Conformational studies on histamine H_2-receptor antagonists: deduction of a simple structure–activity relationship

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For a series of compounds with H_2-antihistaminic activity the most stable conformations were calculated using molecular mechanics methods. For all the drugs studied there are three conformations which exist with equal probabilities with respect to their conformational energies. Two conformations form a ten-membered ring by intramolecular interactions between the aromatic ring and the planar structure at the end of the sidechain. A third conformation has these two parts of the molecule arranged in parallel planes separated by a distance of 3 Å. This was confirmed using semiempirical quantum mechanical methods. In one of the preferred conformations a marked relationship is found between the distances of the amidine structure from the plane of the aromatic moiety and the biological activities of the respective derivatives. When the distance of the sidechain from a hypothetical binding site is varied, there are corresponding differences in the interaction energy. As a consequence, the different biological activities of the compounds can easily be explained.

Keywords: molecular graphics, conformational studies, H_2-receptor antagonists, structure–activity relationship

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H_2-antihistaminergic agents represent a group of conformationally very flexible molecules. The compounds which have been developed are based on the physiological substrate histamine, and are mainly composed of three substructural parts.

- First they contain an imidazole ring or a different aromatic system. Certain specific demands have to be fulfilled. For example the imidazole system has to exist as an N^{τ}–H tautomer so that the unprotonated nitrogen is located in close proximity to the sidechain. This has been demonstrated for several histamine derivatives[1]. Furthermore it has been found that furan derivatives lacking basic properties can exert antihistaminergic action only if a basic dimethylamino group is added as substituent. Also it has been shown that a significant decrease in activity occurs in ranitidine if the furan group is replaced by thiophene or phenyl rings[2].
- The second substructure present in all H_2-antihistaminergic agents is a substituted guanidine or thiourea group that produce a polar, hydrophilic and planar structure possessing a large dipole moment but little or no basic properties.
- Finally a methylthioethyl chain inserted between the two π electron systems fixes them at a certain distance and in a relative location. Also the electron withdrawing characteristics of this structural element cause a decrease in the pK_a of imidazole and therefore favourably influences the 1,4-tautomer equilibrium[3].

From X-ray structures[4–6] and i.r. spectra[7] it has been concluded that intramolecular hydrogen bond formation between the imidazole N^{π} and one of the NH-groups of the guanidine or thiourea regions establishes an 8- or 10-membered ring. It was also proposed that a compact folded ring-structured conformation should be essential as a prerequisite of H_2-antihistaminergic activity.

Synthesis of rigid analogues of cimetidine has led to inactive substances[8]. Investigations using similar rigid derivatives have found that it is mainly the steric factors which govern H_2-antihistaminergic activity[9]. Finally it has been found that physical properties such as solubility or the partition coefficient cannot be used to account for the pharmacological behaviour of the compounds under investigation[10,11].

On the basis of these observations one might argue that a unique conformation is essential for binding of H_2-antihistaminergic agents at the histamine receptor. Therefore the first aim of the work presented here was to calculate the preferred conformations of different H_2-antihistaminergic agents and subsequently search for a possible relationship between the potential existence of a unique 'active' conformer and the known antihistaminergic potencies of the corresponding drug molecules.

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Appropriate pharmacological data can be obtained from several studies in the literature.

METHODS

The calculation of conformational energies was carried out using both molecular mechanic and semiempirical quantum chemical methods. Considering the huge amount of computing time caused by the large number of rotatable bonds, quantum chemical methods were used first of all to check the low energy conformations found with molecular mechanic methods.

From the beginning for burimamide and metiamide a conformational search using CNDO/2[12] was attempted. All torsion angles were rotated in 30° increments and the respective conformational energies were calculated. It was impossible nevertheless to get a significant result in this manner, particularly because of an overestimation of the sulphur–hydrogen interactions which occur using the CNDO/2 method.

Using the Maximin-molecular mechanics method within the Sybyl-program[13] for a series of 8 compounds (Table 1) in a first approach all 8–10 rotors were investigated in 90° increments. Maximin is a minimization method which uses the Simplex algorithm, but allows such options as fixed geometries in parts of the molecule or specified rotatable bonds, i.e. bond length and valence angle minimization is performed simultaneously with slight variations of the torsional angles to get a minimum energy geometry of a certain basic conformer.

These potential energy calculations were carried out using charges calculated by a topological method from Gasteiger and Marsili[14]. Since this method is an extreme approximation for the procedure described above CNDO/2-calculations were also performed.

Then in a second run, using the Search-option, a systematic search for allowed conformations from a steric point of view was performed for metiamide, cimetidine, and ranitidine. Search is a conformational analysis method based on the screening of van der Waals' contact distances. In this procedure three bonds are studied at a time in 30° increments. Conformations are rejected, if they contain interatomic distances shorter than the sum of the respective van der Waals' radii.

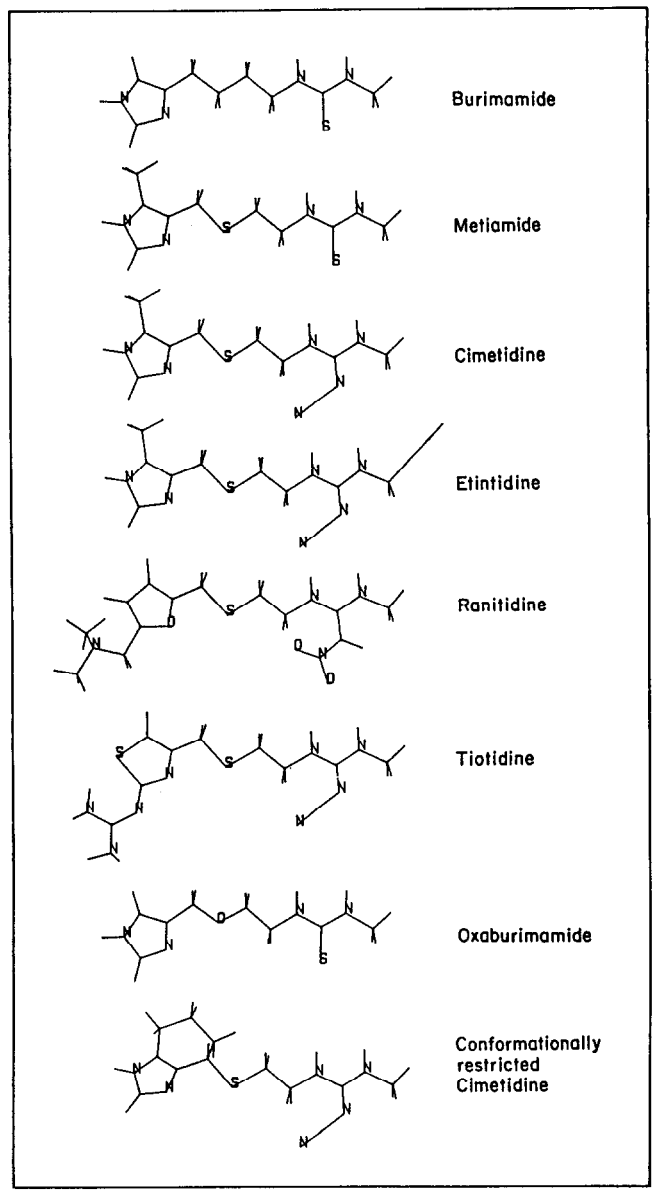
Subsequently energy calculations are performed for the valid Search-conformations using Maximin. As a result the same low energy conformations were obtained as in the first approach. Ranitidine obviously possesses more conformational flexibility than the other compounds, i.e. it is probable that similar additional low energy conformations close to the highly preferred conformations can be found.

The molecular modelling and force field calculations were performed on a VAX 11/730 computer and an Evans and Sutherland PS300 system. Quantum mechanical calculations were performed on an IBM 3038.

RESULTS

For all the compounds studied, except the conformationally restricted cimetidine derivative, three nearly equal or at least very similar preferred conformations I, II, and III (see Figure 1, Table 2) were found. In all three a type of 'head-to-tail' interaction appears. In conformations I and II the postulated hydrogen bond was

Table 1. List of investigated histamine H_2-receptor antagonists



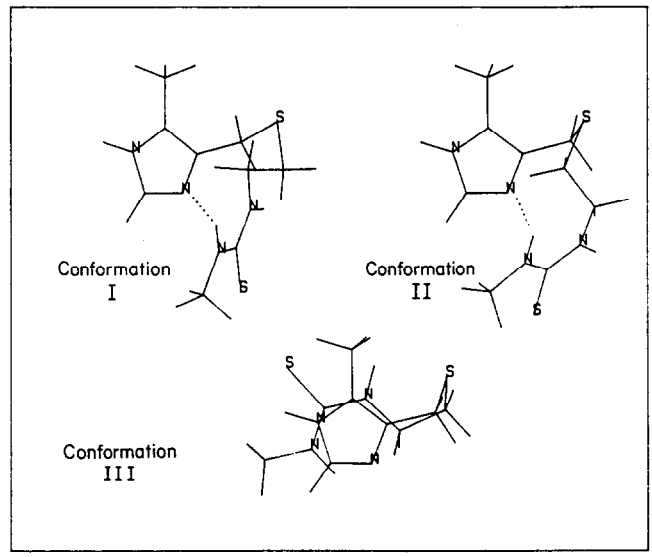


Figure 1. Preferred conformations I, II, and III of metiamide

Table 2. Conformational energies in kcal/mol of the 3 preferred conformations calculated using Maximin molecular mechanic method and CNDO/2

	Relative conformational energies in kcal/mol[a]					
	Maximin			CNDO/2		
	Conf. I	Conf. II	Conf. III	Conf. I	Conf. II	Conf. III
Burimamide	1.12	0.91	0.00	0.00	0.03	1.61
Metiamide	0.83	1.02	0.00	1.14	0.00	2.07
Cimetidine	1.19	1.81	0.00	0.00	0.01	1.32
Etintidine	2.11	1.29	0.00	2.02	0.00	1.66
Ranitidine	1.61	3.31	0.00	0.00	2.05	0.29
Tiotidine	1.09	0.80	0.00	0.00	1.70	0.90
Oxaburimamide	1.01	0.24	0.00	0.98	0.00	0.80
Restricted Cimetidine		0.00	1.16		0.00	3.73

[a]Energy differences are specified relative to the most preferred conformation of each molecule.

formed. Conformation II corresponds to the geometrically optimized X-ray structure of metiamide and cimetidine. In conformation III the aromatic ring and the N-containing sidechain are located in superposed planes separated by 3 Å.

Despite having a different structure, ranitidine also forms comparable 3-D structures. The NH group, necessary for the formation of the 10-membered ring in all the other compounds, takes part in hydrogen bonding between the methylamino group and an oxygen atom of the nitro group. Therefore head-to-tail orientations take place, in which the CH hydrogen of the ethylendiamine group points into the direction of the ring.

The calculated energy differences between the three different preferred conformations make them occur with almost equal probability (see Table 2). The absolute energy minimum in the molecular mechanics calculations in all cases was obtained for the 'sandwich' conformation (conformation III). In conformation III the angle bending and electrostatic energies are slightly decreased whereas the van der Waals energies show a marked increase compared with conformations I and II. All three conformations lie within a 3 kcal/mol energy limit.

CNDO/2 calculations for the preferred molecular mechanics conformations result in similar energies. The values are even more close together, however the two cyclic conformations I and II are favoured over the sandwich form of conformation III.

Similar results were also obtained from investigations using the eht method[15] using metiamide, cimetidine, ranitidine, and tiotidine.

In order to make the comparison between the investigated compounds more accurate they were placed in identical positions using 'Fit'. 'Fit' is an option in the Sybyl-program which performs the transformation of coordinates so that the sum of the square deviation between pairs of atoms from two molecules is minimized. Fitting in order to match the aromatic moieties of all compounds was thought to be convenient if this structure is engaged in binding to a specific primary binding site at the histamine H_2-receptor. It should therefore always be fixed in the same position.

A comparison carried out after the fitting procedure was performed for all three conformations with the ring shifted in a fixed position gives the following features:

- For conformation I no striking differences appear to exist between all computed compounds except conformationally restricted cimetidine (see Colour Plate 1).
- In conformation III there is a large degree of conformity between the different derivatives (see Colour Plate 2). This was also tested using ranitidine as an example, as methylation of the ring changes the conformation with respect to the sidechain. This would explain the variations in H_2-antihistaminergic activity previously found for ranitidine derivates (the 3-methyl-ranitidine derivative is inactive whereas the 4-isomer is highly potent). No such changes were detected.
- Conformation II is formed by the different derivatives with noticeable variation of the distance between the sidechain and the aromatic ring. A marked relationship exists between this distance and the activities of the compounds because as the distance is increased the activity of the compound is increased (see Colour Plate 3).

In order to be able to describe more accurately the conformational properties of the molecules studied in terms of the intramolecular distances the molecules were dissected in four planes. Plane 1 contains the ring structure, plane 2 contains the atoms from the beginning of the chain to the thioether linkage, plane 3 contains the connecting S-C-C-N-chain, and plane 4 the 'guanidine' region as shown in Figure 2 for metiamide. Based on this description it can be stated that:

The torsion angle between plane 1 and 2 (or put another way the distances between atoms of the sidechain) and the plane of the ring undergo a modification in the same sequence which corresponds to the observed pharmacological activities[16] (see Table 3). This is the torsion angle N^{π} -C-C-X (where X = C, S, O) which decreases as the activity of the compounds increases. Alterations of the torsion angle cause different distances between planes 1 and 4, so that the position of plane 4 is changed if plane 1 is kept fixed (see Table 3). If the locations of the sidechains in space are compared then the differences are even more substantial. For burimamide and tiotidine which respectively represent the most and least active congeners of the series the sidechain positions are changed by about 2 Å.

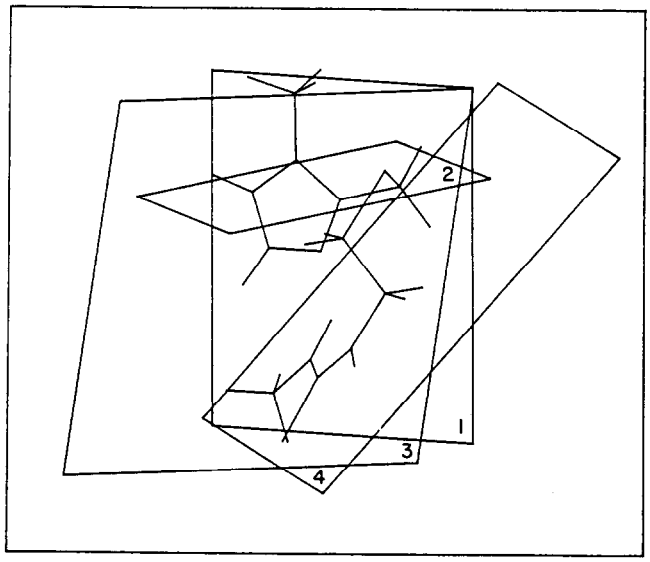


Figure 2. Conformation II of metiamide dissected into 4 planes

Table 3. Characteristic torsion angles, intramolecular distances, and biological activities of H_2-antihistaminergic agents

	Torsion angle plane 1/2 (degrees)	Distances plane1/plane4[a] (Å)			Antagonist activity $K_B \times 10^{-6}$M
Burimamide	85.0	2.70	2.56	1.67	7.8
Metiamide	72.9	3.23	2.84	1.72	0.92
Cimetidine	69.6	3.34	3.21	2.22	0.79
Etintidine	61.1	3.79	3.86	2.89	0.26[b]
Ranitidine	59.3	3.96	4.11	3.16	0.063[c]
Tiotidine	53.4	4.04	4.04	2.96	0.015[d]
Oxaburimamide	83.8	2.85	2.74	1.83	–
Restricted Cimetidine	87.8	2.31	2.06	1.23	–

[a]Distance between normals of plane 1 and N-C-N atoms in plane 4
[b]C.f. 0.61 reported for cimetidine[18]
[c]C.f. 0.28 reported for cimetidine[19]
[d]C.f. 0.36 reported for cimetidine[20]

DISCUSSION

Among H_2-antihistaminergic agents the relative activity/inactivity cannot be linked to the occurrence or nonoccurrence of an intramolecular hydrogen-bonded cyclic structure as was first supposed from the differences in X-ray structures. Also if it is supposed that only a unique conformation fits the receptor, it is impossible to explain the potencies using the preference of one or another specific conformation. The question then arises: is it possible to obtain a relationship between the graduation of activity and the observed differences in geometry?

When constructing a receptor model common binding sites must be found for the characteristic structures of a group of molecules. For H_2-receptor antagonists an acceptable basic idea is that the aromatic ring (as an analogue of the imidazole moiety of histamine) interacts at a primary binding site. The additional binding of the side chain endgroup with a secondary binding site is important in the explanation of the graduation of activities. From the results it can be proposed that for the compounds studied the variation in the position of the sidechain alters the distances of a secondary binding site causing a corresponding graduation in the interaction energies. This supports previous observations that the 3-D structure of these compounds in the biophase is essential for activity.

It has to be stated that the entropic term and also the influence of solvation on intramolecular hydrogen bond formation have not been investigated. However, due to the evident similarity between the structures under question a dramatic change in the influence of the two terms on the conformational behaviour of the single congeners of the series is not to be expected.

In earlier investigations in the laboratory of the authors receptor models were constructed consisting of amino acids as model binding sites for different pharmacologically active molecules[17]. The same approach will be followed for the H_2-receptor antagonists used in this study. Calculations of the interaction energies between the proposed receptor binding conformation of H_2-antagonists and binding site models will be performed using the monopole-bond polarizability method.

Conformational analyses of additional derivatives will also be performed. It will be important to analyse how the newly synthesized rigid analogues which contain diaryl-structures (instead of an aromatic ring plus a four atom chain) are accommodated by this model. At the moment the authors are investigating this problem using ICI127032.

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