamine  $H_2$ -receptors.<sup>11,12</sup> Interestingly, the guanidine 2d differs from the shorter alkylene chain guanidines since it is not a partial agonist but is an H<sub>2</sub>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  $(pK_a = -1.2)$ ,<sup>13</sup> guanidine is one of the strongest organic bases known ( $pK_a$ = 13.6)<sup>14</sup> and the disubstituted guanidine group of  $2\mathbf{d}$ 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.

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

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

T7

Charton obtained an excellent correlation between guanidinium  $pK_a$  and Taft's<sup>16</sup>  $\sigma_I$  values (Figure 1). Although Liler<sup>17</sup> has since argued that a correlation with  $\sigma_m$ would be better justified on theoretical grounds, Charton's data strongly support a correlation with  $\sigma_{I}$  and indicate that the influence of the substituent is largely inductive. The very high  $\rho$  value (-24) for the  $\sigma_{\rm I}$  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.  $\sigma_I$  substituent constants. Data from Charton.<sup>15</sup> The line corresponds to the equation  $pK_a' = 14.20 - 24.1 \sigma_I$ .

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<sub>2</sub>-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.<sup>1,2</sup> 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<sub>2</sub>-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<sup>1</sup> = H) has been shown by UV spectroscopy for aqueous solutions<sup>20</sup> and by NMR for solutions in dipolar aprotic solvents.<sup>21</sup> The cyanoimino tautomer is the only form of cyanoguanidine that has been found in crystal structure determinations by x-ray diffraction<sup>22</sup>

Table II.Comparison of Physicochemical Properties of<br/>Cyanoguanidines and Thioureas $^a$ 

	Ϋ́						
$\mathbf{R}^{1} = \mathbf{R}^{2} = \mathbf{H}$	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)	$119^{a}$	$124,^{o} 120^{c}$					
Acidity $(pK_a)$	d	a . (					
Proton gained at 25 °C	$-1.2^{a}$	-0.4 <sup>e</sup>					
Proton lost at 25 °C	15'	148					
Partition P -	0 00h	0.07h					
$C_{\rm O}$ $/C_{\rm T}$ $\sim$ at 37 °C	0.05	0.01					
Dipole moment.	$4.89^{i}$	$8.16^{j}$					
$\mu$ (dioxane) (D)							
$\mathbf{R}^1 = \mathbf{R}^2 = \mathbf{C}\mathbf{H}_3$		· · ·					
Partition, $P(Oct-H_2O)$	0.58 <sup>h</sup>	0.40 <sup>h</sup>					
at 37 °C							
$\Delta G^+$ for interconv between conformers (kcal mol <sup>-1</sup> )	11.8"	12.4'					
H <sub>3</sub> C CH <sub>2</sub> SCH <sub>2</sub> CH <sub>2</sub> -							
R' = HN N							
$R^2 = CH_3$	metiamide	cimetidine					
Partition, $P$ (Oct-H <sub>2</sub> O at pH 9.2)	$3.2^{h}$	$2.5^{h}$					
Solubility in $H_2O(37 \degree C)$							
w/v, %	$0.32^{h}$	$1.14^{h}$					
Molar, M	0.013	0.045					

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

and neutron diffraction<sup>23</sup> 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<sup>22</sup> (and also N"-cyano-N,N'-dimethylguanidine)<sup>24</sup> are indicative of considerable delocalization of  $\pi$  electrons extending over all six carbon and nitrogen atoms. Both thiourea<sup>25</sup> and cyanoguanidine<sup>26</sup> (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  $\Delta G^*$  for the interconversion between isomers are similar (11.8 kcal/mol for N,N'-dimethylthiourea<sup>27</sup> and 12.4 kcal/mol for the corresponding cyanoguanidine<sup>28</sup>). 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.<sup>29</sup>) 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<sup> $\alpha$ </sup>



$$\mathbf{R}' = \mathbf{CH}_{3}$$

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<sub>2</sub>-receptor antagonist activity, cyanoguanidine and thiourea may be classed as true bioisosteres.<sup>9,10</sup> Similarly, the partial bioisosterism of urea and thiourea in H<sub>2</sub>-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 ( $P_{\text{Oct-H}_2\text{O}} = 0.02$ )<sup>30</sup> 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-4yl)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<sup>31</sup> 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,Zforms (8a,b)] whereas cimetidine assumes only the two staggered (E,Z) configurations (9a,b) of the cyanoguanidine group.<sup>32</sup> 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 metiDurant, Ganellin, et al.



 $R \rightarrow CH_{2}XCH_{2}CH_{2}NHCNHMe$  Ia-4a  $MeNCS \qquad Ia-4a$   $MeNCS \qquad NCN$   $R \rightarrow CH_{2}XCH_{2}CH_{2}NH_{2}$  MeSC(=NCN) MeSC(=NCN)NHMe  $HN \qquad N$   $I0 \qquad Ib-4b$   $MeNH_{2}$   $MeNH_{2}$ 

amide, is excreted largely unchanged, together with small amounts of the thioether sulfoxide.<sup>33</sup> 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<sup>34</sup> and man.<sup>35</sup> 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.<sup>36-40</sup>

Synthesis. N-Methylthioureas 1a-4a and the urea 2c were made from intermediate amines 10 and methyl isothiocyanate or methyl isocyanate. N'-Cyano-Nmethylguanidines 1b-4b were synthesized (Scheme IV) from amines 10 and N-cyano-N', S-dimethylisothiourea<sup>44</sup> (method 1); from 10 and dimethylcyanodithioimidocarbonate<sup>45</sup> 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<sub>3</sub>) 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)-5methylimidazole 10 (X =  $CH_2$ ; R =  $CH_3$ ) was synthesized from N,N'-dibenzoyllysine<sup>46</sup> by a Dakin-West<sup>47</sup> rearrangement followed by cyclization (see the Experimental Section).



## Experimental Section<sup>48</sup>

NMR spectra were recorded on a Varian A-60A instrument using Me<sub>4</sub>Si 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<sup>49</sup> (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<sub>2</sub>O, afforded 1a (28.1 g, 68%).

**N-Methyl-N-[2-(imidazol-4-yl)methylthioethyl]thiourea** (3a). (i) A solution of 4-hydroxymethylimidazole hydrochloride<sup>50</sup> (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<sub>2</sub>O and recrystallized from EtOH to give 4-[(2-aminoethyl)thiomethyl]imidazole dihydrobromide (156 g, 98%): mp 178-179 °C. Anal. (C<sub>6</sub>H<sub>13</sub>Br<sub>2</sub>N<sub>3</sub>S) C, H, N, Br, S.

(ii) A solution of the amine dihydrobromide (10.0 g, 0.031 mol)in H<sub>2</sub>O was basified to pH 11 with K<sub>2</sub>CO<sub>3</sub> (8.7 g) in H<sub>2</sub>O. 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 4hydroxymethyl-5-methylimidazole hydrochloride<sup>51</sup> 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<sub>7</sub>H<sub>15</sub>Br<sub>2</sub>N<sub>3</sub>S) 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<sup>46</sup> (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<sub>2</sub>O. The precipitate was collected and recrystallized from dimethoxymethane to give 4-(4-benzamidobutyl)-2-phenyl-5oxazolone (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<sub>3</sub> and washed with dilute NaOH and dilute HCl and then dried over MgSO<sub>4</sub>. 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  $\delta$  (60 MHz, Me<sub>2</sub>SO-d<sub>6</sub>) 8.5 (t, NH),  $\approx$ 8.3 (br s, NH),  $\approx$ 7.8, 7.4 (m, C<sub>6</sub>H<sub>5</sub>), 4.4 (m, CH), 3.2 (m, NCH<sub>2</sub>), 2.1 (s, CH<sub>3</sub>), 1.5 [m, (CH<sub>2</sub>)<sub>3</sub>].

(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  $\delta$  (60 MHz, D<sub>2</sub>O) 4.3 (t, CH), 3.1 (t, NCH<sub>2</sub>), 2.35 (s, CH<sub>3</sub>), 1.7 [m, (CH<sub>2</sub>)<sub>3</sub>].

(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<sup>44</sup> (22.4 g, 0.17 mol) in acetonitrile (1 L) was heated under reflux for 48 h. Following concentration, the residue was chromatographed (SiO<sub>2</sub>-CH<sub>3</sub>CN) and the product obtained was recrystallized from CH<sub>3</sub>CN 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<sup>45</sup> (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<sub>2</sub> 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<sub>2</sub>O).

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<sub>3</sub>CN (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<sub>2</sub>-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<sub>2</sub>, 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)-5methylimidazole (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<sub>3</sub>; X = CH<sub>2</sub>) (2.27 g, 79%) which was treated directly with MeNH<sub>2</sub> 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<sub>3</sub> (15 mL) and concentrated H<sub>2</sub>SO<sub>4</sub> (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<sub>2</sub>O, the product was recrystallized from water to afford *N*,S-dimethyl-*N'*-nitroisothiourea: mp 149.5-150 °C; NMR  $\delta$  (60 MHz,  $Me_2SO-d_6$ ) 2.5 (s, SCH<sub>3</sub>), 2.9 (d, NCH<sub>3</sub>, J = 5 Hz), 9.0 (br s, NH). Anal. (C<sub>3</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>S) 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-amino-ethyl)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<sub>2</sub>-Me<sub>2</sub>CO). The product crystallized under Et<sub>2</sub>O-MeCOEt to give 2e (1.2 g, 44%).

N<sup>''</sup>-Carbamyl-N-methyl-N<sup>-</sup>[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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