which prevent the close approach of the appropriate γ-H atom to O.

In conclusion, the solid-state photolyses are topochemically controlled, with minimum motion resulting in formation of the *cis*-OH photoproduct (1) (Fig. 3) *via* interaction of *p*-orbital lobes *a* and *b* (Fig. 2), while the less-sterically hindered *trans*-OH compounds [(2) and (4)] are formed in solution reactions.

Asymmetric synthesis

The crystallographic study of 4-chloro-α-(3-methyladamantyl)acetophenone indicated that the material crystallized in the chiral space group $P2_12_12_1$ (Table 1). This suggested the possibility of producing an optically active product mixture from the achiral reactant material (Evans, Garcia-Garibay, Omkaram, Scheffer, Trotter & Wireko, 1986); the important factor is that the (chance) crystallization of the achiral reactant in a chiral space group provides a chiral environment for the reactant. Products formed by photolysis in solution or in a polycrystalline aggregate show no trace of optical activity. However, when a single crystal weighing 313 mg was photolysed, the major product was the *cis*-OH compound (1), with $[\alpha]_D = -21{\cdot}6°$, and an enantiomeric excess of 80% (as determined by the use of a chiral NMR shift reagent). The lack of total stereospecificity may be due to inversion twinning in the crystal, or to disruption of the crystal lattice as the reaction proceeds.

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References

EVANS, S. V., GARCIA-GARIBAY, M., OMKARAM, N., SCHEFFER, J. R., TROTTER, J. & WIREKO, F. (1986). *J. Am. Chem. Soc.* **108**, 5648–5650.

EVANS, S. V. & TROTTER, J. (1988). *Acta Cryst.* B**44**, 63–72.

EVANS, S. V. & TROTTER, J. (1989). *Acta Cryst.* B**45**, 159–162.

International Tables for X-ray Crystallography (1974). Vol. IV, pp. 99–102 and 149. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

OMKARAM, N. (1986). PhD Thesis, Univ. of British Columbia, Canada.

Acta Cryst. (1989). B**45**, 505–512

Structural Study of Histamine H_2-Receptor Antagonists. Five 3-[2-(Diaminomethyleneamino)-4-thiazolylmethylthio]propionamidine and -amide Derivatives

BY TOSHIMASA ISHIDA, YASUKO IN, MITSUNOBU DOI AND MASATOSHI INOUE

Osaka University of Pharmaceutical Sciences, 2-10-65 Kawai, Matsubara, Osaka 580, *Japan*

AND ISAO YANAGISAWA

Central Research Laboratories, Yamanouchi Pharmaceutical Co. Ltd, No. 1–8, Azusawa 1-chome, Itabashi-ku, Tokyo 174, *Japan*

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Abstract

(1) N^2-Cyano-3-[2-(diaminomethyleneamino)-4-thiazolylmethylthio]propionamidine monohydrate, $C_9H_{13}N_7S_2.H_2O$, $M_r = 301{\cdot}39$, $P\bar{1}$, $a = 11{\cdot}089$ (4), $b = 9{\cdot}130$ (6), $c = 7{\cdot}033$ (5) Å, $\alpha = 100{\cdot}99$ (6), $\beta = 83{\cdot}86$ (5), $\gamma = 86{\cdot}80$ (7)°, $V = 692{\cdot}9$ (6) Å^3, $Z = 2$, $D_m = 1{\cdot}443$ (2), $D_x = 1{\cdot}444$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 34{\cdot}86$ cm^{-1}, $F(000) = 316$, $T = 293$ K, $R = 0{\cdot}043$ for 2219 reflections. (2) 3-[2-(Diaminomethyleneamino)-4-thiazolylmethylthio]-N^2-sulfamoylpropionamidine (famotidine) hydrochloride, $C_8H_{15}N_7O_2S_3.HCl$, $M_r = 373{\cdot}90$, Cc, $a = 15{\cdot}205$ (3), $b = 14{\cdot}442$ (3), $c = 9{\cdot}262$ (1) Å, $\beta = 124{\cdot}00$ (5)°, $V = 1686{\cdot}1$ (7) Å^3, $Z = 4$, $D_m = 1{\cdot}470$ (2), $D_x = 1{\cdot}473$ g cm^{-3}, μ(Cu $K\alpha$) = 56·09 cm^{-1}, $F(000) = 776$, $T = 293$ K, $R = 0{\cdot}036$ for 1411 reflections. (3) 3-[2-(Diaminomethyleneamino)-4-thiazolylmethylthio]-propionamide, $C_8H_{13}N_5OS_2$, $M_r = 259{\cdot}35$, $P2_12_12_1$, $a = 5{\cdot}472$ (1), $b = 18{\cdot}260$ (5), $c = 11{\cdot}890$ (3) Å, $V = 1188{\cdot}0$ (5) Å^3, $Z = 4$, $D_m = 1{\cdot}448$ (1), $D_x = 1{\cdot}450$ g cm^{-3}, μ(Cu $K\alpha$) = 39·26 cm^{-1}, $F(000) = 544$, $T = 293$ K, $R = 0{\cdot}036$ for 1260 reflections. (4) 3-{2-[Amino(methylamino)methyleneamino]-4-thiazolylmethylthio}-N^2-cyanopropionamidine, $C_{10}H_{15}N_7S_2$, $M_r = 297{\cdot}40$, $P2_1/c$, $a = 14{\cdot}235$ (5), $b = 5{\cdot}453$ (2), $c = 17{\cdot}782$ (7) Å, $\beta = 90{\cdot}13$ (6)°, $V = 1380{\cdot}2$ (8) Å^3, $Z = 4$, $D_m = 1{\cdot}420$ (1), $D_x = 1{\cdot}431$ g cm^{-3}, μ(Cu $K\alpha$) =

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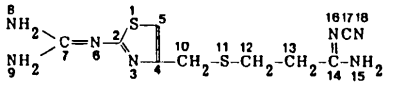
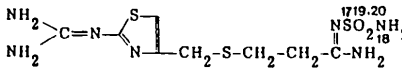
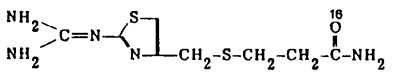
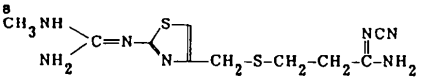
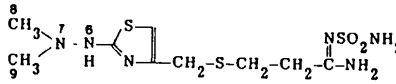
Table 1. *Chemical structures with the atomic numberings and H_2-receptor antagonist activities of famotidine analogues*

	Chemical structure	$ED_{50}(M)$*
(1)		1.8×10^{-7}
(2)		2.7×10^{-7}
(3)		1.0×10^{-6}
(4)		1.2×10^{-6}
(5)		$> 10^{-4}$

*H_2-receptor antagonist activity in guinea pig atrium.

34·39 cm^{-1}, $F(000) = 624$, $T = 293$ K, $R = 0.035$ for 2210 reflections. (5) 3-[2-(*N'*,*N'*-dimethylhydrazino)-4-thiazolylmethylthio]-N^2-sulfamoylpropionamidine–maleic acid (1/1), $C_9H_{18}N_6O_2S_3.C_4H_4O_4$, M_r = 454·53, *P*1, $a = 14.802$ (4), $b = 13.275$ (3), c = 5·236 (2) Å, $\alpha = 93.42$ (2), $\beta = 93.68$ (2), γ = 84·01 (2)°, $V = 1019.8$ (5) $Å^3$, $Z = 2$, $D_m = 1.475$ (2), $D_x = 1.480$ g cm^{-3}, μ(Cu $K\alpha$) = 36·57 cm^{-1}, $F(000)$ = 476, $T = 293$ K, $R = 0.055$ for 3326 reflections. These molecules exhibit different activities as histamine H_2-receptor antagonists. The possible relationship between the molecular conformation and inhibitory activity is discussed.

Introduction

To design a biologically active compound, it is important to identify the key atoms and their spatial orientation responsible for the activity emergency. When information on the stereostructure of the receptor molecule is lacking, an alternative methodology is to compare the molecular conformations in a series of compounds of structural and physicochemical similarities but of different pharmaceutical activities. The conformational characteristics thus obtained would be useful for considering new potent compounds.

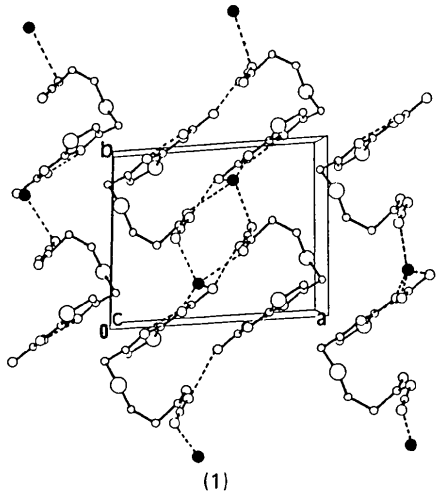
The therapeutic success of cimetidine as a histamine H_2-receptor antagonist (Brogden, Heel, Speight & Avery, 1978) led to the development of more potent and/or longer lasting drugs for human peptic ulcers. Consequently, 3-[2-(diaminomethyleneamino)-4-thiazolylmethylthio]-N^2-sulfamoylpropionamidine (famotidine) was designed as a more-potent ulcer drug (Takeda, Takagi & Maeno, 1981, 1983; Takeda, Takagi, Yashima & Maeno, 1982; Takagi, Takeda & Maeno, 1982; Harada, Terai & Maeno, 1983; Yanagisawa, Hirata & Ishii, 1987). The chemical structure of famotidine differs from cimetidine in the central aromatic ring and the end group of the side chain: a thiazole ring and an amidine group in the former, and an imidazole ring and a guanidine group in the latter.

This paper deals with the X-ray crystal analyses of five famotidine analogues exhibiting different antagonist activities; their chemical formulae with the atomic numberings used are given in Table 1, along with their inhibitory activities (Yanagisawa, Hirata & Ishii, 1984, 1987). The conformational comparison of these compounds with cimetidine and ranitidine is useful for considering the structure–activity relationship of H_2-receptor antagonists (Ishida, In, Shibata, Doi, Inoue & Yanagisawa, 1987).

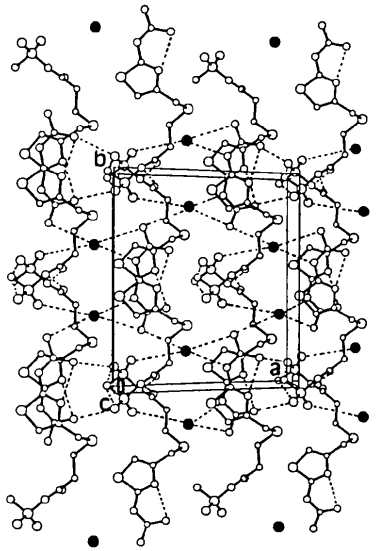
Experimental

Synthesized by the method of Yanagisawa *et al.* (1984, 1987), recrystallized from methanol/acetone/water (1), methanol [(2) and (3)], ethanol (4) and methanol/water (5). Crystal size (mm): (1) 0·1 × 0·2 × 0·5; (2) 0·3 × 0·3 × 0·4; (3) 0·3 × 0·1 × 0·4; (4) 0·2 × 0·2 × 0·4; (5) 0·1 × 0·2 × 0·5. D_m by flotation method (benzene–carbon tetrachloride mixture). Rigaku four-circle diffractometer with graphite-monochromated Cu $K\alpha$ radiation. Cell parameters from 25 reflections with $15 < 2\theta < 30°$. Intensity data measured by ω–2θ continuous scan mode; scan speed 2–4° min^{-1} (θ); scan range $(A + 0.15\tan\theta)°$ with A 0·8 to 1·2°; 5 s stationary background counts; 2θ range 2–130°; *hkl* range: (1) 0–±13, 0–±10, 0–8; (2) 0–±17, 0–16, 0–10; (3) 0–6, 0–21, 0–13; (4) 0–±16, 0–6, 0–20; (5) 0–±17, 0–±15, 0–6. Four standard reflections monitored every 100 reflections; no significant variation of intensities. Corrections for Lorentz and polarization effects; no absorption corrections. Number of measured reflections, number of observed $[I > \sigma(I)]$ reflections in parentheses: (1) 2582 (2219); (2) 1439 (1411); (3) 1269 (1260); (4) 2443 (2210); (5) 3913 (3326). Structure solved by heavy-atom (2) or direct methods, *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). All H atoms located on respective difference Fourier maps. Block-diagonal least-squares refinements with anisotropic temperature factors for non-H atoms and isotropic ones for H atoms. The function minimized was $\sum w(|F_o| - |F_c|)^2$, where the following w was used: $w = 1.0/[\sigma(F_o)^2 + m_1|F_o| + m_2|F_o|^2]$ for $|F_o| > \sigma(F_o)$; values

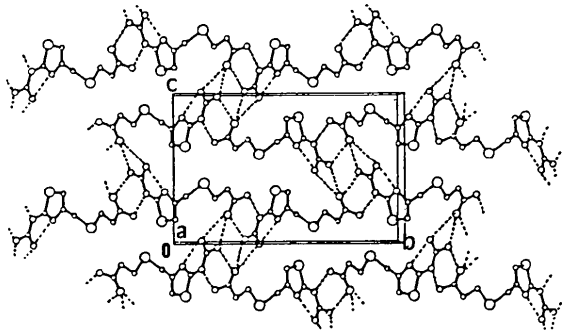
of m_1 and m_2: (1) 0·0302, −0·0004; (2) 0·0417, −0·0004; (3) 0·0454, −0·0006; (4) 0·0324, −0·0003; (5) 0·0627, −0·0009. Final wR and S: (1) 0·053, 1·198; (2) 0·030, 1·052; (3) 0·040, 1·109; (4) 0·034, 1·145; (5) 0·041, 1·326. $(\Delta/\sigma)_{max}$: (1) 0·40; (2) 0·33; (3) 0·38; (4) 0·32; (5) 0·35. $(\Delta\rho)_{max}$ and $(\Delta\rho)_{min}$ (e Å^{-3}): (1) 0·35, −0·28; (2) 0·22, −0·18; (3) 0·25, −0·19; (4) 0·25, −0·15; (5) 0·30, −0·22. Scattering factors from *International Tables for X-ray Crystallography* (1974). All numerical computations performed on an ACOS 900 computer at the Computation Center, Osaka University, using *The Universal Crystallographic Computing System – Osaka* (1979).*



(1)



(2)

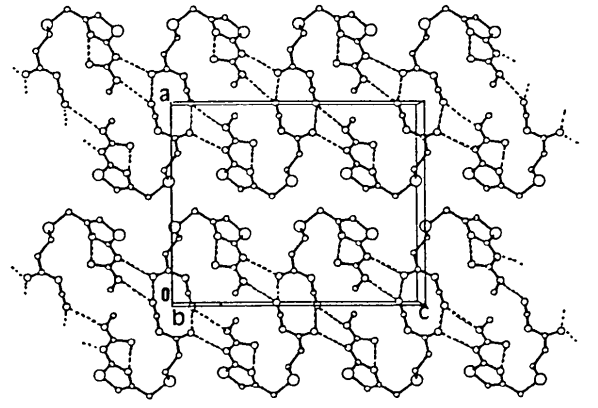


(3)

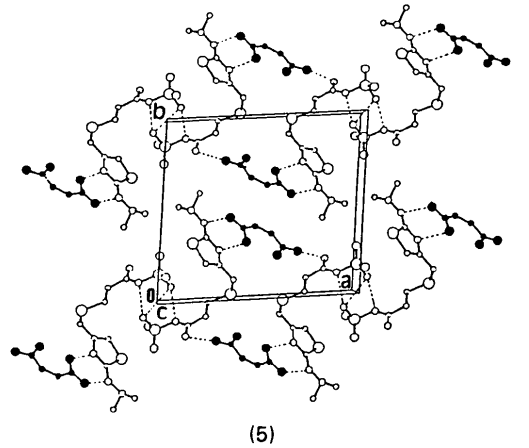
Discussion

Table 2 lists final coordinates and B_{eq} values for the non-H atoms. Fig. 1 shows the views of perspective molecular packings, in which dotted lines represent possible intra- or intermolecular hydrogen bonds. The hydrogen-bond distances and angles are summarized in Table 3.

* Lists of structure factors, anisotropic temperature factors and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51975 (53 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.



(4)



(5)

Fig. 1. Perspective views of crystal packings of (1)–(5). The dotted lines represent hydrogen bonds. The filled circles show waters of crystallization in (1), chloride ions in (2) and maleic acids in (5).

Table 2. *Fractional coordinates and equivalent isotropic temperature factors* (Å^2) *of compounds* (1)–(5)

W represents the water molecule.

$$B_{eq} = \tfrac{4}{3}\sum_i\sum_j \mathbf{a}_i.\mathbf{a}_j B_{ij}.$$

	x	*y*	*z*	B_{eq}
(1)				
S(1)	0·79184 (6)	0·09405 (7)	0·64019 (9)	3·38 (3)
C(2)	0·7598 (2)	0·0187 (3)	0·4068 (3)	2·86 (9)
N(3)	0·8364 (2)	0·0484 (2)	0·2679 (3)	3·26 (9)
C(4)	0·9270 (2)	0·1354 (3)	0·3454 (4)	3·3 (1)
C(5)	0·9161 (2)	0·1696 (3)	0·5426 (4)	3·5 (1)
N(6)	0·6603 (2)	−0·0626 (2)	0·3913 (3)	3·34 (9)
C(7)	0·6196 (2)	−0·1026 (3)	0·2203 (4)	3·5 (1)
N(8)	0·5211 (2)	−0·1864 (3)	0·2193 (4)	4·8 (1)
N(9)	0·6650 (2)	−0·0704 (3)	0·0564 (3)	4·8 (1)
C(10)	1·0213 (2)	0·1841 (3)	0·2072 (4)	3·7 (1)
S(11)	0·95688 (6)	0·31350 (8)	0·0703 (1)	3·71 (3)
C(12)	0·8975 (2)	0·4669 (3)	0·2689 (4)	3·6 (1)
C(13)	0·7837 (3)	0·5472 (3)	0·2191 (4)	3·7 (1)
C(14)	0·6828 (2)	0·4425 (3)	0·1862 (4)	3·3 (1)
N(15)	0·6400 (2)	0·3825 (3)	0·3316 (3)	4·4 (1)
N(16)	0·6366 (2)	0·4072 (2)	0·0195 (3)	3·7 (1)
C(17)	0·6770 (3)	0·4682 (3)	−0·1285 (4)	4·0 (1)
N(18)	0·7044 (3)	0·5140 (3)	−0·2692 (4)	5·3 (1)
O(1)*W*	0·5755 (2)	0·7909 (2)	0·6884 (3)	4·36 (9)
(2)				
S(1)	0·46667 (9)	0·0758 (1)	0·4354 (2)	6·44 (5)
C(2)	0·3604 (3)	0·0053 (3)	0·3760 (6)	4·1 (2)
N(3)	0·2680 (3)	0·0413 (2)	0·2800 (5)	4·1 (1)
C(4)	0·2770 (4)	0·1345 (3)	0·2468 (5)	4·7 (2)
C(5)	0·3767 (4)	0·1629 (3)	0·3218 (7)	5·6 (2)
N(6)	0·3827 (2)	−0·0870 (2)	0·4323 (5)	4·5 (1)
C(7)	0·3060 (3)	−0·1534 (3)	0·3787 (5)	3·6 (1)
N(8)	0·3422 (3)	−0·2401 (2)	0·4385 (5)	4·5 (1)
N(9)	0·2069 (2)	−0·1364 (2)	0·2749 (5)	4·0 (1)
C(10)	0·1776 (4)	0·1899 (3)	0·1387 (5)	4·7 (2)
S(11)	0·1100 (1)	0·21254 (7)	0·2446 (2)	5·30 (4)
C(12)	0·2057 (4)	0·2813 (3)	0·4344 (6)	5·3 (2)
C(13)	0·1990 (3)	0·3831 (3)	0·3907 (5)	4·6 (2)
C(14)	0·2780 (3)	0·4420 (3)	0·5400 (5)	3·5 (1)
N(15)	0·2656 (3)	0·4502 (3)	0·6708 (4)	4·1 (1)
N(16)	0·3500 (2)	0·4801 (2)	0·5258 (4)	3·2 (1)
S(17)	0·43854 (8)	0·54953 (6)	0·6750 (1)	2·85 (3)
N(18)	0·5283 (2)	0·4913 (2)	0·8434 (4)	4·1 (1)
O(19)	0·4891 (2)	0·5894 (2)	0·5968 (4)	4·0 (1)
O(20)	0·3936 (2)	0·6128 (2)	0·7373 (4)	4·1 (1)
Cl(21)	0·10148 (8)	0·66179 (7)	0·2242 (2)	4·16 (3)
(3)				
S(1)	0·8771 (2)	0·54985 (5)	0·65159 (8)	2·87 (4)
C(2)	0·8993 (7)	0·5720 (2)	0·7946 (3)	2·3 (1)
N(3)	1·0785 (6)	0·5379 (2)	0·8464 (3)	2·5 (1)
C(4)	1·2065 (8)	0·4931 (2)	0·7744 (3)	2·5 (1)
C(5)	1·1265 (9)	0·4924 (2)	0·6660 (4)	3·3 (2)
N(6)	0·7329 (7)	0·6205 (2)	0·8340 (3)	2·8 (1)
C(7)	0·7382 (8)	0·6422 (2)	0·9411 (3)	2·6 (1)
N(8)	0·5666 (9)	0·6884 (2)	0·9758 (3)	4·2 (2)
N(9)	0·9027 (9)	0·6207 (2)	1·0154 (3)	4·1 (2)
C(10)	1·4100 (8)	0·4485 (2)	0·8192 (4)	2·9 (2)
S(11)	1·3074 (2)	0·37079 (5)	0·90363 (8)	2·81 (4)
C(12)	1·116 (1)	0·3243 (2)	0·8036 (4)	3·5 (2)
C(13)	0·9547 (9)	0·2691 (2)	0·8609 (4)	3·4 (2)
C(14)	0·7622 (8)	0·2383 (2)	0·7841 (3)	2·7 (1)
N(15)	0·6428 (7)	0·1796 (2)	0·8182 (2)	3·0 (1)
O(16)	0·7168 (7)	0·2675 (2)	0·6917 (3)	3·9 (1)
(4)				
S(1)	0·35214 (4)	0·9111 (1)	0·79372 (3)	3·43 (2)
C(2)	0·3046 (1)	0·6568 (4)	0·7477 (1)	2·71 (8)
N(3)	0·3435 (1)	0·6134 (3)	0·68222 (9)	2·94 (7)
C(4)	0·4120 (1)	0·7841 (4)	0·6663 (1)	2·99 (8)
C(5)	0·4261 (1)	0·9579 (4)	0·7181 (1)	3·56 (9)
N(6)	0·2339 (1)	0·5314 (3)	0·78251 (9)	2·80 (7)
C(7)	0·1896 (1)	0·3555 (4)	0·7441 (1)	2·70 (8)
N(8)	0·1247 (1)	0·2238 (4)	0·7815 (1)	3·31 (8)
C(8)	0·0719 (2)	0·0258 (5)	0·7479 (1)	4·0 (1)
N(9)	0·2025 (1)	0·3047 (4)	0·6720 (1)	3·63 (8)
C(10)	0·4637 (1)	0·7593 (4)	0·5936 (1)	3·56 (9)
S(11)	0·38785 (4)	0·7677 (1)	0·51151 (3)	3·20 (2)
C(12)	0·3323 (1)	1·0612 (4)	0·5279 (1)	3·10 (9)
C(13)	0·2504 (2)	1·1038 (4)	0·4739 (1)	3·42 (9)
C(14)	0·1708 (1)	0·9236 (4)	0·4848 (1)	3·06 (9)

Table 2 (*cont.*)

	x	*y*	*z*	B_{eq}
N(15)	0·1442 (1)	0·7961 (4)	0·4262 (1)	3·43 (8)
N(16)	0·1337 (1)	0·9118 (4)	0·5525 (1)	3·79 (8)
C(17)	0·0600 (2)	0·7655 (5)	0·5635 (1)	3·9 (1)
N(18)	−0·0043 (1)	0·6470 (5)	0·5794 (1)	4·9 (1)
(5)				
S(1)	0·33773 (6)	−0·31250 (7)	0·8029 (2)	3·99 (4)
C(2)	0·2684 (2)	−0·3385 (2)	0·5380 (6)	3·7 (1)
N(3)	0·1992 (2)	−0·2675 (2)	0·5066 (5)	3·7 (1)
C(4)	0·1971 (2)	−0·1899 (2)	0·6989 (6)	3·6 (1)
C(5)	0·2658 (2)	−0·2026 (3)	0·8722 (7)	3·9 (1)
N(6)	0·2835 (2)	−0·4186 (2)	0·3831 (6)	4·7 (1)
N(7)	0·3553 (2)	−0·4927 (2)	0·4597 (6)	4·5 (1)
C(8)	0·4166 (3)	−0·5154 (4)	0·2528 (9)	6·8 (3)
C(9)	0·3145 (3)	−0·5819 (3)	0·536 (1)	6·8 (3)
C(10)	0·1215 (2)	−0·1051 (3)	0·6892 (7)	3·9 (1)
S(11)	0·13001 (5)	−0·02229 (7)	0·4269 (2)	3·78 (3)
C(12)	0·2430 (2)	0·0174 (2)	0·4880 (6)	3·6 (1)
C(13)	0·2506 (2)	0·0907 (3)	0·7197 (7)	4·1 (2)
C(14)	0·3410 (2)	0·1338 (2)	0·7639 (6)	3·4 (1)
N(15)	0·3506 (2)	0·1876 (2)	0·9873 (6)	4·7 (1)
N(16)	0·4018 (2)	0·1114 (2)	0·5892 (5)	3·7 (1)
S(17)	0·50283 (5)	0·15041 (6)	0·6273 (1)	3·22 (3)
N(18)	0·5658 (2)	0·0746 (2)	0·8095 (5)	3·7 (1)
O(19)	0·5382 (2)	0·1343 (2)	0·3797 (4)	4·4 (1)
O(20)	0·5032 (2)	0·2482 (2)	0·7541 (5)	4·8 (1)
Maleic acid				
C(1)	0·9700 (3)	0·3896 (3)	1·2746 (8)	5·3 (2)
C(2)	0·9103 (2)	0·3820 (3)	1·0356 (7)	4·4 (2)
O(3)	0·9264 (2)	0·3096 (2)	0·8786 (5)	5·8 (1)
O(4)	0·8424 (2)	0·4443 (2)	1·0238 (6)	6·2 (2)
C(5)	1·0547 (2)	0·3433 (3)	1·3320 (8)	5·2 (2)
C(6)	1·1115 (2)	0·2683 (3)	1·1774 (7)	4·8 (2)
O(7)	1·0768 (2)	0·2241 (3)	0·9764 (7)	8·9 (2)
O(8)	1·1890 (2)	0·2432 (2)	1·2614 (6)	5·6 (1)

Table 3. *Hydrogen-bond distances* (Å) *and angles* (°)

W and *M* represent water and maleic acid, respectively.

Donor (*D*) at *x*, *y*, *z*	Acceptor (*A*) at	symmetry operation	*D*···*A*	H···*A*	*D*—H···*A*
(1)					
N(8)	N(16)	−*x* + 1, −*y*, −*z*	3·110 (3)	2·31 (3)	140 (3)
N(9)	N(3)	*x*, *y*, *z*	2·686 (3)	1·99 (4)	127 (3)
N(9)	O(1)*W*	*x*, *y* − 1, *z* − 1	2·955 (3)	2·20 (3)	168 (3)
N(15)	N(18)	*x*, *y*, *z* + 1	3·012 (4)	2·16 (3)	170 (3)
N(15)	O(1)*W*	−*x* + 1, −*y* + 1, −*z* + 1	2·941 (3)	2·20 (4)	147 (4)
O(1)*W*	N(6)	*x*, *y* + 1, *z*	2·797 (3)	1·75 (4)	167 (4)
O(1)*W*	N(18)	*x*, *y*, *z* + 1	2·916 (4)	1·83 (4)	167 (3)
(2)					
N(6)	Cl(21)	*x* + 0·5, −*y* + 0·5, *z* + 0·5	3·080 (4)	2·02 (5)	166 (4)
N(8)	O(19)	*x*, *y* − 1, *z*	3·089 (5)	2·33 (5)	139 (4)
N(9)	N(3)	*x*, *y*, *z*	2·721 (5)	1·80 (5)	141 (4)
N(15)	N(16)	*x*, −*y* + 1, *z* + 0·5	2·959 (5)	1·86 (5)	179 (5)
N(18)	O(19)	*x*, −*y* + 1, *z* + 0·5	2·964 (5)	1·89 (5)	180 (4)
(3)					
N(8)	O(16)	−*x* + 1·5, −*y* + 1, *z* + 0·5	2·941 (4)	2·20 (4)	153 (3)
N(8)	O(16)	−*x* + 1, *y* + 0·5, −*z* + 1·5	2·903 (4)	2·00 (4)	169 (3)
N(9)	N(3)	*x*, *y*, *z*	2·691 (4)	2·21 (4)	118 (4)
N(9)	O(16)	−*x* + 1·5, −*y* + 1, *z* + 0·5	3·003 (4)	2·11 (5)	161 (5)
N(15)	N(6)	−*x* + 1, *y* − 0·5, −*z* + 1·5	2·942 (4)	2·00 (4)	151 (3)
(4)					
N(8)	N(18)	−*x*, *y* − 0·5, −*z* + 1·5	3·041 (3)	2·36 (2)	130 (2)
N(9)	N(3)	*x*, *y*, *z*	2·626 (2)	1·95 (3)	134 (2)
N(9)	N(16)	*x*, *y* − 1, *z*	3·171 (3)	2·30 (2)	163 (2)
N(15)	N(6)	*x*, −*y* + 1·5, *z* − 0·5	3·010 (2)	2·08 (2)	168 (2)
N(15)	N(18)	−*x*, −*y* + 1, −*z* + 1	3·132 (3)	2·22 (3)	173 (2)
(5)					
N(6)	O(4)*M*	−*x* + 1, −*y*, −*z* + 1	2·769 (4)	1·83 (4)	178 (4)
N(15)	O(8)*M*	*x* − 1, *y*, *z*	2·901 (4)	1·95 (4)	178 (4)
N(15)	O(20)	*x*, *y*, *z*	2·822 (4)	2·21 (4)	119 (3)
N(18)	O(19)	*x*, *y*, *z* + 1	3·085 (4)	2·12 (4)	179 (3)
N(18)	N(16)	−*x* + 1, −*y*, −*z* + 1	3·155 (4)	2·20 (4)	176 (4)
O(3)*M*	N(3)	−*x* + 1, −*y*, −*z* + 1	2·727 (4)	1·72 (4)	179 (4)
O(7)*M*	O(3)*M*	*x*, *y*, *z*	2·429 (5)	1·54 (4)	155 (4)

Table 4. *Bond lengths* (Å) *of compounds* (1)–(5)

M represents maleic acid.

(1)			
S(1)—C(2)	1·737 (2)	C(7)—N(9)	1·300 (4)
S(1)—C(5)	1·712 (3)	C(10)—S(11)	1·822 (3)
C(2)—N(3)	1·303 (3)	S(11)—C(11)	1·817 (3)
C(2)—N(6)	1·366 (3)	C(12)—C(13)	1·530 (4)
N(3)—C(4)	1·406 (3)	C(13)—C(14)	1·520 (4)
C(4)—C(5)	1·353 (4)	C(14)—N(15)	1·307 (4)
C(4)—C(10)	1·495 (4)	C(14)—N(16)	1·320 (3)
N(6)—C(7)	1·323 (3)	N(16)—C(17)	1·320 (4)
C(7)—N(8)	1·368 (4)	C(17)—N(18)	1·163 (4)
(2)			
S(1)—C(2)	1·720 (5)	C(10)—S(11)	1·804 (5)
S(1)—C(5)	1·717 (6)	S(11)—C(12)	1·826 (5)
C(2)—N(3)	1·279 (6)	C(12)—C(13)	1·513 (7)
C(2)—N(6)	1·403 (6)	C(13)—C(14)	1·490 (6)
N(3)—C(4)	1·404 (6)	C(14)—N(15)	1·332 (6)
C(4)—C(5)	1·331 (7)	C(14)—N(16)	1·295 (5)
C(4)—C(10)	1·494 (7)	N(16)—S(17)	1·627 (4)
N(6)—C(7)	1·370 (6)	S(17)—N(18)	1·619 (4)
C(7)—N(8)	1·356 (6)	S(17)—O(19)	1·439 (3)
C(7)—N(9)	1·278 (6)	S(17)—O(20)	1·440 (3)
(3)			
S(1)—C(2)	1·752 (4)	C(7)—N(8)	1·328 (6)
S(1)—C(5)	1·730 (4)	C(7)—N(9)	1·321 (6)
C(2)—N(3)	1·316 (5)	C(10)—S(11)	1·826 (4)
C(2)—N(6)	1·353 (5)	S(11)—C(12)	1·799 (5)
N(3)—C(4)	1·376 (5)	C(12)—C(13)	1·503 (7)
C(4)—C(5)	1·361 (6)	C(13)—C(14)	1·503 (6)
C(4)—C(10)	1·479 (6)	C(14)—N(15)	1·320 (5)
N(6)—C(7)	1·335 (5)	C(14)—O(16)	1·246 (5)
(4)			
S(1)—C(2)	1·746 (2)	N(8)—C(8)	1·444 (3)
S(1)—C(5)	1·729 (2)	C(10)—S(11)	1·815 (2)
C(2)—N(3)	1·312 (3)	S(11)—C(12)	1·809 (2)
C(2)—N(6)	1·336 (3)	C(12)—C(13)	1·527 (3)
N(3)—C(4)	1·378 (3)	C(13)—C(14)	1·512 (3)
C(4)—C(5)	1·336 (3)	C(14)—N(15)	1·308 (3)
C(4)—C(10)	1·495 (3)	C(14)—N(16)	1·317 (3)
N(6)—C(7)	1·335 (2)	N(16)—C(17)	1·333 (3)
C(7)—N(8)	1·348 (3)	C(17)—N(18)	1·157 (3)
C(7)—N(9)	1·324 (3)		
(5)			
S(1)—C(2)	1·712 (3)	C(14)—N(15)	1·302 (4)
S(1)—C(5)	1·748 (4)	C(14)—N(16)	1·324 (4)
C(2)—N(3)	1·327 (4)	N(16)—S(17)	1·630 (3)
C(2)—N(6)	1·307 (4)	S(17)—N(18)	1·611 (3)
N(3)—C(4)	1·396 (4)	S(17)—O(19)	1·425 (3)
C(4)—C(5)	1·322 (5)	S(17)—O(20)	1·423 (3)
C(4)—C(10)	1·503 (5)	C(1)*M*—C(2)*M*	1·490 (5)
N(6)—N(7)	1·426 (4)	C(1)*M*—C(5)*M*	1·361 (6)
N(7)—C(8)	1·455 (6)	C(2)*M*—O(3)*M*	1·241 (5)
N(7)—C(9)	1·470 (6)	C(2)*M*—O(4)*M*	1·234 (5)
C(10)—S(11)	1·828 (4)	C(5)*M*—C(6)*M*	1·474 (6)
S(11)—C(12)	1·809 (3)	C(6)*M*—O(7)*M*	1·279 (5)
C(12)—C(13)	1·515 (5)	C(6)*M*—O(8)*M*	1·222 (5)
C(13)—C(14)	1·508 (5)		

Table 5. *Bond angles* (°) *of compounds* (1)–(5)

M represents maleic acid.

(1)			
C(2)—S(1)—C(5)	89·9 (1)	N(6)—C(7)—N(9)	126·0 (2)
S(1)—C(2)—N(3)	114·0 (1)	N(8)—C(7)—N(9)	118·2 (2)
S(1)—C(2)—N(6)	117·3 (1)	C(4)—C(10)—S(11)	112·2 (1)
N(3)—C(2)—N(6)	128·6 (1)	C(10)—S(11)—C(12)	100·2 (1)
C(2)—N(3)—C(4)	110·9 (2)	S(11)—C(12)—C(13)	110·6 (1)
N(3)—C(4)—C(5)	114·7 (2)	C(12)—C(13)—C(14)	111·6 (2)
N(3)—C(4)—C(10)	118·5 (1)	C(13)—C(14)—N(15)	117·9 (2)
C(5)—C(4)—C(10)	126·8 (2)	C(13)—C(14)—N(16)	124·1 (2)
S(1)—C(5)—C(4)	110·5 (1)	N(15)—C(14)—N(16)	118·1 (2)
C(2)—N(6)—C(7)	120·2 (2)	C(14)—N(16)—C(17)	119·1 (2)
N(6)—C(7)—N(8)	115·8 (2)	N(16)—C(17)—N(18)	173·2 (2)
(2)			
C(2)—S(1)—C(5)	87·3 (2)	C(10)—S(11)—C(12)	103·4 (2)
S(1)—C(2)—N(3)	116·9 (2)	S(11)—C(12)—C(13)	111·9 (2)
S(1)—C(2)—N(6)	117·1 (2)	C(12)—C(13)—C(14)	114·1 (3)
N(3)—C(2)—N(6)	126·0 (3)	C(13)—C(14)—N(15)	116·3 (3)
C(2)—N(3)—C(4)	109·8 (3)	C(13)—C(14)—N(16)	115·9 (3)
N(3)—C(4)—C(5)	113·8 (3)	N(15)—C(14)—N(16)	127·8 (3)
N(3)—C(4)—C(10)	118·3 (3)	C(14)—N(16)—S(17)	121·3 (2)
C(5)—C(4)—C(10)	127·9 (3)	N(16)—S(17)—N(18)	110·4 (2)
S(1)—C(5)—C(4)	112·2 (2)	N(16)—S(17)—O(19)	103·9 (2)
C(2)—N(6)—C(7)	123·4 (3)	N(16)—S(17)—O(20)	112·3 (2)
N(6)—C(7)—N(8)	115·4 (3)	N(18)—S(17)—O(19)	107·0 (2)
N(6)—C(7)—N(9)	123·0 (3)	N(18)—S(17)—O(20)	106·1 (2)
N(8)—C(7)—N(9)	121·5 (3)	O(19)—S(17)—O(20)	117·0 (2)
C(4)—C(10)—S(11)	113·8 (2)		
(3)			
C(2)—S(1)—C(5)	89·4 (2)	N(6)—C(7)—N(8)	118·0 (3)
S(1)—C(2)—N(3)	113·4 (1)	N(6)—C(7)—N(9)	124·3 (2)
S(1)—C(2)—N(6)	116·2 (1)	N(8)—C(7)—N(9)	117·6 (3)
N(3)—C(2)—N(6)	130·5 (2)	C(4)—C(10)—S(11)	113·2 (2)
C(2)—N(3)—C(4)	111·7 (2)	C(10)—S(11)—C(12)	100·5 (2)
N(3)—C(4)—C(5)	115·5 (2)	S(11)—C(12)—C(13)	111·0 (2)
N(3)—C(4)—C(10)	119·1 (2)	C(12)—C(13)—C(14)	112·7 (3)
C(5)—C(4)—C(10)	125·3 (3)	C(13)—C(14)—N(15)	117·6 (3)
S(1)—C(5)—C(4)	110·0 (2)	C(13)—C(14)—O(16)	121·1 (3)
C(2)—N(6)—C(7)	120·7 (2)	N(15)—C(14)—O(16)	121·3 (2)
(4)			
C(2)—S(1)—C(5)	89·4 (1)	N(8)—C(7)—N(9)	117·6 (1)
S(1)—C(2)—N(3)	113·3 (1)	C(7)—N(8)—C(8)	123·4 (1)
S(1)—C(2)—N(6)	118·1 (1)	C(4)—C(10)—S(11)	113·6 (1)
N(3)—C(2)—N(6)	128·7 (1)	C(10)—S(11)—C(12)	98·7 (1)
C(2)—N(3)—C(4)	111·1 (1)	S(11)—C(12)—C(13)	111·5 (1)
N(3)—C(4)—C(5)	116·3 (1)	C(12)—C(13)—C(14)	113·1 (1)
N(3)—C(4)—C(10)	117·8 (1)	C(13)—C(14)—N(15)	117·3 (1)
C(5)—C(4)—C(10)	125·8 (1)	C(13)—C(14)—N(16)	116·8 (1)
S(1)—C(5)—C(4)	109·9 (1)	N(15)—C(14)—N(16)	125·9 (1)
C(2)—N(6)—C(7)	118·3 (1)	C(14)—N(16)—C(17)	118·7 (1)
N(6)—C(7)—N(8)	117·0 (1)	N(16)—C(17)—N(18)	173·9 (1)
N(6)—C(7)—N(9)	125·4 (1)		
(5)			
C(2)—S(1)—C(5)	89·5 (2)	C(13)—C(14)—N(16)	117·9 (2)
S(1)—C(2)—N(3)	112·3 (1)	N(15)—C(14)—N(16)	127·4 (2)
S(1)—C(2)—N(6)	123·3 (1)	C(14)—N(16)—S(17)	121·2 (1)
N(3)—C(2)—N(6)	124·3 (2)	N(16)—S(17)—N(18)	108·6 (1)
C(2)—N(3)—C(4)	113·6 (2)	N(16)—S(17)—O(19)	104·2 (1)
N(3)—C(4)—C(5)	112·6 (2)	N(16)—S(17)—O(20)	113·3 (1)
N(3)—C(4)—C(10)	119·3 (2)	N(18)—S(17)—O(19)	105·9 (1)
C(5)—C(4)—C(10)	128·1 (2)	N(18)—S(17)—O(20)	105·6 (1)
S(1)—C(5)—C(4)	111·9 (1)	O(19)—S(17)—O(20)	118·8 (1)
C(2)—N(6)—N(7)	117·0 (2)	C(2)*M*—C(1)*M*—C(5)*M*	130·1 (2)
N(6)—N(7)—C(8)	109·5 (2)	C(1)*M*—C(2)*M*—O(3)*M*	119·0 (2)
N(6)—N(7)—C(9)	108·2 (2)	C(1)*M*—C(2)*M*—O(4)*M*	115·6 (2)
C(8)—N(7)—C(9)	113·4 (3)	O(3)*M*—C(2)*M*—O(4)*M*	125·0 (2)
C(4)—C(10)—S(11)	112·5 (1)	C(1)*M*—C(5)*M*—C(6)*M*	129·5 (2)
C(10)—S(11)—C(12)	102·5 (1)	C(5)*M*—C(6)*M*—O(7)*M*	120·1 (2)
S(11)—C(12)—C(13)	113·1 (1)	C(5)*M*—C(6)*M*—O(8)*M*	117·8 (2)
C(12)—C(13)—C(14)	115·2 (2)	O(7)*M*—C(6)*M*—O(8)*M*	121·8 (2)
C(13)—C(14)—N(15)	114·7 (2)		

The crystals are stabilized by intermolecular hydrogen bonds, in addition to van der Waals interactions. All of the H atoms bound to polar N or O atoms participate in hydrogen-bond formation; the bonding parameters are reasonable. It is characteristic that a hydrogen bond is formed between the cyanoamidine [N(15)···N(18)] or between the sulfamoylamidine [N(18)···O(19)] groups.

Water molecules in (1), chloride ions in (2) and maleic acid molecules in (5) exist in the cavities produced by the packing of the title molecules and contribute to the crystal lattice stabilization *via* hydrogen bonds. The water and maleic acid molecules do not appear to influence significantly the molecular conformations of (1) and (5), respectively; maleic acid in (5) exists as a neutral form of HOOCCH=CHCOOH, as evidenced from the difference Fourier map. In contrast, the molecular conformation of (2) appears to be largely affected by

the presence of hydrochloride (salt formation); the H atom of HCl is transferred to the N(6) atom of (2), so that the guanidine group is in a protonated state. There is a hydrogen bond [N(6)···Cl^- = 3·080 Å] and short contacts with the chloride ions [N(8)···Cl^- = 3·349, N(9)···Cl^- = 3·231 and N(15)···Cl^- = 3·235 Å].

The bond lengths and angles of (1)–(5) are listed in Tables 4 and 5. These values are all in the accepted region (Kennard, 1983) within their e.s.d.'s. It is interesting to note that each C—N bond in the guanidine group shows nearly equal double-bond character, and the conformation about C(2)—N(6)—C(7) is fixed to some limited regions because of the resonance between the thiazole ring and the guanidine group. On the other hand, the double-bond character of the amidine group is localized at the C(14)—N(15) and C(14)—N(16) bonds, and the C(4)—C(10)—S(11)—C(12)—C(13)—C(14) bond sequence is likely to rotate freely, judging from the bond lengths and angles.

The molecular conformations of (1)–(5) are shown in Fig. 2, where the dotted lines represent intramolecular hydrogen bonds. A characteristic common to (1)–(4) is the formation of a planar and highly polar six-membered-ring system by means of an intramolecular hydrogen bond [N(9)—H···N(3), see Table 3]. In (5), where such a hydrogen bond is not possible, a planar arrangement is also observed.

The torsion angles defining the side-chain conformation with respect to the thiazole ring are given in Table 6, together with the dihedral angles between the thiazole ring and amidine or amide group. This table also lists torsion angles of cimetidine (Hadicke, Fickel & Franke, 1978), cimetidine monohydrate (Kojić-Prodić, Ružić-Toroš, Bresciani-Pahor & Randaccio, 1980), ranitidine oxalate (Kojić-Prodić, Ružić-Toroš & Toso, 1982) and the free form of famotidine (Yanagisawa *et al.*, 1987). Interestingly, ω_1 and ω_2 torsion angles show the common *gauche* conformations. The same conformational characteristic has also been observed in cimetidine, cimetidine monohydrate, ranitidine oxalate and famotidine free form. This result implies that the conformation about C(4)—C(10)—S(11) is relatively fixed, and the conformational difference among the compounds is determined by ω_3–ω_5. Table 6 also shows that ω_3 and

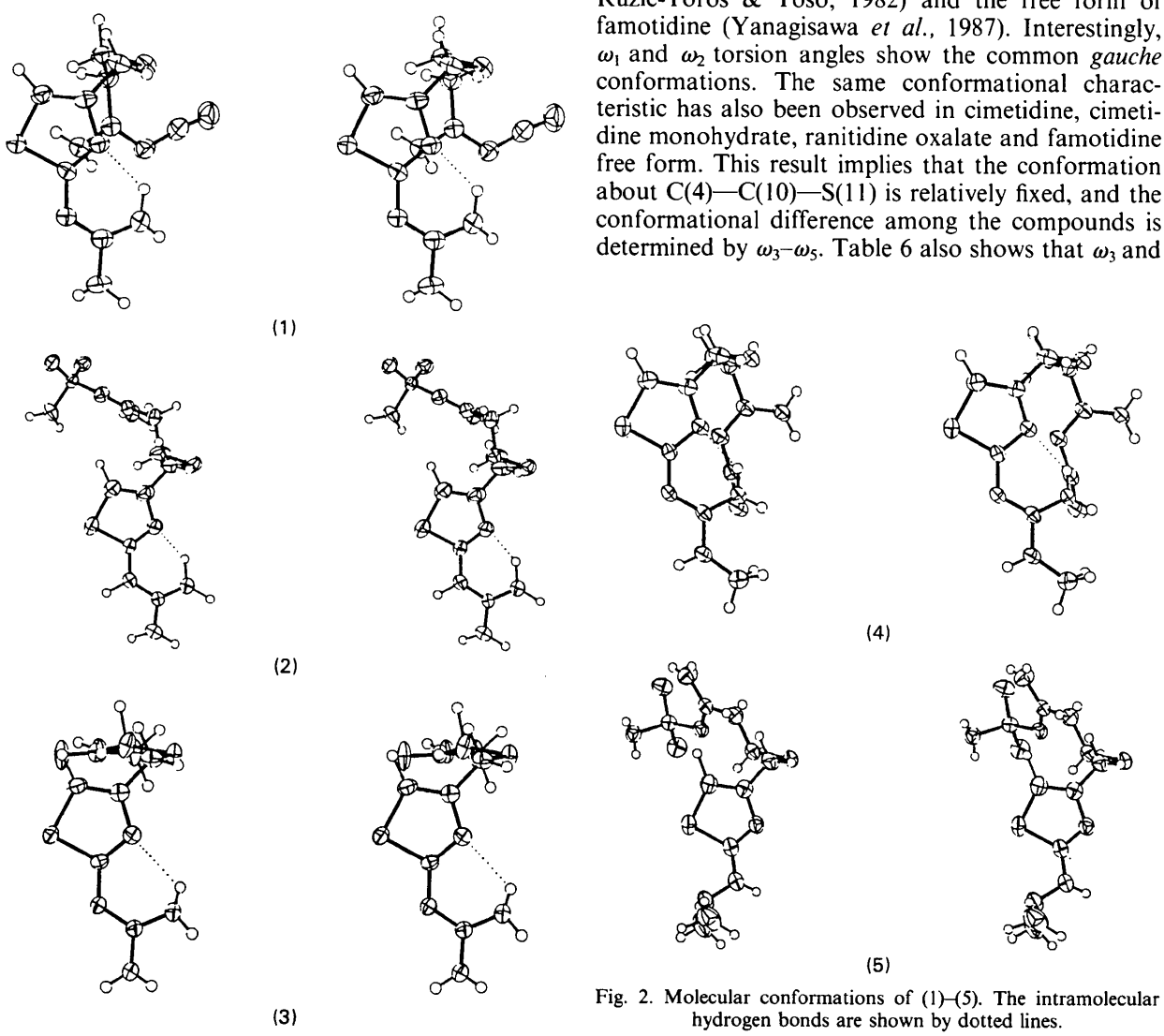


Fig. 2. Molecular conformations of (1)–(5). The intramolecular hydrogen bonds are shown by dotted lines.

Table 6. *Torsion angles (°) and dihedral angles (°) between the thiazole ring and the amidine or amide group*

The torsion angles of the famotidine (free form), cimetidine, cimetidine monohydrate and ranitidine oxalate are also given for comparison. Although the side chains of the cimetidine and ranitidine molecules are longer by an NH group than the present compounds, the listed torsion angles of the former molecules correspond to the latter ones.

Compound	ω_1 N(3)—C(4)— C(10)—S(11)	ω_2 C(4)—C(10)— S(11)—C(12)	ω_3 C(10)—S(11)— C(12)—C(13)	ω_4 S(11)—C(12)— C(13)—C(14)	ω_5 C(12)—C(13)— C(14)—N(15)	Dihedral angle
(1)	65·8 (2)	61·7 (2)	−148·5 (2)	60·9 (2)	61·4 (3)	19·6 (2)
(2)	68·8 (3)	62·5 (3)	84·8 (4)	−178·1 (4)	−67·4 (4)	86·7 (3)
(3)	73·5 (2)	57·0 (2)	−165.0 (3)	170·7 (3)	167·7 (3)	94·2 (2)
(4)	58·4 (1)	56·8 (1)	−170·3 (2)	64·4 (2)	−124·2 (2)	13·3 (1)
(5)	69·6 (2)	55·9 (2)	71·4 (2)	174·4 (3)	172·6 (3)	56·1 (2)
(2) (free form)	56·8	62·7	−170·6	68·1	−129·8	12·6
Cimetidine	69·8	−61·9	−62·6	175·7	−90·6	28·2
Cimetidine monohydrate	70·4	59·5	−137·2	67·6	75·8	10·7
Ranitidine oxalate	114·8	−59·0	−75·5	−176·0	−101·0	74·4

Table 7. *Conformational parameters and their correlation coefficients (r) with inhibitory activities*

The 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 $10^{-7} < ED_{50}$.

Compound	ω_3	Dihedral angle (°)	D_{xy} of N(3)···N(15) (Å)	D_y of N(3)···N(15) (Å)	Activity
(1)	211·5	19·6	0·47	−0·08	3
(2)*	189·4	12·6	3·30	0·60	3
(3)	195·0	94·2	2·88	2·78	2
(4)	189·7	13·3	3·07	0·54	2
(5)	71·4	56·1	5·89	5·56	0
Cimetidine	297·4	28·2	3·90	−1·40	2
Cimetidine†	222·8	10·7	1·00	0·00	2
Ranitidine‡	284·5	74·4	2·80	−0·40	3
Linear correlation coefficient with activity					
r	0·8875	0·5334	0·8113	0·8333	

* Famotidine free form.
† Cimetidine monohydrate.
‡ Ranitidine oxalate.

ω_4 torsion angles are restricted to either *gauche* or *trans*, while ω_5 has conformational freedom.

The geometry observed in the crystal structure may not represent the actual conformation bound to the H_2 receptor. Nevertheless, it is reasonable to consider the possible stereostructure–activity relationship using these X-ray data, particularly as structural data on the receptor binding site are lacking at present. Thus it is assumed that the combination of ω_3–ω_5 torsion angles could be closely related with the H_2-receptor antagonist activity. Before the discussion, it is important to say that the protonated structure of (2) (famotidine) shows a different conformation from the neutral one. The free form of (2) has a folded conformation (Yanagisawa *et al.*, 1987), while the present hydrochloride takes an extended conformation. This drastic conformational change from the neutral to the cationic state has also been observed in cimetidine (Shibata, Kagawa, Morisaka, Ishida & Inoue, 1983) and ranitidine (Ishida *et al.*, unpublished results). Thus it is questionable whether the conformation observed in the (2).HCl crystal reflects the intrinsic form of famotidine. Therefore, the data of (2).HCl were excluded from consideration. The relationships between the conformational parameters and H_2-receptor antagonist activities are given in Table 7.

As was expected, the compounds exhibiting high activities show the *trans* preference at the ω_3 torsion angle, while that without activity is in a *gauche* region ($r = 0{\cdot}8875$). On the other hand, the combination of ω_3, ω_4, ω_5 torsion angles determines the whole molecular conformation, as already stated. For example, when ω_3, ω_4, ω_5 takes the combination *trans, gauche, gauche* or *trans, gauche, anticlinal*, the side chain is folded back and the end group becomes close to parallel with the thiazole ring [(1), (2)(free form) and (4)], which is also observed for the potent cimetidine and ranitidine conformations. Therefore the dihedral angle may be related to the activity, although the correlation coefficient is not so high ($r = 0{\cdot}5334$).

Since the interatomic distances between the central aromatic ring and the side-chain end group are primarily determined by the combination of ω_3, ω_4, ω_5 torsion angles, on the other hand, these parameters were examined in relation to the activities. It is worthwhile to say that, among many possible interatomic pairs, the atomic distance between the thiazole N(3) atom and the end-group N(15) atom

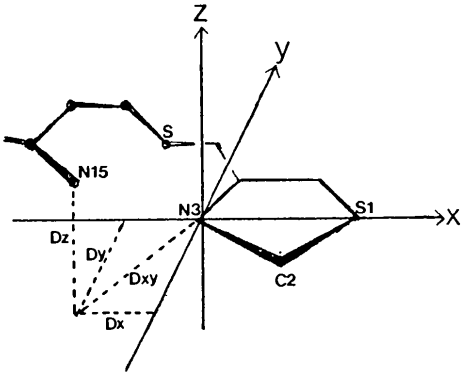


Fig. 3. Definition of D_x, D_y, D_z and D_{xy} distances between N(3) and N(15) atoms.

showed a high correlation. These two atoms could form the hydrogen bonds with the binding site of an H_2 receptor as the electron acceptor and donor atoms, respectively. In particular, the D_{xy} and D_y components of N(3)···N(15), which are defined in Fig. 3, were most strongly correlated with the activities ($r = 0.8113$ and 0·8333, respectively). Thus the linear combination of ω_3, D_{xy} and D_y led to the following correlation:

$$\begin{aligned} \text{activity} &= \underset{(0.9160)}{1.9033} + \underset{(0.0040)}{0.0058\omega_3} - \underset{(0.0987)}{0.2678D_{xy}} - \underset{(0.1233)}{0.1613D_y}, \\ r &= \underset{(0.3012).}{0.9578} \end{aligned}$$

This equation clearly implies that the molecular conformation and spatial disposition of the N(15) atom with respect to the thiazole of imidazole ring are closely related to the emergence of antagonist activity.

References

BROGDEN, R. N., HEEL, R. C., SPEIGHT, T. M. & AVERY, G. S. (1978). *Drugs*, **15**, 93–131.

HADICKE, E., FICKEL, F. & FRANKE, A. (1978). *Chem. Ber.* **111**, 3222–3232.

HARADA, M., TERAI, M. & MAENO, H. (1983). *Eur. J. Pharmacol.* **91**, 371–376.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

ISHIDA, T., IN, Y., SHIBATA, M., DOI, M., INOUE, M. & YANAGISAWA, I. (1987). *Mol. Pharmacol.* **31**, 410–416.

KENNARD, O. (1983). *International Tables for X-ray Crystallography*, Vol. III, edited by C. H. MACGILLAVRY, G. D. RIECK & K. LONSDALE, pp. 275–276. Dordrecht: D. Reidel. (Present distributor Kluwer Academic Publishers, Dordrecht.)

KOJIĆ-PRODIĆ, B., RUŽIĆ-TOROŠ, Ž., BRESCIANI-PAHOR, N. & RANDACCIO, L. (1980). *Acta Cryst.* B**36**,1223–1225.

KOJIĆ-PRODIĆ, B., RUŽIĆ-TOROŠ, Ž. & TOSO, R. (1982). *Acta Cryst.* B**38**, 1837–1840.

MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1978). *MULTAN*78. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

SHIBATA, M., KAGAWA, M., MORISAKA, K., ISHIDA, T. & INOUE, M. (1983). *Acta Cryst.* C**39**, 1255–1257.

TAKAGI, T., TAKEDA, M. & MAENO, H. (1982). *Arch. Int. Pharmacodyn.* **256**, 49–58.

TAKEDA, M., TAKAGI, T. & MAENO, H. (1981). *Jpn J. Pharmacol.* **31**, 222.

TAKEDA, M., TAKAGI, T. & MAENO, H. (1983). *Eur. J. Pharmacol.* **91**, 371–376.

TAKEDA, M., TAKAGI, T., YASHIMA, Y. & MAENO, H. (1982). *Arzneim. Forsch.* **32**, 734–737.

The Universal Crystallographic Computing System – Osaka (1979). The Computation Center, Osaka Univ., Japan.

YANAGISAWA, I., HIRATA, Y. & ISHII, Y. (1984). *J. Med. Chem.* **27**, 849–857.

YANAGISAWA, I., HIRATA, Y. & ISHII, Y. (1987). *J. Med. Chem.* **30**, 1787–1793.

Acta Cryst. (1989). B**45**, 512–518

Structures of Two 2-Oxyimino-α-D-pyranosides

BY ZBIGNIEW CIUNIK* AND HANS PAULSEN

Institut für Organische Chemie und Biochemie, Universität Hamburg, Martin-Luther-King-Platz 6, *D*-2000 *Hamburg* 13, *Federal Republic of Germany*

PETER LUGER

Institut für Kristallographie, Freie Universität Berlin, Takustrasse 6, *D*-1000 *Berlin* 33, *Federal Republic of Germany*

AND ZYGFRYD SMIATACZ AND HENRYK MYSZKA

Instytut Chemii, Uniwersytet Gdański, ul. Sobieskiego 18, 80-952 *Gdańsk, Poland*

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Abstract

1-(3-Acetamido-2-acetoxyimino-4-*O*-acetyl-2,3-dideoxy-α-D-*threo*-pentopyranosyl)pyrazole (I), $C_{14}H_{18}N_4O_6$, $M_r = 338.32$, orthorhombic, $P2_12_12_1$, $a = 9.257$ (2), $b = 9.306$ (2), $c = 19.582$ (5) Å, $V = 1687$ (1) Å^3, $Z = 4$, $D_x = 1.324$ (1) Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 0.907$ mm^{-1}, $F(000) = 712$, room temperature, $R = 0.042$ for 1566 reflections with $I > 2\sigma(I)$. 1-(3,4,6-Tri-*O*-acetyl-2-hydroxyimino-2-deoxy-α-D-*arabino*-hexopyranosyl)-pyrazole (II), $C_{15}H_{19}N_3O_8$, $M_r = 369.33$, monoclinic,

* On leave from Instytut Chemii, Uniwersytet Wrocławski, ul. Fr. Joliot-Curie 14, 50-383 Wrocław, Poland.

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