A theoretical study concerning the mode of interaction of the histamine H_2-agonist dimaprit

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A theoretical study was performed to elucidate the mode of interaction of the histamine H_2-agonist dimaprit with the histamine H_2-receptor. For this purpose receptor mapping techniques, including ab initio *energy calculations, geometry optimizations and molecular electrostatic potential calculations (MEPs), have been used. The characteristics of dimaprit were compared to those of histamine for which the points of interaction with the H_2-receptor are known, as well as its bioactive conformation. In this comparative study two possible models for the interaction of dimaprit with the H_2-receptor were considered. In one model the two nitrogen atoms of the isothiourea moiety of dimaprit play an essential role in the recognition of the ligand by the receptor and have the same function as the nitrogen atoms of the imidazole ring of histamine; in the second model this role is fulfilled by a sulphur and a nitrogen atom of the same isothiourea moiety. The comparison to histamine was based on geometrical resemblance as well as on similarity in MEPs. Also the conformational energy of dimaprit in the two interaction models was considered. Results of the investigations reveal that the isothiourea moiety of dimaprit most probably interacts with the histamine H_2-receptor through the sulphur and nitrogen atom, the first atom acting as a proton acceptor and the second one as a proton donor. Subsequently, three analogues of dimaprit, namely SK&F 91487, SK&F 91488 and SK&F 92054, were studied. It was possible to explain their pharmacological behavior within the proposed model. Furthermore, the new model for the interaction of dimaprit with the H_2-receptor enabled the design of a structurally new histamine H_2-agonist, 2-amino-5-(2-aminoethyl)thiazole.*

Keywords: dimaprit, histamine, H_2-agonist, H_2-receptor

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INTRODUCTION

The first highly specific and active histamine H_2-agonist described was dimaprit. This compound, [S-[3-(N,N-dimethylamino)propyl]isothiourea] (Figure 1), has about 70% of the activity of histamine at the guinea pig right atrium.[1,2] Like histamine, in water dimaprit is a mixture of several protonated forms (Figure 1). The macroscopic ionization constants of dimaprit, pK_{a1} and pK_{a2}, are 8.30 and 9.40, respectively.[1] Therefore, at physiological pH, the predominant species is the dication. To reveal the active molecular species of dimaprit, its molecular features were compared to those of histamine. For histamine it is known that the properties needed for H_2-agonistic activity are a protonated amino group and a planar aromatic amidine system capable of 1,3-prototropic tautomerism (Figure 2); this tautomeric system will probably function as a proton transfer agent at the receptor.[3] These two essential features are present in only one of the ionic species of dimaprit, i.e., in the species in which the isothiourea moiety is neutral and the dimethylamino group is protonated (Figure 1, species II). However, the percentage monocation present at physiological pH is only 12%, of which again only 5% is present in form II. Evidence for the monocationic form of dimaprit being the active molecular species was given in a recent study in which the activity of dimaprit was measured as a function of pH;[4] an increase in the concentration monocation as a result of an increase in the pH from 7.0 to 7.5 led to a concomitant rise in the activity of dimaprit. It was impossible to support these data by studying analogues of dimaprit, as any substitution at the isothiourea part of dimaprit resulted in a complete loss of histamine H_2-activity.[4]

Although it is generally accepted that the monocationic form II of dimaprit is the active molecular species, no detailed studies have been carried out to gain insight into the exact mode of interaction of the isothiourea moiety of dimaprit with the histamine H_2-receptor. However, knowledge on this interaction is important as it will lead to a better understanding of the recognition of histamine H_2-agonists by the receptor, and thereby can result in a better understanding of the activation mechanism.

The isothiourea group in dimaprit is a planar system. As the monocationic form II incorporates a neutral amidine

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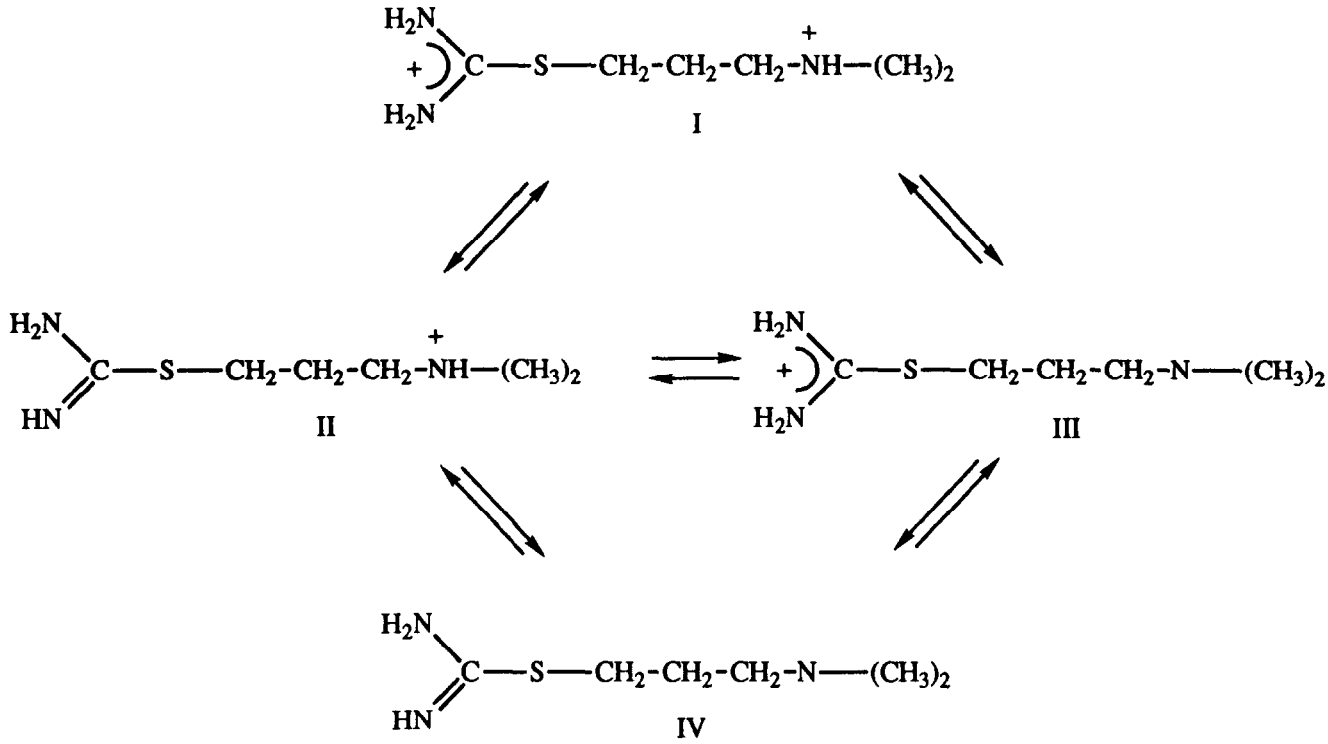


Figure 1. Tautomeric and ionic equilibria of dimaprit.

moiety, it is capable of participating in a proton relay mechanism, being one of the conditions proposed to be essential for H_2-agonistic activity. In general, it is assumed that the function of this amidine moiety is comparable to the function of the imidazole ring of histamine. The single-bonded nitrogen atom of the isothiourea group is considered to be the proton donor whereas the double-bonded nitrogen atom is thought to act as the proton acceptor (Figure 3a). Although this model is generally accepted, a second interaction model for dimaprit has been proposed.[5] In the latter model, which differs from the first only in the mode of interaction of the isothiourea moiety with the histamine H_2-receptor, the sulphur atom of form II acts as the proton acceptor and the single-bonded nitrogen atom of the isothiourea moiety again acts as the proton donor (Figure 3b).

The activation mechanism of the histamine H_2-receptor has been subject of many studies: not only was the pharmacological profile of a large group of histamine analogues investigated, but quantum chemical calculations also were

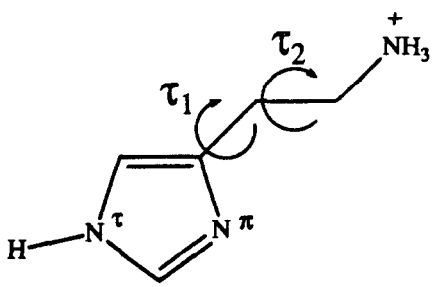


Figure 2. Bioactive conformation of histamine for the histamine H_2-receptor; $\tau_1 = 90°$, $\tau_2 = 180°$.[15]

carried out. As it is most likely that the protonated amino group of histamine binds to a negatively charged group at the histamine H_2-receptor (carboxylate from an ASP or a GLU), the ultimate form of histamine bound at the receptor will be the neutral species. Quantum chemical studies have been carried out to investigate the effect of side chain deprotonation and neutralization upon the properties of the imidazole ring of histamine. For both the monocationic and neutral (or neutralized) species of histamine, MEPs were calculated in the plane of the imidazole ring.[6–8] These studies revealed that deprotonation (or neutralization) results both in a lowering of the MEP minimum near the double-bonded nitrogen atom of the imidazole ring and in a change of the tautomeric preference; whereas the N^{τ}-H form appears to be the preferred tautomeric form of the charged molecule, the N^{π}-H form is the preferred one of the neutral species. These observations led to the hypothesis that a proton transfer mechanism is involved in H_2-receptor activation. This process is suggested to proceed in the following way. When the histamine side chain anchors to an anionic receptor site, the neutralization causes a shift in tautomeric preference from the N^{τ}-H form to the N^{π}-H form. The N^{π}-atom accepts a proton while the N^{τ}-atom donates a proton to a putative proton acceptor site with which the histamine is interacting. In a subsequent study a mechanistic model was introduced, in which the energetics of the assumed proton transfer processes was investigated.[9] The system was modeled by a proton relay chain produced by binding a histamine molecule to a receptor model consisting of an anionic anchoring site, and a proton donor and acceptor site. The anchoring of a histamine cation at a negative receptor site was simulated by the interaction with a hydroxyl anion or by calculations on neutral histamine; the proton donor and acceptor

sites were modeled by ammonium and ammonia groups, respectively. This study was recently extended to various analogues of histamine.[10] An important conclusion can be drawn from these studies: the MEP in the plane of the imidazole ring of histamine is an accurate parameter for describing effects related to H_2-agonistic activity.

Until now no study has been performed to discriminate between the two models of interaction of dimaprit. This is probably due to the high flexibility and size of dimaprit.

The aim of the present study is to obtain insight into the most likely mode of interaction of dimaprit by using molecular modeling as well as quantum chemical techniques. Therefore, dimaprit was fitted onto a proposed active conformation of histamine. Conclusions were validated by investigating close homologues of dimaprit.

METHODS

Quantum chemical calculations

The nonempirical program HFS-LCAO, as developed by Baerends et al.[11] and recently extended with an automatized procedure for geometry optimization,[12] was used for three purposes: to optimize the isothiourea part of dimaprit; to determine the (relative) energies of the conformations of dimaprit obtained from the fitting procedures; and to calculate the molecular electrostatic potentials. For all these calculations a double ζ plus polarization function (DZD) on each of the atoms was used.

MNDO[13] was used for those geometry optimizations in which no delocalization was present and the optimization concerned only C, H and N atoms.

Fitting procedures

Dimaprit was fitted onto histamine using two procedures, a rigid and a flexible molecular fitting procedure. Within the rigid fitting procedure the geometry of the molecule to be superimposed is not changed; only translations and rotations are allowed, to match user-selected atom pairs. During the subsequent flexible fitting procedure torsion angles, bond lengths and bond angles can be varied to improve the fit (usually only torsion angles are varied). To superimpose the selected atom pairs both procedures use penalty functions that depend on a restrain constant and the squared separation distance of the atoms. In the rigid fitting procedure the restrain constants of the various atom pairs have only a relative value; in the flexible fitting procedure, the penalty function (restrain constant times squared separation distance) is added to the molecular mechanics energy of the flexible molecule, and the total energy is minimized. Both fitting procedures are implemented in the molecular modeling package Chem-X.[14]

RESULTS

Conformation of the template molecule histamine

The conformation of histamine as described by Weinstein et al.[9] was used as a template in the fitting procedures. This conformation resembles the crystal structure of histamine, the extended conformation, $\tau_1 \approx 90°$, $\tau_2 \approx 180°$ (Figure 2)[15] and was obtained from a STO-3G optimization of the X-ray structure using GAUSSIAN 80.[9]

Initial conformation of dimaprit

The conformation of dimaprit used in the fitting procedures was derived in two steps. First, the isothiourea part of dimaprit was optimized using the nonempirical HFS-LCAO program; for this purpose the propylene chain of dimaprit was replaced by a methyl group. In all subsequent calculations the geometry of the isothiourea part of dimaprit was kept unchanged. Second, the propyldimethylamino chain was optimized using the semiempirical program MNDO. After optimization the fragments were connected and the resulting conformation was used in the fitting procedures. The reason for using a two-step optimization procedure was the known weakness of MNDO (INDO programs in general) in treating delocalized systems like the isothiourea part of dimaprit;[16] as a result the relative positions of the hydrogen atoms connected to the nitrogens of the isothiourea moiety would not have been calculated properly.

Fitting of histamine and dimaprit

The optimized conformation of dimaprit was fitted onto histamine by first employing a rigid fitting and then a flexible fitting procedure. Within the first procedure only the isothiourea part was matched with the imidazole ring of histamine without changing the conformation of dimaprit. In the second procedure the propyldimethylamino side chain conformation of dimaprit was adjusted to get an overlap between the protonated dimethylamino group of dimaprit and the charged amino group of histamine, and between the side chains of both molecules. Two interaction models for dimaprit were considered.

The results of the fitting procedures are depicted in Figure 3. Figures 3a and 3b display the two interaction models, S-fit and N-fit, respectively. Table 1 gives the final distances

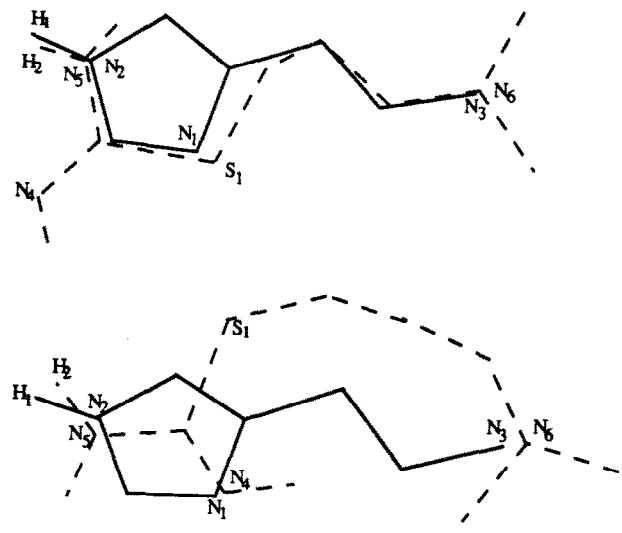
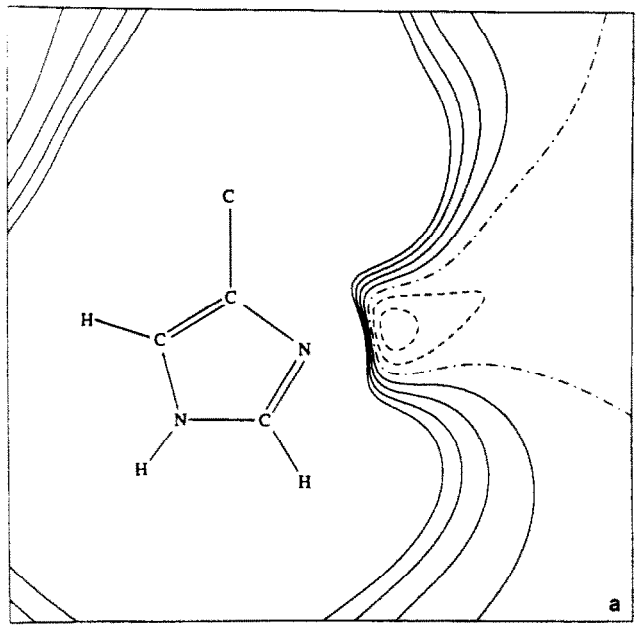
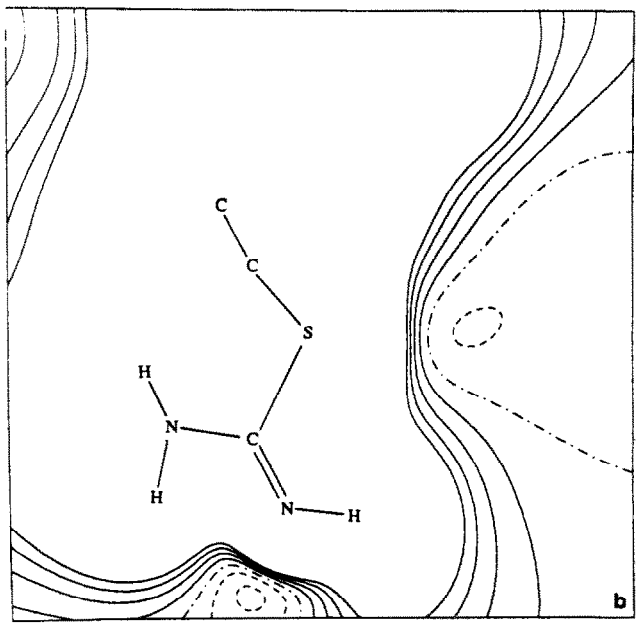


Figure 3. Fitted conformation of dimaprit in comparison with histamine: a, S-fit; b, N-fit; histamine solid lines; dimaprit dashed lines.

Table 1. Final distances between the fitted atom pairs of dimaprit and histamine in the S-fit and N-fit (Å)

S-fit		N-fit	
Fitted atom pairs	Distance (Å)	Fitted atom pairs	Distance (Å)
N_1–S_1	0.313	N_1–N_4	0.075
N_2–N_5	0.100	N_2–N_5	0.381
H_1–H_2	0.204	H_1–H_2	0.252
N_3–N_6	0.276	N_3–N_6	0.152





between the matched atoms of dimaprit and histamine for both models.

In the first model (S-fit) the sulphur atom of the isothiourea moiety of dimaprit is considered to be the proton acceptor and is therefore superimposed on the N^{π}-atom of the imidazole ring of histamine. The NH_2 of the isothiourea is matched with the N^{τ}-H of the imidazole ring. This group is assumed to function as the proton donor. An additional restraint is applied to keep the isothiourea moiety in the same plane as the imidazole ring of histamine (Figure 3a).

In the second model (N-fit) the two nitrogen atoms of the isothiourea part of dimaprit are fitted onto the two nitrogen atoms of the imidazole ring of histamine. The double bonded nitrogen atom of the isothiourea moiety of dimaprit is fitted onto the double bonded nitrogen atom of the imidazole ring of histamine. In this model the NH_2 of the isothiourea moiety again fulfils the role of proton donor and is fitted onto N^{τ}-H of histamine (Figure 3b).

Refinement of the final dimaprit conformations

The conformation of dimaprit obtained from the fitting procedures for both interaction models was further refined using MNDO. These optimizations were performed in such a way that the relative orientation of the isothiourea moiety and the protonated amino group did not change. The geometry of the isothiourea moiety itself was kept frozen.

MEP

The comparison between histamine and dimaprit in the two models also included a comparison of the molecular electrostatic potentials. The MEPs are depicted in Figure 4. All

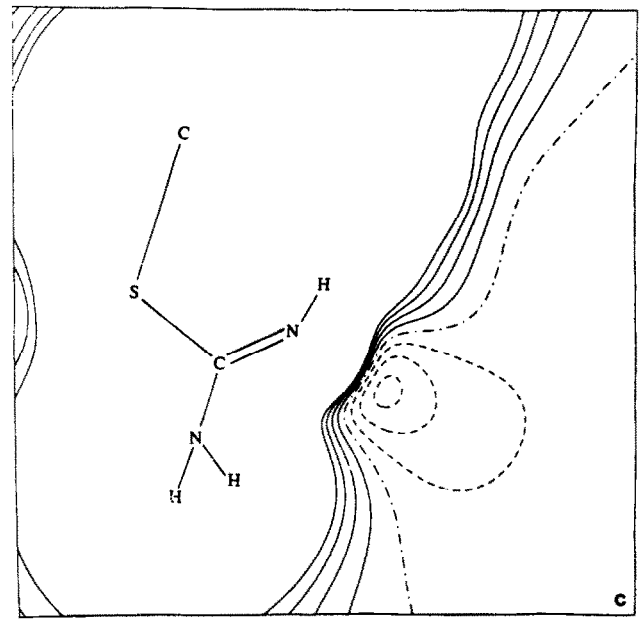


Figure 4. Molecular electrostatic potential maps for a, histamine; b, dimaprit in the S-fit; and c, dimaprit in the N-fit; solid lines, 20.0, 15.0, 10.0, 5.0 kcal/mol; dashed-dotted lines, 0.0 kcal/mol; and dashed lines, −5.0, −10.0 kcal/mol.

MEP calculations were performed in the plane defined by the imidazole ring of histamine and were carried out for the neutral species only.

Conformational energy calculations for dimaprit

The conformational energy of dimaprit has been calculated for both the charged and neutral species using the nonempirical HFS-LCAO program.[11] For the monocationic form, the N-fit conformation is 3.5 kcal/mol more stable compared to the S-fit conformation. For the neutral species the S-fit conformation is stabilized with 4.6 kcal/mol over the N-fit conformation.

β-Methylhistamine

The propyldimethylamino chain of the N-fit conformation of dimaprit displays a considerable deviation from the orientation of the side chain of histamine. The same conformational space is occupied by the methyl group of β-methylhistamine. Therefore, β-methylhistamine was included in this study to be able to discuss the steric freedom of the side chain of histamine. The conformation of β-methylhistamine was optimized using MNDO. Subsequently, the compound was fitted onto the active conformation of histamine. The MNDO energy difference between the fitted and optimized conformation of β-methylhistamine appeared to be only 3.5 kcal/mol. The molecular electrostatic potentials of the imidazole ring strongly resemble the MEP data of histamine; therefore these data are not shown. Figure 5 again shows the N-fit conformation of dimaprit, now superimposed on what should be the bioactive conformation of β-methylhistamine.

A dimaprit analogue

MEP data were calculated for a rigid analogue of dimaprit, 2-amino-5-(2-aminoethyl)thiazole (Figure 6). The results are shown in Figure 7.

DISCUSSION

Three criteria have been used to determine the bioactive conformation of dimaprit: the results of the fitting procedures (Table 1, Figure 3); the MEPs (Figure 4) of the two conformations of dimaprit in comparison to histamine; and their relative energies.

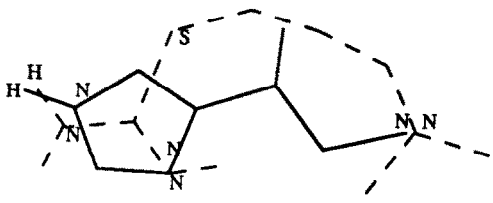


Figure 5. Fitted conformation of dimaprit (N-fit, dotted lines) in comparison to the fitted conformation of β-methylhistamine (solid lines).

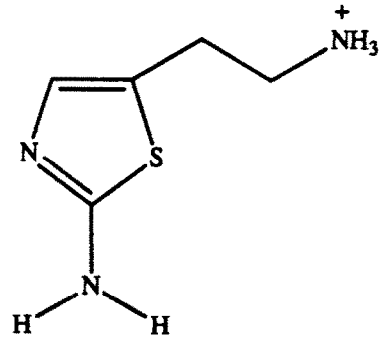


Figure 6. Structure of 2-amino-5-(2-aminoethyl)thiazole, the cyclic analogue of dimaprit.

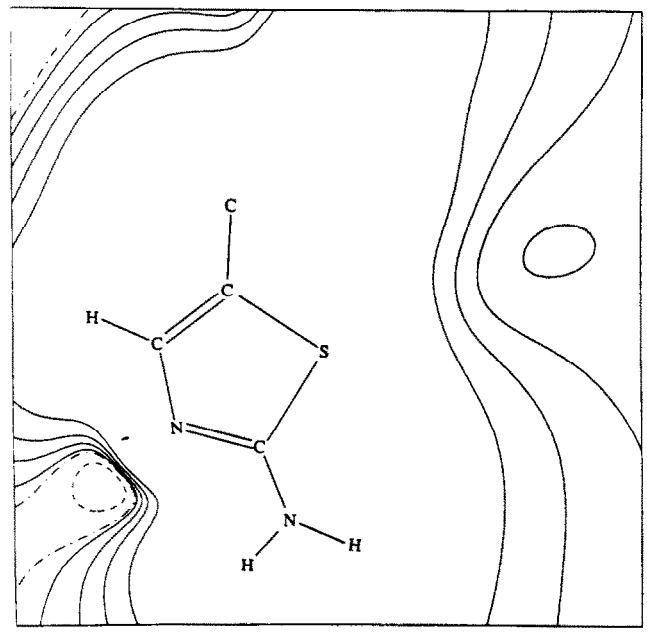


Figure 7. Molecular electrostatic potential map for 2-amino-5-(2-aminoethyl)thiazole: solid lines, 20.0, 15.0, 10.0, 5.0 kcal/mol; dashed-dotted lines, 0.0 kcal/mol; and dashed lines, −5.0, −10.0 kcal/mol.

Comparison between the N-fit and S-fit

When interpreting results from fitting procedures two criteria have to be considered: first, the distances between the fitted atoms, and secondly, the overall geometrical resemblance between the fitted molecules. When comparing the distances between the fitted atoms in the two interaction models for dimaprit (S-fit and N-fit), no large differences are observed (Table 1). In both models the atoms are within 0.5 Å of each other. When the two models are compared with respect to the overall steric fit of dimaprit and histamine (Figures 3a and 3b), the better geometrical overlap in the S-fit is obvious. The question arises whether a large deviation from the side chain of histamine, as is displayed in the N-fit for dimaprit, is allowed. Though the side chain is not expected to contribute to the overall binding energy, its conformational freedom might be limited due to steric interactions with the receptor. This question can be answered

by studying the properties of β-methylhistamine, as its β-methyl group occupies the same conformational space as the side chain of dimaprit in the N-fit.

β-Methylhistamine

β-Methylhistamine is an inactive analogue of histamine, its activity being less than 1% of histamine at the guinea pig right atrium.[17] In principle, the inactivity of the β-methyl derivative of histamine could be explained in two ways: either the conformational energy of the β-methyl derivative after fitting it onto histamine is too high compared to the energy of its optimized conformation, or its MEP data deviate largely from those of histamine. However, β-methylhistamine could be fitted onto histamine with an increase of only 3.5 kcal/mol in conformational energy, and also the electrostatic potentials of the derivative closely resemble those of histamine. So, β-methylhistamine should be able to adopt its bioactive conformation, and contains all features necessary for recognition by the H_2-receptor. Therefore, its inactivity can only be due to unfavorable steric interactions with the receptor caused by the presence of the β-methyl group. As mentioned above, the β-methyl group occupies the same conformational space as the side chain of dimaprit in the N-fit. This implies that the N-fit conformation can be established only at the expense of a large decrease in the apparent interaction energy.

Interpretation of MEP data

After interpreting the results of the fit procedures the MEPs have to be considered. Figure 4 reveals that the potential minima close to those atoms acting as proton acceptors are different: the potential minimum for histamine near the N^{π}-atom has a value of −13.2 kcal/mol; the minimum near the double bonded nitrogen atom of dimaprit in the N-fit is more pronounced than the minimum near the sulphur atom of dimaprit in the S-fit, −15.8 and −5.4 kcal/mol, respectively. However, another difference related to the direction of these MEP minima is observed. The difference in directionality of the MEP minimum of dimaprit relative to the one of histamine can be calculated by drawing a line from the MEP minimum to the corresponding proton acceptor and calculating the angle between the line for dimaprit and the one for histamine. In the N-fit this angle turns out to be almost 60°, whereas in the S-fit this angle is practically 0.

The importance of a proper alignment of the MEP minima is pointed out in a series of studies, which show its relevance both for hydrogen bond formation and for the energetic components of a proton transfer. Vedani and Dunitz[18] studied the deviation of the position of protons involved in hydrogen bonding from the CNC bisector of the imidazole ring, which coincides with the line through the MEP minimum and the N-atom. It was shown that the deviation from the bisector is less than 30° for 95% of all the structures studied. The MEP minimum of dimaprit in the N-fit is clearly not within this range of 30° and is therefore far from optimally positioned for interaction with the proposed proton donor of the receptor.

The necessity of an optimal relative orientation of proton donor and acceptor has also been demonstrated by means of quantum chemical calculations. For various model systems $(H_nX\text{-}H\text{-}YH_m)^+$ Scheiner et al.[19–21] calculated the effects of angular distortions on the energetics of a proton transfer. One type of deformation involved a rotation of one subunit relative to the other. Second and third deformations concerned the rotation of both units by equal amounts in the same or in opposite directions, respectively. The general conclusion drawn was that angular deformations lead to a nonlinear increase of the barrier for proton transfer with increasing deformations. Deformations less than 20° had little effect, whereas at deformations of 40° and larger, effects increased strongly. Furthermore, a destabilization of the complex when compared to the optimal orientation was observed. From these data it can be concluded that the S-fit conformation is more optimally oriented for a possible proton transfer than the N-fit conformation.

Interpretation of conformational energy data

From the relative energies of dimaprit in the two interaction models it is evident that the energy difference between the two conformations is small. Therefore, no additional information is obtained on which conformation would be the preferred one.

Proposed interaction model for dimaprit

Based upon the results of the fitting procedures and the MEP data it can be concluded that both criteria indicate that the conformation of dimaprit in the S-fit is the most likely candidate for the bioactive conformation. This implies that the sulphur atom of the isothiourea moiety of dimaprit will act as a proton acceptor.

Verification of the interaction model

The proposed interaction model for dimaprit can be verified by examining whether the chosen model, in contrast to the other model, can explain the pharmacological behavior of analogues of dimaprit.

The first compound considered is the higher homologue of dimaprit, SK&F 91488, also called homodimaprit.[2] In this compound the length of the chain connecting the isothiourea moiety to the dimethylamino group has been increased by one methylene group, compared to dimaprit. As this compound is more flexible than dimaprit it is obvious that it can easily be fitted onto histamine in a conformation corresponding to both the N-fit and the S-fit conformations of dimaprit. If the S-fit model is chosen as the model representing the bioactive conformation of dimaprit, we might expect homodimaprit to display agonistic activity in an S-fit conformation. If we now compare the S-fit conformation of homodimaprit with the fitted conformation of β-methyl histamine, an overlap is observed between the β-methyl group of β-methylhistamine and the butylene chain of homodimaprit (Figure 8). So, the conclusion must be therefore that although homodimaprit can adopt a conformation in which the sulphur atom of the isothiourea moiety can act as a proton acceptor (S-fit), this conformation is presumably prevented at the receptor due to unfavorable

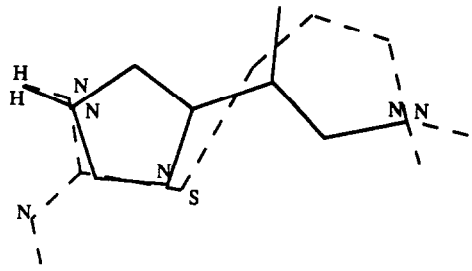


Figure 8. Fitted conformation of homodimaprit (dotted lines) in comparison to the one of β-methylhistamine (solid lines). Both have been fitted on histamine.

steric interactions. This is in agreement with its lack of H_2-activity. However, if the N-fit conformation of dimaprit would have been chosen as its active conformation, the conclusion must be drawn that a deviation from the side chain of histamine is allowed. Homodimaprit shows a comparable deviation when it is fitted onto histamine and should therefore also display H_2-agonistic activity. This would be in contradiction to its pharmacological profile.

The second compound to be considered is the lower homologue of dimaprit SK&F 91487, also called nordimaprit.[2] Nordimaprit was fitted onto histamine in an S-fit conformation. A reasonable fit was found with respect to the fitted atom pairs, although the side chains of histamine and nordimaprit appeared to have a far-from-optimal overall steric resemblance. As was suggested for β-methylhistamine and homodimaprit, this will cause unfavorable steric interactions with the receptor. Any attempt to improve the fit with respect to the side chains failed, as this was always accompanied by a poor fit of the essential atom pairs (i.e., the distance between the two charged nitrogens became about 1.5 Å). So, the inactivity of nordimaprit can be assumed to be caused by a poor fit of proton donor and acceptor atoms as a result of unfavorable steric interactions between the side chain and the receptor. Again, if the N-fit conformation of dimaprit had been chosen to interact with the histamine receptor, the inactivity of nordimaprit could not have been explained, as the N-fit conformation of this derivative deviates from the ethylamino side chain of histamine comparable to the N-fit of dimaprit.

The last dimaprit analogue to be discussed is SK&F 92054.[2] This compound is a derivative of dimaprit in which one of the hydrogen atoms of the NH_2-group of the isothiourea moiety is replaced by a methyl group. This compound is also inactive. Based on NMR data of the thiourea moiety of metiamide[22] it can be reasoned that in the S-fit conformation of SK&F 92054, the methyl group replacing one of the NH_2 hydrogens of the isothiourea moiety, can be present only in such that it coincides with the N^{τ}-H hydrogen atom of the imidazole ring in histamine. As N^{τ}-methylhistamine is an inactive analogue of histamine whose inactivity is most probably due to the loss of the proton donor function in the imidazole ring, the inactivity of SK&F 92054 also can be explained. However, the methylated NH_2-function only coincides with the N^{τ}-H group of histamine when the S-fit is considered. When the N-fit is taken into account, no definite reason can be found to explain the inactivity of SK&F 92054. In the N-fit the methyl group practically overlays the 2-methyl group of the inactive histamine analogue 2-methylhistamine. Although the inactivity of the latter compound might be due to steric interactions with the receptor, the effect can also be caused by the electronic influence of the substituent on the characteristics of the imidazole ring.[22,23] There is however no electronic explanation for the inactivity of the N-fit conformation of SK&F 92054. This can be demonstrated by the small difference in pK_a of the isothiourea of dimaprit and of SK&F 92054, respectively 8.3 and 8.4.[24]

It is concluded that, based upon the proposed active conformation of dimaprit, the known pharmacological behavior of dimaprit analogues, SK&F 91487, SK&F 91488 and SK&F 92054 can be explained, whereas the N-fit conformation of dimaprit would fail to do this in case of SK&F 91487 and SK&F 91488.

Design of new compounds

Finally, the validity of the interaction model for dimaprit can be checked by designing new compounds with a predicted (and desired) biological profile. Based upon the S-fit conformation of dimaprit, replacement of the isothiourea group of dimaprit by a rigid 2-aminothiazole ring could result in an active H_2-agonist (Figure 6). A literature study revealed that such compounds have already been synthesized as analogues of dimaprit. Impicciatore et al.[25] synthesized an extensive series of these dimaprit analogues and studied their activity. Although these authors observed H_2-activity, the final conclusion was that the thiazole ring of these compounds was not bioisostere with the isothiourea group of dimaprit.

It was checked whether the histamine H_2-receptor agonist 2-amino-5-(2-aminoethyl)thiazole (AAT) as synthesized by Impicciatore et al.[25] would fit into our model; the compound appeared to stimulate gastric acid secretion dose dependently in the guinea pig isolated stomach (activity comparable to histamine). First it was checked whether the compound could be fitted onto histamine in a conformation comparable to the N-fit conformation of dimaprit. The nitrogen atom of the thiazole ring was fitted onto N^{π} of the imidazole ring of histamine and the 2-amino function of the thiazole ring was fitted onto N^{τ}-H of the imidazole ring of histamine. After this rigid fit, the charged amino group of AAT could not be fitted onto the protonated amino group of histamine. Only with the sulphur atom acting as a proton acceptor could a good fit be obtained. Within this fit the nitrogen atom of the thiazole ring occupies the same receptor position as the N^{τ} atom of the histamine imidazole ring. For this so-called S-fit a MEP map was calculated (Figure 7). The map of AAT appeared to be very similar to that of dimaprit; only a low MEP value (1.5 kcal/mol) was found for the minimum near the sulphur atom when compared to dimaprit (−5.4 kcal/mol). If the MEP of AAT is compared to the MEP of histamine (Figure 4a) a big difference is observed. Though both compounds have in common the potential minimum near N^{π}, S, AAT has an additional minimum near the double-bonded nitrogen of the thiazole ring. This minimum is at the N^{τ}-H position of histamine, which is thought to interact as a proton donor. It is assumed that at this position of the receptor a proton acceptor function is present.

This will cause a destabilizing interaction with the potential minimum of AAT, thereby lowering the interaction energy. The implications for activation can be given only in a study where a simulation of this process is performed. This is done elsewhere.[28] Summarizing, the series of compounds synthesized by Impicciatore et al.[25] can be considered as cyclic analogues of dimaprit.

It is interesting to note that cyclic analogues of dimaprit like AAT,[25] do not have a proton donor function at the same position as histamine (N^{τ}) or dimaprit (NH_2) in their active conformation: the nitrogen atom of the thiazole ring, which was fitted onto the N^{τ} of the imidazole ring of histamine, is not protonated under physiological conditions. This suggests a possible proton donor role for the 2-amino group of the thiazole ring. Indeed, it is known that the 2-amino function is necessary for a high activity as the 5-ethylaminothiazole compound is less active: AAT is a full agonist with an activity comparable to histamine, whereas the thiazole analogue only has 0.1% of the activity of histamine left (gastric acid secretion of the rat).[3]

A final interesting observation is that the dimaprit analogues are incapable of tautomerism, which was thought to be an essential feature for receptor activation.[3] Although this might lead to the suggestion that a static interaction might be the receptor activation mechanism as proposed earlier,[26] it will be shown that the compounds can participate in a proton relay mechanism. This will be the subject of two different papers.[27,28]

CONCLUSION

Based upon the present results it is clear that the sulphur atom of the isothiourea moiety of dimaprit acts as the proton acceptor. Moreover, this model also explains the inactivity of all known analogues of dimaprit. The inactivity of homo- and nordimaprit is caused by unfavorable steric interactions with the receptor. If the N-fit of dimaprit would have been considered to represent the active conformation it would be impossible to explain the inactivities of these two analogues.

The data found for the 2-aminothiazole analogues of dimaprit open new perspectives for studying H_2-receptor activation, as these compounds do not incorporate the classical tautomeric system.

Finally, this study shows that computer graphics and quantum chemistry techniques can be powerful tools in studying the interaction of biologically active compounds with their receptors and, ultimately, in designing new drugs.

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REFERENCES

1 Parsons, M.E., Owen, D.A.A., Ganellin, C.R. and Durant, G.J. Dimaprit—[S-[3-(N,N-dimethylamino)-propyl]isothiourea]—a highly specific histamine H_2-receptor agonist. Part 1. Pharmacology. *Agents and Actions*. 1977, **7**, 31–37

2 Durant, G.J., Ganellin, C.R. and Parsons, M.E. Dimaprit–[S-[3-(N,N-dimethylamino)-propyl]isothiourea]—a highly specific histamine H_2-receptor agonist. Part 2. Structure activity considerations. *Agents and Actions*. 1977, **7**, 39–43

3 Durant, G.J., Ganellin, C.R. and Parsons, M.E. Chemical differentiation of histamine H_1- and H_2-receptor agonists. *J. Med. Chem.* 1975, **18**, 905–909

4 Sterk, G.J., van der Goot, H. and Timmerman, H. Studies on histaminergic compounds. Part II. Synthesis and histamine H_2-activity of dimaprit and some of its analogues. *Eur. J. Med. Chem.* 1984, **19**, 545–550

5 Green, J.P., Johnson, C.L. and Weinstein, H. *Psychopharmacology: A generation of progress*. Raven, New York (1978), pp. 319–320

6 Weinstein, H., Chou, D., Johnson, C.L., Kang, S. and Green, J.P. Tautomerism and the receptor action of histamine: a mechanistic model. *Mol. Pharm.* 1976, **12**, 738–745

7 Richards, W.G., Wallis, J. and Ganellin, C.R. Imidazole geometry and the calculations of tautomer preference for histamine. *Eur. J. Med. Chem.* 1979, **14**, 9–12

8 Topiol, S., Weinstein, H. and Osman, R. A theoretical investigation of histamine tautomerism. *J. Med. Chem.* 1984, **27**, 1531–1534

9 Weinstein, H., Mazurek, A.P., Osman, R. and Topiol, S. Theoretical studies on the activation mechanism of the histamine H_2-receptor: the proton transfer between histamine and a receptor model. *Mol. Pharm.* 1986, **29**, 28–33

10 Luque, F.J., Illas, F. and Pouplana, R. On the mechanism of histamine H_2-receptor activation. *Mol. Pharm.* 1987, **32**, 557–563

11 Baerends, E.J., Ellis, D.E. and Ros, P. Self-consistent molecular Hartree-Fock-Slater calculations. I. The computational procedure. *Chem. Phys.* 1973, **2**, 41–51

12 Versluis, L. and Ziegler, T. The determination of molecular structures by density functional theory. The evaluation of analytical energy gradients by numerical integration. *J. Chem. Phys.* 1987, **88**, 322–328

13 Dewar, M.J.S. and Thiel, W. Ground states of molecules. 38. The MNDO-method approximation and parameters. *J. Am. Chem. Soc.* 1977, **99**, 4899–4907

14 Chem-X, developed and distributed by Chemical Design Ltd, Oxford, UK

15 Prout, K., Critchley, S.R. and Ganellin, C.R. 2-(4-Imidazolyl)ethylammonium bromide (histamine monohydrobromide). *Acta Crystallogr. Sect. B.* 1974, **30**, 2884–2886

16 Clark, T. *A Handbook of Computational Chemistry*. John Wiley & Sons, New York (1985), Chapter 4.

17 Ganellin, C.R., Port, G.N.J. and Richards, W.G. Conformation of histamine derivatives. 2. Application of molecular orbital calculations of preferred conformations in relation to dual receptor activity. *J. Med. Chem.* 1973, **16**, 616–620

18 Vedani, A. and Dunitz, J.D. Lone-pair directionality in hydrogen bond potential functions for molecular mechanics calculations: the inhibition of human carbonic

anhydrase II by sulfonamides. *J. Am. Chem. Soc.* 1985, **107**, 7653–7658
19 Scheiner, S. Comparison of proton transfers in heterodimers and homodimers of NH_3 and OH_2. *J. Chem. Phys.* 1982, **77**, 4039–4050
20 Scheiner, S. Proton transfers in hydrogen bonded systems. 4. Cationic dimers of NH_3 and OH_2. *J. Chem. Phys.* 1986, **86**, 376–382
21 Scheiner, S. and Bigham, L.D. Comparison of proton transfers in $(S_2H_5)^+$ and $(O_2H_5)^+$. *J. Chem. Phys.* 1985, **82**, 3316–3321
22 Ganellin, C.R. *Pharmacology of histamine receptors.* Wright PSG, Bristol (1982), pp. 81–86
23 Reggio, P., Topiol, S. and Weinstein, H. Molecular determinants for the agonist activity of 2-methylhistamine and 4-methylhistamine at H_2-receptors. *J. Med. Chem.* 1986, **29**, 2412–2415
24 Sterk, G.-J. Studies on histaminergic compounds. Ph.D. thesis, Vrije Universiteit, Amsterdam, 1987
25 Impicciatore, M., Morini, G., Chiavarini, M., Barocelli, E., Bordi, F., Plazzi, P.V. and Vitali, F. 4. Histamine receptors and metabolism. *Agents and Actions* 1987, **20**, 262–264
26 Ganellin, C.R. *Pharmacology of histamine receptors.* Wright PSG, Bristol (1982), pp. 35–39
27 Eriks, J. Ch., Sterk, G.-J., van der Aar, E.M., van Acker, S.A.B.E., van der Goot, H. and Timmerman, H. *New Perspectives in Histamine Research* (H. Timmerman and H. van der Goot, Eds.) Birkhäuser Verlag, Basel (1991), pp. 301–314
28 Haaksma, E.E.J., Donné - Op den Kelder, G.M., Timmerman, H. and Weinstein, H. *New Perspectives in Histamine Research* (H. Timmerman and H. van der Goot, Eds.) Birkhäuser Verlag, Basel (1991), pp. 315–324