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On the Structure-Activity Relationship of Histamine H2-Receptor Antagonists Based on the X-Ray Crystal Structures and ^{1}H-NMR Spectra of Amidine Derivatves

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SUMMARY

The conformation of six amidine compounds, which possess a common 3-[(4-thiazolyl)methylthio]propionylamidine framework but exhibit different activities as histamine H2-receptor antagonists, have been subjected to both single crystal X-ray structural and ^{1}H-NMR analyses.The X-ray studies suggest a correlation between antagonist activity and the relative spatial orientation of the thiazolyl and amidine nitrogen atoms. This correlation is supported by a comparison of the conformations observed for the amidines with those of other H2-receptor antagonists and reveal that a folded conformation, specifically the NH...N intramolecular hydrogen-bonded configuration, is important for antagonist activity. The ^{1}H-NMR measurements on the active amidine compounds show that the intramolecular NH...N bond is likely to be present in solution.

Structural modification of the prototype, histamine, led to the discovery of H2-receptor antagonists, burimamide (1), metiamide (2), and cimetidine (3). The therapeutic success of cimetidine stimulated the development of the more potent antagonists, ranitidine (4), tiotidine (5), etintidin (6), and oxmetidine (7). Furthermore, more potent and longer-lasting drugs than cimetidine are now under study. Some of these compounds contain nonimidazole structures and all of them possess a longer side group than the aminoethyl one in histamine: a methylthioethyl or oxypropyl side chain is connected by an end group such as cyanoguanidine or a substituted heteroaromatic ring. This may suggest either conformational flexibility in the binding site of the histamine H2 receptor or the existence of other receptor sites. Recently, a thiazole derivative with a terminal amidine group, 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]-methyl]thio]-N^2-sulfamoyl-propionamidine (famotidine), was found to be a more potent H2-receptor antagonist than cimetidine (8).

A useful methodology which permits the identification of the key structural features responsible for biological activity is to compare the molecular structures in a series of compounds with chemical and physicochemical similarities but different pharmaceutical activities. Furthermore, the data thus obtained may be used for the design of new and more potent drugs. With this in mind and the aim of clarifying the structure-activity relationship of histamine H2-receptor antagonists, we have undertaken the X-ray single crystal structural and ^{1}H-NMR analyses of the six amidine compounds shown in Table 1.

Materials and Methods

X-ray analyses. All amidine compounds have been chemically synthesized (9). The crystallographic data are given in Table 2. Diffraction intensities were measured on a Rigaku AFC-5 automatic diffractometer operated in the ω-2θ scan mode, using graphite monochormated Cu Kα radiation (λ = 1.5405 Å). Intensities were corrected for Lorentz and polarization effects but not for absorption. Nonhydrogen atom positions were located by either direct methods (10) or Patterson analyses, and refined by block diagonal least squares using anisotropic thermal parameters. In all of the compounds except **5**, hydrogen atoms were obtained from difference Fourier syntheses and included in refinement with isotropic thermal parameters. For compound **5** the hydrogen atoms were included in refinement in their calculated positions. All calculations were performed at the Computation Center of Osaka University using the UNICS system of programs (11). Details of crystal structures will be published elsewhere.

^{1}H-NMR spectra. ^{1}H-NMR spectra were recorded on a Varian XL-300 spectrometer equipped with fast Fourier transform and temperature control units. Chemical shifts were measured with 2,2-dimethyl-2-silapentane-5-sulphonate as internal standard. Solutions were approximately 14 mM in the compounds under study and were prepared using CD_3OD/D_2O (3:2, v/v) mixture without adjustment of pH. All concentrations were determined gravimetrically; although not very accurate, it did not, in general, affect our conclusions. Spectra were recorded at the following temperatures; 5°, 23°, 30°, 40°, and 50°.

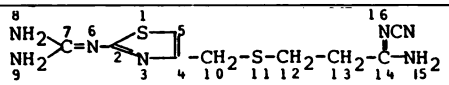
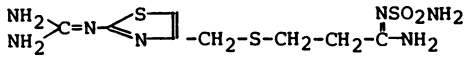
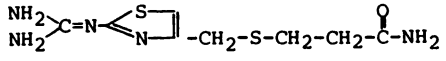
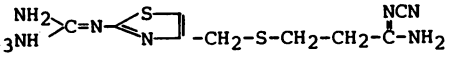
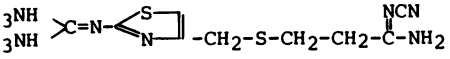
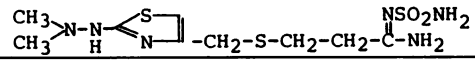
Results and Discussion

Molecular Conformations

Stereoscopic projections of a molecular unit for each of the compounds, viewed perpendicular to the thiazole ring are presented in Fig. 1. A characteristic common to compounds **1–5** is the formation of a planar six-membered ring system by means of an intramolecular hydrogen bond between the thiazole and guanidyl nitrogen atoms. In **6**, where such a hydrogen bond is not possible, a planar arrangement is also found.

TABLE 1

Structure and H2-receptor antagonist activities of amidine compounds

Compound	Chemical structure	ED_{50} (M)[a]	Activity[b]
1[c]		1.8×10^{-7}	3
2		2.7×10^{-7}	3
3		1.0×10^{-6}	2
4		1.2×10^{-6}	2
5		$>10^{-4}$	0
6		$>10^{-4}$	0

[a] H2-receptor antagonist activity in guinea pig atrium, from Ref. 9.

[b] Antagonist activity was classified as 0–3 according to the ED_{50} values: 0 for $ED_{50} > 10^{-4}$, 1 for $10^{-5} < ED_{50} < 10^{-4}$, 2 for $10^{-6} < ED_{50} < 10^{-5}$, and 3 for $10^{-7} < ED_{50} < 10^{-6}$.

[c] The numbers shown in the chemical structure represent the atomic numberings used for the X-ray studies of compounds 1–6.

TABLE 2

Crystallographic data of amidine compounds

Compound	1	2[a]	3	4	5	6[a]
Solvent for crystallization	Methanol/acetone/water	Methanol	Methanol	Ethanol	Ethanol/ethyl acetate	Methanol/water
Crystal system	Triclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Triclinic
Space group	$P\bar{1}$	Cc	$P2_12_12_1$	$P2_1/c$	$P2_1$	$P\bar{1}$
Cell constant						
a, Å	11.089 (4)	15.205 (3)	5.472 (1)	14.235 (5)	6.974 (1)	14.802 (4)
b, Å	9.130 (6)	14.442 (3)	18.260 (5)	5.453 (2)	26.743 (3)	13.275 (3)
C, Å	7.033 (5)	9.262 (1)	11.890 (3)	17.782 (7)	16.847 (2)	5.236 (2)
α, deg.	100.99 (6)	90.0	90.0	90.0	90.0	93.42 (2)
β, deg.	83.86 (5)	124.00 (5)	90.0	90.13 (6)	104.51 (2)	93.68 (2)
γ, deg.	86.80 (7)	90.0	90.0	90.0	90.0	84.01 (2)
Volume, Å^3	692.9 (6)	1685.9 (7)	1188.0 (5)	1380.2 (8)	3042.0 (7)	1019.8 (5)
Z	2	4	4	4	8	2
Formula/asymmetric unit	$C_9H_{13}N_7S_2 \cdot H_2O$	$C_8H_{15}N_7O_2S_3 \cdot HCl$	$C_8H_{13}N_5OS_2$	$C_{10}H_{15}N_7S_2$	$4 \cdot C_{11}H_{17}N_7S_2$[b]	$C_9H_{18}N_6O_2S_3 \cdot C_4H_4O_4$
Molecular weight	301.31	373.89	259.34	297.40	311.42 × 4	454.53
Crystal density						
Observed,[c] g/cm^3	1.443 (2)	1.470 (2)	1.448 (1)	1.420 (1)	1.365 (2)	1.475 (2)
Calculated	1.445	1.473	1.450	1.432	1.360	1.481
μ(Cu Kα), cm^{-1}	34.22	54.58	38.41	33.75	30.83	35.95
F(0 0 0)	316	776	544	624	656	476

[a] Crystals of 2 and 6 were used as HCl and maleic acid salts, respectively.

[b] Since the crystal of 5 had four molecules per asymmetric unit, respective molecules were designated as molecules A, B, C, and D.

[c] Crystal densities were measured by flotation method using C_6H_6/CCl_4 mixture.

The torsion angles defining the conformation of amidine side chain with respect to the thiazole ring are listed in Table 3 along with the dihedral angles between the thiazole ring and the planar amidine moiety. In all of the compounds, the torsion angles of ω1 and ω2 are either (*gauche*·*gauche*) or (−*gauche*·−*gauche*); as **5** has no asymmetric atom (although its space group, $P2_1$, is non-centrosymmetric), the molecules B and D with a (−*gauche*·−gauche) conformation for ω1,ω2 can be converted to (*gauche*·*gauche*) by a mirror operation. This (*gauche*·*gauche*) preference for ω1,ω2 means that the overall conformation of the side chain is determined by a combination of ω3, ω4, and ω5 torsion angles. In this set of torsion angles ω3 and ω4 are seen restricted to either *gauche* or *trans*, whereas ω5 has conformational freedom (*gauche*, −gauche, *trans*, anticlinal, and −anticlinal). When the (ω3,ω4,ω5) combination is (*trans*,*gauche*, *gauche*, or −anticlinal), the thiazole ring and the amidine moiety are close to coplanar as is seen in compounds **1** and **4**. It is interesting to note that the amidine compounds with H2-receptor antagonist activity have a *trans* conformation at ω3 (except the hydrochloride salt of **2**), whereas those without activity (**5** and **6**) are *gauche* at ω3. Thus, it appears that those torsion angles are related to the antagonist activity, with a specific combination leading to the active conformation.

In the crystal packings, neither the water of **1** nor the maleic acid of **6**, which exists as in the neutral form (HOOCH=CHOOH), forms more than one hydrogen bond per molecule. They lie in the cavities provided by the packing and contribute to lattice stabilization. Therefore, they do not appear to significantly influence the conformations of the molecules. In contrast, however, the conformation of **2** appears to be affected by the presence of HCl (a salt formation) significantly: the N6 atom of guanidine was protonated by the hydrogen atom of

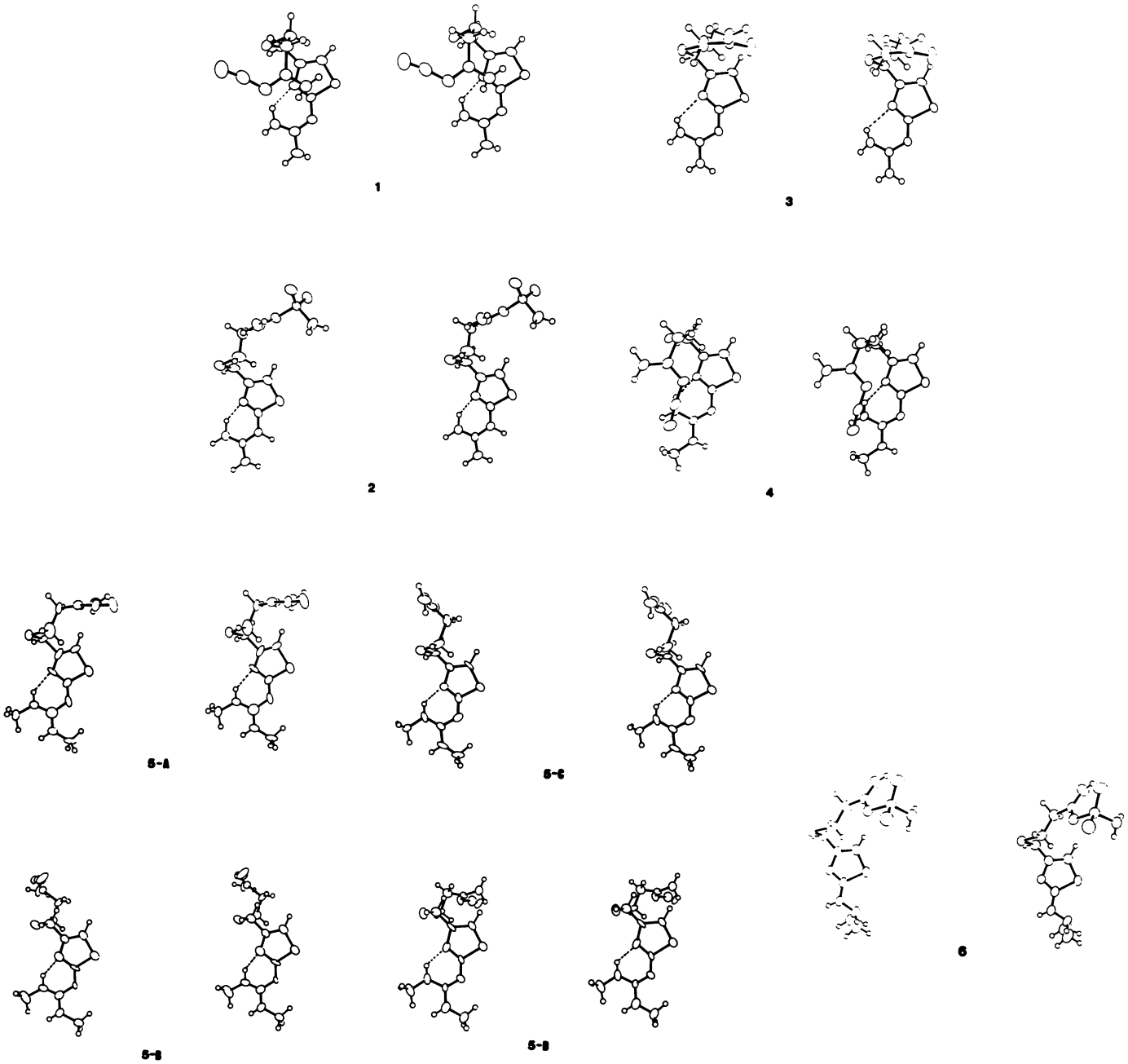


Fig. 1. Stereoscopic projections for one molecule each of amidine compounds **1–6**. – – –, the intramolecular hydrogen bonds. *5-A* to *5-D* represent the molecules A, B, C, and D of compound **5**, respectively.

HCl(N6—H...Cl). Similar conformational differences are also observed between the crystal structures of cimetidine (12) and its hydrochloride salt (13). Therefore, it is questionable whether the conformation found in **2** reflects the stable conformation in its neutral state.

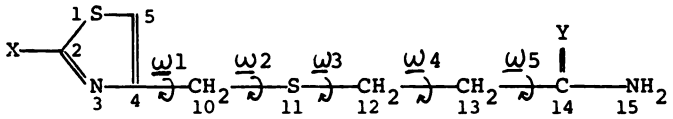
Conformation-Acitivity Relationship

X-ray data. For the purposes of our geometric analysis it is important to consider which atoms participate in binding to the histamine H2 receptor. Although the absence of structural data on the receptor frustrates this consideration, a large volume of structural data on many potent antagonists and conformational analyses on histamine and its analogues (14, 15) suggest the following two nitrogens as the most probable candidates: the thiazole nitrogen as an electron acceptor and the amidinyl NH group as an electron donor. Both of these atoms can simultaneously hydrogen bond to the receptor. With this in mind and remembering that minor modifications in chemical structure of the antagonists can cause drastic changes in their activity (see **1** and **5** and **2** and **6** in Table 1) due to conformational changes, we examined those geometric parameters that appear to be related to the activity. The crystallographic data of **2** HCl were excluded from the analysis, because the existence of HCl influences the molecular conformation (stated above) as well as the chemical structure (cationic form).

(a) The dihedral angle between the thiazole ring and the amidine group, although not correlating directly with activity, may suggest that a parallel alignment of these groups corresponds to the favored active conformation. In the compounds **5** and **6** lacking activity, this angle is far from 0°. Jauregui *et*

TABLE 3

Torsion angles (degrees) with their conformational notations in parentheses and dihedral angles (degrees) between the thiazole ring and amidine group



Compounds	ω1 (N3-C4-C10-S11)	ω2 (C4-C10-S11-C12)	ω3 (C10-S11-C12-C13)	ω4 (S11-C12-C13-C14)	ω5 (C12-C13-C14-N15)	Dihedral angle
1	65.8 (*g*)[a]	61.9 (*g*)	−148.3 (*t*)	60.4 (*g*)	62.0 (*g*)	20.0
2	68.3 (*g*)	63.9 (*g*)	84.8 (*g*)	−177.6 (*t*)	−67.8 (g^-)	87.2
3	73.4 (*g*)	57.2 (*g*)	−164.7 (*t*)	170.1 (*t*)	166.9 (*t*)	85.5
4	58.6 (*g*)	56.6 (*g*)	−170.5 (*t*)	64.6 (*g*)	−124.4 (−*ac*)	13.3
5						
Mol A	65.1 (*g*)	53.3 (*g*)	74.1 (*g*)	−169.9 (*t*)	116.4 (*ac*)	82.3
Mol B[b]	71.1 (*g*)	61.8 (*g*)	70.0 (*g*)	62.3 (*g*)	71.8 (*g*)	80.3
Mol C	64.2 (*g*)	59.2 (*g*)	77.1 (*g*)	61.4 (*g*)	79.4 (*g*)	81.1
Mol D[b]	70.0 (*g*)	58.0 (*g*)	76.7 (*g*)	−170.6 (*t*)	113.9 (*ac*)	78.2
6	68.2 (*g*)	59.8 (*g*)	72.0 (*g*)	173.3 (*t*)	173.8 (*t*)	54.3

[a] Conformational notations: *g*, +*gauche*; g^-, −gauche; *t*, *trans*; *ac*, +anticlinal; −*ac*, −anticlinal.
[b] The conformations of molecules B and D in **5** show the ones converted by a mirror operation (see text).

al. (16) have likewise concluded from their energy calculations on metiamide and cimetidine that a parallel alignment of imidazole ring and endo group is required for interaction with the histamine H2-receptor.

(b) From our crystallographic data it appears that ω3 is also related to antagonist activity, and the high correlation coefficient with the activity, $(r)^1$ of 0.95, implies that a *trans* configuration at ω3 is required.

(c) The other geometric parameters considered are listed in Table 4. Of the distances between the side chain atoms and the N3 thiazole atom, N3-N16 (O16 in **3**) showed good correlation with activity. It is important to note that, although ω3 and N3-N16 parameters are likely to relate to antagonist activity and are useful in distinguishing between active (activity, 2–3) and inactive (activity, 0) conformations, they show no correlation in compounds with activities of 2–3.

Next we examined the structure-activity relationship by resolving the conformations, especially the relative orientation of the thiazole ring and amidine side chain atoms, into three directions (*x*, *y*, *z*) (see Table 4). A high correlation to the activity can be seen in the *y* direction of the N3-N15 and N3-N16 (O16 in **3**) atomic pairs: this value is significantly smaller in all of the active compounds. Furthermore, the d_{xy} distance in the *xy* plane gives good correlation with activity.[2] Similar results are also obtained for N3-C13 and N3-C14 atomic pairs. Thus, it appears that the relative orientation of the amidine side chain with respect to the thiazole ring is important for the emergence of antagonist activity.

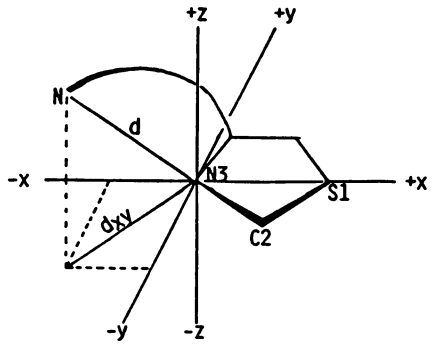
We were interested to know whether the correlation we observed above for our amidine compounds is also found for other H2-receptor antagonists. The compounds structurally analyzed thus far are listed in Table 5 along with their activities and the numbering system employed. The ranking of activity was evaluated from the published pharmaceutical data (23, 24).

TABLE 4

Geometric parameters of the thiazole N3 atom to the amidine N15 and N16 atoms

Compound	N3-N15			N3-N16		
	d[a]	*y*	d_{xy}	*d*	*y*	d_{xy}
1	3.575	−0.07	0.46	4.576	−0.12	1.68
3[b]	6.972	2.80	2.90	5.629	2.59	3.32
4	5.449	0.52	3.06	4.099	−0.30	0.94
5						
A	5.932	4.35	5.11	6.468	3.97	4.20
B[c]	6.834	5.40	5.58	6.479	5.99	6.21
C	7.026	5.43	5.63	6.463	5.99	6.17
D[c]	5.929	4.30	5.10	6.317	3.77	4.02
6	7.270	5.92	6.48	6.165	3.87	4.38
r[d]	0.69	0.93	0.96	0.88	0.88	0.82
a[e]	0.96	0.99	1.00	0.99	0.99	0.98
b[e]	−0.30	0.49	0.69	0.24	0.21	0.11

[a] The values of *d*, *y*, and d_{xy} show the distances (in Å) from the N3 atom (original point) of the thiazole ring to the N15 or N16 atom of the amidine side chain, and are defined as follows:

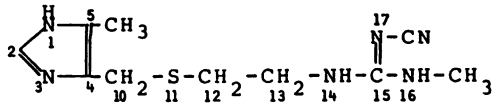
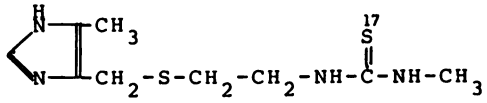
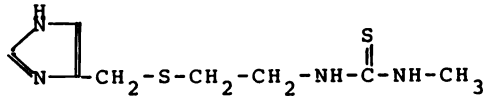
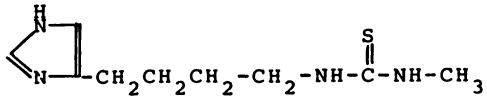
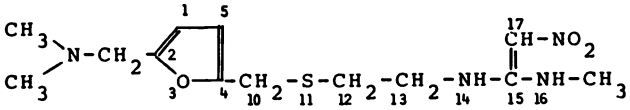
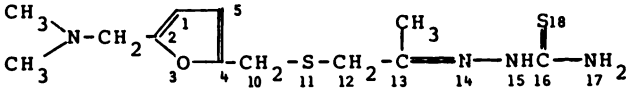
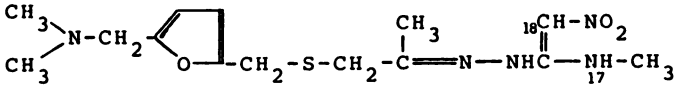


where the thiazole ring lies in the *xy* plane.
[b] The position of O16 in **3** was taken into account for the parameters concerning the N3-N16 pair.
[c] The values obtained by the mirror operation were used.
[d] *r* represents the correlation coefficient of respective headings against the H2-receptor antagonist activities.
[e] The 99% confidence interval at the correlation coefficient (ρ) is represented by $a > \rho > b$.

[1] The number of data (=8) used for the calculation is not enough to give a reliable value of *r*. But the value is useful to assess the conformational characteristics relating to the activty.
[2] The high correlation coefficients for *y* and d_{xy} values were mainly determined by the conformational differences between the nonactive and active compounds. Among the active compounds having activities of 2–3, no high correlation coefficients were obtained.

TABLE 5

The chemical structures, atomic numberings, and activities of other H2-receptor antagonists

No.	Chemical structure[a]	Name	Activity[b]
7		Cimetidine	2
8		Metiamide	2
9		Thiaburimamide	1
10		Burimamide	1
11		Ranitidine	3
12		RANTS	0
13		RANET	0

[a] For cimetidine, the crystal structures of type A (Ref. 12) and Type D (Ref. 17) of free form monohydrate (Ref. 18) and hydrochloride (Ref. 13) were used. The crystal structures of **8–13** were used from Refs. 19–22, respectively.

[b] The ranking of activity was estimated from Refs. 9, 23, and 24. The standard criterion for classifying the activity is the same as that listed in Table 1.

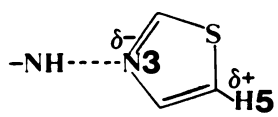
Since the length of the side chain connecting the heteroaromatic ring to the planar end group in these compounds (**7–13**) is different from our amidine compounds (**1–6**), we examined various atomic combinations, bearing in mind that the relative orientation of the heteroatom in the aromatic ring (numbered 3) and the side chain NH group is important. Not unexpectedly, significant correlations with activities were found in the y and d_{xy} values of the following atomic pairs: 3–15 (for **1–6**), 14 (for **7–11**), 15 (for **12,13**), 3–15 (for **1–6**), 16 (for **7–11**), 17 (for **12,13**), and 3–16 (for **1–6**), 17 (for **7–11**), 18 (for **12,13**). The correlation coefficients were as follows:

$r = 0.70$, $a = 0.91$, $b = 0.19$ for y value of 3–15,14,15
$r = 0.79$, $a = 0.94$, $b = 0.38$ for d_{xy} value of 3–15,14,15
$r = 0.68$, $a = 0.91$, $b = 0.17$ for y value of 3–15,16,17
$r = 0.69$, $a = 0.90$, $b = 0.19$ for d_{xy} value of 3–15,16,17
$r = 0.62$, $a = 0.89$, $b = 0.10$ for y value of 3–16,17,18
$r = 0.66$, $a = 0.90$, $b = 0.13$ for d_{xy} value of 3–16,17,18

where the number of data was 19.

These results corroborate our findings for the amidine compounds and show that the spatial orientation of the nitrogen of the side chain to the heteroaromatic ring is important for the emergence of H2-receptor antagonist activity. The y and d_{xy} values of the active antagonists both lie on the range of 0–3 Å. The stereoscopic illustration of the orientations is shown in Fig. 2. From this figure it is seen that the distribution of NH positions falls into two regions corresponding to active and inactive compounds. Most of the active compounds (activity ≥ 2) lie in the region -4 Å $< x < 1$ Å and -2 Å $< y < 2$ Å with no restriction in the z direction. Population analyses by using the active compounds show that the position x=−3 Å, y=z=0 Å represents the preferred position of the NH group with respect to the thiazole ring. Similar results have been deduced by Mitchell (25) and Gilman *et al.* (26). It is worthwhile to note that the two NH groups (N14 and N16) in **7–13** all lie in the same region. Fig. 2 also shows the distribution of the side chain NH groups for **2** and **7** (hydrochloride salts) and both are seen to lie in the region corresponding to inactive compounds.

^{1}H-NMR data. The population analysis above, based on X-ray data, for the amidine and other H2-antagonists suggests that an intramolecular hydrogen bond, NH(amidinyl)... N(thiazole), is important for the emergence of activity. This naturally implies a folded structure for the active conformation. We therefore investigated the ^{1}H-NMR spectra of compounds **1–6** to see whether this hydrogen-bonded form is also present in solution. The participation of the thiazole N3 atom in hydrogen bonding in these compounds could be expected to be accompanied by a decrease in the electron density at the H5 proton resulting from an electron transfer as shown below:



Thus, the chemical shift of this proton should become temperature sensitive. We measured the chemical shifts of H5 for **1–6** and the results are given in Table 6. Immediately striking is the strict correlation between the chemical shifts and activity: the larger the shift the higher the activity. In line with the above arguments, this would mean an electron enrichment at

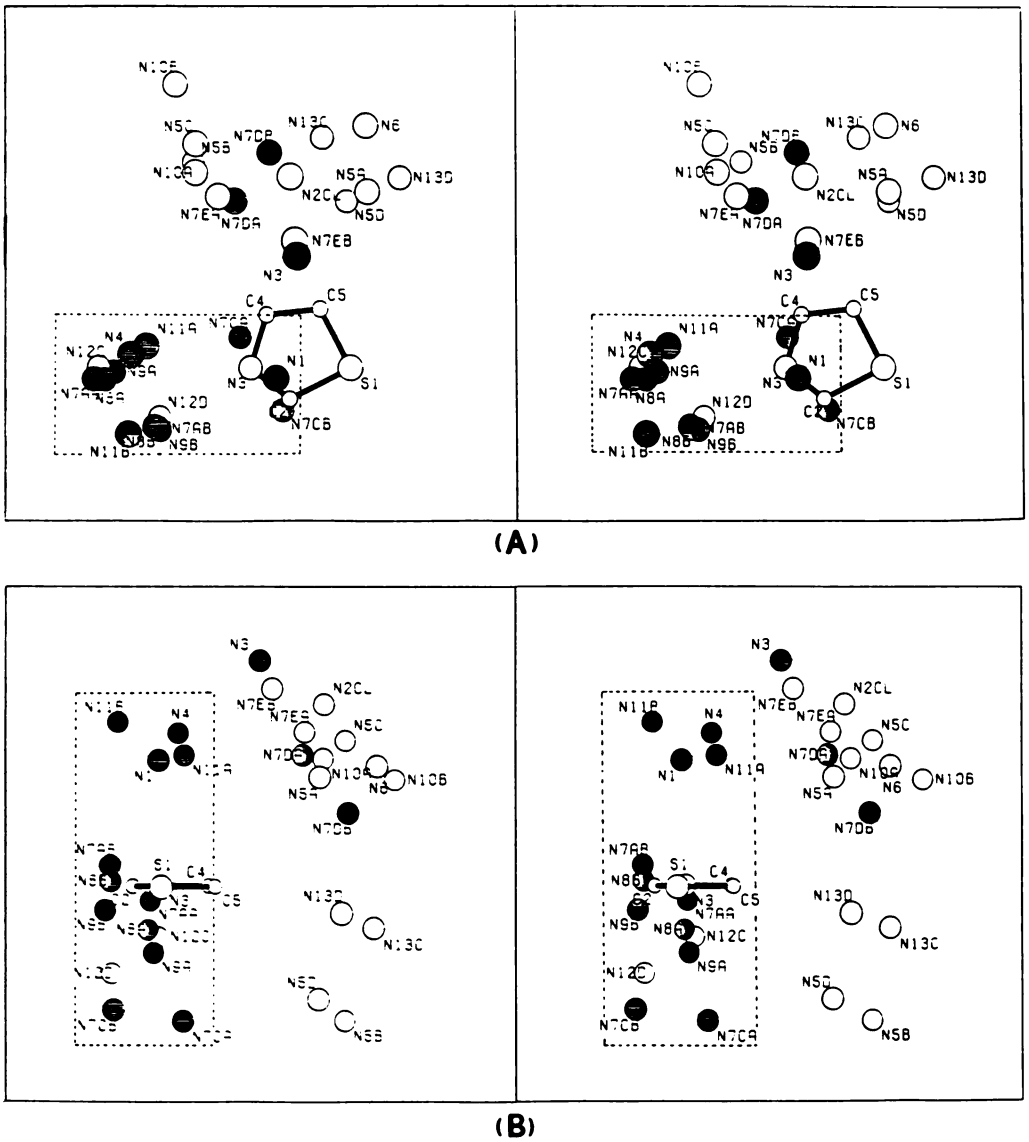


Fig. 2. Stereoscopic drawings of the orientations of NH side atoms to the thiazole (**1–6**), imidazole (**7–10**), or furan (**11–13**) rings. A and B represent the *xy* and *yz* planes of the heteroaromatic rings, respectively. The NH positions of the compounds having the H2 antagonist activities higher than burimamide (**10**) are shown by the *shaded circles*. The NHs of burimamide and the other compounds without activities are shown by the *open circles*. For the HCl salts of **2** and **7**, their atoms are also shown by the *open circles* (see text). The N15 atoms of **1**, **2** (HCl salt), **3**, **4**, **5** (molecules A, B, C, and D), and **6** are shown by: *N1, N2CL, N3, N4, N5A, N5B, N5C, N5D,* and *N6*, respectively. The N14 and N16 atoms of **7** (form A, form C, form D, and HCl salt), **8**, **9**, **10**, and **11** are shown by: *N7AA, N7AB, N7CA, N7CB, N7DA, N7DB, N7EA, N7EB, N8A, N8B, N9A, N9B, N10A, N10B, N11A,* and *N11B*, respectively. The N15 and N17 atoms of **12** and **13** are shown by: *N12C, N12D, N13C,* and *N13D*, respectively. The region enclosed by the *dashed lines* shows the most preferred NH position for the emergency of antagonist activity.

TABLE 6

Temperature dependence of chemical shift (in ppm) of H5 aromatic proton[a]

Compound	Temperature				
	5°	23°	30°	40°	50°
1	6.642	6.638	6.637	6.633	6.629
2 (free form)	6.648	6.640	6.639	6.635	6.631
2 (HCl salt)	7.088	7.089	7.089	7.089	7.088
3	6.623	6.615	6.613	6.610	6.607
4	6.612	6.606	6.603	6.600	6.595
5	6.596	6.600	6.598	6.594	6.590
6	6.315	6.312	6.312	6.312	6.312

[a] Estimated standard error of chemical shift is ±0.001 ppm.

N3, which is of course favored for hydrogen bonding, and breaking this bond by increasing the temperature should give rise to upfield values for the chemical shifts of H5. Indeed, this is what is observed; that is, those amidines (see Table 6) with activity also show a large temperature dependence for the H5 proton. Similar dependence at lower concentration (~7 mM) suggests that the change is mainly due to the effect of intramolecular hydrogen bonding. Therefore, taken together, these data suggest that an intramolecular hydrogen bond, probably N15—H...N3, leads to the active conformation for H2-receptor antagonism, although the direct participation of H5 in hydrogen bonding cannot be excluded. Finally, it is interesting to note that the H5 atom in the hydrochloride salt of **2** does not show any temperature dependence despite having the lowest chemical shift.

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