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A Computational Study of Histamine H1-Receptor Agonist Activity Using QSPR and Molecular Surface Electrostatic Potential

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Abstract: The activity of 12 human and guinea pig histamine H1-receptor agonists are investigated computationally. The mapped electrostatic potentials on the molecular surfaces of each of the structures are analyzed at HF/3-21G level of theory to identify any common features that possibly relate to their subsequent agonistic activities. Statistically derived quantities including potential's minima $V_{S,min}$, maxima $V_{S,max}$, molecular volume, surface area, ε_{HOMO}, and ε_{LUMO} energies were computed. Analysis concluded that both V_{max}, and ε_{HOMO} are of prime significance in the agonist activity. For the same set of agonists, hundreds of calculated descriptors at HF/3-21G* level of theory using CODESSA package followed by analysis of the multiple linear regression techniques, where several models of three to five parameters were produced. All QSPR models were investigated using full cross-validated R^2_{cv} and leave one-out cross-validation. Among the attained models of correlation is a four- and five-parameter equations with $R^2 = 0.995$ and 0.999, and 0.974 and 0.993, $R^2_{cv} = 0.974$ and 0.993, and 0.933 and 0.986 for human and guinea pig histamine H1-receptor agonists respectively. The CODESSA-based models can be useful for the prediction of the activity of the histamine H1-agonists.
Keywords: histamine; H1-agonist; surface potential; HF; Codessa; QSPR.

Introduction

Histamine is a biogenic amine chemical which is produced by a specific type of white blood cell, and mast cells in response to foreign pathogens in the body. It assists in immune response and acts as a neurotransmitter, besides regulating physiological and biological functions in the body such as digestion, orgasm, and sleep.[1]

Chemically, two major structural constituents can be distinguished in the histamine molecule; the imidazole ring and the aminoethyl side chain. Histamine exerts its effects by activating histamine receptors, of which four subtypes have been classified and designated H1 through H4.[2] 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.[2-4]

The histamine H1 receptors are considered the classical histamine receptor, where they are found throughout the whole body, specifically; on the smooth muscle tissue of the internal organs, the endothelium lining blood vessels, and central nervous system tissue. The interaction of histamine with these H1 receptors results in hives, itching and swelling due to insect bites and similar allergic reactions, and allergic rhinitis, or cold-like symptoms due to allergic reaction.[5]

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. Several modifications in histamine's imidazole ring and/or the aminoethyl side chain have been reported to obtain active H1 agonists and led to a strong decrease or complete loss of its activity.[6-8]

In order to improve agonistic activity, efforts have been made to modify the structures of so far effective molecules. While modifications in the ethylene side chain of histamine have not produced promising H1 agonists, modifying the imidazole ring has developed the most potent and selective H1-agonists known thus far.[9]

The interaction of a histamine H1 agonist with a receptor is an example of a bimolecular recognition process, in which the H1 agonist recognizes that the histamine has certain key features that will promote their relation. Such key features have often been identified through the analysis of the electrostatic potential $V_{(r)}$ that

is created in the space surrounding a molecule by its nuclei and electrons. It is through this potential that a molecule interacts with other systems in its vicinity. The affinity of a particular molecule for a specific receptor has been shown in a number of cases to depend upon the degree to which the electrostatic potential of the former possesses certain characteristics that have been established as being necessary for effectively interacting with that receptor.[10-12]

CODESSA (comprehensive descriptors for structural and statistical analysis) represents a QSPR approach that computes hundreds of structural parameters using the constitutional, topological, geometrical, electrostatic, and quantum chemical descriptors of the chemical compounds.[13-14] The computed descriptors are used to develop multi-linear regression (MLR) models of the investigated property. CODESSA was successfully employed in QSPR studies in variety of applications.[15-18]

In the present investigations, we utilize a QSPR model that uses theoretical descriptors of the chemical structure. All QSPR and QSAR models are based on the assumption that the properties of a substance, like the physicochemical behavior, reactivity, or biological activity, are ultimately determined by its molecular structure. To correlate the molecular structure and properties, the chemical compounds must be adequately characterized with structural descriptors.

Our objective here has been to use the molecular electrostatic potential $V_{(\mathbf{r})}$ as a tool for comparing and analyzing a group of human and Guinea Pig histamine H1 agonists. All of them exhibit H1 agonistic activity to varying degrees.[3] Our approach has been to qualitatively analyze the electrostatic potentials on the molecular surfaces of **1-12** in terms of relative patterns of positive and negative regions. Therefore, the focus here is primarily upon the most positive and most negative values of potentials $V_{S(r)}$, the $V_{S,max}$ and the $V_{S,min}$, respectively.

The electrostatic potential $V_{(\mathbf{r})}$ created in the space surrounding a molecule by its nuclei and electrons is given rigorously by eq. (1), 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. [19]

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

Sites reactive toward electrophiles can be identified and ranked by means of the locations and magnitudes of $V_{S,min}$, while $V_{S,max}$ play an analogous role for nucleophilic attack.[11]

Computational Method

The optimized structures with the Hartree-Fock HF/3-21G* procedure and the Gaussian 03 for windows were properly attributed to their local minima.[20] Local charges, electrostatic potential, local charges at each atom, dipole moment, ε_{HOMO} and ε_{LUMO} were calculated for each of the compounds.

1- Potential surface calculations:

The electrostatic potentials on the molecular surfaces of **1-12** were computed and mapped using eq. (1) at the same level utilizing Spartan 08 package for windows.[21] Following Bader *et al* [22], the surfaces were taken to be the 0.002 au contour of the molecular electronic density, $\rho_{(\mathbf{r})}$. The values of the $V_{S,min}$, $V_{S,max}$, surface area (A^2), molecular volume (A^3) and the polar surface area, PSA (A^2), were calculated.

The Polar Surface Area (PSA) is the surface sum over all polar atoms; O and N. For molecules to act on receptors in the central nervous system through penetrating the blood-brain barrier, PSA should be less than 60 A^2. However, molecules with PSA > 140 A^2 are usually poor at permeating cell membranes.[23]

2- QSPR calculations:

The optimized structures of 12 H1-agonists **(1-12)** were analyzed by the CODESSA program to exploit constitutional, topological, geometrical, electrostatic, and quantum mechanical descriptors. The CODESSA heuristic method (HM) was then employed to the dataset looking for a pre-selection step for the many available descriptors and to select the rough starting regression models.

Starting from computing all possible one-parameter regression models, a stepwise addition of descriptors is examined to find the best multiparameter regression models with optimal values of the statistical parameters including highest values of R^2, the cross-validated R^2_{cv}, and the Fisher F-criterion value. Descriptors for which values could not be calculated and/or those of low variance in the dataset were discarded.

Results and Discussion

Examples of the molecular surface electrostatic potentials of **1-12** are shown in Figures 1 for histamine (**1**), 2-(3-methylphenyl)histamine (**7**) and 2-(4-Methylphenylthio- methyl)histamine (**12**). In general, the most positive potentials (blue regions) are associated with amine hydrogens in the imidazole ring (H1); the most negative (red regions) are due to nitrogen lone pairs of the aminoethyl side chain. As seen in Figures 1, the local maxima and minima are generally in opposite proximity, on ends of the molecules. The computed surface properties of **1-12** are presented in Table 1 along with the activities of guinea pig H1 agonists (gpH1R) and the human H1 agonists (hH1R) taken from reference 3.

While the imidazole ring is a common element of the molecules, and each molecule contains one to two

of five-, or six-membered rings, there are also significant differences in the computed surface related quantities. There is a considerable range of sizes, the surface areas being between 142 and 277 A^2.

The PSA of these molecules provide additional distinction. As mentioned above, the strongest positive potentials, with $V_{S,max}$ between 268 and 322 kJ/mole, are produced by amine hydrogens (H_1). However, in other systems where no such hydrogens available, their $V_{S,max}$ and PSA were found to be much weaker than the preceding numbers indicating the significance of both quantities.

On the other hand, the negative surface regions, while less widespread in area, are much more consistent in strength. The $V_{S,min}$ are all within a relatively narrow range, –245 to –297 kJ/mole. It may be reasonable to infer that these negative potentials are of primary importance in H1 agonistic activity.

It is interesting to note that the surface electrostatic potentials of the least three active structures, **4, 6** and **12** do not differ dramatically from those of the others, where their relative small H1 agonistic activities may reflect an interaction of several factors. This virtual interaction may also explain the very close agonism of structures **7** and **11** for example, though they yielded different mapped features and computed quantities.

Linear regression analysis was used to estimate the possible correlations of human H1 and pig H1 agonist activities with the MSEP based computed quantities using SPSS for Windows,[24] where V_{max} showed minor correlation with H1 agonism with R^2 of 0.7 in case of gp-ileum and 0.4 in case of gpH_1R.

Employing Codessa based QSAR; several quantities were computed and are displayed in Table 2 for the structures **1-12.** A particularly remarkable note is the repeated similarities among these computed values. The maximum partial charges for both a H, $Q_{max,H}$ and a N atom, $Q_{max,N}$ of each molecule have extrapolated values of 0.05 and 0.09 kJ/mole respectively, with very insignificant differences. Also, the computed polarity of the molecules (except for molecule **16**) shows small changes relating to the substituent itself but not its position, where seven out of 12 structures have a polarity of 0.175. Thus the internal charge separations in these molecules are quite significant.

On the other hand, HM of the descriptor selection implemented in Codessa was utilized, where the attained correlations of the best one-, two-, three-, four-, and five- parameters with the histamine H1-agonists; gpH1R and hH1R, along with their statistical data are displayed in Table 3. In these models, the correlation coefficient, R^2, measures the fit of the regression equation, while, F, the Fisher test value, reflects the ratio of the variance explained by the model and the variance due to the error in it. s^2 is the standard deviation of the regression. The discussion here will focus only on the four- and five-parameter models for each of hH1R and gpH1R, where, the same descriptors were retained in the different correlation models of hH1R, with varying coefficients, while different descriptors were retained in the correlation models for gpH1R.

The four- and five- parameter correlations of the hH1R were given in eq. (2) and eq. (3) respectively, while depicted in Figures 3a and 3b.

$$\text{Agonist}_{(hH1R)} = 14.543 - 635730*P_{\mu} + 2.1869*FHASA + 290.89*SE_{OK} - 83.337*P^2_f \quad (2)$$

$$N=12,\ R^2=0.9946,\ F=320.34,\ s^2=10.13,\ R^2cv=0.9737$$

$$\text{Agonist}_{(hH1R)} = 7.1327 - 635730 * P_{\mu} + 2.1398 * FHASA + 250.33 * SE_{OK} - 75.285 * P^2_f + 1682.2 * HASA \quad (3)$$

$$N=12,\ R^2=0.9989,\ F=1088.67,\ s^2=2.40,\ R^2cv=0.9931$$

$$\text{Agonist}_{(gpH1R)} = 7365.2 - 779110*P_{\mu} - 47093.0*BO_{max,C} + 32.325*YZ_{shadow} + 196.27*\varepsilon_{HOMO-LUMO} \quad (4)$$

$$R^2=0.9728,\ F=62.58,\ s^2=1297.19,\ R^2=0.9333$$

$$\text{Agonist}_{(gpH1R)} = 76809 - 1.6161e+06*P_{\mu} - 38384.0*BO_{max,C} + 33.913 * YZ_{shadow} + 85807.0 * (HACA-1) - 3942.2 * MVCA \quad (5)$$

$$R^2=0.9980,\ F=605.19,\ s^2=110.0837,\ R^2cv = 0.9862$$

It was attention-grabbing that no constitutional, geometrical, or topological descriptors have been driven out in the correlation models of hH1R in eqs. (2), and (3), where each of the two equations has only one electrostatic descriptor while the others are quantum chemicals. Similarly, in eqs. (4), and (5) for the correlation of gpH1R, only one geometrical descriptor has been derived while the rest three or four are quantum chemical descriptors. The lack of a major contribution for electrostatic descriptors in any of the correlation equations is in agreement with the previous investigations using MSEP.

Though the maximum number of descriptors used in the multiple linear regression was set to 5. However, this would not maintain the recommended ratio between the number of descriptor exploited and the available known molecules as 1:5.[25] this may lead to over-correlated equations, primarily in the five-parameter models; eqs. (3) and (5). Therefore. the three- and four-parameter correlations in eqs. (2) and (4) are much more trusted correlations.

In eqs. (2-5), the descriptor P_μ is the minimum atomic orbital electronic population deals with the nucleophilicity of the molecule. P_μ has negative coefficients in all models which imply consistent inverse proportion with H1 agonism. *FHASA* is the fraction of the total molecular surface area associated with hydrogens which can be donated. *HASA* is the hydrogen acceptor dependent surface area. The image of the Onsager-Kirkwood solvation energy (SE_{OK}) is a ratio between the dipole moment of the molecule calculated on the basis of Mulliken charges and its subsequent molecular weight. SE_{OK} is a measure of the polarity of the solvent. The former three descriptors have positive coefficients everywhere in the models implying a direct proportional of hydrogen bonding and polarity on H1 agonistic activities. P^2_f is a measure of the ratio of Polarity parameter to square distance. A negative sign of P^2_f points out that a decrease in its magnitude favors the exhibition of the H1 agonistic activity of the compounds. The electrostatic descriptors, hydrogen bond acceptor charged surface area/total molecular surface area *(HACA-1/TMSA)*, describe the hydrogen bonding donor properties of the compounds.

In eqs. (4) and (5), the maximum bond order of a carbon atom, $BO_{max,C}$ is a valency-related descriptor describes the strength of intramolecular bonding interactions including multipole interactions involving C atom. *YZ Shadow* (YZ_{Shadow}); a geometrical descriptor reflects the shape of the molecule projected onto the planes oriented with respect to its moments of inertia. It has a positive coefficient with subsequent direct proportional with H1 agonist activity. $\varepsilon_{HOMO\text{-}LUMO}$ is the energy gap between the highest occupied molecular orbitals and the lowest unoccupied molecular orbitals which helps to estimate the relative reactivity of the molecules of a given series of compounds.

Several descriptors have a high incidence in the set of 10 correlations presented in Table 3. The minimum atomic orbital electronic population appears in nine correlations. The repeated appearance of HASA related and SE_{OK} the molecular weight descriptors in all hH1R correlations demonstrates that the H1 agonist activity is determined mainly by the tendency of forming hydrogen bonds and by the molecular polarity.

Conclusion:

In the present study, the computed descriptors for 12 histamine H1 agonists have been correlated with their activity in both human and Guinea Pig using Spartan 8, Gaussian 03, and Codessa package. The most negative potential, electrostatic descriptors including potentials minima $V_{S,min}$ showed insignificant role in the H1 agonistic activity. QSPR analysis produced three- to five-parameter equations that could be working properly to predict the potency of unknown H1 agonists. Hydrogen bonding and polarity related descriptors constituted the major variables in the correlated models.

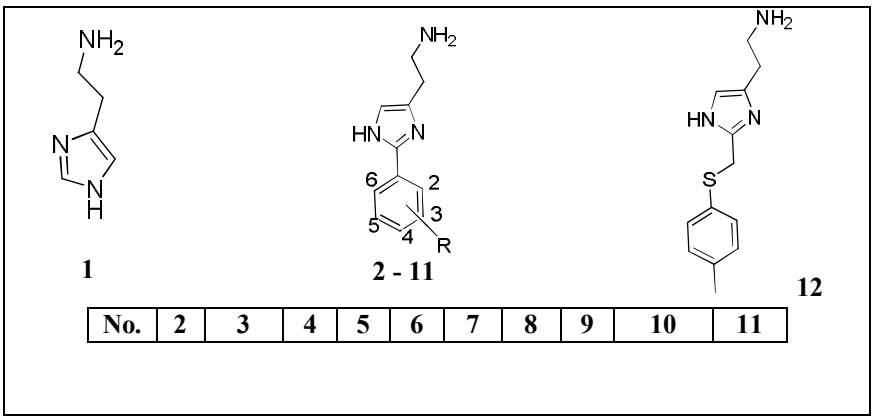

Figure 1: Structures of H1R agonists. 1: histamine; 2-11: 2-phenylhistamine derivatives; 12: thioether compound related to 11.

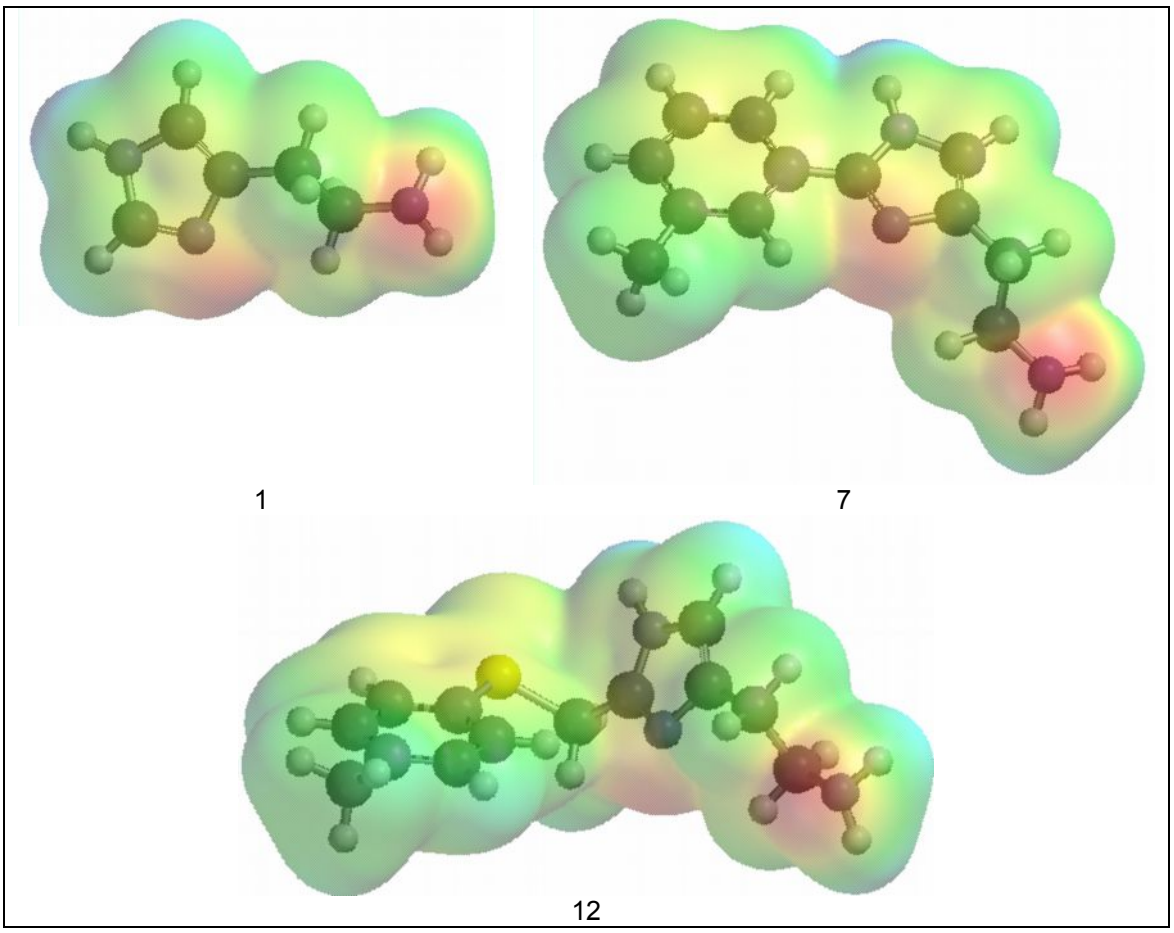

Figure 2: Computed electrostatic potential on the molecular surface of histamine H1 agonists (1, 7, 12) optimized at HF/3-21G*. The potential ranges, in kJ/mole, according to the color code: red (most negative) < orange < yellow < green < blue (most positive).

Table 1: Calculated Statistical related properties to molecular Surface Electrostatic Potential of histamine H1 agonists

	H1 Agonist		MSEP						
sys	gpH1R	hH1R	$V_{S,min}$	$V_{S,max}$	Area	Vol	PSA	ε_{HOMO}	ε_{LUMO}
optimized at HF/3-21G:									
1	100.00	100.00	-272.990	286.922	142.30	122.26	43.58	-832.380	518.439
2	137.50	21.00	-258.384	292.505	218.29	203.87	47.79	-759.131	292.702
3	164.20	17.00	-259.575	288.370	237.62	223.08	50.81	-755.416	297.749
4	28.90	6.60	-297.068	287.783	222.64	206.81	56.54	-786.898	279.552
5	301.40	26.90	-249.019	310.663	222.37	206.58	52.32	-784.125	259.442
6	37.50	5.50	-248.309	308.489	222.40	206.54	49.91	-772.734	281.717
7	271.60	42.40	-248.333	312.580	236.88	222.63	43.46	-784.118	254.626
8	415.10	87.60	-248.470	309.917	241.24	227.33	42.53	-780.996	257.845
9	550.00	83.60	-249.412	310.060	250.78	238.64	43.25	-780.805	255.317
10	366.70	70.20	-260.757	289.710	246.89	231.38	58.34	-759.786	296.396
11	386.00	41.80	-244.800	322.202	248.29	231.10	61.83	-795.701	230.928
12	29.00	7.20	-255.342	267.535	277.02	266.18	50.32	-780.582	377.406

hH1R: potency in human, gpH1R: potency in Guinea Pig, $V_{S,min}$ and $V_{S,max}$: minimum and maximum potentials (KJ/mol), surface area (A^2), molecular volume (A^3), PSA: polar surface area (A^2), ε_{HOMO} and ε_{LUMO}: energy of highest and lowest occupied orbitals (KJ/mol).

Table 2: Calculated Codessa based descriptors for histamine H1 agonists optimized at HF/3-21G*

sys	P_μ	*FHASA*	SE_{OK}	P^2_f	*HACA-1*	MW_R	$Max_{\pi-\pi}$	V_N^{max}	D_T	$BO_{max,C}$	ε_{H-L}	YZ_{shadow}	V_C^{max}	$Q_{max,H}$	$Q_{max,N}$
1	7.00E-05	1.16E-01	1.48E-01	3.70E-03	0.012	6.538	0.945	3.224	4.060	1.634	14.000	21.780	3.969	0.0507	-0.0886
2	1.00E-04	6.02E-02	3.89E-02	3.75E-03	6.63E-03	6.935	0.939	3.232	2.697	1.625	10.884	29.000	3.976	0.0516	-0.0865
3	1.00E-04	5.20E-02	5.49E-02	3.73E-03	5.74E-03	6.709	0.940	3.2322	3.324	1.625	10.866	32.800	3.986	0.0516	-0.0865
4	1.30E-04	6.05E-02	9.35E-02	0.1201	6.50E-03	7.601	0.939	3.2272	4.381	1.627	11.054	28.680	3.969	0.0622	-0.084
5	1.00E-04	5.94E-02	8.42E-02	0.1179	6.51E-03	7.601	0.937	3.235	4.157	1.622	10.817	29.780	3.977	0.0585	-0.0857
6	1.00E-04	5.59E-02	3.33E-02	0.1178	6.16E-03	7.601	0.939	3.231	2.616	1.627	10.929	28.700	3.974	0.0576	-0.086
7	1.00E-04	6.22E-02	1.01E-01	3.76E-03	6.73E-03	8.211	0.937	3.234	4.723	1.623	10.749	31.920	3.994	0.0518	-0.0859
8	0.00E+00	5.55E-02	5.99E-02	3.76E-03	6.06E-03	9.857	0.938	3.233	3.992	1.624	10.783	35.240	4.004	0.0517	-0.0861
9	0.00E+00	5.26E-02	4.93E-02	3.76E-03	5.78E-03	11.598	0.938	3.233	3.929	1.624	10.766	37.820	3.986	0.0516	-0.0864
10	1.00E-04	9.53E-02	7.26E-02	5.61E-03	6.69E-03	7.009	0.938	3.234	3.972	1.623	10.946	32.720	3.976	0.0518	-0.0860
11	1.00E-04	5.70E-02	1.15E-01	4.07E-03	6.15E-03	8.508	0.937	3.233	5.408	1.623	10.641	35.240	3.976	0.1743	-0.0858
12	1.00E-04	3.79E-02	2.90E-02	3.72E-03	7.79E-03	7.275	0.944	3.230	2.680	1.640	12.048	40.761	3.989	0.0515	-0.0868

P_μ: Min atomic orbital electronic population (quantum. mechanical), ***FHASA***: Fractional HASA (HASA/TMSA) [Quant-Chem PC], SE_{OK}: Image of the Onsager-Kirkwood solvation energy, P^2_f: Polarity parameter / square distance, ***HACA***: HACA-1/TMSA [Zefirov's P, MW_R: Relative molecular weight, $Max_{\pi-\pi}$: Max PI-PI bond order, V_N^{max}: Max valency of a N atom, D_T: Tot dipole of the molecule, $BO_{max,C}$: Max bond order of a C atom, ε_{H-L}: HOMO - LUMO energy gap, V_C^{max}: Max valency of a C atom, $Q_{max,H:}$ maximum partial charge for H atom, $Q_{max,N}$: maximum partial charge for N atom.

Table 3*: Statistical parameters and correlated descriptors with histamine H1 agonist in human (hH1R), and guinea pig (gpH1R).

	hH1R						gpH1R					
model	**R^2**	**F**	**s^2**	**R^2cv**	**descriptor**	**cof**	**R^2**	**F**	**s^2**	**R^2cv**	**descriptor**	**cof**
1	0.541	11.8	598.8	0.435	Intercept P_μ	9.4042e+01 -6.1870e+05	0.558	12.6	14757.5	0.458	Intercept MW_R	-4.7418e+02 8.8837e+01
2	0.931	60.7	100.1	0.902	Intercept P_μ FHASA	3.0397e+01 -6.3304e+05 1.0173e+03	0.773	15.3	8432.0	0.628	Intercept P_μ $Max_{\pi-\pi}$	3.6910e+04 -2.5179e+06 -3.8827e+04
3	0.982	145.4	29.4	0.960	Intercept P_μ FHASA SE_{OK}	1.1668e+01 -6.7898e+05 2.3229e+00 2.8930e+02	0.908	26.3	3836.8	0.785	Intercept P_μ V_N^{max} D_T	-8.5875e+04 -2.3879e+06 2.6606e+04 8.5726e+01
4	0.995	230.3	10.1	0.974	Intercept P_μ FHASA SE_{OK} P^2_f	1.4543e+01 -6.3573e+05 2.1869e+00 2.9089e+02 -8.3337e+01	0.973	62.6	1297.2	0.933	Intercept P_μ $BO_{max,C}$ YZ_{Shadow} $\varepsilon_{HOMO-LUMO}$	7.3652e+04 -7.7911e+05 -4.7093e+04 3.2325e+01 1.9627e+02
5	0.999	1088.7	2.4	0.993	Intercept P_μ FHASA SE_{OK} P^2_f HASA	7.1327e+00 -6.3740e+05 2.1398e+00 2.5033e+02 -7.5285e+01 1.6822e+03	0.998	605.2	110.1	0.986	Intercept P_μ $BO_{max,C}$ YZ_{Shadow} HACA-1/TMSA V_C^{max}	7.6809e+04 -1.6161e+06 -3.8384e+04 3.3913e+01 8.5807e+04 -3.9422e+03

- Abbreviations similar to those used in Table 2

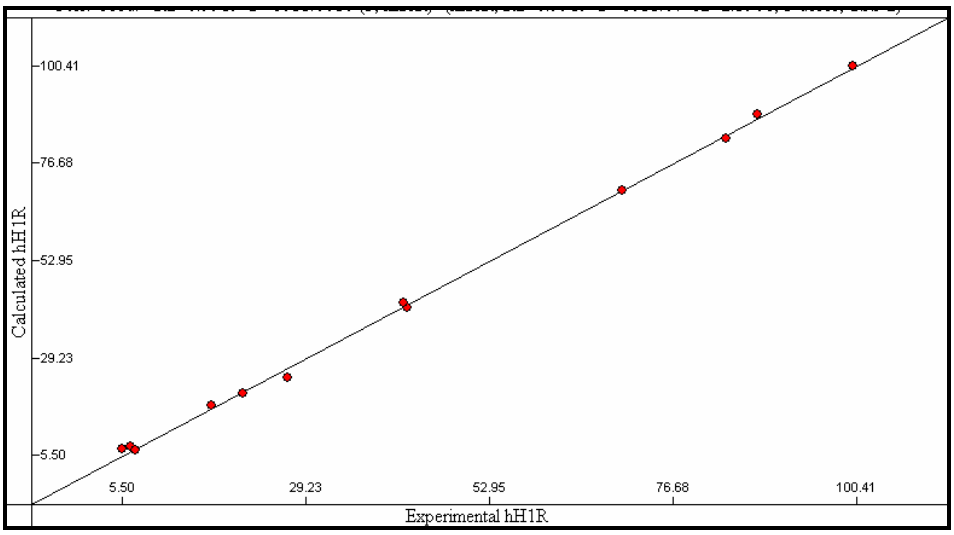

Figure 3a. Correlation of human histamine H1-agonist with calculated descriptors. A plot of the calculated versus observed data for five molecular descriptors from the CODESSA Program. (eq. 3; N= 12, R^2=0.9989, F=1088.67, s^2=2.40, R^2cv=0.9931

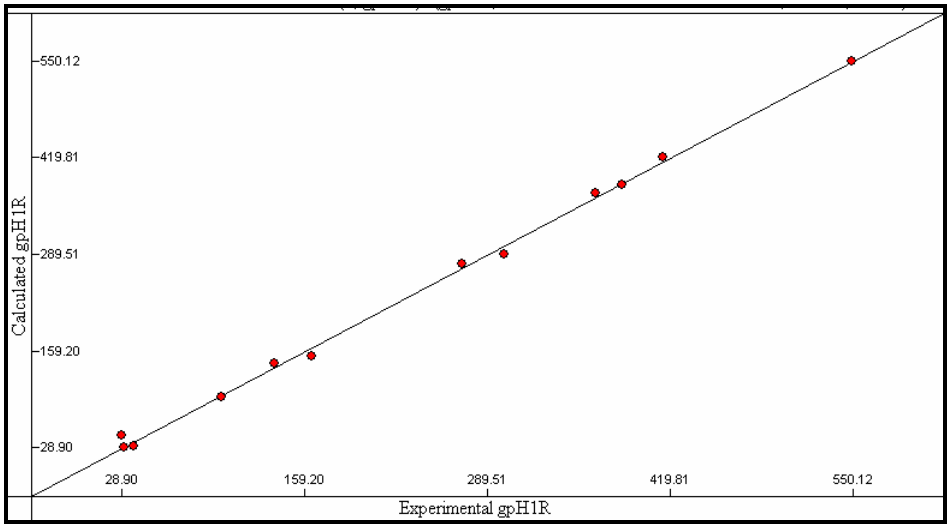

Figure 3b. Correlation of guinea pig histamine H1-agonisim with calculated descriptors. A plot of the calculated versus observed data for five molecular descriptors from the CODESSA Program. (eq. 5; n=12, R^2=0.9980, F=605.19, s^2=110.0837, R^2cv = 0.9862)

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