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The computational design of test compounds with potentially specific biological activity: Histamine-H_2 agonists derived from 5-HT/H_2 antagonists*

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SUMMARY

The previously proposed models for the recognition and activation of 5-HT and histamine-H_2 receptors, which were employed to explain the antagonist activity of LSD at both of these receptors, as well as the selective antagonism for H_2 receptors by SKF-10856 and 9,10-dihydro-LSD, are used herein to design a compound to test the H_2-receptor model. The design strategy attempts to construct a compound with potentially selective H_2 agonism. The design scheme maintains features which were previously used to explain selective recognition of SKF-10856 and 9,10-dihydro-LSD as well as reintroduces the chemical features proposed to be responsible for H_2 activation. The existence of the H_2 recognition and activation features in the proposed compound is verified, in a previously proposed model, by computational studies of the molecular electrostatic potentials and shifts in the tautomeric preference.

INTRODUCTION

The rational design of new compounds with specific biological activity is generally based on the use of a model or hypothesis which explains the activities of existing compounds. Such models may be rooted in computational chemical methods and, therefore, require the establishment of a correspondence between computationally derived characteristics and biochemically observed properties. Thus, we have associated the recognition of compounds (represented by physicochemical properties) with binding affinities, and the activation by these compounds (represented by molecular processes) with biochemical responses [1]. In previous studies, we have used this scheme to understand the activities of various ligands of 5-hydroxytryptamine (serotonin, 5-HT) [1–4]

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and histamine receptors [5–8]. These models were then used to explain the antagonism of LSD at both of these receptor systems [1,2]. The same models can be used to explain the selective H_2 antagonism of the LSD analogues SKF-10856 and 9,10-dihydro-LSD. These studies are briefly reviewed herein.

Based on the histamine-H_2 activation model, a compound whose structure is also derived from the LSD framework is proposed. This compound should maintain the selectivity for recognition at the histamine-H_2 receptor while also regaining the characteristic features proposed to be responsible for activation at the histamine-H_2 receptor. Presented herein are computational chemical studies which verify the existence of the proposed recognition features, as evidenced by features of the molecular electrostatic potentials, and which verify the existence of activation features, as evidenced by tautomeric properties of the proposed compound. Thus, the activity of the proposed compound is tested in existing computational chemical models.

METHODS

For the purpose of generating molecular electrostatic potential (MEP) maps, the structure of LSD was obtained from the Cambridge Crystallographic Data Base (entry LSDIBZ) [9]. For simplification, the amide ethyl groups were changed into methyl groups. The structures of all other compounds were obtained from this framework by the deletion or change of the appropriate atoms and by the complete relaxation of hydrogen atoms which were added in order to satisfy valence requirements. The relaxation was performed with the use of version 2.0 of Biograf [10] with BioDesign's proprietary molecular mechanics force field [11]. During the relaxation of these added hydrogen atoms, the positions of other atoms were optimized as described here: *9,10-dihydro-LSD,* the carbon and hydrogen atoms at the 9 and 10 positions (with the assumption of a chair conformation of the piperidine ring); *5-HT (serotonin),* the hydroxyl oxygen atom, the two methylene carbon atoms of the aminoethyl side chain (and their hydrogen atoms), and the carbon atom *ortho* to both the hydroxyl group and 5-membered ring (to relieve strain); *histamine,* the nitrogen atom (formerly a carbon atom) at the 1 position and both hydrogen atoms on the methylene carbon atom which is bonded to the amino group; *our proposed agonist,* the nitrogen atom (formerly a carbon atom) at the 1 position of the imidazole ring and the 9 and 10 hydrogen and carbon atoms (with the assumption of a chair piperidine ring).

The MEPs were evaluated, in planes parallel to each structure's 5-membered aromatic ring, at the ab initio Hartree–Fock level directly from the STO-3G basis set [12] charge distribution with the use of the GAUSSIAN 86 system of programs [13]. The geometries and energies of the model compound were optimized at the MNDO level [14] with the use of the program AMPAC (version 1.00) [15]. With the GAUSSIAN 86 system of programs [13], the energies of the derived structures were then evaluated at the ab initio Hartree–Fock level with the STO-3G basis set [12]. The notation X//Y is used herein to denote that the energy was evaluated with method X using the optimized structure determined with method Y.

RESULTS AND DISCUSSION

Model for 5-HT receptors

The previously proposed model for recognition at 5-HT receptors contains two main features

[1,2]. The first feature is based on the fact that 5-HT exists as the protonated form (at the ethylamine side chain) at physiological pH. The primary feature responsible for recognition was therefore postulated to be the cationic amine which would interact with some neutralizing anchor of the receptor. It has been shown [1, 2] that this neutralized form has recognition properties similar to those of neutral 5-HT; therefore, neutral 5-HT is employed in this model. Interestingly, recent site-directed mutagenesis studies suggest such a similar anchoring role for the Asp^{113} residue of the β-adrenergic receptor in the binding of agonists and antagonists [16]. The second recognition characteristic proposed for 5-HT receptors is the electronic properties over the indole ring of 5-HT. This is based on the observations that indoles tend to form stacking complexes with, e.g., imidazoliums [17]. Specifically, the molecular electrostatic potential (MEP) over the indole ring was suggested to embody a representation of the required electrostatic properties for binding at 5-HT receptors (see Fig. 1). The use of electrostatic properties to represent recognition characteristics is consistent with the notion that recognition is a long-range effect, and that electrostatic properties are long-ranged in nature. Computational studies were used to verify that indeed the reactivity characteristics of complexes of 5-HT correlate with these electrostatic properties. An essential feature of the MEP of 5-HT (see Fig. 1) is the ellipsoidal shape resulting from the pair of negative minima. These recognition features have been reported in other analogues [8].

While the above summarizes *properties* used in a model for recognition, a molecular model for activation must represent some molecular *process* which would be initiated by an agonist. The molecular process which has been proposed as a model for activation of 5-HT receptors is the transfer of a proton from an imidazolium to ammonia acting as a proton donor/acceptor pair [3,4] (see Fig. 2). Previous computational chemical studies showed that the interaction of 5-HT with such a proton-transfer model is consistent with the recognition model described above [3,4]. Furthermore, the computational results verify that the interaction of 5-HT with this proton-transfer model induces such a proton-transfer process. This is achieved in two ways. The presence of 5-HT lowers the energy of the imidazole/ammonium complex relative to that of imidazolium/ammonia, thereby providing a thermodynamic facilitation of the proton-transfer process. Furthermore, the presence of the indole π-cloud serves to bring the two ends (donor and acceptor) closer together, and to reduce the energy of the transition state. These combined effects provide a facilitation of the kinetics of the proton-transfer process.

Further refinement of this overall model would obviously be necessary to explain ligand activity at 5-HT receptor subtypes. For the present purposes of designing histamine-H_2 agonists, this stage of the refinement of the model is sufficient.

Model for histamine-H_2 receptors

The proposed model for ligand action at histamine-H_2 receptors is analogous to the 5-HT receptor model described above [5–7]. At physiological pH, the ethylamine side chain of histamine is protonated and serves as a primary feature for the recognition model at the receptor. With a neutralized structure (e.g., the deprotonated form or a complex with an electron-rich moiety [18]) the MEP at 1.6 Å over the imidazole region (see Fig. 1) serves as an indicator of the reactivity characteristics in potential stacking interactions. For reasons elaborated below, the N3 tautomer of the imidazole ring is used at this stage. We note the triangular shape of the MEP at 1.6 Å, with one dominant minimum. The proposed model for the process responsible for activation of the histamine-H_2 receptor would suggest that the properties of the MEP in the plane of the imidazole should also be considered (see below). This MEP is also shown in Fig. 1.

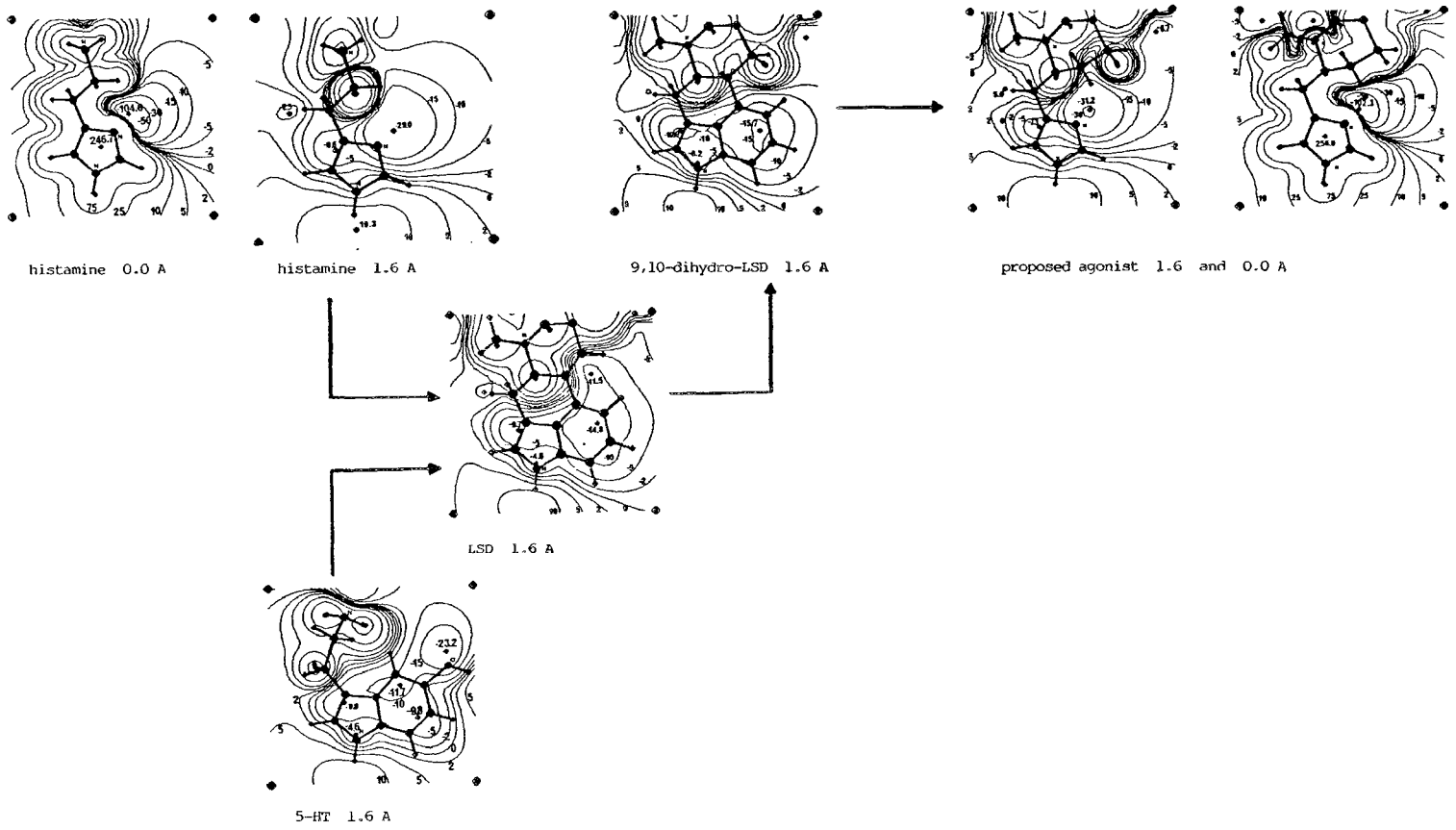

Fig. 1. MEPs of histamine, 5-HT, LSD, 9,10-dihydro-LSD, and the proposed histamine-H_2 receptor agonist. The MEPs were evaluated from the STO-3G charge distribution in planes (i.e., distances below the aromatic ring system) indicated below each map. Because the region of space considered in the calculation of the MEPs was limited in order to highlight their essential features, some structures appear to be truncated in this figure; however, for each structure, the complete set of atoms, as described in the Methods section, were used in the calculations (see Fig. 4 for a complete representation of our proposed agonist).

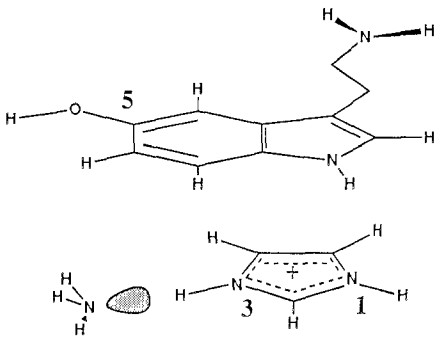

Fig. 2. Schematic representation of the proton-transfer model for activation of the 5-HT receptor.

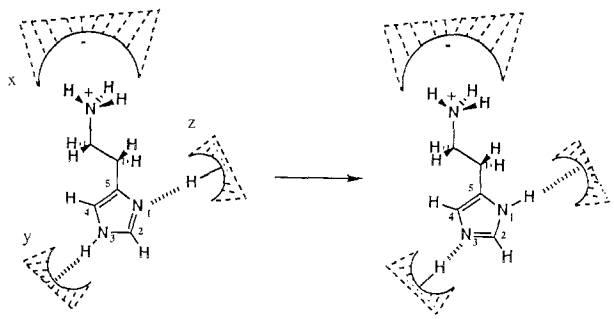

Fig. 3. Schematic representation of the proton-relay model for activation of the histamine-H_2 receptor. The geometric shapes surrounding histamine are meant to represent portions of the receptor with which it interacts; x indicates a negative region which neutralizes the cation, y is a proton acceptor, and z is a proton donor.

The proposed molecular process responsible for activation of the histamine receptor can be summarized as follows [6]. At physiological pH, with the ethylamine side chain protonated, histamine exists primarily as the N3 tautomer. Upon neutralization of the side chain (a primary event in the binding process) the N1 tautomer becomes preferred. Prior to the actual activation process, histamine would still be in its N3 tautomeric form (albeit preferring the N1 form), and therefore the neutral N3 tautomeric form is used in generating the MEP to represent the recognition features. The activation model then assumes that the imidazole ring of histamine is situated between a potential proton donor (to N1) and proton acceptor (from N3; see Fig. 3). The corresponding donation of a proton to N1 and acceptance of a proton from N3 results in the favorable change of histamine to the N1 tautomeric form. With respect to the receptor, histamine may be considered to have completed a circuit allowing a proton-relay process to take place, thereby initiating some series of events which eventually lead to a measurable response.

It has been proposed that the 5-HT and histamine receptor models described herein can be unified into a single system which can then be used as an example for a general model for the origin of receptors [19].

LSD and related analogues

The above models for the two receptor systems discussed herein have been successfully tested on other closely related ligands [6–8]. More challenging and convincing is the ability of the models to explain the activities of compounds not clearly related to the endogenous ligands. Such examples are available [1,2,20]. We focus here on LSD and 9,10-dihydro-LSD [1,2,20]. LSD acts as an antagonist at both 5-HT and histamine-H_2 receptors. Because antagonism requires recognition (but not activation) at the receptor, one would expect to find the recognition characteristics of both 5-HT and H_2 receptors in LSD. As can be seen in Fig. 1, both sets of features can be identified in the MEP of LSD. This example illustrates a virtue of such computational models in helping to identify similarities between compounds not obviously present in comparing the molecular structures. For example, one of the negative regions in the MEP of 5-HT (the one resulting from a lone pair of the 5-hydroxyl oxygen atom) is reproduced by the double bond between C9 and

C10. From Fig. 1, it is evident that while this minimum in LSD is necessary to generate those features in its MEP required for the 5-HT recognition model, they are not needed for the histamine-H_2 receptor model. Employing this analysis, one can understand why saturation of this bond should, and indeed did, result [1] in a compound, 9,10-dihydro-LSD, with dramatically reduced affinity for 5-HT receptors, but with virtually no change in affinity for H_2-receptors.

Proposed histamine-H_2 agonist

The previous section illustrates the utilization of the recognition models for 5-HT and histamine-H_2 receptors to explain the recognition of LSD at both of these receptors, and the design of a compound with only H_2-binding activity. The design of 9,10-dihydro-LSD resulted in a compound in which recognition properties for 5-HT receptors were lost, and activation properties for 5-HT and H_2 receptors were absent. It is of obvious interest to see if this approach can be taken one step further, e.g., the employment of the activation portion of the histamine-H_2 receptor model to introduce those features necessary for the activation process at this receptor. It is hoped that this could result in a compound which preserves the high potency of LSD at H_2 receptors while being able to act as an agonist at these receptors. Such a proposed compound is illustrated in Fig. 4. The design strategy simply assumes that while the indole ring system of 9,10-dihydro-LSD may be recognized at the H_2 receptor, it cannot undergo the tautomerism required for activation. Therefore, the indole ring system of 9,10-dihydro-LSD is replaced with an imidazole ring. This modification introduces additional flexibility into the molecule. It is then assumed that the remainder of 9,10-dihydro-LSD contains properties (in common with LSD), which impart effective recognition characteristics (as opposed to unfavorable steric effects), and these are therefore maintained in the new compound. From Fig. 1, it is evident that the MEP of this compound is still similar to that of histamine. Thus we would expect the recognition properties to be preserved. It is also reasonable to expect that properties such as pK_a, hydrophobicity, transport, etc., of the 'parent' compounds will be preserved.

As a computational model to test whether neutralization of the side chain of histamine induces the requisite shift in tautomeric preference, a simple model was employed [5]. In this scheme, the difference in tautomeric preference for the neutral form of histamine was compared to that of the cationic form so that the 'tautomeric shift' can be calculated (see Table 1). In this analysis, the

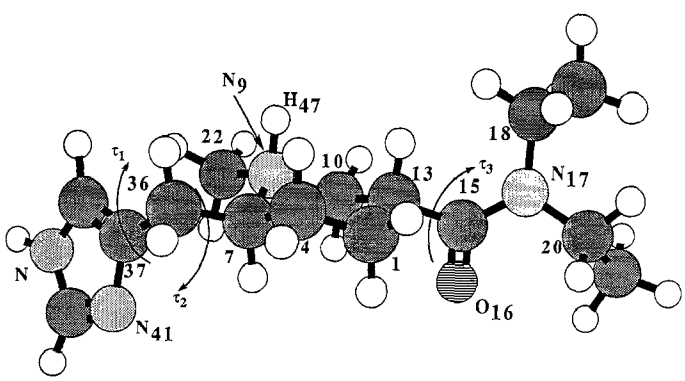

Fig. 4. The proposed histamine-H_2 receptor agonist with atoms numbered and dihedral angles τ_1, τ_2, and τ_3 labeled ($\tau_1 \equiv N_{41}$–C_{37}–C_{36}–C_7, $\tau_2 \equiv C_{37}$–C_{36}–C_7–C_4, and $\tau_3 \equiv O_{16}$–C_{15}–C_{13}–C_1).

TABLE I
THE GEOMETRIES AND ENERGIES OF THE PROPOSED COMPOUND[1]

Conformer	Piperidine substitution (axial versus equatorial)			Average geometry[2] (degrees)			E[N3]–E[N1] (kcal/mol)		Shift in tautomeric preference (kcal/mol)	Hydrogen bond?[3]
	Methyl	Amide	Imidazole	τ_1	τ_2	τ_3	Neutral	Cation		
Histamine	–	–	–	–	–	–	0.14	−8.39	8.53	
							1.15	−10.26	11.41	
A	e	e	e	109	−59	−73	0.01	−5.95	5.96	
							1.24	−7.34	8.59	
B	e	e	e	32	−140	75	−0.53	−9.33	8.80	
							0.15	−9.97	10.11	
C	e	e	e	−70	−60	76	−0.41	−8.09	7.68	
							0.24	−8.82	9.06	
D	e	e	e	−134	−146	74	−0.37	−9.41	9.04	yes
							0.82	−10.08	10.91	
E	a	e	e	100	−74	−72	−0.52	−6.11	5.59	
							0.33	−7.48	7.81	
F	a	e	e	64	−172	74	0.10	−10.92	11.02	yes
							0.94	−14.49	15.43	
G	a	e	e	−51	−158	76	−0.53	−11.25	10.72	yes
							0.85	−15.24	16.08	
H	a	e	e	−138	−173	74	−0.97	−11.25	10.28	
							−0.64	−15.24	14.60	
I	a	e	e	−73	−70	76	0.35	−8.22	8.57	
							1.26	−9.47	10.73	
J	e	a	e	111	−61	−51	−0.02	−7.86	7.88	yes
							1.26	−8.96	10.22	
K	e	a	e	106	−79	−67	0.19	−7.86	8.05	yes
							2.84	−8.96	11.80	
L	e	a	e	−69	−72	−71	−0.21	−8.54	8.32	yes
							0.41	−8.90	9.32	

[1] See Fig. 4 for the numbering of the atoms and the definitions of the dihedral angles τ_1, τ_2, and τ_3. The first set (i.e., the first row) of energies for each conformation are the MNDO//MNDO values and the second set corresponds to the STO-3G//MNDO calculations.

[2] $\tau_1 \equiv N_{41}$–C_{37}–C_{36}–C_7, $\tau_2 \equiv C_{37}$–C_{36}–C_7–C_4, and $\tau_3 \equiv O_{16}$–C_{15}–C_{13}–C_1. The values of the dihedral angles τ_1, τ_2, and τ_3 reported in this table were obtained by averaging those of the structures representing the same conformer; i.e., for some conformation sets, all four species (neutral and protonated N1 and N3 tautomers) were not necessarily included in the calculation of the average because at least one of them may be equivalent to a conformation in another set.

[3] D, F, and G have intramolecular hydrogen bonds between N_{41} and H_{47} in the N3 cationic form. J, K, and L have intramolecular hydrogen bonds between O_{16} and H_{47} in the N3 cationic forms. A hydrogen bond between O_{16} and H_{47} also exists in the N1 cationic form of L.

neutral form of histamine serves as the model for histamine at the receptor, following neutralization of the side chain. Later studies, simulating an actual proton-relay process induced by a neutralizing group (OH^-), confirmed that the calculated tautomeric preference serves as an adequate indicator of the proposed tautomeric shift [6]. For the present study, we again use these differences in tautomeric preference as a test of the proposed mechanistic model. In Table 1, we present the results of structural optimizations (at the MNDO level) of neutral and cationic forms of the N1 and N3 tautomers of our model compound at various conformational minima (the corresponding results for histamine are also included). Two sets of energies are reported for every entry in Table 1, i.e., the MNDO//MNDO and STO-3G//MNDO energies. Previous calibration studies of the tautomeric shifts in histamine indicate that the MNDO//MNDO calculations are in good qualitative agreement with the ab initio STO-3G//STO-3G results, while the STO-3G//MNDO calculations are in good quantitative agreement with the STO-3G//STO-3G results [21]. In the remainder of the discussion, we will therefore refer to the STO-3G results in Table 1.

We note that the methyl, amide, and imidazole substituents of the piperidine ring can each assume either equatorial or axial positions. Accordingly, the various local minima presented in Table 1 are designated by the piperidine substitution of these groups. The various substitution patterns are designated by, e.g., eee for equatorial methyl, amide, and imidazole, with similar names for the other structures. eee corresponds to the conformation of LSD. It should be noted that the piperidine nitrogen atom is easily inverted, i.e., eee and aee are interconvertible. We have therefore included the aee structures herein. eae structures have also been included although they are not interconvertible with eee structures. Note that the presumably high-energy eea, aea, eaa, and aaa conformations were excluded from this study. Other major conformational features, i.e., the conformational angles τ_1, τ_2, and τ_3 (see Fig. 4), and the existence of intramolecular hydrogen bonds, are also indicated in Table 1.

The first entry in Table 1, having the methyl, amide, and imidazole groups all in equatorial positions (eee) corresponds most closely to that of LSD. This set of structures prefers the N1 tautomer by 1.24 kcal/mol in the neutral form and prefers the N3 tautomer by 7.34 kcal/mol in the cationic form, i.e., a 'tautomeric shift' of 8.59 kcal/mol (at the STO-3G//MNDO level). This is similar to the corresponding value of 11.41 kcal/mol for histamine. Thus, in the LSD-like conformations, the LSD-like compound would be expected to undergo the appropriate shift in tautomeric preference postulated to be necessary for activation of the H_2 receptor. Previous studies of histamine in this model have suggested that histamine would undergo this shift in tautomeric preference while its side chain assumes an extended conformation. Two of the other eee sets of structures (B and D) have similar conformations for τ_1 and τ_2. They too have a shift in tautomeric preference of 10.11 and 10.91 kcal/mol, respectively, which are similar to that of histamine. There are also three groups of aee structures (F, G, and H) for which the appropriate tautomeric shift is observed (15.43, 16.08, and 14.60 kcal/mol, respectively). In fact, for any set of structures within a set of conformations in Table 1, the tautomeric shift occurs.

It is also worth noting that six of the conformational sets (D, F, G, J, K, and L) contain structures with intramolecular hydrogen bonds. In sets D, F, and G, there is a hydrogen bond between N_{41} and H_{47} (see Fig. 4 for labeling) in the cationic tautomer corresponding to N3 of histamine. This results in an additional stabilization of this cationic form. The tautomeric shifts for these entries tend to be larger than those for the other entries in Table 1, i.e., 14–16 kcal/mol as opposed to 8–12 kcal/mol. However, while the tautomeric shift is somewhat larger, the result is qualitative-

ly the same. The analogous situation clearly exists with histamine and has been previously discussed [5–8,18,21]. This intramolecular hydrogen bond involves direct interaction with the imidazole group which is central to the activation model. The second type of intramolecular hydrogen bond observed in sets J, K, and L, takes place between O_{16} and H_{47} in the cationic (and/or neutral) states corresponding to the N3 tautomer of histamine. In these instances, both the qualitative and quantitative tautomeric shifts are similar to those for structures without intramolecular hydrogen bonds.

In Table 2, we examine the results where the lowest-energy conformation is used for each state (neutral, cationic, N1, N3). The results for the axial and equatorial positions of the methyl group on the piperidine ring were combined because of the ease of inversion of the piperidine nitrogen atom; all entries in Table 2 are derived from calculations in which the positions (axial versus equatorial) of the other piperidine substituents are not varied. For each of these sets of structures (eee, aee, and eae) we again find the analogous shift in tautomeric preference. Finally, the last set of entries in Table 2 corresponds to the results obtained when the lowest-energy structure is used for each state, regardless of the conformation; again, the same tautomeric shift is found. This last entry is somewhat artificial as it involves both chair (first row) and boat (second row) forms of the piperidine ring which are not interconvertible.

The qualitative results are quite clear. Regardless of the conformation, or group of conformations used, a shift in tautomeric preference is observed for the model compound which parallels that of histamine. The use of the different conformational structures only affects the magnitude of the shift. Thus, the compound proposed herein could serve in a manner similar to that of histamine in the proposed process ascribed to an activation model. Coupled with the observation that the recognition elements of the proposed compound, as indicated through similarities in the

TABLE 2
MNDO//MNDO AND STO-3G//MNDO CALCULATIONS OF THE SHIFT IN TAUTOMERIC PREFERENCE USING THE LOWEST-ENERGY CONFORMATIONS OF THE PROPOSED H_2-RECEPTOR AGONIST

Piperidine substitution (axial versus equatorial)			E[N3]–E[N1] (kcal/mol)[a]				Shift
Methyl	Amide	Imidazole	Neutral		Cationic		(kcal/mol)
e/a	e	e	−0.156	(2C-2G)	−10.924	(2D-2B)	10.768
			0.236	(2C-2C)	−14.471	(2D-2C)	14.707
e	a	e	−0.082	(3C-3B)	−7.858	(3C-3B)	7.776
			0.514	(3C-3B)	−8.904	(3C-3C)	9.418
Substitution ignored			−0.156	(2C-2G)	−9.178	(2D-3B)	9.022
			0.236	(2C-2C)	−13.911	(2D-3C)	14.147

[a] The two lines of data for each piperidine substitution pattern (see the previous table) correspond to the MNDO//MNDO and STO-3G//MNDO calculations, respectively. The symbols in parentheses correspond to the conformation set (see supplementary material) from which the neutral or protonated tautomers were selected. Note that the lowest STO-3G energies may not necessarily be associated with the lowest-energy (MNDO) conformations derived from the geometry optimizations.

MEPs, agree with those of histamine, the proposed compound should provide an interesting candidate for testing the histamine-H_2 receptor model for agonists reviewed herein.

Supplementary material available

Tables of all of the structural parameters obtained at the MNDO level and total energies at the MNDO//MNDO and STO-3G//MNDO levels for the model structure are available from the authors.

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