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Dedicated to Professor Ionel Haiduc
on the occasion of his 70th anniversary

CONFORMATIONAL ANALYSIS FOR A SERIES OF IMIDAZOLE LIGANDS ACTING AS ANTAGONISTS ON THE HISTAMINE H3 RECEPTOR

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A conformational analysis was performed using the MM+ force field and the semiempirical AM1 method for a series of 30 imidazolic derivatives containing carbamate as a polar group substituted by different linear or branched alkyl moieties. The best conformers have helical shapes with a turn around the carbamate function and with the hydrogen atom and carbonyl bond of the amidic groups in syn orientation. Both methods give a large number of conformers that populate the low-energy levels of the potential energy surface (PES). Many of them could be present in the synthesized product. The best AM1 conformer of the most active H3 antagonist of the series has twelve rotation barriers. Nine of them have energy values lower than 3 kcal/mol allowing easy interconversions between conformers in the receptor ligand binding domain. Data obtained in this work suggest that the antagonist activity of these compounds does not depend significantly on their steric behavior.

INTRODUCTION

Histamine is a biogenic amine that plays many physiological roles. The major functions for histamine have been largely defined by the activity of the H1-H4 receptors. The H3 receptor is involved in neurotransmitter release in the central nervous system (CNS). Histamine H_3 antagonists are designed for potential therapeutic applications in different CNS diseases: depression,[1] bulimia,[2] epilepsia,[3,4] schizophrenia,[5,6] Alzheimer's syndrome,[6,7] temporary loss of memory,[6,8] and incapacity of learning.[8-13] Of the high active H_3 antagonists, thioperamide and clobenpropit are still considered among the prototypes of H3 agonists. However, these compounds contain hepatotoxic groups of thiourea or isothiourea and for this reason they were not introduced in clinical trials. Searching for less toxic compounds with high activity and selectivity on the H_3 receptor, Schunack et al.[14] synthesized compounds similar to clobenpropit containing a carbamate group instead of thiourea. We have chosen these series of compounds for a conformational study of the steric behavior of possible low-energy conformers. The number of conformers and their steric properties are important in searching pharmacophore patterns for antagonists of the histamine H3 receptor.

METHODS

The 3D-equilibrium geometry of the compounds has been obtained using a molecular mechanics method, the MM+ force field, and a semiempirical quantum chemical method, AM1,[15] both implemented in the HyperChem7.52 package.[16] The conformational analysis was performed with the Conformational Search module also included in HyperChem7.52. The compounds have 7 to 15 rotatable bonds and all have been considered in conformational search. The corresponding dihedrals have been varied with steps of 60°. In order to obtain the conformer in the lowest minimum on the potential energy surface, an energy criterion of 10 kcal/mol above the best conformer was used. Maximum number of optimization cycles was set to 5000 and the lowest 100 conformers above the best conformer were kept. All conformers resulted from conformational search have been further fully optimized using the AM1method. Geometry optimizations have been carried out using the Polak-Ribiere conjugate gradient algorithm, an SCF convergence of 10^{-5} and as stop criterion a RMS gradient of 0.01 kcal/Åmol. For racemates two series of geometries, containing either (R) chiral atoms or (S) chiral atoms, have been optimized. Energy barriers have

been obtained from single point calculations on conformers resulted by modifying the dihedrals of the best conformer with steps of 15°.

RESULTS

The compounds in this series of classical H3 antagonists have a general structure containing an imidazolic ring substituted in 4-position by a propyl group which is bound to an oxygen atom of a carbamate group. The carbamate group is bound through its nitrogen atom to a hydrophobic alkyl ending group. Applying the MM+ and AM1 methods for geometry optimization some general observations resulted. Both methods give the best conformers of all the 30 compounds of this series with a helical shape where the turn occurs around the carbamate group. Due to this turning effect the peptidic bond is in *syn* instead of *anti* conformation.

We have chosen to discuss the results obtained for the most active ligand in this series. The numbering for its heavy atoms is displayed in Fig 1. It has twelve flexible bonds that have been rotated in conformational searching.

Of the 100 MM+ conformers on optimization at the AM1 level remained 94 distinct conformers. The helical shape of the best conformers resulted from both methods can be observed in Fig 2. In general, the conformers with this shape have a more limited access to the receptor ligand binding domain (LBD) than the conformers with extended conformations.

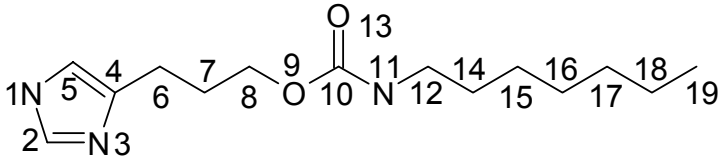

Fig. 1 – Atom numbering in heptyl-carbamic acid 3-(1*H*-imidazol-4-yl)-propyl ester, the most active ligand in the series.

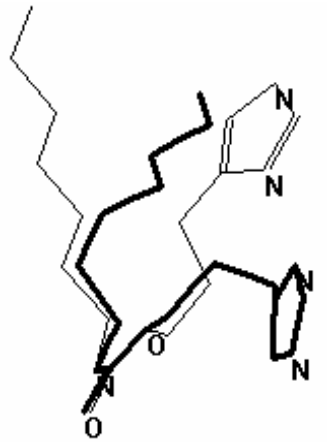

Fig. 2 – Superposition of the best MM+ conformer (thick line), of the best AM1 conformer and their helical shape.

The packing degree of conformers given by the two methods can be appreciated from the histograms in Fig 3a and 3b where the number of conformers is represented function of the distance between the C5 and C19 unbound atoms. One can observe that the least distances (of 3.5-5 Å) between the C5 and C19 unbound atoms are given by the MM+ force field. Thus, this method provides most of conformers with a high intramolecular packing, while the AM1 method gives a distribution closer to a normal one, the majority of conformers having the mean distance between the C5 and C19 unbound atoms between 4.5 and 8 Å.

Figures 4a and 4b show the normal distribution of the 100 distinct lowest-energy conformers obtained in conformational search with the MM+ force field and the normal distribution of those obtained through the AM1 optimization. In these figures the number of molecules is plotted function of the differences between the total energy of each conformer and the total energy of the best conformer resulted from each of the two methods. Total energies of the best MM+, and the best AM1 conformers are 12.078 kcal/mol and -78398.21 kcal/mol, respectively. The MM+ force field gives a distribution shifted to the right (9 conformers have

energy differences between 0 and 0.4 kcal/mol and 91 are contained in an energy range between 0.4 and 1.1 kcal/mol), while the AM1 method gives a distribution shifted to the left (87 conformers have energies differences between 0 and 2.5 kcal/mol). The distribution of the AM1 heat of formation is similar to the distribution of the AM1 total energy.

Figures 4a and 4b show that there are many low-energy conformers on the PES that could be obtained in final product by synthesis. All energy barriers have been calculated in order to find out if these conformers could pass different energy barriers and could rearrange in other low-energy conformers with a more suitable conformation for interacting with amino acid residues from the receptor LBD (Fig 5).

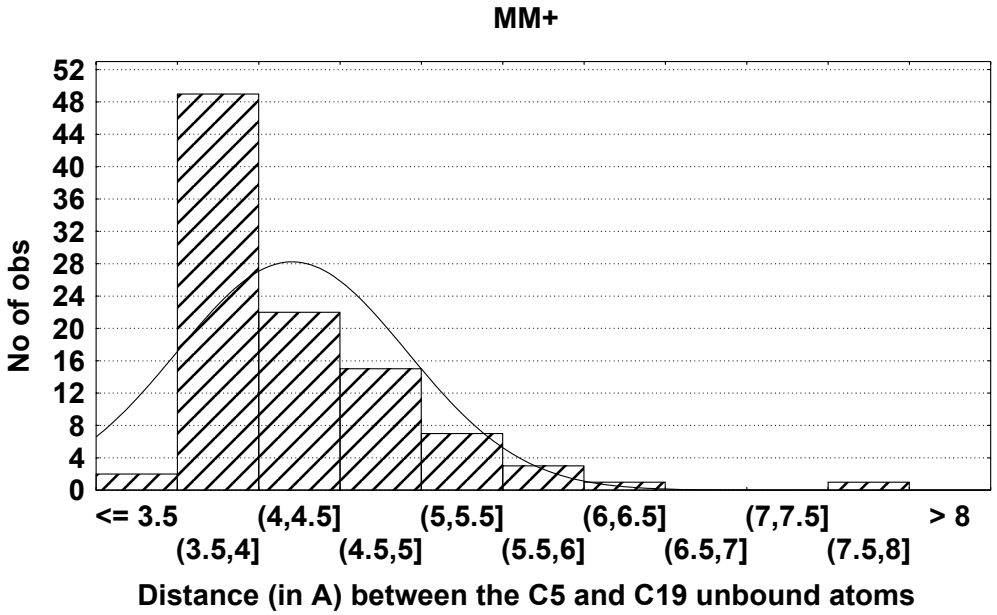

Fig. 3a – The number of the MM+ conformers against the distance between the C5 and C19 unbound atoms.

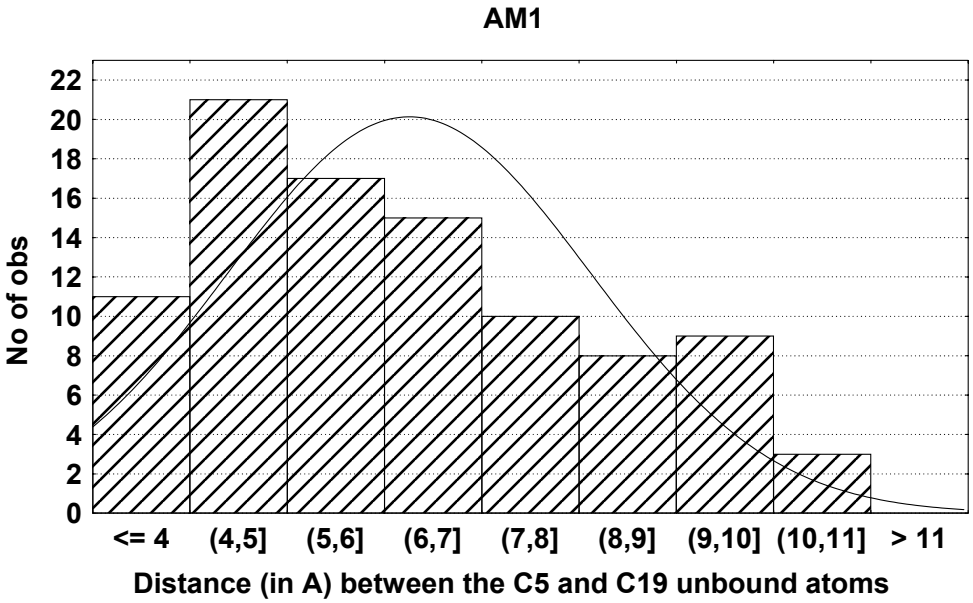

Fig. 3b – The number of the AM1 conformers against the distance between the C5 and C19 unbound atoms.

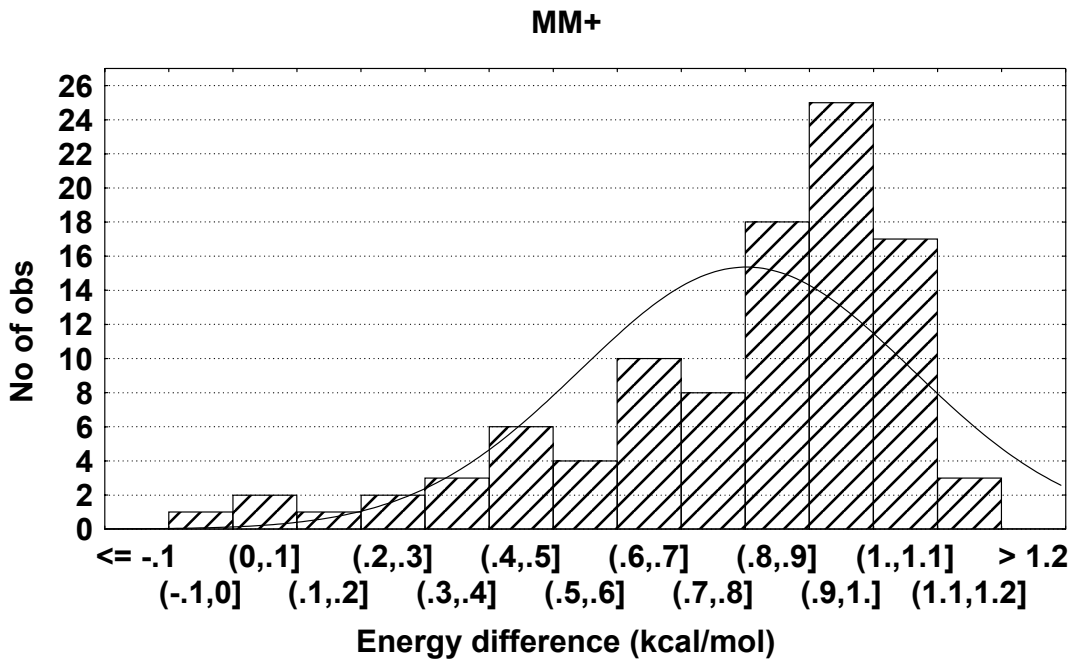

Fig. 4a – The number of the MM+ conformers against the difference between the energy of each of the 99 MM+ conformers and the energy (12.078 kcal/mol) of best MM+ conformer.

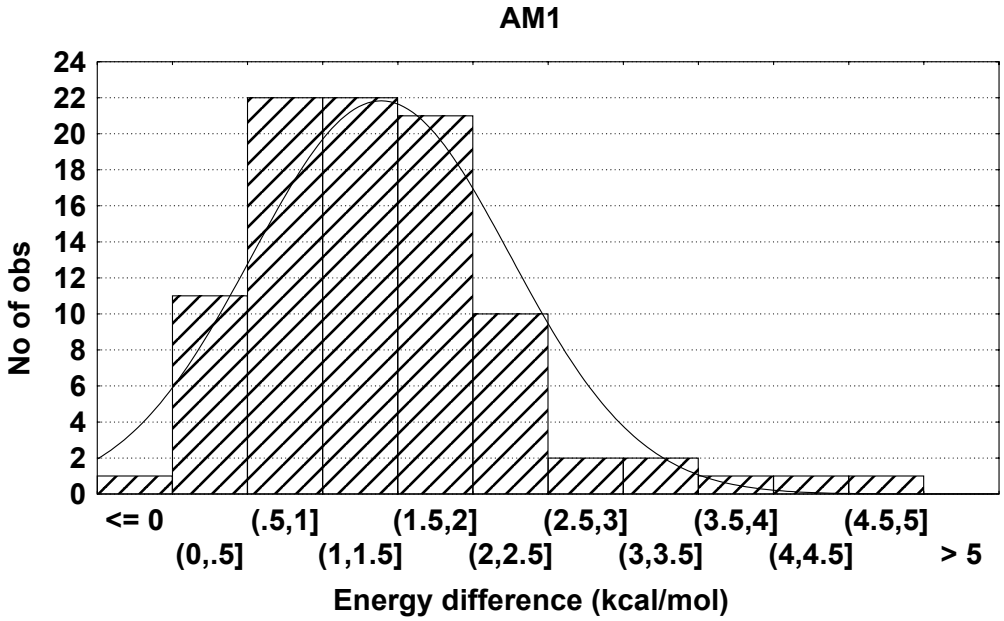

Fig. 4b – The number of the AM1 conformers against the difference between the energy of each of the 93 MM+ conformers and the energy (-78398.21 kcal/mol) of best AM1 conformer.

There is only one energy barrier over 5000 kcal/mol at the rotation of the C5-C4-C6-C7 dihedral around the C4-C5 bond. Stable conformers can have the C5-C4-C6-C7 dihedral between150-360°. Other two barriers have energy over 100 kcal/mol. They correspond to the rotation of the C8-O9 and O9-C10 bonds. Stable conformers have the C7-C8-O9-C10 and C8-O9-C10-N11 dihedrals in the range 90 and -120°. The O9-C10-N11-C12 dihedral can have only two values around 0 and -165. Except for the above three dihedrals that could lead to high energy barriers, the rest of dihedrals can take values in a large range between 60 and -60°. Conformers with

dihedrals in this interval have energy barriers lower than 3 kcal/mol. The low-energy rotation barriers of the majority of rotatable bonds suggest that many conformers can be obtained by synthesis and that these conformers can easily convert in other conformations more suitable for interaction with amino acids from the receptor active site. Due to the large number of possible conversions between conformers, the highest active as well as the least active compounds have equal chances to convert in the receptor LBD in conformers with productive ligand-receptor interactions. These results suggest that the steric interactions could have at most a modest influence on the biological activity of this class of imidazolic derivatives.

A supplementary argument according to which the activity of these compounds does not depend on the detrimental sterical interactions with the receptor walls is presented in Fig. 6a and 6b where the superpositions of the most active and the most inactive derivatives are displayed.

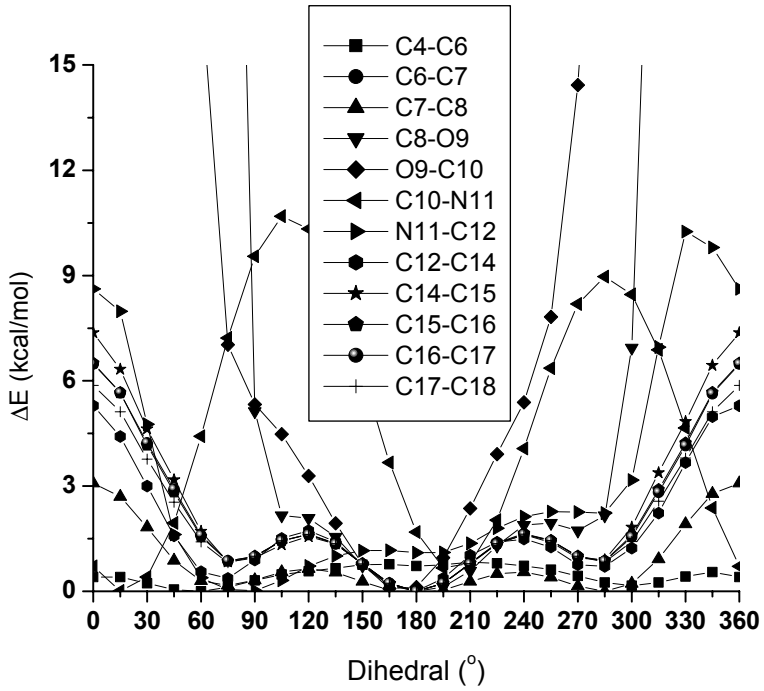

Fig. 5 – The AM1 barriers to rotation of the 12 flexible bonds in the legend. ΔE (the difference between the total energy of each conformer and the total energy of the best conformer) is plotted against the dihedral values.

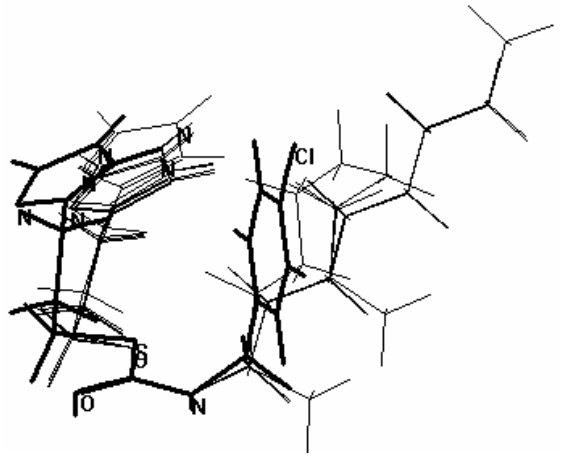

Fig. 6a – Superposition of clobenpropit (thick lines) and the AM1 best conformers of the highest active (five) ligands.

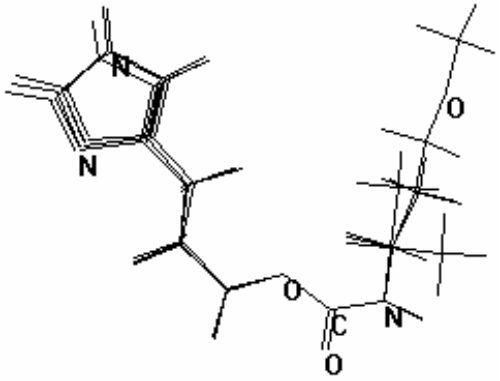

Fig. 6b – Superposition of the AM1 best conformers of the lowest active (three) ligands.

One can observe that the dimensions of the least active compounds are lesser than the dimensions of the highest active compounds. It is possible that the activity of these compounds depends significantly on their hydrophobicity, rather than their steric properties.

CONCLUSIONS

The MM+ force field, as well as the AM1 method give the lowest-energy conformers with the aminic hydrogen and carbonylic oxygen of the amidic groups in *syn* positions suggesting that in vacuum the packed shapes are preferred to the extended conformations.

Molecular mechanics and the semiempirical AM1 method give for the H3 antagonists of this series many low-energy conformers suggesting that from synthesis could result a mixture of many conformers. The barriers to rotation of the flexible bonds have generally low values allowing easy interconversions in the receptor LBD. The low activity of the weak antagonists of the series is not due to the detrimental steric interactions with the receptor walls.

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