Guanidine Derivatives Acting at Histaminergic Receptors

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1 Introduction

This review concerns compounds that are derived from the two biologically important organic bases, imidazole and guanidine. These bases are contained in the essential amino-acids histidine and arginine, respectively, and in many naturally occurring polypeptides derived therefrom. Guanidine itself is one of the strongest known organic bases (pK_a 13.6)[1] and at a physiological pH of 7.4 it will exist almost exclusively as the cationic species [(1a), Z = H, Figure 1]. Imidazole is a tautomeric base with $pK_a = 7.03$;[2] for 4-substituted imidazoles significant populations of cationic (2a) and tautomeric neutral species (2b and 2c) are likely to be present at a physiological pH of 7.4 (Figure 2). Imidazole is the strongest base

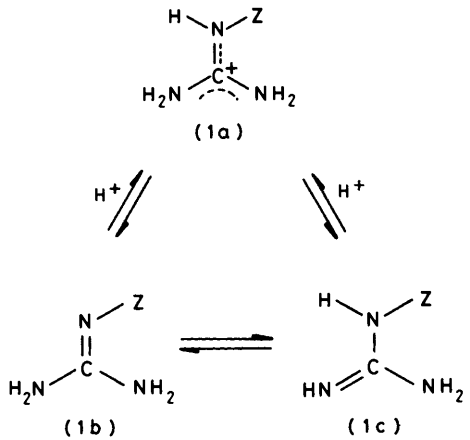


Figure 1 *Guanidine species equilibria*

that can exist in the free base form in the pH range at which most enzymes act. This property may contribute to the unique properties of histidine units at the active site of most enzymes where they can act as either proton donor or acceptor.

Compounds containing guanidine groups in their structure have been shown to exert a variety of physiological or pharmacological effects.[3,4] For example, the

[1] S. J. Angyal and W. K. Warburton, *J. Chem. Soc.*, 1951, 2492.
[2] A. H. M. Kirby and A. Neuberger, *Biochem. J.*, 1938, **32**, 1146.
[3] G. J. Durant, A. M. Roe, and A. L. Green, *Prog. Med. Chem.*, 1970, **7**(1), 124.
[4] G. J. Durant, M. E. Parsons, and J. W. Black, *J. Med. Chem.*, 1975, **18**, 830.

naturally occurring guanidine derivative creatine is important to muscle activity. Some guanidines affect the cardiovascular system, and many guanidines possess antimicrobial activity. Many imidazoles also exert important biological actions, particularly histamine (3), which is the decarboxylated product from histidine.

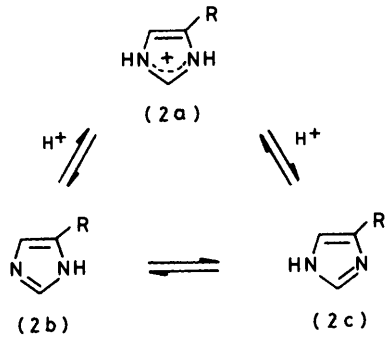
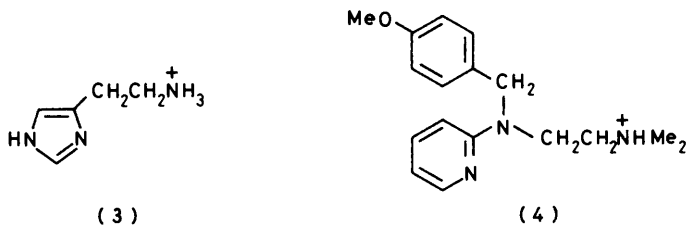


Figure 2 *Imidazole species equilibria*



This review primarily concerns molecules containing both imidazole and guanidine or closely related groups in their structures and which exert pharmacological effects at histaminergic receptors.

2 The Development of Histamine H_2-Receptor Antagonists

Histamine stimulates contraction of smooth muscle from various organs such as the gut and bronchi and this effect can be suppressed by low concentrations of conventional antihistaminic drugs. These latter compounds, typified by mepyramine (4), comprise a group of lipophilic tertiary amines that were originally discovered in the 1940s and subsequently produced a large family of histamine antagonists. This field has been reviewed recently.[5,6] The pharmacological receptors involved in these mepyramine-sensitive responses have been defined as histamine H_1-receptors.[7] Histamine also stimulates secretion of acid by the stomach and increases the heart rate. The failure of conventional antihistamines to

[5] C. R. Ganellin in 'Pharmacology of Histamine Receptors', ed. C. R. Ganellin and M. E. Parsons, J. Wright and Sons, London 1982.

[6] G. J. Durant, C. R. Ganellin, R. Griffiths, C. A. Harvey, D. A. A. Owen, and G. S. Sach, in 'Frontiers in Histamine Research', ed. C. R. Ganellin and J. C. Schwartz, Pergamon Press, Oxford, 1985.

[7] A. S. F. Ash and H. O. Schild, *Br. J. Pharmacol.*, 1966, **27**, 427.

block these effects of histamine led to the initiation of a research programme at Smith Kline & French Laboratories (Welwyn) in which an antagonist of these non-H_1-receptor (subsequently[8] termed H_2-receptor) effects of histamine was sought. The discovery of an effective inhibitor of histamine-stimulated gastric acid secretion was envisaged as a potential means of controlling the hypersecretion of gastric acid in patients. The structure of histamine (3) was used as a chemical starting point with the objective of designing a structure that would bind more strongly than histamine but not trigger off the usual physiological response (*i.e.*, in the pharmacological terminology of receptor occupancy theory,[9] to reduce efficacy but to retain or enhance affinity). After four years of research, the guanidine derivative of histamine, N^{α}-guanylhistamine (5), provided a much sought-after lead following the discovery that it was a weakly active partial agonist at histamine H_2-receptors.[4] In extremely high doses, inhibition of histamine-stimulated gastric acid secretion in the anaesthetized rat was observed (ID_{50}, 800 μmole/kg, *i.v.*) and high concentrations of N^{α}-guanylhistamine antagonized histamine-induced contractions on guinea-pig right atrium *in vitro* (Table 1). As an agonist, N^{α}-guanylhistamine elicits weak submaximal responses in both of these histamine H_2-receptor systems.[4] This guanidine derivative was originally selected for synthesis based on literature analogies for guanidine structures exerting inhibitory effects at enzymes or receptor sites which are normally responsive to amines.[4] It appeared conceivable that these precedents for guanidines exerting opposing effects to amines could be related to the formation of cyclic hydrogen-bonded structures between guanidinium ions and anionic counter ions (6). Such complexes have been observed in crystal structures of some guanidinium salts with oxyanions. The higher homologue, 3-(imidazol-4-yl)propylguanidine [(7), Table 1] was slightly more potent as an antagonist but was also a partial agonist.[10] It appeared likely that the agonist activity of these guanidinium compounds was related to the high basicity of guanidine and that the presence of the cationic charge on these molecules might enable them to mimic histamine under some circumstances. Analogous thioureas *e.g.* SK&F 91581 (8), which are polar but neutral structures with $pK_a \simeq 0$, were found to be devoid of agonist activity, but antagonist activity was weak (Table 1). However, further chain extension of the thiourea derivative led to an increase in antagonist activity and afforded the first fully characterized histamine H_2-receptor antagonist burimamide.[8] Burimamide (9) was devoid of agonist activity and was shown to be a selective antagonist of histamine on non-H_1 tissue systems (Table 1), thereby defining histamine H_2-receptors and characterizing burimamide as a histamine H_2-receptor antagonist.[8] The analogous thiourea metiamide (10) is more potent as an antagonist than burimamide (Table 1) and this compound was initially selected to explore the clinical potential of H_2-receptor antagonists.[11,12] Metiamide was

[8] J. W. Black, W. A. M. Duncan, G. J. Durant, C. R. Ganellin, and M. E. Parsons, *Nature (London)*, 1972, **236**, 385.

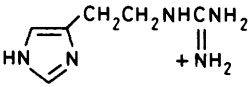
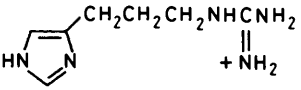
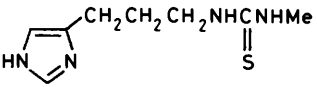
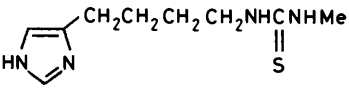
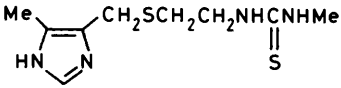
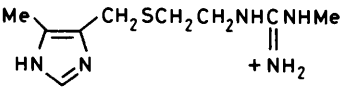
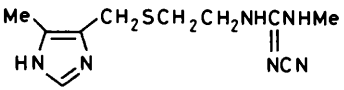
[9] R. P. Stephenson, *Br. J. Pharmacol.*, 1956, **11**, 379.

[10] M. E. Parsons, R. C. Blakemore, G. J. Durant, C. R. Ganellin, and A. C. Rasmussen, *Agents Actions*, 1975, **3**, 133.

[11] J. W. Black, G. J. Durant, J. C. Emmett, and C. R. Ganellin, *Nature (London)*, 1974, **248**, 65.

[12] J. W. Black, W. A. M. Duncan, J. C. Emmett, C. R. Ganellin, T. Hesselbo, M. E. Parsons, and G. J. Wyllie, *Agents Actions*, 1973, **3**, 133.

Table 1 *Some key compounds in the development of the H_2-receptor antagonist cimetidine*

Compound (No.)	*Structure*	*H_2-Receptor Antagonist Activity in vitro*[a] pA_2	*in vivo*[b] ID_{50} (μmol/kg)
N^{α}-Guanylhistamine (5)		3.9	800
SK&F 91486 (7)		4.65	100
SK&F 91581 (8)		3.8	*c*
Burimamide (9)		5.11	6.1
Metiamide (10)		6.04	1.6
Guanidine isostere (11)		4.80	12
Cimetidine (12)		6.10	1.4

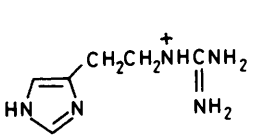
[a] $pA_2 = -\log K_B$ where K_B is the dissociation constant ($\times 10^{-6}$M) determined *in vitro* on guinea-pig atrium against histamine stimulation. Statistical limits and slopes of regressions are omitted. [b] ID_{50} is the intravenous dose required to produce 50% inhibition of near maximal histamine-stimulated gastric acid secretion in anaesthetized rats using a lumen-perfused preparation (*ref.* 8). [c] No antagonism observed up to an intravenous dose of 256μmole/kg

shown to be highly effective clinically in reducing hypersecretion of gastric acid and proved to be of therapeutic value in duodenal ulcer disease. However, the occurrence of a reversible granulocytopenia in a small number of patients limited the use of metiamide and the possibility existed that this effect was related to the presence of the thiourea group. Fortunately, non-thiourea structures had already been considered,[13,14] including guanidines. The guanidine analogue (11) (see Table

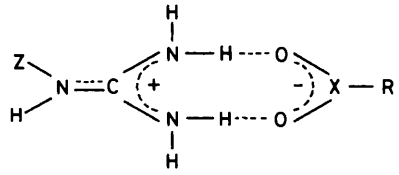
[13] R. W. Brimblecombe, W. A. M. Duncan, G. J. Durant, J. C. Emmett, C. R. Ganellin, and M. E. Parsons, *J. Int. Med. Res.*, 1975, **3**, 86.

[14] G. J. Durant, J. C. Emmett, C. R. Ganellin, P. D. Miles, M. E. Parsons, H. D. Prain, and G. R. White, *J. Med. Chem.*, 1975, **20**, 901.

1) was found to be an antagonist but was approximately an order of magnitude less potent that metiamide.[14] Interestingly, this compound differs from the shorter-chain guanidine structures in that it is not a partial agonist. It appears to be a competitive antagonist but of lower potency than metiamide (Table 1). Since guanidine is considerably more basic than thiourea and will exist overwhelmingly as the protonated species at physiological pH, we considered whether activity could be increased by reducing the basicity of the guanidine.

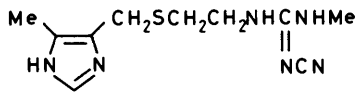


(5)



(6)

Guanidine basicity is highly sensitive to substituent effects. Electron withdrawing substituents increase the acidity of the proton on the adjacent nitrogen atom and stabilize the guanidine base as the imino tautomer [(1b) Figure 1]. Charton[15] has demonstrated a correlation between guanidine pK_a and the inductive substituent constant σ_I. The strongly electron-withdrawing cyano and nitro groups reduce pK_a by over 14 pK_a units to around zero and approximately to the pK_a of thiourea. These guanidine substituents were found to increase antagonist activity and the cyanoguanidine analogue (12) is at least as potent as metiamide as an H_2-receptor antagonist[13,14] (Table 1). This compound cimetidine (Tagamet) was selected for development and was subsequently launched on to the market in the U.K. in 1976, and soon afterwards in most other countries in the world. Cimetidine proved to be a highly effective and successful drug therapy in peptic ulcer disease in many millions of patients.[16] Furthermore, cimetidine is free from the side-effect of granulocytopenia that limited the use of metiamide.



(12)

The importance of guanidine structures in the discovery and development of H_2-receptor antagonists and cimetidine is evident from Table 1, in which are listed the structures and activities of some of the key compounds synthesized *en route* to cimetidine.

[15] M. Charton, *J. Org. Chem.*, 1965, **30**, 969.
[16] For example 'Cimetidine in the 80s', ed. J. H. Baron, Churchill Livingstone, Edinburgh, 1981.

The similarity of cimetidine and metiamide in their activity as H_2-receptor antagonists was also observed in other pairs of imidazole-derived cyanoguanidines and thioureas and these groups provide an interesting example of chemical equivalence in biologically active molecules[14] (bioisosterism). Some physicochemical properties of cyanoguanidine and thiourea are compared in Table 2 and the similarity in their acid–base characteristics, polarity, lipophilicity, and geometry is apparent. The crystal structures of cimetidine and metiamide, are near-identical and both form 10-membered intramolecularly hydrogen-bonded ring structures.[17] It should be added that the bioisosterism of cyanoguanidine and thiourea is not universal and for several other biological actions these groups are not equivalent.

3 Histamine Antagonists Based on Isocytosine Structures

Further isosteres of thiourea or cyanoguanidine have been utilized in novel H_2-receptor antagonist structures derived from metiamide or cimetidine. One example is the nitrodiaminoethene analogue (13) (see Table 3) which is approximately equipotent as an H_2-receptor antagonist. In these carbon isosteres of guanidine it appears that the nitro substituent is essential to act inductively as a powerful electron-withdrawing group and also mesomerically in order to stabilize the negative charge on an adjacent carbon atom. The derivation and utilization of the nitrodiaminoethene group in H_2-receptor antagonists has been described.[18,19] The properties of this group are compared with those of cyanoguanidine and thiourea in Table 2. This group was subsequently utilized by research workers from Glaxo Laboratories in the development of the drug, ranitidine.[20]

Isocytosine (2-aminopyrimidin-4-one) may be regarded as a guanidine derivative in which substituents on two nitrogen atoms are incorporated into a 6-membered ring. Isocytosine was originally selected for synthesis since it is a planar conformationally restricted neutral guanidine structure with additional sites for potentially increasing affinity by ring substitution. Isocytosine is slightly more basic and more acidic than thiourea or cyanoguanidine but its neutral form should predominate at physiological pH. Properties of isocytosine are compared with those of thiourea and cyanoguanidine in Table 2. The isocytosine analogue (14) is less active as an H_2-receptor antagonist than the corresponding thiourea or cyanoguanidine, namely metiamide or cimetidine (Table 3). However, 5-substituted isocytosines have provided a family of structures which are highly effective as histamine receptor antagonists. Examples include oxmetidine (15) (see Table 3) which contains a 3,4-methylenedioxybenzyl substituent in the 5-position of the isocytosine ring and SK&F 93241 (16) (see Table 4) which contains a 6-

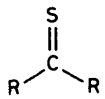
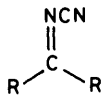
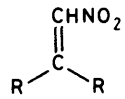
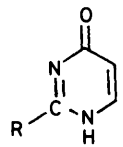
[17] K. Prout and C. R. Ganellin in 'Structural Studies on Molecules of Biological Interest', ed. G. Dodson, J. P. Glusker, and D. Sagre, Clarendon Press, Oxford, 1981.

[18] C. R. Ganellin, *J. Med. Chem.*, 1981, **24**, 913.

[19] G. J. Durant, T. H. Brown, J. C. Emmett, C. R. Ganellin, H. D. Prain, and R. C. Young, in 'The Chemical Regulation of Biological Mechanisms', ed. A. M. Creighton and S. Turner, R. S. C. Special Publication, No. 42, The Royal Society of Chemistry, London, 1982, p. 27.

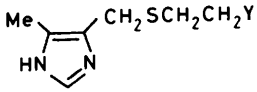
[20] J. Bradshaw, M. E. Butcher, S. W. Clitherow, M. D. Dowle, R. Hayes, D. B. Judd, J. M. McKinnon, and B. J. Price, in *ref.* 19, p. 45.

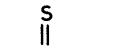
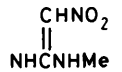
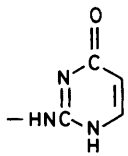
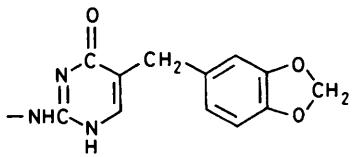
Table 2 *Comparison of some physicochemical properties of thiourea, cyanoguanidine, 1,1diamino-2-nitroethene, and isocytosine*[a]

	R	 *thiourea*	 *cyano-guanidine*	 *diamino-nitroethene*	 *isocytosine*
Proton Dissociation					
pK_a (acid, 25 °C)	NH_2	15	14		9.6
	NHMe			14	
pK_a (base, 25 °C)	NH_2	−1.2	−0.4		4.0
	NHMe			2.7	
Polarity					
dipole moment	NH_2	4.89	8.16		
μ(Debye)	NMe_2			7.64	
partition (octanol:water)					
log P (37 °C)	NH_2	−1.05	−1.15		−0.97
	NHMe	−0.24	−0.40	−1.28	−0.55
Geometry					
C–N length Å	NH_2	1.34	1.33	1.321; 1.315[b]	1.32 (1.36)
N–C–N angle (degrees)	NH_2	119	120	119.4	119
restricted bond					
rotation, ΔG	NHMe	11.8	12.4		
(kcal/mole)	NMe_2		9.2	11.8	

[a] See reference 19 for original literature references. [b] Data for ranitidine hydrogen oxalate (B. Kojic-Prodic, Z. Ruzic-Tolos, and R. Toso, *Acta Crystallogr., Sect. B*, 1982, **38**, 1837.)

Table 3 *H_2-Receptor antagonist potencies of metiamide, cimetidine, diaminonitroethene, and isocytosine analogues*



Compound No.	*Y*	*H_2-Receptor Antagonist Activity*	
		in vitro[a] pA_2	*in vivo*[b] ID_{50} (μmol/kg)
10		6.04	1.6
12		6.10	1.4
13		5.85	1.0
14		5.13	8.4
15		7.69	0.09

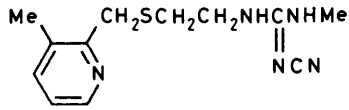
[a,b] See footnotes to Table 1

methyl-3-picolyl substituent in this position. Oxmetidine is about sixteen times more potent than cimetidine as an H_2-receptor antagonist and has been shown to be effective in patients with peptic ulcer disease.[21,22] SK&F 93479 (17) (see Table 4), which contains a 6-methyl-3-picolyl substituent in the 5-position of the

[21] R. C. Blakemore, T. H. Brown, G. J. Durant, J. C. Emmett, C. R. Ganellin, M. E. Parsons, and A. C. Rasmussen, *Brit. J. Pharmacol.*, 1980, **70**, 105P.

[22] R. Corinaldesi, A. Galassi, C. Borghi, R. Pasquali, M. Miglidi, T. Sacco, and L. Barbara, *Hepato-Gastroenterology*, 1981, **28** (6), 319.

isocytosine ring and the 5-dimethylaminomethylfuran-2-yl ring in place of imidazole, is a highly potent and selective H_2-receptor antagonist in animals and man and has an extended duration of action.[23,24]



(18)

The 3-methylpyrid-2-yl analogue (18) of cimetidine is comparable in potency as an H_2-receptor antagonist *in vitro* (atrial pA_2 6.0). In isocytosine structures, substituting pyridine for imidazole also leads to a retention of H_2-receptor antagonist activity but additionally there is an increase in H_1-receptor antagonist activity. Thus, whereas oxmetidine and its picolyl isocytosine analogue (16) (see Table 4) possess only weak H_1-receptor antagonist activity, analogues in which the imidazole ring is replaced by pyridine are considerably more active as H_1-receptor antagonists. In these structures (19), it has been demonstrated by G. S. Sach and co-workers of these laboratories[25] that both H_1- and H_2-receptor antagonist activity are dependent upon the bulk of the substituent, R(3), adjacent to the side chain and that these activities have different optima with respect to the 'Verloop' steric parameter[26] for R(3). The two activities are nearly in balance where R(3) = OMe, and with this compound [SK&F 93319 (20)], combined antagonism at H_1 and H_2 receptors *in vivo* has been demonstrated.[27] SK&F 93319 has been studied in man and may have therapeutic utility in conditions, including some inflammatory skin diseases, which require simultaneous antagonism of histamine at H_1 and H_2 receptors.[27]

A particularly interesting finding with SK&F 93319 was its negligible ability to penetrate into the CNS in animals.[27] This observation led to a research programme directed to the design of a selective H_1-receptor antagonist free from the centrally mediated side-effects which characterized previous compounds in this therapeutic class. For structures (19) it has been shown[25] that maximum H_1-receptor antagonist activity together with the greatest separation from H_2-antagonism occurs where R(3) = Br, Me, or NH_2. Further studies showed that activity was also strongly influenced by 5-pyridyl substituents, R(5), in 3,5-disubstituted compounds (19) which enabled H_1-receptor antagonist activity to be raised and H_2-receptor antagonist activity to be reduced. QSAR analysis indicated the

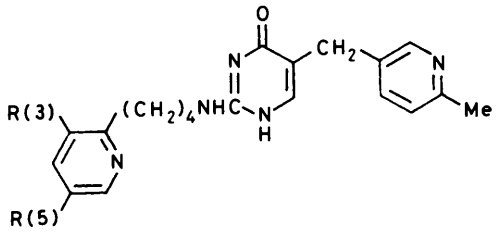
[23] R. C. Blakemore, T. H. Brown, G. J. Durant, C. R. Ganellin, M. E. Parsons, A. C. Rasmussen, and D. A. Rawlings, *Br. J. Pharmacol.*, 1981, **74**, 200P.

[24] T. Gledhill, J. G. Mills, A. Clancy, M. Buck, R. H. Hunt, and W. L. Burland, *Gut*, 1982, **23**, A455.

[25] R. C. Blakemore, T. H. Brown, D. G. Cooper, G. J. Durant, C. R. Ganellin, R. J. Ife, M. E. Parsons, A. C. Rasmussen, and G. S. Sach, Poster Presentation (P7), 2nd SCI/RSC Medicinal Chemistry Symposium, Cambridge, 1983.

[26] A. Verloop, W. Hoogenstraaten, and J. Tipker, *Drug Design*, 1976, **7**, 165.

[27] C. R. Ganellin, R. C. Blakemore, T. H. Brown, D. G. Cooper, G. J. Durant, C. A. Harvey, R. J. Ife, D. A. A. Owen, M. E. Parsons, A. C. Rasmussen, and G. S. Sach, New England and Regional Allergy Proceedings, 1985, in press.



(19)

importance of a steric factor for R(3) and electronic factors for R(3) and R(5).[28] With SK&F 93944 [(19) R(3) = Me, R(5) = Br], H_1-receptor antagonist activity has been increased over the combined antagonist SK&F 93319 by two orders of magnitude and H_2-receptor antagonist activity has been reduced by about two orders of magnitude [(21) Table 4].[28,29] SK&F 93944 has a potency at least equal to that of the conventional H_1-receptor antagonist mepyramine *in vitro* on guinea-pig ileum and *in vivo* in antagonizing histamine-induced bronchconstriction in guinea-pigs and also in other *in vivo* assays for H_1-receptor antagonist activity.[29,30] Negligible penetration of labelled SK&F 93944 into the central nervous system of anaesthetized male rats has been demonstrated.[31] In its chemical properties, SK&F 93944 differs from most previously described H_1-receptor antagonists in lacking a tertiary amino-group and being of markedly reduced basicity.[28] SK&F 93944 is a completely novel H_1-receptor antagonist which offers the prospects of being a truly non-sedative antihistaminic drug and clinical studies are in progress.

4 Guanidine Structures Containing Two Heteroarylalkyl Substituents

A. Histamine H_2-Receptor Antagonists.—The imidazole-containing guanidinium structures described earlier in this review appear to exhibit relatively low affinity for H_2-receptors either as partial agonists or as antagonists (Table 1). The guanidinium analogue (11) of cimetidine is an antagonist with $pA_2 = 4.8$, on guinea-pig atrium. Additional examples, listed in Table 5, include the des-methyl imidazol-4-yl analogues (22) and (23) and thiazol-2-yl analogues which exhibit similar activity to corresponding imidazoles in the guanidinium structure (24) and in the more active cyanoguanidine (25). In contrast, the 3-(thiazol-2-yl)-propyl derivatives (26) and (27) are less active. Structures that contain two imidazolyl-(or thiazolyl)-alkyl substituents are considerably more potent as H_2-receptor antagonists (Table 6), and the increase in activity due to the second substituent is particularly pronounced for the guanidinium compounds. The symmetrically substituted guanidinium derivative containing two 'cimetidine side-chain' sustituents (28), which has $pA_2 =$

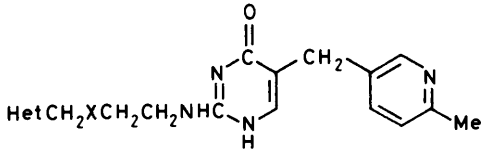
[28] D. G. Cooper, G. J. Durant, C. R. Ganellin, C. A. Harvey, M. L. Meeson, D. A. A. Owen, G. S. Sach, and M. A. Wilczynska, Proceedings of VIIIth International Symposium on Medicinal Chemistry, Vol. 2, Swedish Pharmaceutical Press, Stockholm, 1985, p. 198.

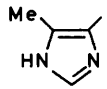
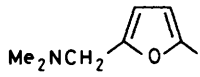
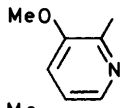
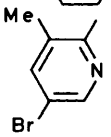
[29] G. J. Durant, C. R. Ganellin, R. Griffiths, C. A. Harvey, R. J. Ife, D. A. A. Owen, M. E. Parsons, and G. S. Sach, *Br. J. Pharmacol.*, 1984, **82**, 232P.

[30] E. A. Brown, R. Griffiths, C. A. Harvey, and D. A. A. Owen, *Br. J. Pharmacol.*, 1985, submitted for publication.

[31] E. A. Brown, C. R. Calcutt, R. Griffiths, B. Jackson, B. K. Leigh, D. A. A. Owen, and I. R. Smith, unpublished results.

Table 4 *H_1 and H_2-Receptor antagonist potencies of some isocytosine derivatives*



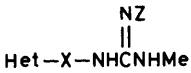
Compound No.	*Het*	*X*	*SK&F No.*	*Antagonist Activity in vitro* pA_2 (H_1)[a]	pA_2 (H_2)[b]
16		S	93241	5.49[c]	7.05[c]
17		S	93479	approx. 4.2[d]	7.78[d]
20		CH_2	93319	7.77[e]	7.49[e]
21		CH_2	93944	9.55[f]	approx. 5.9[f]

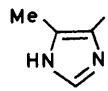
[a,b] $pA_2 = -\log K_B$ where K_B is the dissociation constant determined against histamine stimulation on guinea-pig ileum (H_1) and guinea-pig atrium (H_2) (*ref.* 8). [c] R. C. Blakemore and M. E. Parsons (SK&F Research Ltd.) – unpublished results. [d] *Ref.* 23. [e] *Ref.* 27. [f] *Ref.* 29, 30.

6.7 on guinea-pig atrium, demonstrates an activity increase of nearly two orders of magnitude at H_2-receptors due to the introduction of a second heteroarylalkyl substituent in place of methyl[32,33] [*cf.* (11)]. The thiazole-containing substituents also show an increase in potency and in the guanidinium structures (32) and (36) the 3-(thiazol-2-yl)propyl substituent appears to lead to an activity increase, compared with methyl [*cf.* (11 and 26)] similar in magnitude to that of a 'cimetidine side-chain' substituent. The magnitude of the increase due to the second heteroarylakyl substituent is generally less marked in the neutral cyanoguanidines. However, it is interesting to compare cyanoguanidines (33) with (31) in which the 3-(thiazol-2-yl)propyl substituent appears to be more effective than the analogous longer chain thioether substituent, although the reverse is true in the *N*-methylcyanoguanidines (25) and (27) (Table 5). Thus, di-heteroarylalkylguanidines are generally more potent as H_2-receptor antagonists than monoheteroarylalkyl-guanidines and the results in Tables 5 and 6 are consistent with the presence of an additional binding site, or accessory binding area, at the H_2 receptor that can

[32] C. R. Ganellin, G. J. Durant, J. C. Emmett, D. W. Hills, R. J. Ife, P. D. Miles, and M. E. Parsons, Proceedings of VIIIth International Meeting on Medicinal Chemistry, Uppsala, Sweden, 1985.
[33] G. J. Durant and C. R. Ganellin, *British Patent*, 1 431 589, 1976.

Table 5 *H_2-Receptor antagonist potencies of mono-heteroarylalkylguanidines*



Compound No.	*Het*	*X*	*Z*	*in vitro*[a] pA_2	*in vivo*[b] ID_{50} (μmoles/kg)
(11)		$CH_2SCH_2CH_2$	H	4.8	12
(12)			CN	6.1	1.4
(22)		$CH_2SCH_2CH_2$	H	4.4	76
(23)			CN	5.9	5.0
(24)		$CH_2SCH_2CH_2$	H	5.0	8.5
(25)			CN	6.1	2.6
(26)		$CH_2CH_2CH_2$	H	4.2	(+ve)[c]
(27)			CN	<3.3	(+ve)[c]

[a,b] See footnotes to Table 1. [c] Weak inhibitory activity observed at doses of 54 μmoles/kg and higher

accommodate a second heteroarylalkyl substituent. The magnitude of the increased potency for this substituent in the guanidinium structures indicates the possibility that electrostatic interactions may be involved in the increased affinity of these molecules for the H_2-receptor. However, the favourable influence of the 3-(thiazol-2-yl)propyl substituent in the cyanoguanidine (33) indicates that an accessory binding area may also favour interactions of neutral ligands.

Questions concerning the presence of additional binding sites at H_2-receptors, or even to the proximity of receptor sites, also seem pertinent to the activity of the polymethylene bis-guanidines (Table 7). Linking two of the imidazolylalkyl-substituted guanidinium structures with a polymethylene chain *via* the two guanidinium groups afforded the series of compounds (38) to (46) and leads to an enhancement in antagonist potency that is dependant upon the length of the bridging chain.[32,34] Activity appears to be optimized with a bridge of eight carbon atoms, and the octamethylene guanidinium analogue (43) is approximately three

[34] G. J. Durant and C. R. Ganellin, *British Patent*, 1 493 931, 1977.

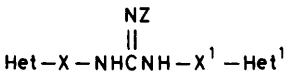
orders of magnitude more potent than the corresponding monoguanidinium structure (11) (Table 5). An enhancement in potency is also observed with corresponding thiazolyl-substituted structures [compare (47) with (24)], although the magnitude of the effect is less striking than for the corresponding imidazoles. The enhancement in potency which accompanies bridging of these guanidine structures appears to require charged guanidine groups since the corresponding bis-*N*-cyanoguanidine (48) does not show any increase in activity over the corresponding mono-*N*-cyanoguanidine [cimetidine (12)]. These observations are suggestive of differences in the mode of interaction of bis-guanidinium compounds and *N*-cyanoguanidines with H_2-receptors. The requirement for the charged guanidinium groups in this activity enhancement may indicate that mutual charge repulsion has a beneficial conformational effect on the linking side-chain that is absent in the neutral bis-*N*-cyanoguanidines. Comparison of the activity of (43) with (49), (50), and (51) (Table 7) suggests that both of the 'cimetidine side-chains' and both guanidinium groups are involved in specific interactions with the histamine H_2-receptor, and also that the second guanidine group is not functioning merely as an additional cationic head.

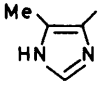
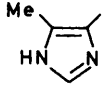
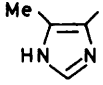
B. Histamine H_2-Receptor Agonists.—3-(Imidazol-4-yl)propylguanidine (7) and its *N*-methyl derivative (52) (Table 8) are both weakly active partial agonists at H_2-receptors. Structural modifications, analogous to those described above for the antagonist structure (11), lead to a marked increase in potency at histamine H_2-receptors (Table 8). Bis-3-(imidazol-4-yl)propylguanidine (53) is about 25 times more potent than (52) as an H_2-receptor agonist on guinea-pig atrium and the octamethylene bis-guanidine (54) is more than 150 times as potent. The latter compound retains the partial agonist character of (52) in eliciting sub-maximal responses on guinea-pig atrium which enabled it to be tested as an antagonist of histamine in this H_2-receptor preparation. The pA_2 value (7.7) for this compound indicates that there is an affinity increase at H_2-receptors of nearly three orders of magnitude accompanying the linking of these structures by an octamethylene bridge. This factor is similar to that observed in the corresponding antagonists (43) and (11). It is worth noting that the unsymmetrical structure (55), which contains one 3-(imidazol-4-yl)propyl guanidine linked by a chain of eight carbon atoms to a guanidine group containing a 'cimetidine side-chain', is a partial agonist at H_2-receptors of comparable potency to (54).

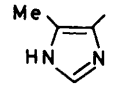
C. Impromidine.—An exceedingly potent H_2-receptor agonist,[35] impromidine (56), has a structure comprising a guanidine group substituted by two different imidazole-containing side-chains. It may be considered as being derived from the partial structures 3-(imidazol-4-yl)propylguanidine or its *N*-methylguanidine derivative (52) (partial agonist) and 2-[(5-methylimidazol-4-yl)methylthio]ethyl-guanidine or its *N*-methylguanidine derivative (52) (an antagonist) (Figure 3). As

[35] G. J. Durant, W. A. M. Duncan, C. R. Ganellin, M. E. Parsons, R. C. Blakemore, and A. C. Rasmussen, *Nature* (*London*), 1978, **276**, 403.

Table 6 *H_2-receptor antagonist potencies of di-heteroarylalkylguanidines*[33]

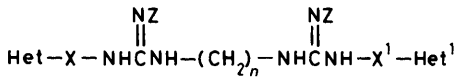


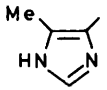
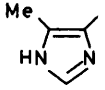
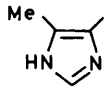
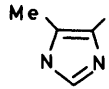
Compound No.	*Het*	*X*	*Het*[1]	*X*[1]	*Z*	*H_2-Receptor Antagonist Activity* *in vitro*[a] pA_2	*in vivo*[b] ID_{50} (μmol/kg)
(28)		$CH_2SCH_2CH_2$		$CH_2SCH_2CH_2$	H	6.7 (0.8)	0.12
(29)					CN	6.7 (0.9)	1.5
(30)		$CH_2SCH_2CH_2$		$CH_2SCH_2CH_2$	H	6.1 (1.3)	1.3
(31)					CN	6.0 (1.0)	2.0

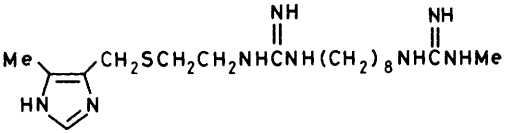
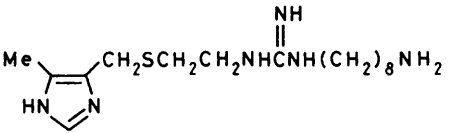
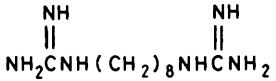
(32)		$CH_2SCH_2CH_2$		$CH_2CH_2CH_2$	H	6.5 (0.88)	0.91
(33)					CN	6.7 (1.25)	0.16
(34)		$CH_2SCH_2CH_2$		$CH_2SCH_2CH_2$	H	5.9 (0.81)	3.8
(35)					CN	6.6 (0.72)	1.1
(36)		$CH_2CH_2CH_2$		$CH_2CH_2CH_2$	H	6.15 (0.87)	4.9
(37)					CN	5.0 (0.75)	25.8

[a,b] See footnotes to Table 1. [c] Bracketed figures refer to slopes of regressions of $\log(DR^{-1})$ against log(Antagonist Concentration)

Table 7 *H_2-Receptor antagonist potencies of polymethylene bis-heteroarylalkylguanidines*[34]

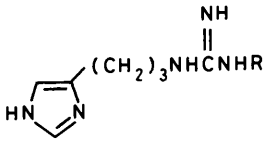


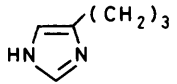
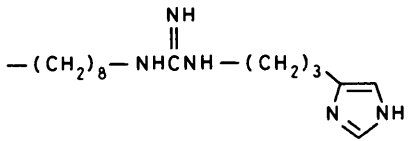
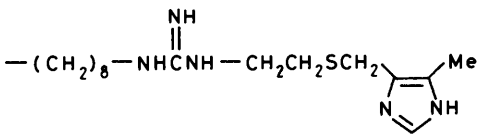
Compound No.	*Het*	*X*	*Z*	*n*	*Het*[1]	*X*[1]	*H_2-Receptor Antagonist Activity* *in vitro*[a] pA$_2$	*in vivo*[b] ID_{50} (μmol/kg)
(38)		$CH_2SCH_2CH_2$	H	2		$CH_2SCH_2CH_2$	6.1	1.2
(39)	„	$CH_2SCH_2CH_2$	H	3	„	$CH_2SCH_2CH_2$	5.9	1.3
(40)	„	$CH_2SCH_2CH_2$	H	5	„	$CH_2SCH_2CH_2$	6.1	1.6
(41)	„	$CH_2SCH_2CH_2$	H	6	„	$CH_2SCH_2CH_2$	6.7	0.66
(42)	„	$CH_2SCH_2CH_2$	H	7	„	$CH_2SCH_2CH_2$	7.5	0.10
(43)	„	$CH_2SCH_2CH_2$	H	8	„	$CH_2SCH_2CH_2$	8.1	0.04
(44)	„	$CH_2SCH_2CH_2$	H	9	„	$CH_2SCH_2CH_2$	7.3	0.13
(45)	„	$CH_2SCH_2CH_2$	H	10	„	$CH_2SCH_2CH_2$	6.7	0.11
(46)	„	$CH_2SCH_2CH_2$	H	12	„	$CH_2SCH_2CH_2$	5.8	—
(47)		$CH_2SCH_2CH_2$	H	8		$CH_2SCH_2CH_2$	6.9	0.7
(48)		$CH_2SCH_2CH_2$	CN	8		$CH_2SCH_2CH_2$	5.9	2.9

(49)		—	7.3	0.9
(50)		—	5.7	3.2
(51)		—	4.0	50

[a,b] See footnotes to Table 1

Table 8 3-(*Imidazol-4-yl*)*propylguanidine derivatives*



Compound No.	*R*	*H_2-Receptor Activities in vitro*[a] *Agonist Activity*[b] *Potency relative to Histamine = 1*	*% Max. response*	*Antagonist Activity*[c] pA_2
(51)	H	0.04	31	4.7
(52)	Me	0.2	60	4.9
(53)		4.8	100	—
(54)		33	62	7.7
(55)		22	39	8.0

[a] Determined on guinea-pig atrium. [b] Relative agonist activities were assessed from cumulative dose–response curves. Construction of complete dose–response curves to histamine and test compounds were used to determine maximum responses obtainable and relative potencies were determined from concentration required to elicit 50% of maximal responses. [c] See footnote *a*, Table 1.

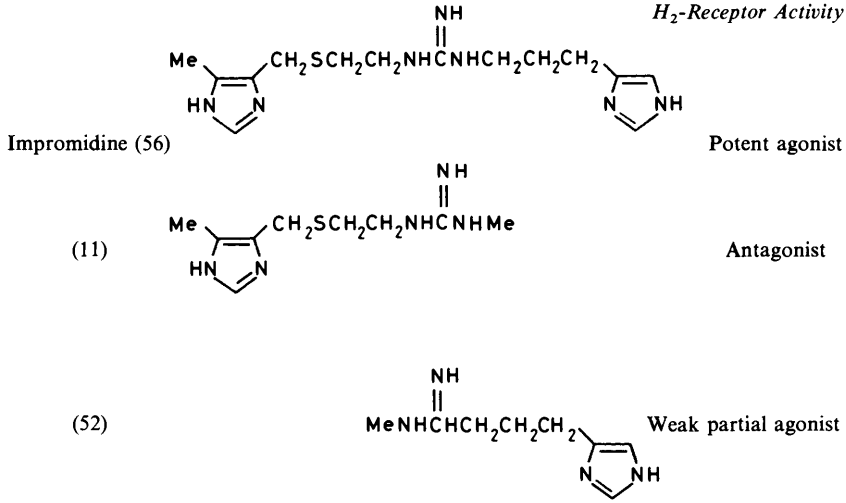


Figure 3 *Chemical structures of impromidine and its 'partial' structures*

an agonist, impromidine is between 10 and 50 times as potent as histamine *in vitro* and *in vivo*, and elicits a near-maximal response in most of these test systems.[35] Impromidine, which is an exceedingly potent stimulant of gastric acid secretion in animals and man, has been used clinically to study the potency and duration of action of novel histamine H_2-receptor antagonists.[36] It has been suggested that treatment with this compound may offer a new therapeutic approach to patients with catecholamine-insensitive congestive heart failure.[37]

Numerous analogues of impromidine including modifications to both of the side-chains and to the guanidine group have been synthesized and compared with impromidine[38] (Tables 9, 10, and 11). Analogues (57)—(60) in which the 'cimetidine side-chain' of impromidine is replaced by the alternative side-chains listed in Table 9 are also powerful agonists on guinea-pig atrium. These side-chains appear to be associated with affinity for H_2-receptors and there are many examples of guanidinium structures containing these side-chains that are antagonists, for example the *N*-methylguanidines [(22), (24), and (26)] (Table 5) and particularly compounds in the series of bis-heteroarylalkyl guanidine derivatives (Table 6). It therefore appears likely that this side-chain substituent in impromidine and congeners is associated with affinity for H_2-receptors.

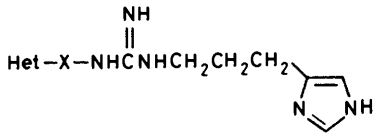
The 3-(imidazol-4-yl)propyl substituent present in impromidine appears to be

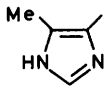
[36] R. H. Hunt, J. G. Mills, J. Beresford, J. A. Billings, W. L. Burland, and G. J. Milton-Thompson, *Gastroenterology*, 1980, **78**, 505.

[37] G. Baumann, B. Permanetter, A. Wirtzfeld, and H. Blomer, *Eur. Heart J.*, 1984, **5**, *Suppl.* 1, 34, *Abstr.* 125; G. Baumann *et al.*, *J. Cardiovascular Pharmacol.*, 1983, **5**, 618.

[38] G. J. Durant, C. R. Ganellin, D. W. Hills, P. D. Miles, M. E. Parsons, E. S. Pepper, and G. R. White, *J. Med. Chem.*, 1985, **28**, 1414.

Table 9 *H_2-Receptor agonist potencies of impromidine analogues*

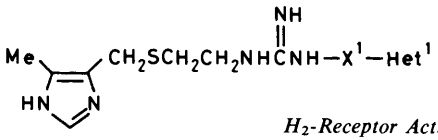


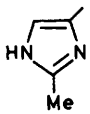
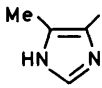
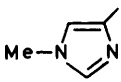
Compound No.	*Het*	*X*	*H_2-Receptor Agonist Activities in vitro*[a] *Potency relative to Histamine = 1*	*% Max. response*
Impromidine (56)		$CH_2SCH_2CH_2$	48	99
(57)		$CH_2SCH_2CH_2$	5.4	95
(58)		$CH_2CH_2CH_2CH_2$	12.4	86
(59)		$CH_2SCH_2CH_2$	24.4	91
(60)		$CH_2CH_2CH_2$	26.7	87

[a,b] See footnotes *a,b*, Table 8

crucial for H_2-receptor agonist activity, as indicated by the effect of structural modification (Table 10). The lower homologue of impromidine containing the 2-(imidazol-4-yl)ethyl substituent (61) is considerably less active as an agonist and the higher homologue (62) is an H_2-receptor antagonist which exhibits a weak sub-maximal response at H_2-receptors on guinea-pig atrium (Table 10). Methyl substituents in the 2- and 4-position of the imidazole ring are reasonably well-accommodated and the impromidine analogues containing these substituents [(63) and (64)] are nearly full agonists approximately four to six times less potent than

Table 10 *H_2-Receptor activities of impromidine analogues*

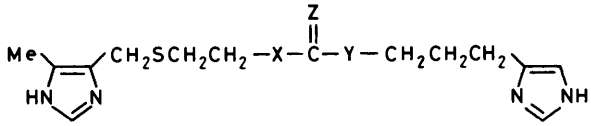


Compound No.	*Het*[1]	*X*[1]	*H_2-Receptor Activities in vitro*[a] *Agonist Activity*[b] *Potency relative to Histamine = 1*	*% Max. response*	*Antagonist Activity*[c] pA_2
Impromidine (56)		$CH_2CH_2CH_2$	48	99	—
(61)		CH_2CH_2	1.9	100	—
(62)		$CH_2CH_2CH_2CH_2$	0.8	20	5.9
(63)		$CH_2CH_2CH_2$	12	100	—
(64)		$CH_2CH_2CH_2$	8.1	85	—
(65)		$CH_2CH_2CH_2$	0.01	11	5.8
(66)		$CH_2CH_2CH_2$	2	47	5.6

[a,b,c] See footnotes *a,b,c*, Table 8

impromidine. The influence of methyl substituents in the 2- and 4-positions of this imidazole ring is therefore in contrast with that previously observed for histamine where 2-methyl substitution leads to a much greater reduction in agonist activity at histamine H_2-receptors than does this substitution at the 4-position of the imidazole ring.[8] In impromidine, methylation of the imidazole ring nitrogen atom leads to a marked reduction in agonist activity, the 3-(1-methylimidazol-4-yl)propyl analogue (65) being only a weakly active partial agonist at histamine H_2-receptors. As noted previously, the 3-(thiazol-2-yl)propyl analogue (32) is an H_2-receptor antagonist and the results for these two compounds suggest that the tautomeric imidazole ring is necessary for agonist activity. The relatively weak activity of the 1,2,4-triazole analogue (66) demonstrates that, unlike for histamine,[8] this ring system is not an effective substitute for imidazole in the impromidine series of H_2-receptor agonists.

Table 11 *H_2-Receptor activities of impromidine analogues*



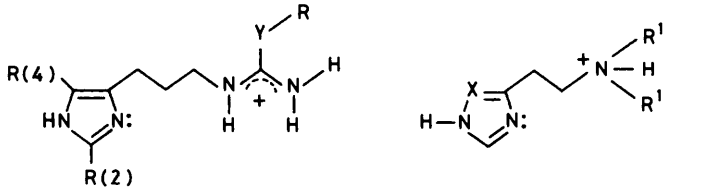
Compound No.	X	Y	Z	H_2-Receptor Activities in vitro[a] Agonist Activity[b] Potency relative to Histamine = 1	% Max. response	Antagonist Activity[c] pA_2
Impromidine (56)	NH	NH	NH	48	99	—
(67)	NH	NH	NCN	—	—	6.2
(68)	NH	NH	S	—	—	5.9
(69)	NH	NH	O	—	—	5.2
(70)	S	NH	NH	6.9	83	—
(71)	NH	S	NH	—	—	5.5
(72)	NH	NH	NCH_3	0.06	91	—
(73)	NH	NH	SCH_3	0.01	17	4.8

[a,b,c] See footnotes *a,b,c*, Table 8

Modifications to the guanidine group of impromidine are listed in Table 11. Analogues [(67), (68), and (69)] in which the basic guanidine group is replaced by the neutral groups, cyanoguanidine, thiourea, or urea are H_2-receptor antagonists essentially devoid of agonist activity. However, the mere presence of a basic group is insufficient to endow agonist activity. The isothiourea group is strongly basic (*S*-methylisothiourea, pK_a 9.78 at 20 °C)[39] and will exist predominantly as a protonated species at physiological pH. The isothiourea analogues of impromidine show interesting differences, since the isothiourea (70) resembles impromidine in acting as a strong agonist on guinea-pig atrium whereas the isomer (71) is an

[39] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 505.

antagonist essentially devoid of agonist activity. These results suggest that for agonist activity it is important for the atom bearing the 3-(imidazol-4-yl)propyl side-chain to possess a proton, whereas a proton on the atom bearing the 2-[(5-methylimidazol-4-yl)methylthio]ethyl side-chain is not essential for the agonist activity of impromidine and related compounds. The *N*-methylguanidine (72) and the *S*-methylisothiourea (73) are both weakly active as H_2-receptor agonists on guinea-pig atrium—results consistent with the view that an amidinium structure containing an $-NH_2$ substituent is important for the agonist activity of impromidine (and analogues) at H_2-receptors on guinea-pig atrium.



(74) (75)

Impromidine Congeners	*Histamine Congeners*
Cationic amidinium group	Cationic ammonium group
R(2) and R(4) = H or Me	R^1 = H or Me
Y = S or NH	X = CH, CMe or N
R = 'affinity' group	N^{τ}-H tautomer of imidazole

Figure 4 *Chemical properties of impromidine and histamine that may be associated with agonist action at H_2-receptors*

One extrapolation from the limited series of structural modifications listed in Tables 9, 10, and 11 is that the 3-(imidazol-4-yl)propyl amidinium structural fragment (74) is important for H_2-receptor agonist activity where R(2) and R(4) are optional 2- or 4-methyl substituents, Y = S or NH, and R is a typical substituent that contributes affinity in H_2-receptor antagonist structures (Figure 4). This fragment may be compared with the structure of histamine, and the structural features (75), and chemical criteria that have been considered necessary for its agonist action at H_2-receptors.[40] Clearly there are similarities and the presence of a tautomeric ring system linked by an alkylene chain to a protonated ligand appears to be important for agonist activity in both series of agonists, but there are also differences as indicated in Figure 4. In preliminary attempts to correlate structure and H_2-receptor agonist activity, conformational space and molecular surfaces of the monocations of histamine and impromidine have been compared.[41]

5 Summary

Many biologically active guanidines and imidazoles have been reported. The initial attempt to combine these groups within one molecule by replacing the amino-

[40] G. J. Durant, C. R. Ganellin, and M. E. Parsons, *J. Med. Chem.*, 1975, **18**, 905.
[41] E. K. Davies and K. Prout, (Oxford University), unpublished results.

group of histamine by guanidine led to the molecule N^{α}-guanylhistamine (5) which is a weak partial agonist at histamine H_2-receptors. However, subsequent structural elaboration has led to a series of compounds that exhibit high levels of activity at histaminergic receptors. A notable example is the cyanoguanidine derivative, cimetidine (12), which is highly effective clinically as a histamine H_2-receptor antagonist. Subsequent developments led to a family of isocytosines, which afforded potent H_2-receptor antagonists, *e.g.* oxmetidine (15) and SK&F 93479 (17), the combined H_1-/H_2-receptor antagonist SK&F 93319 (20) and the selective H_1-receptor antagonist SK&F 93944 (21). Guanidine structures containing more than one imidazole ring structure have exhibited exceedingly high potency at histamine H_2-receptors, either as antagonists or as agonists [*e.g.* impromidine (56)]. Our understanding of the molecular events underlying the pharmacological actions described in this review is rudimentary at the present time, but in future we hope for a greater comprehension of why the combination of the two moieties imidazole and guanidine within a single molecule leads to compounds that exhibit profound biological effects at histaminergic receptors.

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