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A Density Functional Based Molecular Surface Electrostatic Potentials of Histamine H1-Agonists

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Abstract: A computational analysis of the electrostatic potentials of nine histamine H1 agonists of various structural modifications has been carried out at the *density functional B3P86*/6-31G** level of theory. It focuses upon the relationships between these potentials and the H1-agonistic activities of the molecules through identifying any common features. Analysis of several statistically based properties of the surface potentials has revealed that H1-Agonism is a linear function with of the potential's maxima, $V_{S,\max}$, the averages of the positive values on the surface, $\bar{V}_S^+$, and the average potential over the entire surface, $\bar{V}_S$. The statistical parameters for this linearity has been found as $R^2 = 0.999$, $R_{cv}^2 = 0.998$, F = 683.200, and standard error = 2.188. The reached correlation has been used to predict the activities of three H1 agonists, where the results revealed correct trend of agonism, if not the numerical values.

Keywords: histamine; H1-agonist; surface electrostatic potential; DFT, B3P86

Introduction

Histamine belongs to a group of most important biological amines and plays an essential role both in regulation of many physiological functions and in development of a number of serious pathological states. Histamine exerts its effects by activating histamine receptors, of which four subtypes (H1, H2, H3 and H4) are recognized. Specific activation or blockade of these receptor subtypes has led to a tremendous increase in the knowledge of the roles of histamine in physiology and pathology and the mechanisms involved.[1]

H1- agonists are drugs that bind to and activate histamine receptors. Such compounds are of importance for fundamental research on the function of H1 receptors in several physiological and pathophysiological conditions. Although, for therapeutic application, potent and specific H1 agonists do not seem to have any role, such compounds are of importance for fundamental research on the function of H1 receptors. The interaction of a histamine H1 agonist with a receptor is a bimolecular recognition process, where each of them is expected to have a key feature promoting their mutual reception.

The H1 agonists are all closely related to the histamine structure (1) and some rules have been derived for their H1 activity. Thus an H1 agonist consists of an aromatic system with an unsubstituted nitrogen atom at the position adjacent to an ethylamine side chain. This ethylamine group is preferably a primary amine.

Efforts have been made to modify both constituents in order to improve agonistic activity. Modifications in the ethylene side chain of histamine have not revealed interesting H1 agonists. Methylation of the alpha or beta position leads to reduction of H1 activity.[2] Methylation of the amino group of histamine

yields an active H1 agonist as well. Alkylation with higher alkyl groups leads to a strong decrease in H1 agonistic activity.[3] Replacement of the aminoethyl side chain by more rigid moieties also causes a strong decrease in activity.[4] However, modifying the imidazole ring has developed the most potent and selective H1-agonists known thus far.[2-5] In a previous work we presented a research paper employing QSAR and MSEP to seek a correlation between the several computed descriptors and the agonistic activities of the modified histamines imidazole rings.[6]

The electrostatic potential V(r) created in the space around a molecule by its nuclei and electrons is well recognized as a mean for the clarification of molecular reactive behavior, such as electrophilic, nucleophilic and recognition interactions.[7-10] V(r) is defined by eq. (1),[11] where Z_A is the charge on nucleus A, located at $\mathbf{R}_A$. The sign of $V_{(\mathbf{r})}$ at any point **r** is the net result of the positive and negative contributions of the nuclei and electrons.

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r' - r|} \qquad (1)$$

Politzer *et al* has introduced several statistically defined quantities that explicitly reflect the magnitude of V(r) at each point on the surface.[11-12] It was shown that different subsets of these quantities can be used to develop analytical representations of good accuracy for a variety of solution, liquid and solid phase properties that depend upon noncovalent interactions. Also, this approach was extended to interactions in biological systems, such as anticonvulsant drugs and HIV (human immunodeficiency virus) enzyme inhibitors.[13]

Another group of likely prospects is the average potential over the entire surface, $\bar{V}_S$, and the averages of the positive and negative values, $\bar{V}_S^+$ and $\bar{V}_S^-$,[11]

$$\bar{V}_S = \frac{1}{n}\sum_{i=1}^{n} V_S(r_i) \qquad (2)$$

$$\bar{V}_S^+ = \frac{1}{\alpha}\sum_{j=1}^{\alpha} V_S^+(r_j) \qquad (3)$$

$$\bar{V}_S^- = \frac{1}{\beta}\sum_{k=1}^{\beta} V_S^-(r_k) \qquad (4)$$

$\bar{V}_S$ has not proven to be quite similar for most molecules and therefore not very useful. Of much greater importance has been the average deviation from $\bar{V}_S$, which is Π :

$$\Pi = \frac{1}{n}\sum_{i=1}^{n} \left| V_S(r) - \bar{V}_S \right| \qquad (5)$$

Obviously, Π is size-independent. It is an index of the internal charge separation that is present even in molecules that have zero dipole moments. It has been effectively correlated with various empirical measures of polarity.[14]

The total variance, σ_{tot}^2, and its positive and negative components are other quantities that measure the level of charge separation in a molecule with the advantage of being more sensitive than Π to the extremes of $V_S(\mathbf{r})$.[15]

$$\sigma_{tot}^2 = \sigma_+^2 + \sigma_-^2 = \frac{1}{a}\sum_{j=1}^{\alpha}\left[V_S^+(r_j) - \bar{V}_S^+\right]^2 + \frac{1}{\beta}\sum_{k=1}^{\beta}\left[V_S^-(r_k) - \bar{V}_S^-\right]^2. \qquad (6)$$

$\sigma_+^2, \sigma_-^2, and\ \sigma_{tot}^2$ reflect the spreads of values of the positive, negative, and total surface potentials.

Due to the squared terms in Eq. (6), σ_{tot}^2 covers a much larger range than does Π; this can be seen in Table I, which lists our computed surface quantities for the H1 agonists. Although there is an element of similarity in their definitions, Π and σ_{tot}^2 describe distinctly different aspects of the surface potential.

Computational Method

The objective in this paper has been to use the computed V(**r**) as a tool for comparing and analyzing a group of differently modified histamine H1-agonists. Therefore, the concern here is not with the potential throughout the space around a molecule but rather with its pattern on the molecule's surface. Hence we aim at qualitatively analyzing the electrostatic potentials on the molecular surfaces of **1-9** in terms of relative patterns of positive and negative regions.

For this purpose, the electrostatic potentials V(**r**) of optimized molecules 1-9 were computed at the B3P86/6-31G** level[16-17], using the Gaussian programs.[18] The surface was defined according to Bader et al.,[19] as the 0.001 electrons/bohr^3 contour of the electronic density ρ(**r**). This surface potential was then characterized by means of several statistical quantities that reflect its physically-meaningful features. They are given by eqs. (2) – (6), and include potentials' most positive and negative values, $V_{S,max}$ and $V_{S,min}$, the average absolute deviation, Π, and the variances, σ_{tot}^2.

The statistical analysis package; SPSS for windows[20] is then employed to seek the subset of computed quantities to which the molecules' **1-6** known experimental H1-agonist activities fit. This approach can be expressed conceptually in terms of a general function as in eq. (7).

HistamineH1-agonism=

$$f\left[V_{S,\min}, V_{S,\max}, \bar{V}_S^{+}, \bar{V}_S^{-}, \Pi, \sigma_+^2, \sigma_-^2, \sigma_{tot}^2, A_S^+, A_S^-\right]. \quad (7)$$

Results and Discussion

Examples of the molecular surface electrostatic potentials of **1-9** are shown in Figure 2 for histamine **1**, 2-(1H-imidazole-4-yl)-N-methylethanamine **2**, 2-(2-thiazolyl) ethanamine **4**, and 2-(3-Bromophenyl)histamine **6**. The computed surface properties of **1-9** are presented in Table 1 along with the experimental histamine H1 agonism taken from reference.[21] Similarly to our previous study,[6] the most positive potentials (blue regions) are associated with amine hydrogens in the imidazole ring (H1) while the most negative (red regions) are due to nitrogen lone pairs of the aminoethyl side chain.

Table I shows that there is no systematic variation among the computed quantities, where out of nine molecules, four molecules have $A_S^+ > A_S^-$, eight molecules have $\left|\bar{V}_S^{-}\right| > \bar{V}_S^{+}$, and six molecules have $\sigma_-^2 > \sigma_+^2$, and $\left|V_{S,\min}\right| > V_{S,\max}$. Also, there is a considerable range of sizes, the surface areas being between 155 and 264 Å^2.

The strongest positive potentials, with $V_{S,max}$ between 25.0 and 56.6 kcal/mole, are produced by amine hydrogens. However there are no such hydrogens in **4, 5,** and **9**, and their $V_{S,max}$ are consequently much weaker, between 25 and 29.6 kcal/mole. These three molecules also have among the lowest σ_+^2 indicating that the positive regions on their surfaces are relatively weak.

On the other hand, the negative surface regions, while less extensive in area, are much more uniform in strength. The $V_{S,min}$ are all within a relatively narrow range, –37.8 to –44.9 kcal/mole, as are the σ_-^2, 69.9 to 153.8 (kcal/mole)^2; in contrast to the σ_+^2 which are between 33.8 and 146.0 (kcal/mole)^2. Therefore, as before, it may be logical to say that the negative potentials are of primary importance in histamine H1 agonist activity.

The local polarity, Π, in table 1 is above the usually reported values,[22-23] where its values are between 10 and 15.3 kcal/mole. This suggests that the internal charge separations in molecules 1-9 are significant and there is a need for a substantial extent of hydrophilic character.

Using SPSS three correlated equations of the best one-, two-, and three-, computed statistically derived quantities were produced. The mathematical details of these equations are presented in Table 2, where the correlation coefficient, R^2, measures the fit of the regression equation, while R_{cv}^2 is the corrected correlation coefficient, F is the Fisher test value which reflect the ratio of the variance explained by the model and the variance due to the error in it, and s^2 is the standard deviation of the regression.

$$\text{H1-Agonism} = -64.263 + 2.806 * V_{S,\max} \quad (8)$$

$R^2 = 0.858$, $R_{cv}^2 = 0.822$, F = 24.064, std. error = 18.708

$$\text{H1-Agonism} = -144.135 + 1.666 * V_{S,\max} + 11.027 * \bar{V}_S^{+} \quad (9)$$

$R^2 = 0.971$, $R_{cv}^2 = 0.951$, F = 49.021, std. error = 9.859,

$$\text{H1-Agonism} = -151.966 + 2.788 * V_{S,\max} + 7.875 * \bar{V}_S^{+} + 17.399 * \bar{V} \quad (10)$$

$R^2 = 0.999$, $R_{cv}^2 = 0.998$, F = 683.200, std. error = 2.188,

Obviously, the three eqs. (8-10) correlate the histamine H1 agonism with the maximum potential on the molecular surface, $V_{S,\max}$, the averages of the positive potential values, $\bar{V}_S^+$, and the average potential over the entire surface, $\bar{V}_S$. The positive coefficient of $V_{S,\max}$ in each of the correlations indicates a systematic linear proportional relation between $V_{S,\max}$ and H1 agonism. The close values of R^2 and R_{cv}^2 indicates a good stability of the model in eq. (10).

The unavailable values of H1-agonism for structures **7**, **8**, and **9** were calculated according to eq. (10), and found to be 85.1, 76.4, and 56.7 respectively. Being smaller than the agonism of histamine molecule itself (100), these values agree qualitatively if not quantitatively with what has been reported in literature.

Conclusion

In the present study, the mapped electrostatic potential on the surfaces of 9 histamine H1-agonists have been correlated with statistically derived quantities from the potential. Potentials' most positive value, $V_{S,\max}$ has showed significant role in expressing the agonism quantitatively through the relation *H1-agonism*= $f\left[V_{S,\max}, \bar{V}_S^+, \bar{V} \right]$. The density functional B3P86 is a good level of theory to be employed to computationally investigate the biophysical applications.

Figure 1: Structures of histamine H1-agonists.

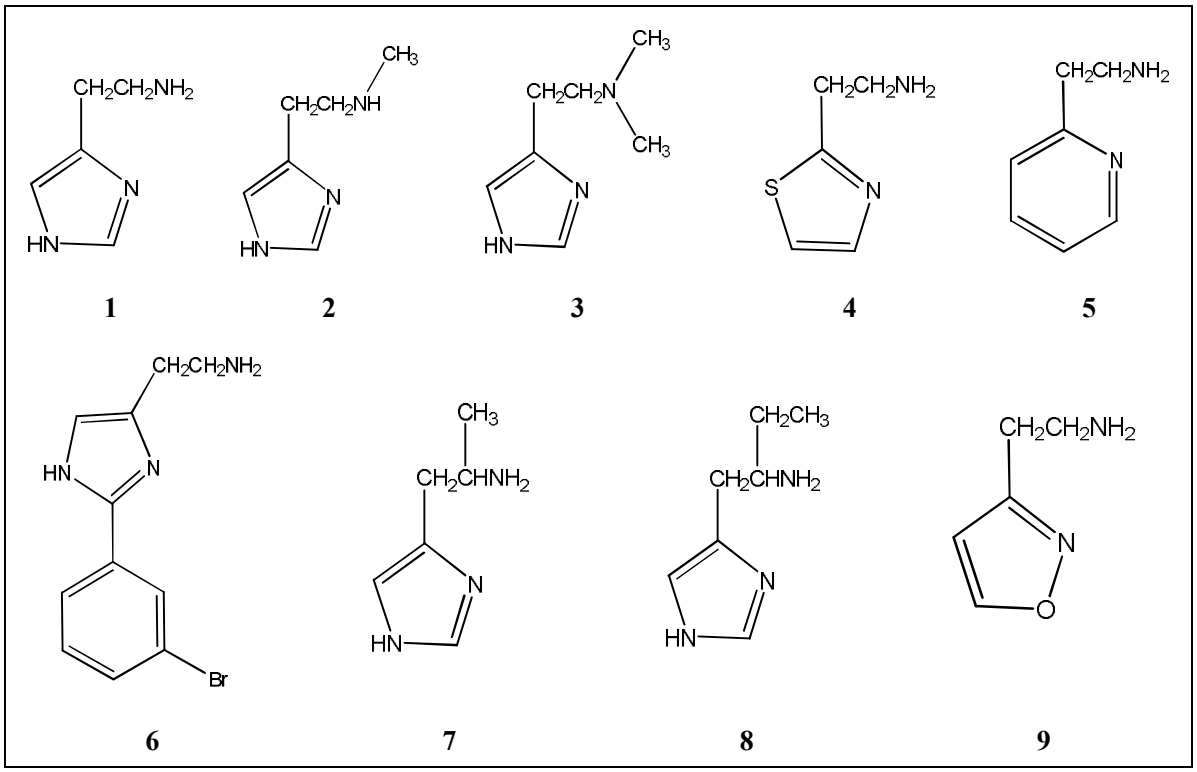

Table 1: Computed Surface Quantities as in eqs. (1-6)] at B3P86/6-31G**

hist	Exp Ago.	Calc Ago.	A	A_S^+	A_S^-	$\bar{V}$	$\bar{V}_S^+$	$\bar{V}_S^-$	$V_{S,\min}$	$V_{S,\max}$	Π	σ_{tot}^2	σ_+^2	σ_-^2
1	100.0	98.1	158.20	80.73	77.48	-0.59	14.38	-16.18	-44.81	52.75	15.28	286.94	135.65	151.29
2	72.0	73.7	178.33	84.01	94.33	-1.09	12.52	-13.21	-43.79	52.39	12.87	282.73	145.98	136.75
3	56.4	55.4	194.43	93.12	101.31	-1.12	10.29	-11.60	-43.44	52.30	10.98	269.40	144.86	124.54
4	11.2	10.5	163.46	94.21	69.25	0.98	9.59	-10.72	-43.26	25.07	9.95	145.28	33.81	111.47
5	5.6	6.2	173.94	96.87	77.08	0.34	10.28	-12.16	-41.78	25.59	11.08	144.48	34.24	110.24
6	112.2	113.2	264.08	118.80	145.28	-0.7	13.78	-11.40	-43.13	56.62	12.46	190.17	120.29	69.88
7	--	85.1	174.05	83.48	90.57	-0.93	13.63	-14.34	-44.89	52.33	13.98	286.68	132.85	153.82
8	--	76.4	192.97	91.98	100.99	-0.85	12.36	-12.87	-44.65	52.29	12.62	281.38	130.99	150.39
9	--	56.7	154.79	92.35	62.44	1.36	13.01	-15.86	-37.77	29.62	13.94	180.87	58.62	122.25

$units. A_S^+, A_S^-$ *are in* A^2; $\Pi, V_{S,\min}, V_{S,\max}, \bar{V}_S^+$, *and* $\bar{V}_S^-$ *are kcal/mol, and* σ_+^2, σ_-^2, *and* σ_{tot}^2 *are in* $(kcal/mol)^2$.

Exp Ago, and Calc Ago are experimental and calculated histamine H1 agonisim

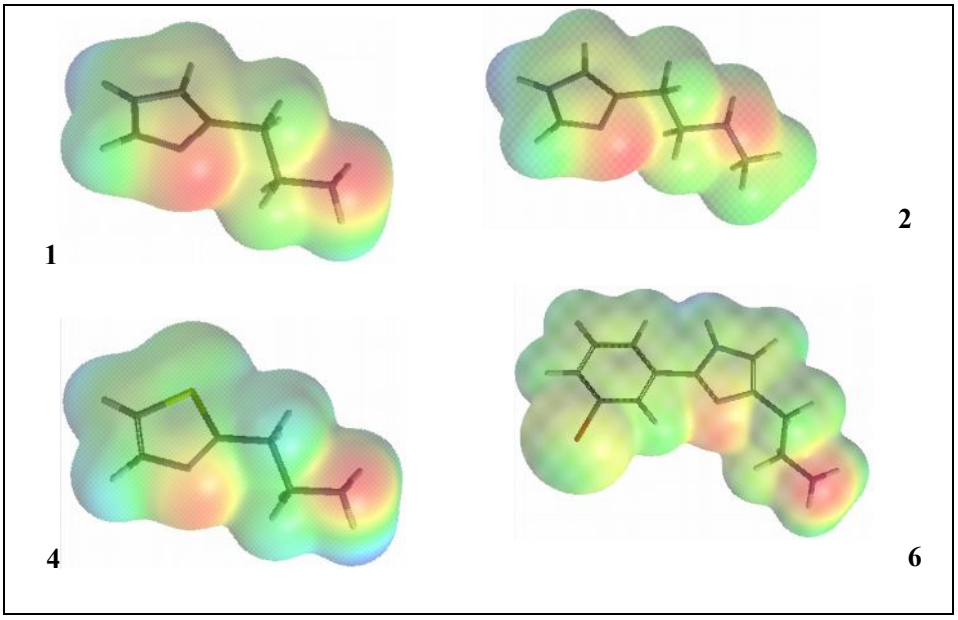

Figure 2: Computed electrostatic potential on the molecular surface of histamine H1 agonists (1, 2, 4, 6) optimized at B3P86/6-31G. The potential ranges according to the color code: red (most negative) < orange < yellow < green < blue (most positive).**

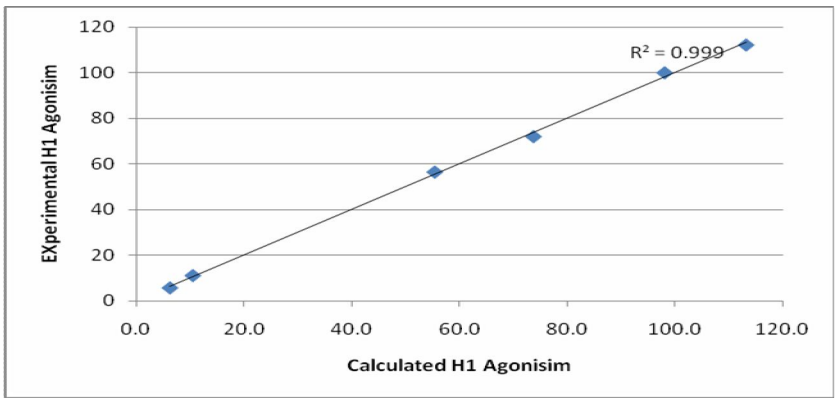

Figure 3: Comparison of experimental and calculated histamine H1-agonism from the regressional analysis in eq. (10). R^2 = 0.999, R^2_{cv} = 0.998, F = 683.200, std. error = 2.188

Table 2: Linear correlations of histamine H1-agonism as in eqs. (8-10)

Model	R^2	$R^2_{adjusted}$	Coefficients	F	S^2
constant $V_{S,\max}$	0.858	0.822	-64.263 2.806	53.562	18.694
constant $V_{S,\max}$ $\bar{V}_S^+$	0.971	0.951	-144.135 1.666 11.027	56.203	9.807
constant $V_{S,\max}$ $\bar{V}_S^+$ $\bar{V}^-$	0.999	0.998	-151.966 2.788 7.875 17.399	110.200	2.163

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