Cardiotonic Agents. 6. Histamine Analogues as Potential Cardiovascular Selective H_2 Agonists

John W. Lampe,* Reda G. Hanna, Thomas A. Piscitelli, Yuo-Ling Chou, Paul W. Erhardt, William C. Lumma, Jr., Stanley S. Greenberg, William R. Ingebretsen, Dennis C. Marshall, and Jay Wiggins

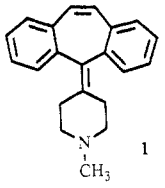
Berlex Laboratories, Inc., 110 East Hanover Avenue, Cedar Knolls, New Jersey 07927. *Received July 24, 1989*

Twenty-six alkyl and aralkyl histamine analogues were prepared as potential cardiotonic agents. Compounds were designed to allow interaction with a putative secondary aryl binding site at the H_2 receptor, the presence of which was inferred from the structure of cyproheptadine, which is known to have H_2-antagonist properties. The compounds were examined for inotropic activity in ferret papillary muscle. Potent inotropic activity was generally found in *N*-alkyl- and *N*,*N*-dialkylimidazole-4-ethanamines, whereas *N*-(amidoalkyl)imidazole-4-ethanamines and *N*-alkylimidazole-4-propanamines were at best weakly active. Five compounds were examined in screens designed to assess hemodynamic effects and gastric acid secretion in vivo. Two of these compounds, α-(3-phenyl-2-*trans*-propenyl)-1*H*-imidazole-4-ethanamine and *N*-heptyl-1*H*-imidazole-4-ethanamine, showed positive inotropic activity with minimal effects on heart rate and mean arterial pressure in vivo; however, both compounds were found to stimulate gastric acid secretion. These results demonstrate that selectivity between various H_2-receptor-mediated activities can be obtained with substituted histamine analogues.

Among the various possible approaches to the treatment of congestive heart failure with cardiotonic agents, the use of histamine H_2 agonists has been comparatively little investigated.[1] Support for this approach may be found in clinical studies which have shown significant improvement in cardiac function in patients with catecholamine-insensitive congestive cardiomyopathy who were treated with the H_2 agonist impromidine.[2] However, this approach presents challenging selectivity problems: in order for an H_2 agonist to be acceptable as a cardiotonic agent, its H_2/H_1 selectivity would have to be high, its chronotropic effects would have to be minimized, and its stimulatory effects on acid secretion at the inotropic dose would have to be negligible. In this paper we present the results of one approach to the solution of these problems.

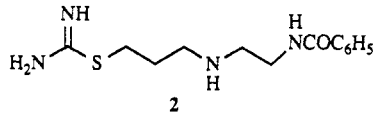
Target Design

Our basic design concept was to combine structural features taken from a known histamine antagonist with those features found in the endogenous agonist histamine itself which are known to be essential to its H_2-agonist properties. We planned in this way to generate partial agonist structures which combined potent positive inotropy with reduced efficacy for other histaminergic effects. We used cyproheptadine (1) as the starting point for this design process. Cyproheptadine is known to have histamine H_1- and H_2-antagonist activity.[3] We made the assumption that 1 fits the H_2 receptor in such a way that its tertiary amine interacts with the histamine NH_2 binding site and one of its phenyl rings is accommodated near the histamine imidazole binding site. In this binding scheme, 1 is an antagonist since it lacks a proton-relay system such as an imidazole, and thus cannot activate the receptor.[4] This receptor binding mode is shown schematically in Figure 1.



1

This mode of binding suggests the existence of a region which tolerates aromatic rings adjacent to the primary binding site of the H_2 receptor, since both aromatic rings of 1 are accommodated by the receptor. The existence of an auxiliary phenyl binding site is consistent with our finding that the benzamide-containing dimaprit analogue 2 is an H_2 agonist of modest activity, whereas its acetamide



2

analogue is inactive.[5] The recent work of Sterk and coworkers,[6] in which H_2-agonist activity was found in a series of phenyl analogues of impromidine, also lends support to this concept; however, studies by Emmett and coworkers[7] suggest that if such a binding region exists, it must be somewhat removed from the chain nitrogen binding site, since *N*-benzylhistamine is essentially inactive. We reasoned that analogues of histamine in which the histamine nucleus has been substituted by groups designed to interact with this putative phenyl binding site should still be able to fit the cardiac H_2 receptor, based on the binding concepts presented above. They should also be able to activate the receptor, since they would contain the proton-relay system necessary for activation, and thus they should retain inotropic activity. However, the compounds might be expected to display H_1-antagonist activity, by virtue of their similarity to 1. This combination of H_2-agonist and H_1-antagonist activity has previously been proposed as a beneficial one in the setting of congestive heart failure.[6] Additionally, we hoped that this structural modification might provide a way to reduce the activity of these compounds at noncardiac H_2 receptors and thus give inotropic selective compounds. The notion that some measure of cardioselectivity might be obtained in a compound series by the proper choice of a substituent which is otherwise unessential for activity has been exploited very successfully in the area of β-adrenergic agents.[8]

* Author to whom correspondence should be addressed.

(1) Erhardt, P. W. *J. Med. Chem.* **1987**, *30*, 231.
(2) Baumann, G.; Permanetter, B.; Wirtzfeld, A. *Pharmacol. Ther.* **1984**, *24*, 165.
(3) Green, J. P.; Maayani, S. *Nature* **1977**, *269*, 164.
(4) (a) Durant, G. J.; Ganellin, C. R.; Parsons, M. E. *J. Med. Chem.* **1975**, *18*, 905. (b) Weinstein, H.; Chou, E.; Johnson, C. L.; Kang, S.; Green, J. P. *Mol. Pharmacol.* **1976**, *12*, 788.
(5) Owens, A. H.; Goehring, R. R.; Lampe, J. W.; Erhardt, P. W.; Lumma, W. C., Jr.; Wiggins, J. *Eur. J. Med. Chem.* **1988**, *23*, 295.
(6) (a) Sterk, G. J.; Van der Goot, H.; Timmerman, H. *Eur. J. Med. Chem.* **1986**, *21*, 305. (b) Sterk, G. J.; Koper, J.; Van der Goot, H.; Timmerman, H. *Eur. J. Med. Chem.* **1987**, *22*, 491.
(7) Emmett, J. C.; Durant, G. J.; Ganellin, C. R.; Roe, A. M.; Turner, J. L. *J. Med. Chem.* **1982**, *25*, 1168.

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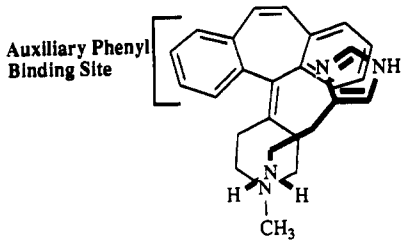


Figure 1. Overlap of 1 (solid lines) with histamine (bold lines).

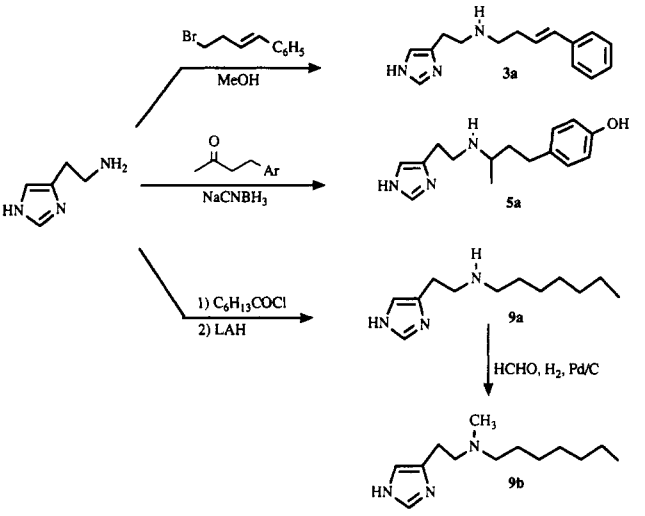
We therefore prepared a series of histamine analogues designed to be able to fit the H_2 receptor in a manner similar to that envisioned for 1. The compounds chosen for synthesis and testing fall into two main structural classes, as shown in Table I. In one class, histamine has been substituted either on or α to its chain nitrogen with alkyl or aralkyl groups of various sizes and substitution patterns. In some of the compounds, for example, **3a**, unsaturation has been introduced into the alkyl chain, in order to mimic more closely the unsaturated structure of 1. Some analogues have been prepared in which the histamine side chain has been lengthened by one carbon (**18**, **19**) so as to determine the optimum length of the side chain in these aralkyl histamines, since in some histamine analogues, such as *N*-guanylhistamine, three carbon chains are know to be preferred.[9] Two *N*-heptyl-substituted compounds were also included in the series (**9a**, **9b**), in order to test whether a simple large lipophilic alkyl group would function as well as similarly lipophilic alkyl groups containing aromatic rings.

In the other main structural class, the histamine nucleus has been substituted on the chain nitrogen by acylaminoethyl groups, in analogy to compound **2**. Several analogues in this class have been additionally substituted by methyl groups at the imidazole 5-position, a substitution known to impart H_2-receptor selectivity.[4a,10]

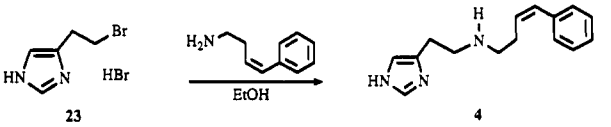
In both of the above structural classes, several nitrogen substituents have been included which have been shown previously to impart cardioselectivity to β-adrenergic agents. Substituents both which contained (**5**, **6**) and which did not contain (**10**, **17**) aromatic rings were selected, so that in these compounds as well the importance of a putative aryl binding site could be assessed.

Representative analogues were examined by using molecular modeling techniques. Structures were minimized by using molecular mechanics calculations, and low-energy conformations were compared to 1.[11] In this way we were able to show that the target structures have accessible conformations in which their imidazole, amino, and aryl groups are arranged in space in a fashion similar to the amino and two phenyl groups of 1, consistent with the putative requirements for interaction of the rigid molecule 1 with the H_2 receptor. Examples of these structural comparisons may be seen in Figure 2. Overlaps of 1 with **4** and of 1 with **20** are shown, demonstrating for these compounds the good correspondence between the structural features in question.

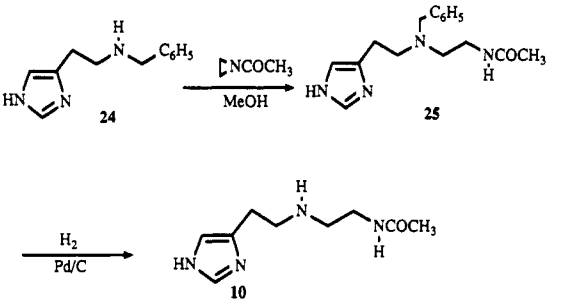
Scheme I



Scheme II



Scheme III



Chemistry

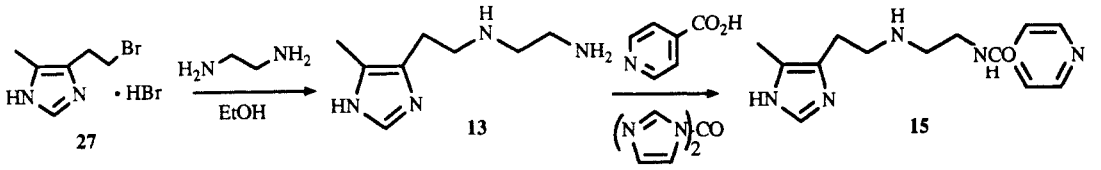
Many of the compounds in this study could be prepared conveniently by alkylation of histamine itself, either by direct alkylation with an appropriate alkyl halide (**3a**), by reductive alkylation with a carbonyl compound and $NaCNBH_3$ using the method of Borch[12] (**5a**, **7a**, **8**, **12**), or by acylation with an acid chloride followed by $LiAlH_4$ reduction of the resulting amide (**9a**). Tertiary amine products were then prepared by further reductive alkylation of the secondary amines, either by the method of Borch (**3b**, **5d**, **7b**) or by hydrogenation in the presence of excess aldehyde (**5b**, **5c**, **9b**). Representative examples are shown in Scheme I.

Other syntheses were used when either the availability of appropriate starting materials or unfavorable reactivity did not allow the use of the above methods. Two compounds (**4**, **6**) were best prepared by reaction of 4-(2-bromoethyl)imidazole hydrobromide (**23**) a compound readily available by using the preparation of Bloemhoff and Kerling,[13] with excess amine in an alcoholic solvent, as shown in Scheme II.

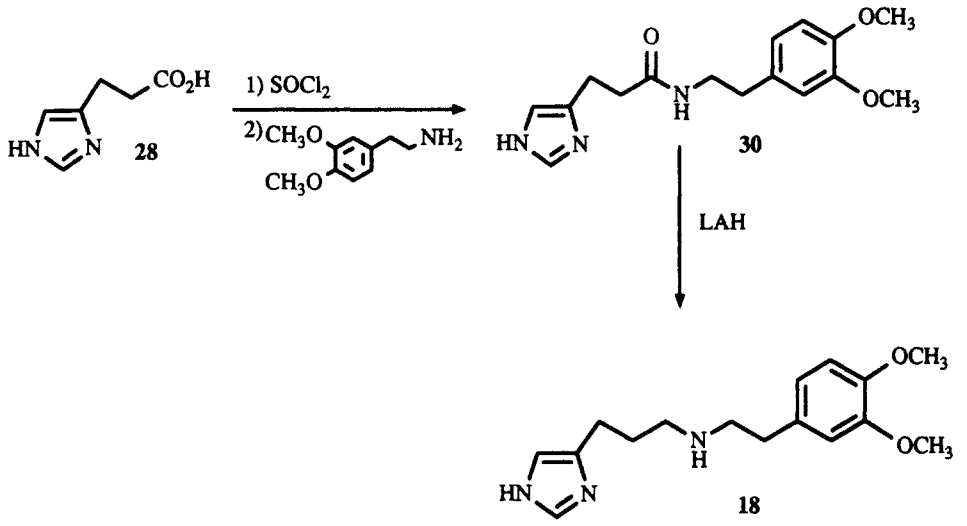
Compounds of the type **10**, **11**, and **14**–**17** were prepared by one of two routes. In the first of these routes, shown

(8) Smith, L. H. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 201. See also references to β-agonists found in ref 1.
(9) Parsons, M. E.; Blakemore, R. C.; Durant, G. J.; Ganellin, C. R.; Rasmussen, A. C. *Agents Actions* **1975**, *5*, 464.
(10) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Roe, A. M.; Slater, R. A. *J. Med. Chem.* **1976**, *19*, 923.
(11) Molecular mechanics calculations were carried out with the use of the MMFF program within CHEMLAB-II, Revision 9.1, a product of Molecular Designs, Ltd., San Leandro, CA 94577. Structures were compared within CHEM-X, developed and distributed by Chemical Design, Ltd., Oxford, England.
(12) (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (b) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.
(13) Bloemhoff, W.; Kerling, K. E. T. *Recl. Trav. Chem. Pays-Bas* **1970**, *89*, 1181.

Scheme IV



Scheme V



in Scheme III, *N*-benzylhistamine **24** was treated with an *N*-acylaziridine[14] to give the corresponding amidoalkylated product (**25**, **26**), which was then debenzylated to give the desired target compound (**10**, **11**) in fair yield. The second route, which provided somewhat better overall yields, is shown in Scheme IV. Reaction of 4-(2-bromoethyl)-5-methylimidazole (**27**) with excess ethylenediamine, by analogy to the method of Durant and co-workers,[15] led easily to the *N*-(2-aminoethyl)histamine compound **13**. In the case of the arylamides **14–16**, selective acylation of **13** to give the desired amides was best carried out by the reaction of the amine with the corresponding aroylimidazole. Compound **7** proved resistant to this approach; however, it was found that reaction of 2 equiv of **13** with phenyl morpholine-4-carboxylate in the absence of solvent provided the desired urea **17** in acceptable yield.

Compounds **18** and **19**, in which the histamine side chain has been lengthened by one carbon atom, were conveniently prepared by reaction of an amine with the acid chloride from dihydrourocanic acid, **29**, followed by $LiAlH_4$ reduction of the resulting amide, as shown in Scheme V. This provides a ready route to the three carbon chain analogues, which might otherwise be difficult to obtain.

A somewhat more involved approach proved necessary for the preparation of α-branched compounds **20** and **21**, shown in Scheme VI. Alkylation of malonate **32** with 4-(chloromethyl)imidazole hydrochloride[16] led under most conditions to decomposition of the halo compound; however, if the alkylation was carried out at low temperature in THF containing the minimal volume of ethanol necessary to dissolve the halo compound, good yields on the alkylation product **33** were obtained. Decarboethoxylation of **33** using the method of Krapcho[17] followed by ester

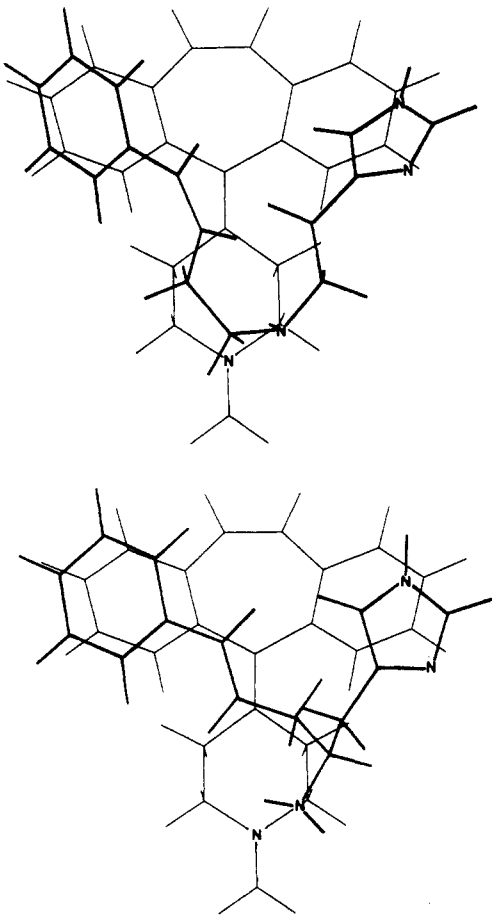


Figure 2. Overlap of **1** (solid lines) with **4** (bold lines) (top). Overlap of **1** (solid lines) with **20** (bold lines) (bottom).

hydrolysis provided acid **35**; attempted direct hydrolytic decarboxylation under acidic or basic conditions led to complex product mixtures. Reaction of acid **35** with diphenyl phosphorazidate[18] gave an isocyanate which cy-

(14) (a) Goldberg, A. A.; Kelly, W. *J. Chem. Soc.* **1948**, 1919. (b) Bestian, H. *Ann.* **1950**, *566*, 210.
(15) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Roe, A. M. GB 1341375 (19 December 1973).
(16) Kelley, J. L.; Miller, C. A.; McLean, E. W. *J. Med. Chem.* **1977**, *20*, 721.
(17) Krapcho, A. P. *Synthesis* **1982**, 805, 893.

Table I. Compounds Studied

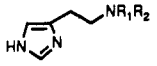
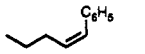
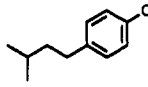
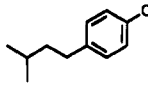
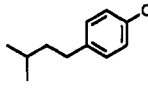
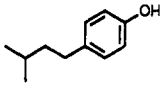
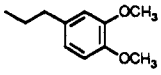
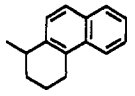
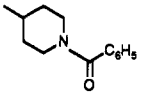
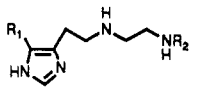
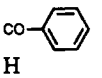
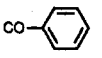
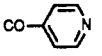
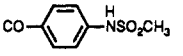
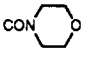
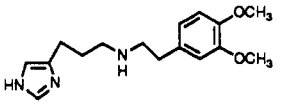
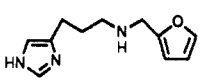
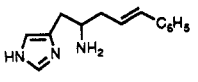
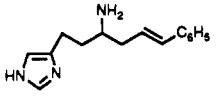
	no.	R_1	R_2
	**3a**	H	
	3b	CH_3	
	4	H	
	5a	H	
	5b	CH_3	
	5c	C_2H_5	
	5d	nC_3H_7	
	6	H	
	7a	H	
	7b	CH_3	
	8	H	
	9a	H	nC_7H_{15}
	9b	CH_3	nC_7H_{15}
	22	H	COC_6H_{13}
	12	H	
	**10**	H	$COCH_3$
	11	H	
	13	CH_3	H
	14	CH_3	
	15	CH_3	
	16	CH_3	
	17	CH_3	
	**18**		
	**19**		
	**20**		
	**21**		

Table II. In Vitro Inotropic Activity

compd	ferret papillary:[a] C_{20}, μmol/L	nadolol block[b]	cimetidine block[c]
3a	14, 21	B	
3b	1, 6	B	NB
4	13, 41		
5a	2, 5	B	NB
5b	0.13, 0.16	NB	B
5c	4, 6	B	B
5d	4.9 (0.7–10)	B	B
6	2, 5	B	B
7a	27 (0.2–50)	B	
7b	6.7 (1–10)	NB	B
8	>10 (1–20)[d]		
9a	1, 11	NB	B
9b	>57 (13–NR)		
10	46, 85		
11	>66 (43–NR)		
12	>27 (2–60)[d]		
13	NR, NR		
14	27 (1–47)		
15	NR, NR		
16	20, 40		
17	>90 (70–NR)		
18	(–)2, (–)5[e]		
19	33 (15–67)		
20	13 (2–30)	NB	B
21	NR, NR, (–)45[e]		
22	7.3 (1–10)	NB	B
40 (histamine)	0.42 (0.1–1)	NB	B
41 (4-methylhistamine)	0.70 (0.1–2)	NB	B
42 (dimaprit)	4, 13	NB	B

[a] Concentration of drug which gives a 20% increase in the force contraction. Data reported are values from individual experiments; where three or more experiments were run, data are reported as the mean and range of values. NR = not reached. [b] Results of inotropy blocking studies in the presence of 100 μM nadolol. B = blocked, NB = not blocked. [c] Results of inotropy blocking studies in the presence of 10 μM cimetidine. B = blocked, NB = not blocked. [d] One of four preparations did not respond. [e] Concentration of drug which gives a 20% decrease in the force of contraction.

clized to give the imidazopyrimidine **36** in good yield. Basic hydrolysis then afforded the desired amine **20**. A similar but slightly modified synthesis was used to prepare compound **21**.

Pharmacology

Test compounds were initially examined in ferret papillary muscle[19] to assess their inotropic activity. Compounds showing a 20% increase in contractile force at less than 15 μM were judged to be active. These compounds were further investigated in papillary muscle in the presence of nadolol (100 μM), in order to eliminate the possibility that their activity was due to β-adrenergic-mediated pathways, and then in the presence of cimetidine (10 μM), in order to judge how much of their activity was due to stimulation of H_2-receptors. Dose–response relationships were determined in the presence of each of the antagonists; an increase of at least 1 order of magnitude in the measured C_{20} was taken as indicative of a blocked inotropic response. In this way, five compounds, **5b**, **7b**, **9a**, **20**, and **22**, were identified which were potent inotropes and whose inotropic activity stemmed from an H_2-receptor-mediated mechanism. The data from these screens are shown in Table II.

These five compounds were studied in screens designed to assess their selectivity. Compounds were examined in

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(19) Hagedorn, A. A., III; Erhardt, P. W.; Lumma, W. C., Jr.; Wohl, R. A.; Cantor, E.; Chou, Y.-L.; Ingebretsen, W. R.; Lampe, J. W.; Pang, D.; Pease, C. A.; Wiggins, J. *J. Med. Chem.* **1987**, *30*, 1342.

Scheme VI

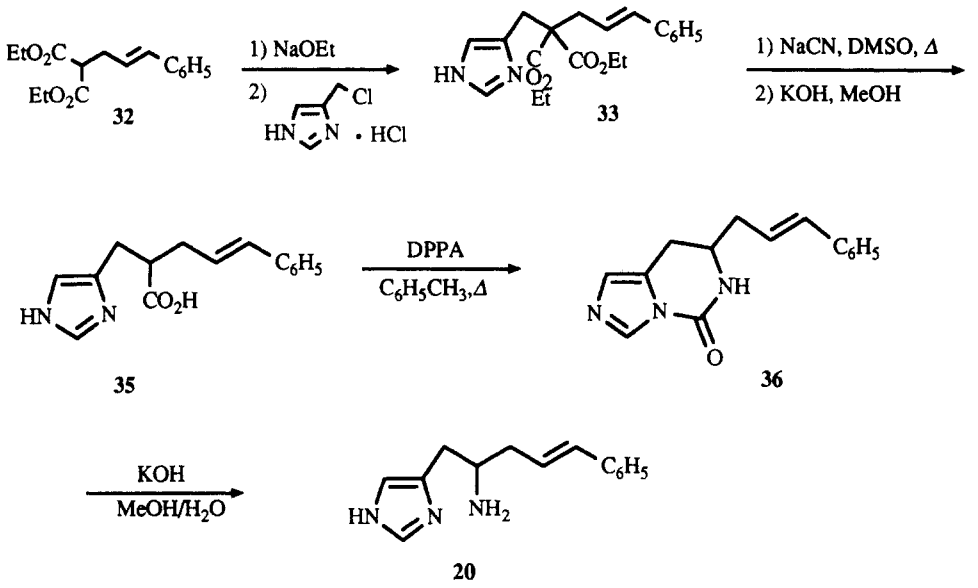

Table III. Guinea Pig in Vitro Activity

compd	atrium: EC_{50}, μmol/L[a]	ileum: EC_{50}, μmol/L[b]
5b	NR	128[c]
7b	NR	165 ± 5.0
9a	71.0[c]	7.88 ± 0.25
20	184[c]	7.23 ± 1.7
22	NR	50.6 ± 1.7
40 (histamine)	0.98 ± 0.65	0.24 ± 0.01
41 (4-methylhistamine)	3.3 ± 0.25	13.8 ± 1.6
42 (dimaprit)	4.6 ± 0.38	10.4 ± 0.60

[a] Concentration of drug which gives 50% of the chronotropic effect of histamine at 5 μg/mL. Values are expressed as the mean ± SEM for three separate dose-response determinations. NR = not reached. [b] Concentration of drug which gives 50% of the contractile response of histamine at 0.5 μg/mL. Values are expressed as the mean ± SEM for three separate dose-response determinations. [c] Inhibits. Values indicate the IC_{50} in μmol/L.

spontaneously beating guinea pig right atria by using the method of Black and co-workers[20] as a measure of their chronotropic activity. Since H_1-agonist activity would be undesirable in an H_2-agonist cardiotonic, and since an H_1 agonist would be expected to show inotropic activity in the above ferret papillary muscle screen, activity at H_1 receptors was determined in vitro by measuring the effect of the compounds on the contractile response of guinea pig ilea, using the method of Magnus and Arch.[21] In both screens, the responses to active compounds were shown to be sensitive to the appropriate antagonists (cimetidine and mepyramine, respectively). These data may be seen in Table III.

Two methods were used to assess the effects of the test compounds on gastric acid secretion in vivo. Stimulation of secretion in rats was measured by using the method of Hagiwara and co-workers.[22] Compounds were additionally studied in a previously unpublished model which allows the simultaneous determination of effects of compounds on gastric acid secretion, cardiac contractility, arterial pressure, and airway resistance in pentobarbital-anesthetized guinea pigs. The animals' stomachs were prepared with ligatures to allow containment of gastric fluids, and test compounds were infused (iv) over a 60-min period during which the hemodynamic parameters were monitored. The doses used in each study were chosen on the basis of the relative inotropic doses measured in papillary muscle. At the end of the experiment the stomachs were removed and their contents were analyzed for volume and total milliequivalents of acid. Results from the in vivo tests are shown in Table IV.

Results and Discussion

Many of the compounds studied displayed potent inotropic activity in papillary muscle. Essentially all of the potent compounds derived at least part of their inotropy from H_2-receptor-mediated pathways, as evidenced by the cimetidine blocking studies; however, many of them displayed β-receptor-mediated inotropy as well. Several structure–activity relationships are apparent in the data and are worthy of mention. Alkyl- and aralkyl-substituted histamines were among the more potent compounds prepared; in contrast, amidoalkyl-substituted histamines were less potent. Intriguingly, compounds in which the histamine chain nitrogen is substituted with two alkyl groups, one of which is methyl, tended to be very potent, and were generally more potent than the corresponding secondary amine compounds (for example, **5b** compared to **5a**). This stands in contrast to work of Durant and co-workers[10] and Ganellin and co-workers,[23] who found that for histamine itself, activity decreases with increasing chain nitrogen methylation. Substitution of larger alkyl groups (**5c**, **5d**) for methyl resulted in a loss in activity. The activity of the amide analogue **22** is very surprising, as a basic nitrogen is generally assumed to be necessary for H_2-agonist activity.[4a] The possibility that **22** causes stimulation of H_2 receptors by way of some indirect mechanism cannot be eliminated by our data and would provide an explanation for the unexpected activity of this compound. Finally, three-carbon homologues of alkyl histamines (**18**, **19**) were less potent than the corresponding two carbon compounds, in agreement with the results seen with histamine itself.[24]

(20) Black, J. W.; Duncan, W. A. M.; Durant, C. J.; Ganellin, C. R.; Parsons, E. M. *Nature* **1972**, *236*, 385.
(21) Magnus, R.; Arch, F. D. *Ges. Physiol.* **1904**, *102*, 123.
(22) Hagiwara, M.; Watanabe, H.; Kawata, K.; Watanabe, K. *Yakugaku Zasshi* **1984**, *104*, 1090.
(23) Ganellin, C. R.; Port, G. N. J.; Richards, W. G. *J. Med. Chem.* **1973**, *16*, 616.
(24) Paton, D. M. In *Histamine and Antihistamines*; Schachter, M., Ed.; Pergamon Press: Oxford, 1973; Vol. 1, Chapter 1, pp 3–24.

Surprisingly, none of the five compounds chosen for further study displayed any agonist activity in guinea pig atria; in fact, two compounds, **9a** and **20**, were modest inhibitors of the histamine induced chronotropic response (Table III). This could suggest the existence of different H_2-receptor subtypes mediating inotropic and chronotropic effects; alternatively, different tissue selectivities could be responsible for the differing activities. The inhibition shown by **9a** and **20** suggests in addition that these compounds are partial H_2 agonists. All compounds tested showed modest H_1-agonist activity in guinea pig ilea, with the exception of **5b**, which was an antagonist. Mixed H_2-agonist/H_1-antagonist activity of this type has been reported previously by Sterk and co-workers.[6] The ratio of H_2 activity, as measured in papillary muscle, to H_1 activity in ileum was greater than that seen for histamine (**40**) for all compounds tested, and was between that seen for dimaprit (**42**) and 4-methylhistamine (**41**) for all compounds except **20**. This comparison shows that these compounds have selectivity for the inotropic H_2 receptor and suggests that at least part of their activity stems from direct action at the receptor.

Two compounds, **5b** and **7b**, were essentially inactive when examined in vivo. The three remaining compounds were generally comparable to dimaprit in overall selectivity, although they were substantially less potent. Compounds **9a** and **20** showed proportionately less stimulation of heart rate, in agreement with the results seen in vitro in atria. The possibility that these modest in vivo heart rate effects stem from a nonhistaminergic mechanism cannot be eliminated by our data. All test compounds showed an increase in airway resistance comparable to that shown by histamine, again suggesting H_1 activity in these compounds. No evidence for selectivity for inotropy over acid secretion stimulation was observed for the test compounds in the guinea pig. The effects of acid secretion seen in the rat generally support those seen in guinea pig; compound **20** was found to be inactive in the rat assay, however.

The compounds in this study demonstrate that it is possible to make substantial modifications on the histamine nucleus and still retain significant H_2-histaminergic activity. Additionally, we have shown that this modification can lead to compounds with improved inotropic selectivity, at least when compared to chronotropy. We were unable to obtain any significant reduction in the acid secretion stimulatory activity of these compounds by using the substitutions studied here. No strong evidence for or against the existence of an aryl binding site was found in this limited compound set, as both alkyl and aralkyl compounds proved active; however, the compounds do support the existence of a site which tolerates large lipophilic groups. Nevertheless, this work demonstrates in principal the validity of the substituted histamine approach to the preparation of inotropic selective H_2 agonists.

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Sargent-Welch 3-300 or a Beckman Acculab 2 infrared spectrometer. NMR spectra were recorded at 60 MHz on a Varian EM-360 or at 300 MHz on a Varian XL-300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal standard of tetramethylsilane for all solvents except D_2O, where sodium 3-(trimethylsilyl)propionate was used as standard. Elemental analyses were performed by Galbraith Laboratories, Microlit Laboratories, or the Berlex Analytical Section; results are within ±0.4% of the calculated values unless otherwise stated. Organic extracts were dried over magnesium sulfate prior to evaporation. Solid products were routinely dried at 60 °C under reduced pressure for a minimum of 12 h. Reactions were monitored by thin-layer chromatography on silica gel (Merck) and alumina (Merck) plates and visualized by UV and iodoplatinate reagent.

***N*-(4-Phenyl-3-*trans*-butenyl)-1*H*-imidazole-4-ethanamine Dihydrochloride (3a).** Histamine (20.94 g, 188 mmol) and *trans*-1-iodo-4-phenyl-3-butene[25] (9.93 g, 38.5 mmol) were combined in 300 mL of methanol, and the mixture was heated at reflux for 48 h. The mixture was then evaporated, and the residue was dissolved in aqueous HCl (pH = 1). The mixture was extracted twice with Et_2O, and the pH was adjusted to 10 with concentrated NH_4OH. Extraction of this mixture with CH_2Cl_2 (three times) followed by drying of these extracts and evaporation gave a residue, which was converted to its HCl salt by treatment with ethanolic HCl. Recrystallization of the salt from methanol gave 2.64 g (22%) of the title compound as an off-white solid: mp 246–249 °C; ^{1}H NMR (DMSO-d_6) δ 2.62 (quar, 2 H), 3.07 (t, 2 H), 3.15 (t, 2 H), 3.30 (m, 4 H), 6.32 (dt, 1 H), 6.53 (d, 1 H), 7.24 (t, 1 H), 7.33 (t, 2 H), 7.43 (d, 2 H), 7.56 (s, 1 H), 9.05 (s, 1 H), 9.47 (br s, 2 H). Anal. ($C_{15}H_{19}N_3$·2HCl) C, H, N.

***N*-(2-Furanylmethyl)-1*H*-imidazole-4-ethanamine Dihydrochloride Hydrate (7a).** A mixture of 27.60 g (0.150 mol) of histamine dihydrochloride, 17.4 g (0.181 mol) of furfural, 12.30 g (0.150 mol) of sodium acetate, and 80 g of 3-Å molecular sieves in 500 mL of methanol was stirred for 45 min at room temp. Sodium cyanoborohydride (6.28 g, 0.100 mol) was then added, and the mixture was stirred for 1.5 h. The mixture was then filtered, and the filtrate was diluted with 400 mL of 1 N NaOH and extracted with seven 300-mL portions of CH_2Cl_2. The extracts were dried and evaporated, and the residue was chromatographed on silica gel, eluting with 94.5:5:0.5 CH_2Cl_2/methanol/concentrated NH_4OH to give an oil which was converted to its HCl salt with methanolic HCl. Recrystallization of this salt from ethanol gave 10.32 g (24%) of the title compound as a white solid: mp 200–204 °C; ^{1}H NMR (DMSO-d_6) δ 3.16 (t, 2 H), 3.26 (t, 2 H), 4.24 (s, 2 H), 6.52 (m, 1 H), 6.70 (d, 1 H), 7.53 (s, 1 H), 7.77 (s, 1 H), 9.07 (s, 1 H). Anal. ($C_{10}H_{13}N_3O$·2HCl·H_2O) C, H, Cl, N.

***N*-[3-(4-Hydroxyphenyl)-1-methylpropyl]-1*H*-imidazole-4-ethanamine Dihydrochloride (5a).** Reaction of histamine dihydrochloride with 4-(4-hydroxyphenyl)-2-butanone on a 18.3-mmol scale following the procedure used for the preparation of **7a** gave 2.25 g (37%) of the title compound as a white solid after recrystallization from ethanol/Et_2O: mp 233–234 °C; ^{1}H NMR (DMSO-d_6) δ 1.33 (d, 3 H), 1.74 (m, 1 H), 2.05 (m, 1 H), 2.50 (m, 1 H), 2.60 (m, 1 H), 3.0–3.6 (m, 5 H), 6.71 (d, 2 H), 7.05 (d, 2 H), 7.58 (s, 1 H), 9.08 (s, 1 H), 9.26 (br s, 1 H), 9.35 (br s, 2 H). Anal. ($C_{15}H_{21}N_3O$·2HCl) C, H, N.

***N*-(1,2,3,4-Tetrahydrophenanthren-1-yl)-1*H*-imidazole-4-ethanamine Dihydrochloride Hemihydrate (8).** Reaction of histamine dihydrochloride with 1,2,3,4-tetrahydrophenanthren-1-one on a 24-mmol scale for 14 days, following the procedure used for the preparation of **7a**, gave 6.56 g of the crude salt, which was recrystallized from methanol/Et_2O to give 2.77 g (31%) of the title compound as a white solid: mp >250 °C; ^{1}H NMR (D_2O) δ 1.98–2.22 (m, 3 H), 2.36 (m, 1 H), 3.00 (m, 1 H), 3.28 (m, 3 H), 3.52 (t, 2 H), 4.67 (t, 1 H), 7.41 (d, 1 H), 7.45 (s, 1 H), 7.66 (m, 2 H), 7.83 (d, 1 H), 7.95 (m, 1 H), 8.07 (m, 1 H), 8.67 (d, 1 H). Anal. ($C_{19}H_{21}N_3$·2HCl·0.5H_2O) C, H, N.

***N*-(1-Benzoylpiperidin-4-yl)-1*H*-imidazole-4-ethanamine Dihydrochloride (12).** Reaction of histamine dihydrochloride with 1-benzoyl-4-piperidone on a 25.1-mmol scale, following the procedure used for the preparation of **7a**, with the additional modification that sodium acetate was omitted, gave on evaporation of the reaction mixture a residue which was partitioned between EtOAc and saturated aqueous K_2CO_3. The EtOAc extracts were dried and evaporated to give a residue which was chromatographed on silica gel, with use of a gradient elution from 99:1 to 90:10 acetonitrile/concentrated NH_4OH. The chromatographed material was converted to its HCl salt in methanol, and the salt was recrystallized from 2-propanol to give 2.81 g (30%) of the title compound as a white solid: mp 192–194 °C dec; ^{1}H NMR (D_2O) δ 1.56–1.84 (m, 2 H), 2.11 (br d, 1 H), 2.33 (br d, 1 H), 3.01 (br t, 1 H), 3.23 (t, 2 H), 3.25 (m, 1 H), 3.47 (t, 2 H), 3.60 (m, 1 H),

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Table IV. In Vivo Pharmacology

	hemodynamic guinea pig[a]						
compd	n	dose, mg/kg per h	dP/dt	heart rate	mean arterial pressure	airway overflow	total acid secretion	rat gastric acid secretion:[b] ED_{50}, mg/kg (sc)
5b	2	10	29 ± 9	−9 ± 13	5 ± 8	39 ± 39	22 ± 27	NC
7b	2	10	−6 ± 27	−8 ± 4	−22 ± 9	51 ± 38	221 ± 29	15.3 ± 1.7
9a	5	75	155 ± 46	14 ± 4	15 ± 9	150 ± 20	220 ± 16	10.7 ± 1.2
20	6	30	68 ± 15	5 ± 4	−18 ± 6	45 ± 9	169 ± 18	NC
22	6	7.5	146 ± 39	41 ± 9	33 ± 11	197 ± 27	160 ± 20	5.9 ± 0.4
40	6	1	132 ± 35	30 ± 2	1 ± 13	109 ± 21	123 ± 25	2.7 ± 0.4
42	6	1	93 ± 32	19 ± 6	−25 ± 9	11 ± 8	91 ± 25	3.1 ± 0.1

[a] Values indicate average maximum percent change from control during the 10-min period subsequent to completion of the infusion for the parameters in question, and are expressed as the mean ± SEM. [b] Values indicate the dose necessary to give a 50% increase in acid secretion over control and are expressed as the mean ± SEM for three separate dose–response determinations. NC = no change.

3.86 (br d, 1 H), 4.66 (br d, 1 H), 7.45 (m, 3 H), 7.54 (m, 3 H), 8.69 (d, 1 H). Anal. ($C_{17}H_{22}N_4O$·2HCl) C, H, N.

***N*-[2-(1*H*-Imidazol-4-yl)ethyl]heptanamide (22).** To a suspension of 46.0 g (250 mmol) of histamine dihydrochloride in 500 mL of pyridine at 0 °C was added 42.6 mL (275 mmol) of heptanoyl chloride. The mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was concentrated, and the residue was dissolved in water. The pH of the mixture was adjusted to 9 with NaOH, and the mixture was extracted three times with CH_2Cl_2. On concentration of the CH_2Cl_2 a solid appeared, which was collected by filtration and recrystallized from ethanol/EtOAc to give 17.0 g (30%) of the title compound as a white solid: mp 134–136 °C; ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 3 H), 1.23 (m, 6 H), 1.46 (t, 2 H), 2.03 (t, 2 H), 2.60 (t, 2 H), 3.24 (quar, 2 H), 6.76 (s, 1 H), 7.50 (s, 1 H), 7.84 (s, 1 H), 11.82 (s, 1 H). Anal. ($C_{12}H_{21}N_3O$) C, H, N.

***N*-Heptyl-1*H*-imidazole-4-ethanamine Dihydrochloride (9a).** To a solution of 3.08 g (81.4 mmol) of $LiAlH_4$ in 300 mL of THF at 0 °C was added in a slow stream a solution of 15.2 g (67.8 mmol) of **22** in 1 L of THF (some warming is necessary to prepare this solution). The mixture was then heated at reflux for 18 h. The reaction mixture was cooled, 17 mL (17 mmol) of a 1.0 M solution of $LiAlH_4$ in THF was added, and the mixture was heated at reflux for 4 h. The mixture was cooled, and the reaction was quenched by sequential addition of 4 mL of water, 4 mL of 15% aqueous NaOH, and 12 mL of water. The mixture was filtered through Celite, and the filtrate was concentrated to an oil, which was converted to its HCl salt by treatment with ethanol and saturated ethereal HCl. Recrystallization of the salt from ethanol/acetonitrile gave 8.95 (47%) of the title compound as a white solid: mp 235–237 °C; ^{1}H NMR (DMSO-d_6) δ 0.77 (t, 3 H), 1.17 (br s, 8 H), 1.56 (br s, 2 H), 2.78 (br s 2 H), 3.08 (d, 2 H), 3.15 (br s, 2 H), 7.47 (s, 1 H), 9.00 (s, 1 H), 9.39 (br s, 2 H). Anal. ($C_{12}H_{23}N_3$·2HCl) H, N, Cl; C: calcd, 51.06; found, 50.60.

***N*-[3-(4-Hydroxyphenyl)-1-methylpropyl]-*N*-propyl-1*H*-imidazole-4-ethanamine (5d).** Reaction of **5a** with propionaldehyde on a 15.3-mmol scale following the procedure used for the preparation of **7a** gave a crude product which was chromatographed on silica gel, with use of a gradient elution from 99:1 to 97:3 acetonitrile/concentrated NH_4OH, to give 1.31 g (28%) of the title compound as an orange oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H), 0.89 (d, 3 H), 1.40 (m, 3 H), 1.62 (m, 1 H), 2.50 (m, 9 H), 3.0–4.0 (br m, 1 H), 6.60 (d, 1 H), 6.75 (s, 1 H), 7.00 (d, 1 H), 7.54 (s, 1 H), 9.0–9.4 (br s, 1 H). Anal. ($C_{18}H_{27}N_3O$) C, H, N.

***N*-(2-Furanylmethyl)-*N*-methyl-1*H*-imidazole-4-ethanamine Diphosphate (7b).** To a suspension of 7.92 g (30.0 mmol) of **7a** in 100 mL of acetonitrile was added 2.40 mL (2.60 g, 32.1 mmol) of 37% aqueous formaldehyde and 2.30 g (36.6 mmol) of sodium cyanoborohydride, and the mixture was stirred for 2 h. To this mixture was added 200 mL of 1 N NaOH, and this solution was extracted four times with CH_2Cl_2 (150 mL). The organic extracts were washed with 200 mL of brine, dried, and evaporated. The residue was chromatographed on silica gel, eluting with 94.5:5:0.5 CH_2Cl_2/methanol/concentrated NH_4OH, and the chromatographed material was further purified by crystallization of its oxalate salt from methanol/2-propanol. The oxalate was converted by way of the free base to the corresponding phosphate salt, which was crystallized from methanol to give 1.52 g (13%) of the title compound as a white solid: mp 173–179 °C; ^{1}H NMR (D_2O) δ 2.92 (s, 3 H), 3.26 (t, 2 H), 3.50 (t, 2 H), 4.48 (s, 2 H), 6.56 (m, 1 H), 6.76 (d, 1 H), 7.32 (s, 1 H), 7.65 (s, 1 H), 8.58 (s, 1 H). Anal. ($C_{11}H_{15}N_3O$·$2H_3PO_4$) C, H, N.

***N*-Methyl-*N*-(4-phenyl-3-*trans*-butenyl)-1*H*-imidazole-4-ethanamine Ditosylate 0.25-Hydrate (3b).** Methylation of **3a** on a 16-mmol scale following the procedure used for the preparation of **7b** gave a crude product which was chromatographed on silica, eluting with 97:3 acetonitrile/concentrated NH_4OH. The chromatographed material was crystallized as its ditosylate salt from methanol/Et_2O to give 830 mg (9%) of the title compound as a white solid: mp 147–150 °C; ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 6 H), 2.58 (quar, 2 H), 2.86 (s, 3 H), 3.12 (t, 2 H), 3.27 (t, 2 H), 3.42 (m, 2 H), 6.21 (m, 1 H), 6.55 (d, 1 H), 7.12 (d, 4 H), 7.27 (d, 1 H), 7.38 (t, 2 H), 7.41 (d, 2 H), 7.50 (d, 4 H), 7.58 (s, 1 H), 9.04 (s, 1 H). Anal. ($C_{16}H_{21}N_3$·$2C_7H_8O_3S$·$0.25H_2O$) C, H, N, S.

***N*-Ethyl-*N*-[3-(4-hydroxyphenyl)-1-ethylpropyl]-1*H*-imidazole-4-ethanamine (5c).** A mixture of 14.2 g (42.6 mmol) of **5a** as its dihydrochloride salt, 18.8 mL (426 mmol) of acetaldehyde, and 7 g of 10% Pd/C in 700 mL of ethanol was shaken on a Parr apparatus under a hydrogen atmosphere of 45 psi for 24 h. The mixture was filtered through Celite, and the filtrate was evaporated. The resulting oil was converted to its free base by partitioning between saturated aqueous $NaHCO_3$ and CH_2Cl_2, and the CH_2Cl_2 extracts were dried and evaporated. Chromatography of the resulting oil on silica gel, eluting with 98:2 acetonitrile/concentrated NH_4OH, afforded 4.2 g (34%) of the title compound as an orange oil: ^{1}H NMR (DMSO-d_6) δ 0.89 (d, 2 H), 0.95 (t, 3 H), 1.42 (m, 1 H), 1.62 (m, 1 H), 2.30–2.73 (m, 9 H), 3.4 (br s, 1 H), 6.64 (d, 1 H), 6.67 (s, 1 H), 6.95 (d, 1 H), 7.48 (s, 1 H), 9.15 (br s, 1 H). Anal. ($C_{17}H_{25}N_3O$·$0.25H_2O$) C, H, N.

***N*-[3-(4-Hydroxyphenyl)-1-methylpropyl]-*N*-methyl-1*H*-imidazole-4-ethanamine (5b).** Reaction of **5a** and 37% aqueous formaldehyde on a 27-mmol scale for 48 h following the procedure used for the preparation of **5c** gave a crude oil which was chromatographed on silica gel, with use of a gradient elution from 100% acetonitrile to 97.5:2.5 acetonitrile/concentrated NH_4OH. The pure fractions were pooled and evaporated from methanol, and the resulting oil was dried at 70 °C and 0.1 Torr to give 2.1 g (27%) of the title compound as a methanol-containing orange oil: ^{1}H NMR (DMSO-d_6) δ 0.88 (d, 1 H), 1.40 (m, 1 H), 1.64 (m, 1 H), 2.14 (s, 3 H), 2.50 (m, 7 H), 3.30 (s, ~1 H, methanol), 6.24 (d, 2 H), 6.64 (s, 1 H), 6.74 (d, 2 H), 7.50 (s, 1 H), 9.20 (br m, 1 H). Anal. ($C_{16}H_{23}N_3O$·$0.35\ CH_3OH$) C, H, N.

***N*-Heptyl-*N*-methyl-1*H*-imidazole-4-ethanamine (9b).** Reaction of **9a** and 37% aqueous formaldehyde on a 20.8-mmol scale for 48 h following the procedure used for the preparation of **5c** gave the crude product as an oil which was chromatographed on silica gel, with use of a gradient elution from 100% acetonitrile to 97:3 acetonitrile/concentrated NH_4OH, to afford 2.2 g (47%) of the title compound as an orange oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H), 1.28 (s, 8 H), 1.47 (m, 2 H), 2.29 (s, 3 H), 2.41 (t, 2 H), 2.65 (t, 2 H), 2.77 (t, 2 H), 6.78 (s, 1 H), 7.51 (s, 1 H), 10.75 (br s, 1 H). Anal. ($C_{13}H_{25}N_3$) H, N; C: calcd, 69.91: found, 69.48.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1*H*-imidazole-4-ethanamine Dihydrochloride (6).** A mixture of 3.9 g (21 mmol) of 3,4-dimethoxyphenethylamine and 1.80 g (7.0 mmol) of 4-(2-bromoethyl)imidazole hydrobromide[13] in 25 mL of ethanol was heated at reflux for 30 h. The mixture was evaporated, the residue was dissolved in 50 mL of saturated aqueous Na_2CO_3, and this

solution was extracted with CH_2Cl_2 (4 × 75 mL). The organic extracts were dried and evaporated, and the residue was triturated with 2:1 Et_2O/hexane. The residue was then chromatographed on silica gel, by eluting with 87:10:3 CH_2Cl_2/ethanol/concentrated NH_4OH. The chromatographed material was converted to its HCl salt with the use of ethanolic HCl and was recrystallized from ethanol/Et_2O to give 610 mg (25%) of the title compound as a white solid: mp 215–216 °C; ^1H NMR (DMSO-d_6) δ 2.93 (m, 2 H), 3.15 (m, 4 H), 3.29 (m, 4 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 6.77 (d, 1 H), 6.89 (s, 1 H), 6.91 (d, 1 H), 7.55 (s, 1 H), 9.05 (d, 1 H), 9.50 (br s, 1 H). Anal. ($C_{15}H_{21}N_3O_2$·2HCl) C, H, N.

***N*-(4-Phenyl-3-*cis*-butenyl)-1*H*-imidazole-4-ethanamine 0.4-Hydrate (4).** Reaction of *cis*-4-phenyl-3-butenamine[26] with 4-(2-bromoethyl)imidazole hydrobromide[13] on a 27-mmol scale following the method used for the preparation of **6** gave 2.40 g (37%) of the title compound as an orange oil after chromatography on silica gel, eluting with 98:2 acetonitrile/concentrated NH_4OH: ^1H NMR (DMSO-d_6) δ 2.43 (quar, 2 H), 2.60–2.75 (m, 6 H), 2.9–3.8 (br s, 2 H), 5.70 (m, 1 H), 6.43 (d, 1 H), 6.72 (s, 1 H), 7.20–7.40 (m, 5 H), 7.48 (s, 1 H). Anal. ($C_{15}H_{19}N_3$·0.4H_2O) C, H, N.

***N*-[2-[[2-(1*H*-Imidazol-4-yl)ethyl](phenylmethyl)amino]ethyl]benzamide (26).** A mixture of 5.81 g (28.9 mmol) of *N*-benzylhistamine and 4.14 g (28.1 mmol) of *N*-benzoylaziridine[14] in 8 mL of methanol was heated at 50 °C for 3.5 h. An additional 1.0 g of *N*-benzoylaziridine was added, and heating was continued for 3 h. Then 1.0 g of *N*-benzoylaziridine was again added, and heating was continued for 24 h. The mixture was diluted with 10 mL of methanol and chromatographed on silica gel, with use of a gradient elution from 98:2 to 92:8 acetonitrile/concentrated NH_4OH. Fractions containing the desired product were pooled and rechromatographed on silica gel, eluting with 97.5:2.5 acetonitrile/concentrated NH_4OH, to give 3.5 g (35%) of the title compound as an oil, which was used directly in the next reaction: ^1H NMR (DMSO-d_6) δ 2.68 (m, 4 H), 3.40 (m, 4 H), 3.68 (s, 2 H), 6.76 (s, 1 H), 7.30 (m, 4 H), 7.50 (m, 4 H), 7.85 (d, 2 H), 8.40 (s, 1 H).

***N*-[2-[[2-(1*H*-Imidazol-4-yl)ethyl](phenylmethyl)amino]ethyl]acetamide (25).** Reaction of *N*-benzylhistamine and *N*-acetylaziridine[14] on a 38.8-mmol scale following the procedure used for the preparation of **26** gave a crude product which was chromatographed twice on silica gel, with use of a gradient elution from 100% acetonitrile to 94:6 acetonitrile/concentrated NH_4OH, to afford 2.0 g (18%) of the title compound as an oil, which was used directly in the next reaction: ^1H NMR ($CDCl_3$) δ 1.92 (s, 3 H), 2.60 (t, 2 H), 2.77 (m, 4 H), 3.28 (quar, 2 H), 3.61 (s, 2 H), 6.74 (s, 1 H), 6.84 (br s, 1 H), 7.17 (d, 2 H), 7.27 (m, 3 H), 7.59 (s, 1 H), 8.64 (br s, 1 H).

***N*-[2-[[2-(1*H*-Imidazol-4-yl)ethyl]amino]ethyl]benzamide Dihydrochloride (11).** A mixture of 3.5 g (10 mmol) of **26**, 1 equiv of 2 N HCl, 0.55 g of 10% Pd/C in 10 mL of methanol, and 1 mL of water was shaken on a Parr apparatus under a hydrogen atmosphere at 50 psi for 24 h. The mixture was filtered through Celite, the filtrate was evaporated, and the residue was chromatographed on silica gel, eluting with 95:5 acetonitrile/concentrated NH_4OH. The chromatographed material was converted to its toluenesulfonic acid salt and the salt was crystallized from acetone/acetonitrile. The salt was converted to its HCl salt. Recrystallization of this salt from methanol/acetonitrile gave 1.4 g (40%) of the title compound as a white solid containing a trace amount of NaCl: mp 202–204 °C; ^1H NMR (DMSO-d_6) δ 3.10–3.50 (br m, 6 H), 3.64 (quar, 2 H), 7.55 (m, 4 H), 8.00 (d, 2 H), 8.93 (t, 1 H), 9.06 (s, 1 H), 9.50 (br s, 2 H). Anal. ($C_{14}H_{18}N_4O$·2HCl·0.23NaCl) C, H, Cl, N, Na.

***N*-[2-[[2-(1*H*-Imidazol-4-yl)ethyl]amino]ethyl]acetamide Methanesulfonic Acid Salt (10).** Hydrogenolysis of **25** on a 7.0-mmol scale following the conditions used for the preparation of **11** gave a crude product which was chromatographed with use of a gradient elution from 95:5 to 82:18 acetonitrile/concentrated NH_4OH. The chromatographed material was converted to its methanesulfonic acid salt, which was crystallized from methanol/acetonitrile to give 1.1 g (33%) of the title compound as a white solid: mp 147–149 °C; ^1H NMR (DMSO-d_6) δ 1.86 (s, 3 H), 2.20 (s, 9 H), 3.04 (m, 4 H), 3.30 (m, 4 H), 7.57 (s, 1 H), 8.14 (t, 1 H), 8.62 (br s, 2 H), 9.08 (s, 1 H), 10.20 (br s, 1 H), 10.38 (br s, 1 H). Anal. ($C_9H_{16}N_4O$·3CH_4O_3S) C, H, N, S.

4-(2-Bromoethyl)-5-methyl-1*H*-imidazole Hydrobromide (27). A solution of 25.00 g (0.198 mol) of 5-methyl-1*H*-imidazole-4-ethanol[27] in 450 mL of 48% HBr was heated at reflux for 4 days. The mixture was evaporated, and the residue was dissolved in 300 mL of water, charcoal treated, and evaporated. This residue was evaporated three times from 300 mL of 2-propanol and was then recrystallized twice from 2-propanol/Et_2O to give 27.48 g (51%) of the title compound as a tan solid: mp 150–151 °C; ^1H NMR (D_2O) δ 2.40 (s, 3 H), 3.30 (t, 2 H), 3.70 (t, 2 H), 8.43 (s, 1 H). Anal. ($C_6H_9BrN_2$·HBr) C, H, N.

***N*-(2-Aminoethyl)-5-methyl-1*H*-imidazole-4-ethanamine Trihydrochloride 0.75-Hydrate (13).** A solution of 26.48 g (89.2 mmol) of **27** in 350 mL of ethanol was added to 350 mL of ethylenediamine, and the resulting mixture was heated at reflux for 2 h. The mixture was evaporated, the residue was dissolved in 200 mL of ethanol and treated with 7.0 g of NaOH in 100 mL of H_2O, and the mixture was evaporated again. This residue was dissolved in 200 mL of ethanol and evaporated three times, and the resulting oil was dissolved in 200 mL of ethanol, filtered, and evaporated. The residue was converted to the HCl salt with methanol/2 N HCl, and the salt was crystallized from methanol/Et_2O to give 21.27 g (82%) of the title compound, sufficiently pure for further use. An additional crystallization from methanol/Et_2O gave an analytical sample as a tan solid: mp 190–195 °C; ^1H NMR (D_2O) δ 2.32 (s, 3 H), 3.16 (t, 2 H), 4.43 (m, 6 H), 8.55 (s, 1 H). Anal. ($C_8H_{16}N_4$·3HCl·0.75H_2O) C, H, Cl, N.

***N*-[2-[[2-(5-Methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]pyridine-4-carboxamide Trihydrochloride 0.25-Hydrate (15).** A mixture of 1.79 g (14.5 mmol) of isonicotinic acid and 2.3 g (14.6 mmol) of carbonyldiimidazole in 100 mL of CH_2Cl_2 was stirred for 1.5 h under a nitrogen atmosphere, after which the mixture was added to a solution of **13** as its free base in 200 mL of CH_2Cl_2. The mixture was stirred for 14 h and was then evaporated, and the residue was chromatographed on silica gel, eluting first with 90:10:1 CH_2Cl_2/ethanol/concentrated NH_4OH, then with 90:10:2 CH_2Cl_2/ethanol/concentrated NH_4OH. The chromatographed material was converted to its HCl salt by using methanolic HCl, and the salt was recrystallized from methanol/Et_2O to give 1.95 g (35%) the title compound as a white solid: mp 270–273 °C dec; ^1H NMR (DMSO-d_6) δ 2.28 (s, 3 H), 3.14 (m, 4 H), 3.28 (m, 2 H), 3.68 (m, 2 H), 8.28 (br s, 2 H), 8.98 (m, 3 H), 9.63 (br s, 3 H). Anal. ($C_{14}H_{19}N_5O$·3HCl·0.25H_2O) C, H, Cl, N.

***N*-[2-[[2-(5-Methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]benzamide Maleate (1:2) (14).** Reaction of benzoic acid with the free base of **13** on a 1.00-mmol scale following the procedure used for the preparation of **15** gave, after chromatography of the crude material on a carboxylic acid ion exchange resin eluting first with methanol and then with 0.5 M NH_3 in methanol, and crystallization of the chromatographed material from methanol/Et_2O as its maleate salt, 100 mg (20%) of the title compound as a white solid: mp 147–148 °C; ^1H NMR (DMSO-d_6) δ 2.19 (s, 3 H), 2.87 (t, 2 H), 3.17 (m, 4 H), 3.33 (br s, 4 H), 3.57 (quar, 2 H), 6.04 (s, 4 H), 7.53 (m, 3 H), 7.87 (d, 2 H), 8.71 (m, 1 H). Anal. ($C_{15}H_{20}N_4O$·2$C_4H_4O_4$) C, H, N.

***N*-[2-[[2-(5-Methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]-4-[(methylsulfonyl)amino]benzamide Fumarate 0.5-Hydrate 0.1-2-Propanol Solvate (16).** Reaction of 4-[(methylsulfonyl)amino]benzoic acid with the free base of **13** on a 14.5-mmol scale in 1:1 THF/CH_2Cl_2 following the procedure used for the preparation of **15** gave 3.87 g of crude material. This material was chromatographed first on silica gel, eluting with first 99:1, then 98:2 ethanol/concentrated NH_4OH, and then on a carboxylic acid ion exchange resin, eluting first with water and then with 0.5 N NH_3, to give a partially purified material which was crystallized as its fumarate salt from methanol/2-propanol to give 1.89 (26%) of the title compound as a white solid: mp 193–197 °C; ^1H NMR (D_2O) δ 2.30 (s, 3 H), 3.14 (m, 2 H), 3.18 (s, 3 H), 3.38 (m, 4 H), 3.78 (m, 2 H), 6.48 (s, 2 H), 7.34 (d, 2 H),

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7.80 (d, 2 H), 8.51 (s, 1 H). Anal. ($C_{16}H_{23}N_5O_3S \cdot C_4H_4O_4 \cdot 0.5H_2O \cdot 0.1C_3H_8O$) C, H, N, S.

***N*-[2-[[2-(5-Methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]-4-morpholinecarboxamide Maleate (1:2) (17).** Phenyl morpholine-4-carboxylate (4.00 g, 19.3 mmol) and 6.48 g (38.5 mmol) of **13** as its free base were combined neat and heated to 70–80 °C under a nitrogen atmosphere for 24 h. The mixture was then chromatographed on activity grade III alumina, with use of a gradient elution from 98:2 to 90:10 acetonitrile/concentrated NH_4OH. The chromatographed material was converted to its maleate salt in ethanol, and the salt was recrystallized from ethanol/Et_2O to give 3.46 g (35%) of the title compound as white needles: mp 145–146 °C; ^1H NMR (D_2O) δ 2.30 (s, 3 H), 3.12 (t, 2 H), 3.20 (t, 2 H), 3.34 (t, 2 H), 3.38 (t, 4 H), 3.49 (t, 2 H), 3.72 (t, 4 H), 6.31 (s, 4 H), 8.53 (s, 1 H). Anal. ($C_{13}H_{23}N_5O_2 \cdot 2C_4H_4O_4$) C, H, N.

1*H*-Imidazole-4-propanoyl Chloride Hydrochloride (29). 1*H*-Imidazole-4-propanoic acid (20.20 g, 144 mmol) was dissolved in 100 mL of thionyl chloride and allowed to stand at room temperature overnight. Evaporation of the excess thionyl chloride followed by evaporation of the residue twice from 100 mL of CH_2Cl_2 gave 27.14 g (97%) of the title compound as a crude oil, which was used directly without further characterization.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1*H*-imidazole-4-propanamide (30).** To a suspension of 12.29 g (63.0 mmol) of **29** in 300 mL of CH_2Cl_2 at 0 °C were added 30.4 g (0.300 mol) of triethylamine and 27.2 g (0.150 mol) of 3,4-dimethoxyphenethylamine. The mixture was allowed to warm to room temperature and was stirred for 18 h. The mixture was then washed with saturated aqueous Na_2CO_3, and the aqueous washes were extracted with EtOAc. The combined organic extracts were dried and evaporated to an oil, which was crystallized from acetonitrile to give 6.43 g (34%) of the title compound as a white solid: mp 111–114 °C; ^1H NMR ($CDCl_3$) δ 2.42 (t, 2 H), 2.65 (t, 2 H), 2.81 (t, 2 H), 3.39 (quar, 2 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 6.59–6.72 (m, 5 H), 7.40 (s, 1 H). Anal. ($C_{16}H_{21}N_3O_3$) C, H, N.

***N*-(2-Furanylmethyl)-1*H*-imidazole-4-propanamide (31).** Reaction of **29** and furfurylamine on a 61-mmol scale following the procedure used for the preparation of **30** gave 7.6 g (57%) of the title compound. Recrystallization from EtOAc/hexane gave an analytical sample: mp 106–109 °C; ^1H NMR ($CDCl_3$) δ 2.42 (t, 2 H), 2.65 (t, 2 H), 2.81 (t, 2 H), 3.39 (quar, 2 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 6.59–6.72 (m, 5 H), 7.40 (s, 1 H). Anal. ($C_{11}H_{13}N_3O_2$) C, H, N.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1*H*-imidazole-4-propanamine Dihydrochloride (18).** To a solution of 3.20 g (11 mmol) of **30** in 120 mL of THF under a nitrogen atmosphere was added 0.65 g (17 mmol) of $LiAlH_4$. The mixture was heated at reflux for 2 days. The reaction was quenched with 1 N HCl sufficient to dissolve the aluminum salts, and the mixture was washed with CH_2Cl_2. The aqueous phase was made basic with 4 N NaOH and was extracted with EtOAc. The EtOAc extracts were dried and evaporated to an oil, which was chromatographed on silica gel, eluting with 97:3 acetonitrile/concentrated NH_4OH. The chromatographed material was converted to its HCl salt with use of ethanol/1 N HCl, and the salt was recrystallized from ethanol to give 830 mg (21%) of the title compound as a white solid: mp 178–180 °C; ^1H NMR (DMSO-d_6) δ 1.92–2.20 (m, 2 H), 2.79 (t, 2 H), 2.84–3.00 (m, 4 H), 3.07 (br s, 2 H), 3.71 (s, 3 H), 3.74 (s, 3 H), 6.70–7.00 (m, 3 H), 7.54 (s, 1 H), 9.08 (s, 1 H), 9.55 (br s, 2 H). Anal. ($C_{16}H_{23}N_3O_2 \cdot 2HCl$) C, H, N.

***N*-(2-Furanylmethyl)-1*H*-imidazole-4-propanamine Dihydrochloride (19).** Reaction of **31** with $LiAlH_4$ on a 13-mmol scale following the procedure used for the preparation of **18** gave 1.40 g (39%) of the title compound as an off-white solid after recrystallization from ethanol: mp 158–160 °C; ^1H NMR (DMSO-d_6) δ 2.08 (quin, 2 H), 2.79 (t, 2 H), 2.88 (t, 2 H), 4.20 (s, 2 H), 6.51 (quar, 1 H), 6.70 (d, 1 H), 7.51 (s, 1 H), 7.76 (d, 1 H), 9.08 (d, 1 H), 10.00 (br s, 1 H). Anal. ($C_{11}H_{15}N_3O \cdot 2HCl$) C, H, N.

Diethyl 2-(3-Phenyl-2-*trans*-propenyl)propanedioate (32). Diethyl malonate (122 mL, 129 g, 804 mmol) was added to a solution of sodium ethoxide, generated from 9.22 g (401 mmol) of sodium, in 400 mL of ethanol, at 0 °C under a nitrogen atmosphere, and the mixture was stirred for 10 min. To this mixture was added cinnamyl bromide (78.83 g, 400 mmol), and the mixture was allowed to warm to room temperature and then was stirred for 3 h. The mixture was then diluted with 700 mL of brine and was then extracted four times with Et_2O (500 mL). The combined organic phases were washed with 400 mL of brine, dried, and evaporated to give 226 g of the crude product, which was distilled to give 83.5 g (76%) of the title compound as a colorless liquid: bp 154–155 °C (0.05 Torr); ^1H NMR ($CDCl_3$) δ 1.26 (t, 6 H), 2.80 (t, 2 H), 3.49 (t, 1 H), 4.21 (quar, 4 H), 6.17 (dt, 1 H), 6.49 (d, 1 H), 7.26 (m, 5 H).

Diethyl 2-[(1*H*-Imidazol-4-yl)methyl]-2-(3-phenyl-2-*trans*-propenyl)propanedioate (33). To a solution of sodium ethoxide, generated from 14.21 g (618 mmol) of sodium, in 1250 mL of THF and 250 mL of ethanol at 20 °C under a nitrogen atmosphere, was added 77.63 g (281 mmol) of **32** and the mixture was cooled to −50 °C. A solution of 43.00 g (281 mmol) of 4-(chloromethyl)-1*H*-imidazole hydrochloride[16] in 200 mL of ethanol was added dropwise over 45 min, after which the mixture was stirred at −50 °C for 1 h. The mixture was allowed to warm to room temperature and washed twice with water (250 mL), and the water washes were extracted twice with CH_2Cl_2. The combined organic phases were dried and evaporated to an oil, which was chromatographed on silica gel, by eluting with 95:5 EtOAc/methanol, to give 76.83 g (77%) of the title compound as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 1.19 (t, 6 H), 2.82 (d, 2 H), 3.27 (s, 2 H), 4.16 (m, 4 H), 6.12 (dt, 1 H), 6.43 (d, 1 H), 6.81 (s, 1 H), 7.28 (m, 5 H), 7.53 (d, 1 H). Anal. ($C_{20}H_{24}N_2O_4$) C, H, N.

Ethyl α-(3-Phenyl-2-*trans*-propenyl)-1*H*-imidazole-4-propanoate (34). A mixture of 60.75 g (171 mmol) of **33** 16.7 g (341 mmol) of sodium cyanide, and 6.2 mL of water in 175 mL of DMSO was heated at 120 °C under a nitrogen atmosphere for 48 h. The mixture was then cooled, diluted with 500 mL of water, and extracted four times with CH_2Cl_2 (500 mL). The combined organic extracts were washed three times with water (500 mL), dried, and evaporated to a dark oil. Chromatography on silica gel, eluting with 97:3 EtOAc/methanol, gave 21.70 g (45%) of the title compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.16 (t, 3 H), 2.50 (m, 2 H), 2.78–3.06 (m, 3 H), 4.09 (m, 2 H), 6.12 (dt, 1 H), 6.39 (d, 1 H), 6.81 (s, 1 H), 7.29 (m, 5 H), 7.55 (d, 1 H), 8.98 (br s, 1 H).

Satisfactory elemental analysis could not be obtained for this compound; however, NMR analysis indicated that the material produced was >95% pure, and it proved adequate for use in further transformations.

α-(3-Phenyl-2-*trans*-propenyl)-1*H*-imidazole-4-propanoic Acid (35). A solution of 21.08 g (74.1 mmol) of **34** and 12.48 g (222 mmol) of potassium hydroxide in 500 mL of methanol was heated at reflux for 3 days. The mixture was then cooled to room temperature, 18.5 mL of concentrated HCl was added, and the solvent was evaporated. The residue was twice dissolved in 100 mL of 2-propanol and the solvent evaporated, after which the residue was triturated with 300 mL of hot 2-propanol and filtered to remove the undissolved salts. Evaporation of the solvent afforded 19.79 g (100%) of the title compound as a white, hygroscopic solid, which was used immediately in the next reaction: ^1H NMR (DMSO-d_6) δ 2.26 (m, 1 H), 2.46 (m, 3 H), 2.78 (m, 1 H), 6.30 (m, 2 H), 6.69 (s, 1 H), 7.18 (t, 1 H), 7.30 (m, 4 H), 7.45 (s, 1 H).

5,6,7,8-Tetrahydro-5-oxo-7-(3-phenyl-2-*trans*-propenyl)-imidazo[1,5-*c*]pyrimidine (36). To a suspension of 18.10 g (70.6 mmol) of **35** in 100 mL of toluene was added 9.9 mL (7.2 g, 71 mmol) of triethylamine and 15.3 mL (19.5 g, 71.0 mmol) of diphenyl phosphorazidate, and the mixture was heated at 90 °C, at which temperature vigorous nitrogen evolution occurred. After 3 h the mixture was cooled, diluted with 200 mL of water, and extracted three times with CH_2Cl_2 (200 mL). The combined organic phases were washed with 150 mL of brine, dried, and evaporated to an oil, which was triturated with Et_2O to give 14.27 g (80%) of the title compound as a tan solid. Analytically pure material was obtained by charcoal treatment of this material followed by recrystallization from ethanol, yielding 5.77 g (32%) of white solid: mp 148–150 °C; ^1H NMR ($CDCl_3$) δ 2.52 (m, 2 H), 2.77 (dd, 1 H), 3.09 (dd, 1 H), 3.79 (m, 1 H), 6.13 (dt, 1 H), 6.30 (br s, 1 H), 6.53 (d, 1 H), 6.84 (s, 1 H), 7.34 (m, 5 H), 8.11 (s, 1 H). Anal. ($C_{15}H_{15}N_3O$) C, H, N.

α-(3-Phenyl-2-*trans*-propenyl)-1*H*-imidazole-4-ethanamine Dihydrochloride (20). A suspension of 4.04 g (15.9 mmol)

of **36** in 50 mL of methanol and 50 mL of 2 N aqueous KOH was heated at reflux for 24 h. The mixture was then cooled, diluted with 100 mL of water, and extracted three times with CH_2Cl_2 (200 mL). The combined organic phases were washed with 150 mL of brine, dried, and evaporated to 3.45 g of a crude oil, which was converted to its HCl salt by using ethanolic HCl. Recrystallization from ethanol gave 2.95 g (62%) of the title compound as a white solid: mp 228–231 °C; ^1H NMR (D_2O) δ 2.66 (m, 2 H), 3.21 (d, 2 H), 3.81 (quint, 1 H), 6.21 (dt, 1 H), 6.60 (d, 1 H), 7.43 (m, 6 H), 8.62 (d, 1 H). Anal. ($C_{14}H_{17}N_3 \cdot 2HCl$) C, H, N.

Diethyl 2-[(1*H*-Imidazol-4-yl)ethyl]-2-(3-phenyl-2-*trans*-propenyl)propanedioate (37). To a solution of sodium ethoxide, generated from 2.90 g (126 mmol) of sodium, in 200 mL of ethanol at 0 °C under a nitrogen atmosphere was added 16.58 g (60.0 mmol) of **32**. The mixture was stirred for 10 min, after which time 15.36 g (60.0 mmol) of 4-(2-bromoethyl)imidazole hydrobromide[13] was added. The mixture was then stirred for 6 h at room temperature, after which the solvent was evaporated. The residue was dissolved in 200 mL of water, and the solution was extracted four times with CH_2Cl_2 (200 mL). The extracts were dried and evaporated to give an oil, which was triturated with three 200-mL portions of hexane. Chromatography of the residue on silica gel, eluting first with 80:20 CH_2Cl_2/ethanol, then with 80:20:2 CH_2Cl_2/ethanol/concentrated NH_4OH, gave 17.01 g (77%) of the title compound as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 1.24 (t, 6H), 2.29 (m, 2 H), 2.62 (m, 2 H), 2.85 (d, 2 H), 4.18 (m, 4 H), 6.06 (dt, 1 H), 6.44 (d, 1 H), 6.67 (s, 1 H), 7.28 (m, 5 H), 7.55 (s, 1 H), 9.55 (br s, 1 H). Anal. ($C_{21}H_{26}N_2O_4$) C, H, N.

α-(3-Phenyl-2-*trans*-propenyl)-1*H*-imidazole-4-butanoic Acid (38). A solution of 6.12 g (16.5 mmol) of **37** in 400 mL of water was heated at reflux for 7 days. The water was then evaporated, and the residue was twice dissolved in 200 mL of ethanol, and the solvent was evaporated. Recrystallization of the residue from ethanol gave 3.31 g (74%) of the title compound as a white solid: mp 175–176 °C; ^1H NMR (DMSO-d_6) δ 1.80 (m, 2 H), 2.42 (m, 5 H), 6.21 (dt, 1 H), 6.43 (d, 1 H), 6.74 (s, 1 H), 7.20 (t, 1 H), 7.30 (t, 2 H), 7.36 (d, 2 H), 7.51 (d, 1 H), 12.11 (br s, 2 H). Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

2-(Trimethylsilyl)ethyl [1-[2-(1*H*-Imidazol-4-yl)ethyl]-4-phenyl-3-*trans*-butenyl]carbamate (39). To a suspension of 7.62 g (28.2 mmol) of **38** in 40 mL of toluene were added 3.9 mL (2.8 g, 28 mmol) of triethylamine and 6.1 mL (7.8 g, 28 mmol) of diphenyl phosphorazidate, and the mixture was heated to 80 °C. Nitrogen evolution occurred, and the mixture became homogeneous. After 2 h, 8.1 mL (6.7 g, 57 mmol) of 2-(trimethylsilyl)ethanol was added, and heating was continued for an additional 22 h. The mixture was then cooled, the solvents were evaporated, and the residue was dissolved in 300 mL of CH_2Cl_2. The solution was washed twice with saturated aqueous Na_2CO_3 (100 mL), twice with 0.25 N aqueous NaOH (100 mL), and twice with brine (100 mL), dried, and evaporated to give a dark oil. Chromatography of the crude product on silica gel, using gradient elution from 99.5:0.5 to 98:2 acetonitrile/concentrated NH_4OH, gave 5.81 g (53%) of the title compound as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 0.96 (m, 2 H), 1.75 (m, 2 H), 2.37 (m, 2 H), 2.60 (m, 1 H), 2.79 (m, 1 H), 3.85 (m, 1 H), 4.17 (dt, 2 H), 4.68 (d, 1 H), 6.12 (m, 1 H), 6.42 (d, 1 H), 6.81 (s, 1 H), 7.29 (m, 5 H), 7.57 (s, 1 H). Anal. ($C_{21}H_{31}N_3O_2Si$) C, H, N.

α-(3-Phenyl-2-*trans*-propenyl)-1*H*-imidazole-4-propanamine Dimaleate 0.25-Hydrate (21). A solution of 5.05 g (13.1 mmol) of **39** and 2.39 g (15.7 mmol) of cesium fluoride in 50 mL DMF was heated at 70 °C under a nitrogen atmosphere for 24 h. An additional 1.20 g (7.90 mmol) portion of cesium fluoride was added, and heating was continued for 20 h. The solvent was removed by vacuum distillation, and the residue was dissolved in 100 mL of water and extracted twice with CH_2Cl_2 (100 mL) and twice with 1-butanol (100 mL). The combined organic extracts were evaporated, and the residue was dissolved in 200 mL of CH_2Cl_2, dried, and evaporated. The crude product was treated with 3.71 g of maleic acid to give the salt, which was crystallized from ethanol/Et_2O to give 2.39 g (38%) of the title compound as a white solid: mp 138–141 °C; ^1H NMR (D_2O) δ 2.11 (m, 2 H), 2.65 (m, 2 H), 2.92 (t, 2 H), 3.50 (quin, 1 H), 6.24 (dt, 1 H), 6.28 (s, 4 H), 6.63 (d, 1 H), 7.27 (s, 1 H), 7.33 (t, 1 H), 7.40 (t, 2 H), 7.46 (d, 2 H), 8.56 (d, 1 H). Anal. ($C_{15}H_{19}N_3 \cdot 2C_4H_4O_4 \cdot 0.25H_2O$) C, H, N.

Pharmacology. Experimental procedures for ferret papillary muscle,[19] guinea pig atrium,[20] guinea pig ileum,[21] and rat gastric acid secretion[22] studies have been previously reported.

Hemodynamic/Gastric Guinea Pig Model. Male guinea pigs (0.7–1.0 kg) were anesthitized with pentobarbital sodium (50 mg/kg, ip). The animal was ventilated via a tracheotomy with room air (60 respirations per min, stroke volume, 3–4 mL). The left carotid artery and right jugular vein were cannulated for measurement of arterial pressure and for infusion of test compound, respectively. The abdomen was opened, the pylorus was ligated, and a ligature was placed around the cardiac aspect of the stomach, after which the abdomen was closed. The heart was exposed via a left thoracotomy, and a 22-gauge needle was inserted into the left ventricle for measurement of left ventricular pressure.

The animal was allowed to stabilize for 30 min, after which blood pressure, heart rate, left ventricular end diastolic pressure, and maximum rate of pressure development ($LV\,dp/dt_{max}$) were measured at 1-min intervals. Test compound was infused for 60 min, after which the hemodynamic parameters were monitored for an additional 10 min. At the end of the experiment, the abdominal incision was opened, the cardiac ligature was tied, and the stomach was removed. The gastric contents were analyzed for volume, pH, and total acid by titration against 0.1 N NaOH.

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Registry No. **3a**, 126376-87-2; **3a** free base, 126376-88-3; **3b**, 126376-90-7; **3b** free base, 126376-91-8; **4**, 126376-92-9; **5a**, 126376-93-0; **5a** free base, 126376-94-1; **5b**, 126376-95-2; **5b** free base, 126376-96-3; **5c**, 126376-97-4; **5d**, 126376-98-5; **5d** free base, 126376-99-6; **6**, 126377-00-2; **6** free base, 126377-01-3; **7a**, 126377-02-4; **7a** free base, 126377-03-5; **7b**, 126377-05-7; **7b**·oxalate, 126377-06-8; **7b** free base, 126377-04-6; **8**, 126377-07-9; **8** free base, 126377-08-0; **9a**, 126377-09-1; **9a** free base, 126377-10-4; **9b**, 126377-11-5; **10**, 126377-13-7; **10** free base, 126377-12-6; **11** free base, 126377-14-8; **11**·toluenesulfonic acid, 126377-15-9; **12**, 126421-33-8; **12** free base, 126377-16-0; **13**, 126377-17-1; **13** free base, 126377-18-2; **14**, 126377-20-6; **14** free base, 126377-19-3; **15**, 126377-21-7; **15** free base, 126377-22-8; **16**, 126377-24-0; **16** free base, 126377-23-9; **17**, 126377-26-2; **17** free base, 126377-25-1; **18**, 126377-27-3; **18** free base, 126377-28-4; **19**, 126377-29-5; **19** free base, 126377-30-8; **20**, 126377-31-9; **20** free base, 126377-32-0; **21**, 126377-34-2; **21** free base, 126377-33-1; **22**, 126377-35-3; **25**, 126377-36-4; **26**, 126377-37-5; **27**, 126377-38-6; **29**, 124369-95-5; **30**, 126377-39-7; **31**, 126377-40-0; **32**, 63082-55-3; **33**, 126377-41-1; **34**, 126377-42-2; **35**, 126377-43-3; **36**, 126377-44-4; **37**, 126377-45-5; **38**, 126377-46-6; **39**, 126377-47-7; *trans*-1-iodo-4-phenyl-3-butene, 56399-99-6; histamine, 51-45-6; histamine dihydrochloride, 56-92-8; furfural, 98-01-1; 4-(4-hydroxyphenyl)-2-butanone, 5471-51-2; 1,2,3,4-tetrahydrophenanthren-1-one, 573-22-8; 1-benzoyl-4-piperidone, 24686-78-0; heptanoyl chloride, 2528-61-2; acetaldehyde, 75-07-0; 3,4-dimethoxyphenethylamine, 120-20-7; 4-(2-bromoethyl)imidazole hydrobromide, 30290-07-4; *cis*-4-phenyl-3-butenamine, 93085-47-3; *N*-benzylhistamine, 7728-61-2; *N*-benzoylaziridine, 7646-66-4; *N*-acetylaziridine, 460-07-1; 4-[(methylsulfonyl)amino]benzoic acid, 7151-76-0; phenyl morpholine-4-carboxylate, 69630-20-2; 1*H*-imidazole-4-propanoic acid, 1074-59-5; furfurylamine, 617-89-0; cinnamyl bromide, 26146-77-0; 4-(chloromethyl)-1*H*-imidazole hydrochloride, 38585-61-4; 4-(2-hydroxyethyl)-5-methyl-1*H*-imidazole, 54732-98-8; isonicotinic acid, 55-22-1; diethyl malonate, 105-53-3.