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A quantum chemical study on a set of non-imidazole H_3 antihistamine molecules

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ABSTRACT

Molecular orbital calculations were carried out on a set of 28 non-imidazole H_3 antihistamine compounds using the Hartree–Fock method in order to investigate the possible relationships between electronic structural properties and binding affinity for H_3 receptors (pK_i). It was observed that the frontier effective-for-reaction molecular orbital (FERMO) energies were better correlated with pK_i values than highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy values. Exploratory data analysis through hierarchical cluster (HCA) and principal component analysis (PCA) showed a separation of the compounds in two sets, one grouping the molecules with high pK_i values, the other gathering low pK_i value compounds. This separation was obtained with the use of the following descriptors: FERMO energies (ε_{FERMO}), charges derived from the electrostatic potential on the nitrogen atom (N^1), electronic density indexes for FERMO on the N^1 atom ($\sum_{(FERMO)} c_i^2$), and electrophilicity (ω'). These electronic descriptors were used to construct a quantitative structure–activity relationship (QSAR) model through the partial least-squares (PLS) method with three principal components. This model generated $Q^2 = 0.88$ and $R^2 = 0.927$ values obtained from a training set and external validation of 23 and 5 molecules, respectively. After the analysis of the PLS regression equation and the values for the selected electronic descriptors, it is suggested that high values of FERMO energies and of $\sum_{(FERMO)} c_i^2$, together with low values of electrophilicity and pronounced negative charges on N^1 appear as desirable properties for the conception of new molecules which might have high binding affinity.

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1. Introduction

Arrang et al. discovered the histamine H_3 receptors in 1983 [1]. Autoradiographic studies showed that in the human brain H_3 receptors are predominantly located in areas associated with cognition, *i.e.*, hippocampus, basal ganglia and cortical center [2]. In these regions, the neurotransmitter histamine associates with other amines synthesized by the human organism (acetylcholine, dopamine, noradrenaline and serotonin) which control some (patho)physiological processes [3]. Investigating the role of the histamine neurotransmitter, it was found that it inhibits its own release [4] and synthesis [5] in the central nervous system (CNS), via interaction with H_3 receptors; histamine also modulates the release of other neurotransmitters [6]. Because of these functions, research into the development of new substances (antagonists) that present inverse performance, has increased, mainly on account of their therapeutic applications in a number of CNS disorders [2,3], such as deficits in learning and memory, Alzheimer's disease, epilepsy, sleep disorders and obesity.

Since the 1980s, efforts have been directed towards the discovery of potent H_3 antagonist ligands. The main structural feature of the first class of ligands was the imidazole ring, which is inherent to histamine, connected to a polar group and a lipophilic residue. However, substances that have the imidazole ring in their structure present an undesirable potential metabolic liability [7–8]. In view of this fact, it is important to identify ligands without this inconvenience, and the latest discoveries of some compounds without the imidazole ring represent a breakthrough in this search. Recent studies [9] show that the number of patents for non-imidazole compounds has overtaken the number of those for compounds with the imidazole ring. This is an indication of the importance of experimental and theoretical studies of this class of compounds in the development of new H_3 receptor antagonists.

A pharmacophore model that has been used in the field of non-imidazole H_3 ligands has the following structural characteristics: (1) two basic character nitrogen atoms, (2) an aromatic ring, and (3) a polar group adjacent to the aromatic ring. A group of compounds that display these characteristics is shown in the general structure represented in Fig. 1(a), which led to the discovery of a potent antagonist (see Fig. 1(b)) [10]. Recently, Dvorak et al. [11] performed a structure activity relationship (SAR) study of two series of antihistamine H_3, with structures similar to the pharmacophore model shown in Fig. 1(a). This study was

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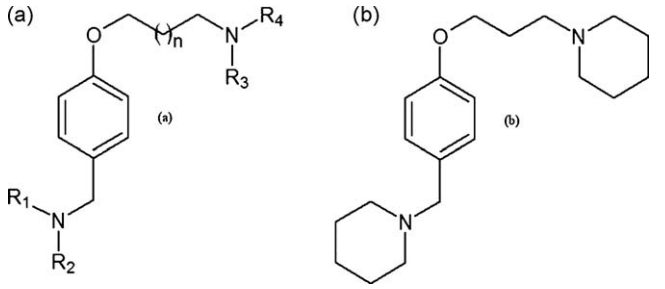


Fig. 1. (a) Structural representation model of a series of 4-(aminoalkoxy)benzylamines which are non-imidazole histamine H_3 receptor ligands; members of this series have alkyl linker ($-CH_2(CH_2)nCH_2-$), an alkylamine group ($-NR^3R^4$), the benzylamine group ($-NR^1R^2$) (chemical structures of alkyl linkers and groups may be found in Ref. [27]); (b) chemical structure of a potent H_3 antagonist (see Refs. [10,27]).

intended to verify the influence of substituent groups in the two nitrogen atoms and to determine whether the 4-hydroxypiperidine group was an appropriate substituent for the propyloxypiperidine moiety, present in the compound shown in Fig. 1(b).

We studied a set of potent non-imidazole H_3 ligands synthesized and characterized by Dvorak et al. [11] in the attempt to evaluate which physicochemical and electronic descriptors might enhance the H_3 histamine receptor binding affinity. A rather novel descriptor is also used: the energies of the frontier effective-for-reaction molecular orbital (FERMO). These values were first introduced and employed by Da Silva et al. [12] to be correlated with pK_a values of carboxylic acids, alcohols and phenols. They suggested that either HOMO or another occupied orbital close to it could be the electron donor for another molecule capable of accepting electrons in its LUMO (see Fig. 2). This option was not discarded by Fukui [13] when commenting on the limitations of the HOMO–LUMO model for electron transfer. Using different methodologies, Fujimoto et al. [14–16] and Hirao and Ohwada [17–20] maintained similar ideas to those of Da Silva et al. [12].

According to Da Silva et al. [12], the choice of the appropriate $HOMO_x$ to be FERMO and thus command the reaction, should obey the following rule: the particular occupied molecular orbital

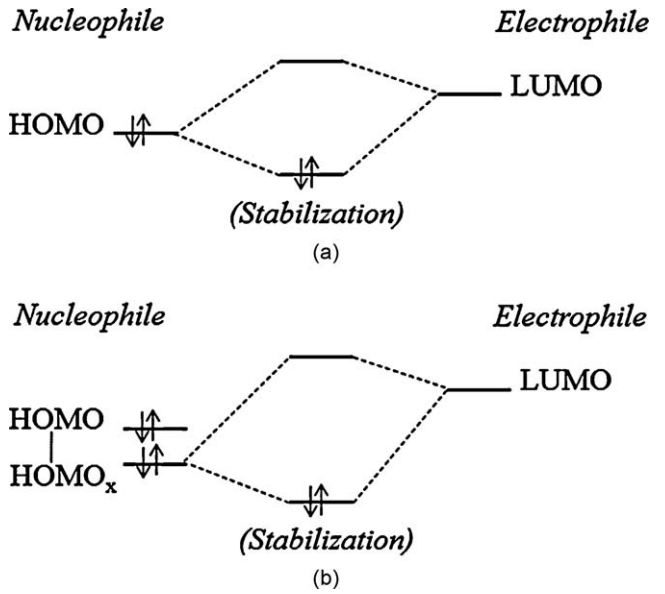


Fig. 2. (a) and (b) are modes of possible molecular orbital interactions between a nucleophile and an electrophile, suggested by Da Silva et al. [12], considering that the HOMO or other occupied molecular orbital ($HOMO_x$) of the nucleophile could be the electron donor to the LUMO of the electrophile.

presents the greatest contribution in the atom or group of atoms which form the reactive center, as calculated using the procedure described by Solomon et al. [21].

2. Methodology

Tables 1 and 2 present the structures of the 28 compounds studied, all derivatives of 4-phenoxipiperidine. The binding affinity values for H_3 receptors (pK_i) for these molecules were measured recently [11].

The molecules were submitted to a preliminary geometry optimization using molecular mechanics force field (MM+) employing the HyperChem 6.0 software [22] to generate the initial coordinates. In addition, the geometries were refined through the Hartree–Fock–Roothaan scheme [23] as implemented in the Gaussian 03 package [24]; Pople's 6-31(d,p) basis was employed for the present quantum chemical calculations. For the statistical calculations the MINITAB program [25] was used.

The calculated descriptors are listed and commented on below:

(a) Charge derived from the electrostatic potential [26] on the N^1 nitrogen atom (N^1 charge), present in all the 28 compounds.

Table 1
Chemical structures of 4-hydroxypiperidines used in the present investigation (group I) and their binding affinities for the human H_3 receptor (pK_i).

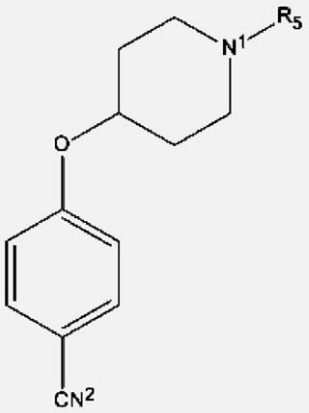
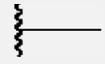
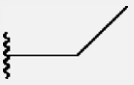
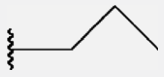
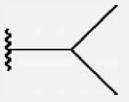
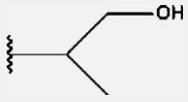
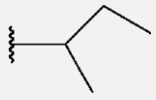
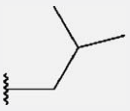
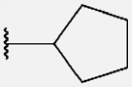
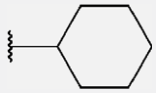
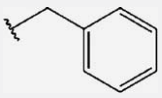
Basic structure of group I	Number	R_5	pK_i
	1		5.37
	2		7.09
	3		6.97
	4		7.55
	5		6.12
	6		7.82
	7		7.18
	8		7.89
	9		7.49
	10		5.27

Table 2
Chemical structures of 4-hydroxypiperidines used in the present investigation (group II) and their binding affinities for the human H_3 receptor (pK_i).

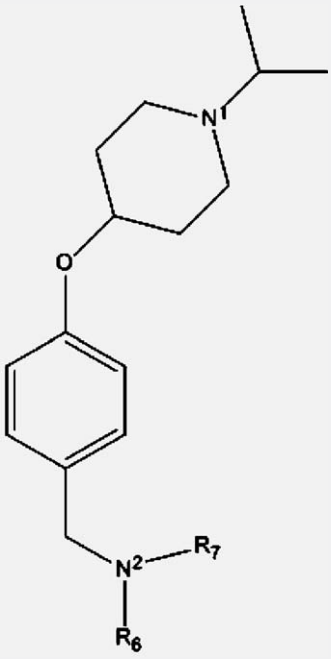
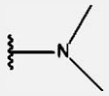
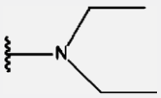
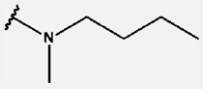
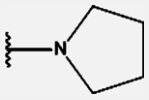
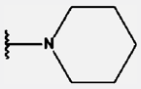
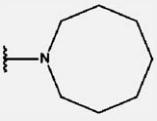
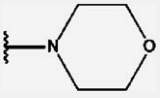
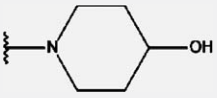
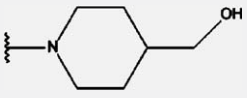
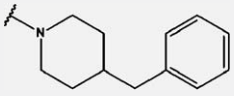
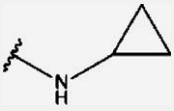
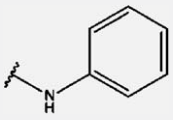
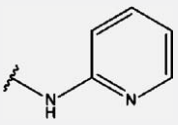
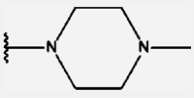
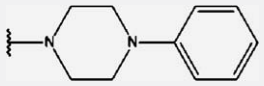
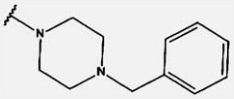
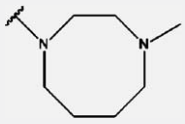
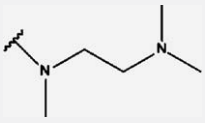
Basic structure of group II	Number	$N^2R_6R_7$	pK_i
	11		8.52
	12		8.91
	13		8.83
	14		8.71
	15		9.20
	16		8.77
	17		8.67
	18		8.85
	19		9.00
	20		8.84
	21		8.79
	22		8.26
	23		8.65
	24		9.13

Table 2 (*Continued*)

Basic structure of group II	Number	$N^2R_6R_7$	pK_i
	25		8.70
	26		8.70
	27		9.00
	28		8.94

This descriptor seems significant as a result of the observation by Apodaca et al. [27] that the loss of the nitrogen atom severely reduces the pK_i value, as illustrated in Fig. 3.

(b) Dipole moment (DM). The purpose for considering this descriptor is to evaluate whether the H_3 receptors favor the binding with polar molecules or, alternatively, with non-polar molecules.

(c) Isotropic first order polarizability (α) [28]. The value of α indicates the facility with which the molecule would create an induced dipole due to the vicinity of other structures; this could be related to the ability to react with amino acids.

(d) Hyperpolarizability or second order polarizability (β) [28]. This property is related to the electrophilic character of a molecule, that is, the larger the value of β, the greater the molecule's capacity to receive electrons.

(e) The molecular volume (V). This is relevant when estimating steric effects in the H_3 antagonists.

(f) The energies of the frontier orbitals HOMO (ε_{HOMO}) and LUMO (ε_{LUMO}). These descriptors are related to the electron donating or accepting character of a given compound [29–31].

(g) The energies of the FERMOs (ε_{FERMO}). For the 28 molecules studied, the N^1 atom was selected as the reactive center, for the same reason that its charge was chosen as an important parameter, as explained in item (a) above. The particular choice of FERMO for some molecules is shown in Fig. 4. It is remarkable the extent to which FERMO showed the best behavior, not necessarily corresponding to the same orbital for each of the molecules. This is shown in Fig. 4 for four orbitals. In this figure we can observe that FERMO has the same shape in each case, coinciding alternatively with $HOMO_{-1}$ for the first two molecules, $HOMO_{-2}$ for the third, and $HOMO_{-3}$ for the forth. In Fig. 5, the energy correlation diagram for the same molecules is shown.

(h) Electronic density indexes for HOMO ($\sum_{(HOMO)} c_i^2$), LUMO ($\sum_{(LUMO)} c_i^2$), and FERMO ($\sum_{(FERMO)} c_i^2$) for the N^1 atom. The summation is for the coefficients (c_i) of the atomic orbitals of the respective MO. This kind of index was used successfully by Subramanian et al. [32] in a quantum chemical and chemometric study of the activity of lapachol and some derivates of 1.4-naphthoquinones against carcinosarcoma Walker 256, showing satisfactory performance as electronic descriptors.

(i) Absolute softness (S), absolute hardness (η), electronic chemical potential (μ), absolute electronegativity (χ), and electrophilicity indexes (ω) were also calculated. The calculation of these indexes employs five different equations [33,34] that have ε_{HOMO} and ε_{LUMO} as variables, *e.g.*, $\mu = (\varepsilon_{LUMO} - \varepsilon_{HOMO})/2$.

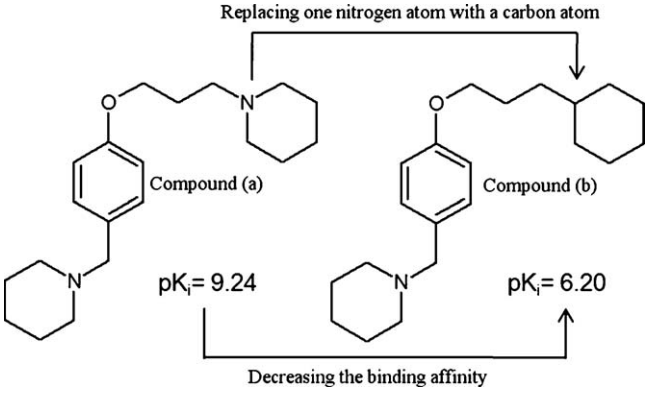


Fig. 3. Apodaca and collaborators [27] confirmed a decrease in binding affinity values for the H_3 receptor when one nitrogen atom is replaced by a carbon atom in 1-[4-(3-piperidin-1-ylpropoxy)benzyl]piperidine, compound (a), producing compound (b), 1-[4-(3-cyclohexylpropoxy)benzyl]piperidine. The study of compounds (a) and (b) with their binding affinity values and chemical structures are presented in Ref. [27].

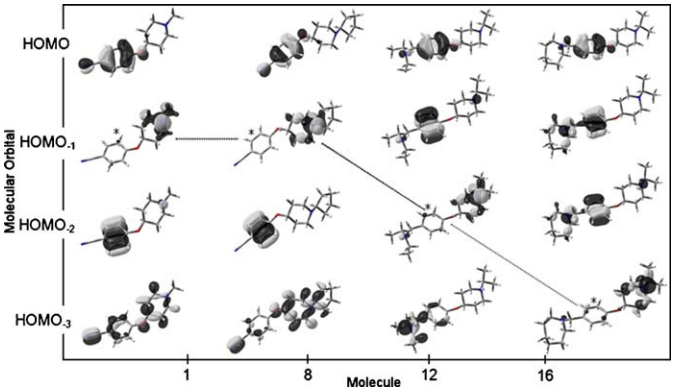


Fig. 4. The shapes of the highest occupied molecular orbital for four molecules: 1, 8, 12, and 16; for the numeration of the molecules see Tables 1 and 2. *Indicates the FERMO. Similar trends for molecular orbitals are confirmed for the other 24 molecules.

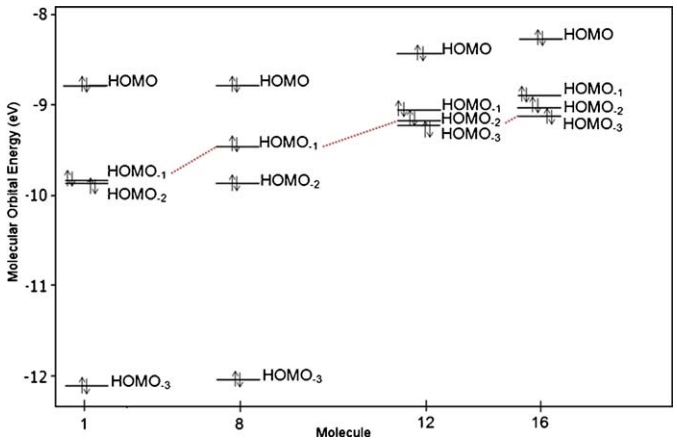


Fig. 5. Molecular orbital energy level diagram for molecules 1, 8, 12, and 16 showing the correlation between the FERMOs which are connected by dashed lines.

(j) The former indexes S, η, μ, χ, ω were recalculated using the FERMO energies, instead of the HOMO energies, generating new reactivity indexes labeled as S', η', μ', χ', ω'. This strategy was partially employed by Da Silva et al. [35] to explain the behavior of some acids and bases with more than one reaction center using Person's hardness and softness indexes [33].

3. Results and discussion

3.1. Statistical analysis for correlation with pK_i

Linear correlation between the MO energies and the pK_i values is reported through the regression parameters shown in Table 3. Evaluating the statistical significance of the linear model, Fisher's F-value should have at least 10 times the value of the Fisher statistical test ($F_{(1,26)} = 9.41$, 99.9% confidence level) [36]. One can confirm that the energy of FERMO is better correlated with the pK_i measurements, since the F-value obtained is 139.47, more than 10 times the acceptable value, while for HOMO and LUMO values were 22.00 and 68.88, respectively. In addition, the regression employing the ε_{FERMO} energies presents the lowest standard deviation, 0.447, the lowest pK_i error, 0.200, and the square of the correlation coefficient (R^2) is 0.843. Thus, the second type of quantum indexes S', η', μ', χ', ω', and $\sum_{(FERMO)} c_i^2$ were chosen to assist in the selection of variables responsible for influencing the binding affinity.

The set of pre-selected properties (ε_{FERMO}, S', η', μ', χ', ω', and $\sum_{(FERMO)} c_i^2$) together with DM, α, β, V, and charges on the N^1 nitrogen atom were analyzed by multivariate methods [37], PCA and HCA. The descriptors ε_{FERMO}, N^1 charge, $\sum_{(FERMO)} c_i^2$, and ω' appear to be the basis of a relevant separation of the compounds in two groups.

The PCA analysis shows that the three first principal components, PC1, PC2 and PC3 appear as significant and explain 98.3% of the total variance. Scores and loadings for the first two components are presented in Figs. 6 and 7. The HCA dendogram produced by the HCA analysis is exhibited in Fig. 8.

Table 3
Linear regression parameters for pK_i values *vs.* LUMO, HOMO and FERMO energies as calculated with HF/6-31G(d,p).

Orbital	R^{2a}	pK_i erro	s^b	F^c	$F_{(1,26)}{}^d$
LUMO	0.726	0.348	0.590	68.88	9.41
HOMO	0.461	0.686	0.828	22.00	
FERMO	0.843	0.200	0.447	139.47	

[a] The square of the correlation coefficient.
[b] Standard deviation.
[c] The Fisher F-value of the linear regression.
[d] The statistical Fisher test (99% reliability level).

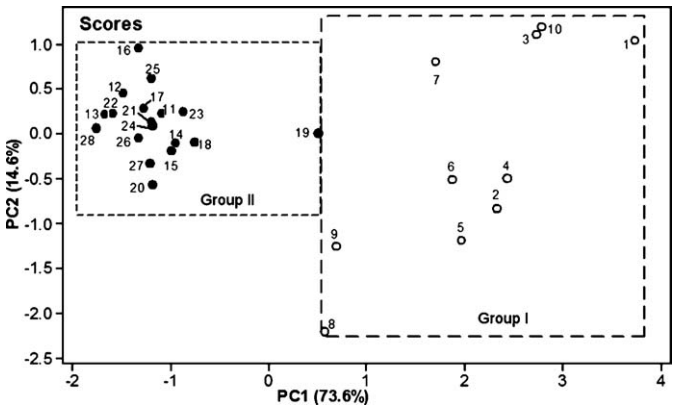


Fig. 6. Scores plot of PC2 against PC1 for the 28 compounds. Group II compounds are located on the left side, and group I compounds on the right side.

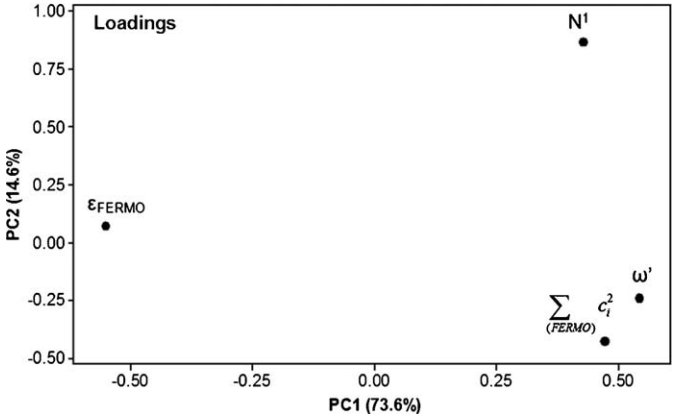


Fig. 7. PC1–PC2 loadings plot using the four descriptors indicated in Section 3.1.

Fig. 6 indicates a clear distinction between two groups of compounds: ligands with lower binding affinity values (compounds 1–10) are grouped on the right-hand side, while those with higher binding affinity values (compounds 11–28) are located on the left side. In addition, as a complement to the former observation, in Fig. 7 for the loadings it is confirmed that the compounds with higher binding affinity values, located on the left side present a contribution of the ε_{FERMO} descriptor, situated on the

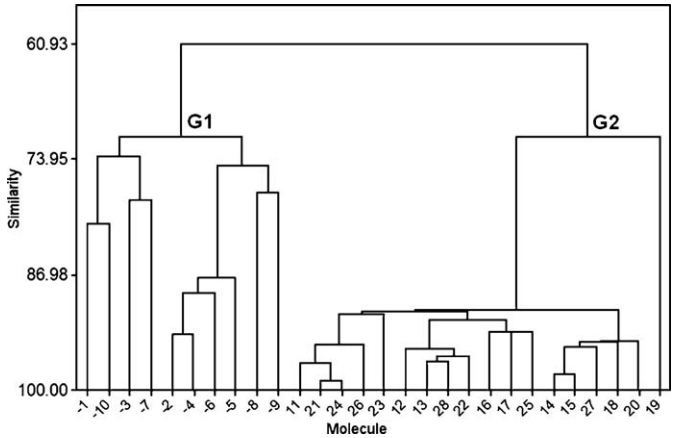


Fig. 8. HCA dendogram with the high binding affinity compounds (with no sign) and the low binding affinity compounds (with negative signs). G1 and G2 are the clusters.

Table 4
The selected quantum chemical descriptors for the 28 compounds.

Group	Compound	pK_i	Quantum chemical descriptors			
			ε_{FERMO} (eV)	N^1 charge (a.u.)	ω' (eV)	$\sum_{(FERMO)} c_i^2$
I	1	5.37	−9.836	−0.512	0.468	0.508
	2	7.09	−9.571	−0.635	0.439	0.526
	3	6.97	−9.495	−0.514	0.431	0.516
	4	7.55	−9.564	−0.613	0.437	0.525
	5	6.12	−9.587	−0.671	0.444	0.516
	6	7.82	−9.481	−0.629	0.429	0.516
	7	7.18	−9.292	−0.551	0.411	0.511
	8	7.89	−9.469	−0.768	0.431	0.499
	9	7.49	−9.345	−0.702	0.418	0.503
	10	5.27	−9.697	−0.530	0.450	0.490
II	11	8.52	−9.144	−0.665	0.257	0.478
	12	8.91	−9.181	−0.678	0.275	0.451
	13	8.83	−9.182	−0.698	0.274	0.449
	14	8.71	−9.135	−0.675	0.258	0.490
	15	9.20	−9.137	−0.681	0.258	0.490
	16	8.77	−9.139	−0.640	0.257	0.457
	17	8.67	−9.177	−0.677	0.274	0.462
	18	8.85	−9.187	−0.670	0.253	0.493
	19	9.00	−9.290	−0.621	0.257	0.525
	20	8.84	−9.139	−0.708	0.259	0.489
	21	8.79	−9.145	−0.675	0.257	0.476
	22	8.26	−9.160	−0.692	0.276	0.453
	23	8.65	−9.153	−0.661	0.295	0.474
	24	9.13	−9.150	−0.677	0.260	0.476
	25	8.70	−9.169	−0.655	0.267	0.462
	26	8.70	−9.156	−0.691	0.262	0.472
	27	9.00	−9.112	−0.693	0.247	0.490
	28	8.94	−9.177	−0.708	0.273	0.449

same side in Fig. 6. On the other hand, compounds with lower binding affinity values, on the right side, have more pronounced contributions from the other descriptors.

The selected descriptors, ε_{FERMO}, N^1 charge, $\sum_{(FERMO)} c_i^2$, and ω', were used to construct the dendogram (see Fig. 8) that indicates that the compounds with lower binding affinity (with negative sign) are grouped together in the G1 cluster. The other molecules, with higher binding affinity values (with no sign), are gathered in the cluster denominated G2. These results agree with what we found through the PCA analysis.

3.2. Analysis of descriptors that influence the binding affinity values

Table 4 shows the calculated values for the four descriptors which were selected for further study, *i.e.*, ε_{FERMO}, N^1 charge, $\sum_{(FERMO)} c_i^2$ and ω' for the 28 compounds. The pK_i values allow a neat distinction between the two groups, I and II (see Table 4).

Table 4 also confirms that the compounds with higher pK_i values, belonging to group II, have ε_{FERMO} values equal to −9.292 eV or higher. Compounds with lower binding affinity, constituents of group I, have values lower or equal to −9.290 eV. On this basis, it is suggested that the molecules with higher nucleophilic character tend to have higher binding affinity values.

The values of electrophilicity (ω'), also shown in Table 4, were clearly different for groups I and II. Indeed, group II shows values between 0.247 and 0.295 eV, whereas for group I, values vary from 0.431 to 0.468 eV. This result suggests that the lower the tendency of the molecules to attract electrons, the greater the binding affinity of the H_3 receptor.

As for the electronic density values ($\sum_{(FERMO)} c_i^2$) in Table 4, there is no apparent difference between groups I and II. Perhaps the correlation between pK_i and $\sum_{(FERMO)} c_i^2$ might be better understood by the regression equation obtained using the PLS method (see Refs. [37–39]). This approach led to Eq. (1), as we discuss in Section 3.3 below. Similar considerations may apply to the performance of the N^1 charge values. Indeed, the use of both descriptors, $\sum_{(FERMO)} c_i^2$ and N^1, seems to be justified through the statistical validation of Eq. (1).

3.3. PLS regression equation

Employing three principal components for the PLS methodology [37–39] with 23 compounds (1–3, 6, 8–10, 12–20, 22–28), and validated through a leave-one-out cross-validation procedure, the external validation set (4, 5, 7, 11, 21), we arrive at Eq. (1) employing the four descriptors previously selected:

$$pK_i = 2.565(\varepsilon_{FERMO}) - 4.510(N^1) + 9.016\left(\sum_{(FERMO)} c_i^2\right) - 5.867(\omega') + 26.571 \quad (1)$$

The statistical validity of this equation may be assessed by the values of the parameters R^2, 0.927, and Q^2, 0.880, as shown in Table 5. Considering these values, it appears that Eq. (1) explains 92.7% of the variance of the pK_i values and predicts 88.0% of the pK_i values. In addition, the correlation has a standard error validation close to zero (0.141) and a *F* Fisher value of 80.11. The differences between the experimental binding affinities and calculated values were relatively low, except for molecules 5 and 6 for which the

Table 5
Experimental and calculated binding affinities using the PLS regression equation.

Compound	p$K_{i(experimental)}$ [a]	pK_i (this work)	Δ (p$K_{i(experimental)}$ − pK_i (this work)) [b]
1	5.37	5.49	−0.12
2	7.09	7.05	0.04
3	6.97	6.65	0.32
4 [c]	7.55	6.97	0.58
5 [c]	6.12	7.05	−0.93
6	7.82	7.22	0.60
7 [c]	7.18	7.42	−0.24
8	7.89	7.72	0.17
9	7.49	7.85	−0.36
10	5.27	5.86	−0.59
11 [c]	8.52	8.92	−0.40
12	8.91	8.53	0.38
13	8.83	8.60	0.23
14	8.71	9.09	−0.38
15	9.20	9.11	0.09
16	8.77	8.62	0.15
17	8.67	8.64	0.03
18	8.85	8.98	−0.13
19	9.00	8.76	0.24
20	8.84	9.21	−0.37
21 [c]	8.79	8.94	−0.15
22	8.26	8.66	−0.40
23	8.65	8.62	0.03
24	9.13	8.92	0.21
25	8.70	8.60	0.10
26	8.70	8.92	−0.22
27	9.00	9.29	−0.29
28	8.94	8.67	0.27

Statistical parameters	Values
R^2 [d]	0.927
Q^2 [e]	0.880
SEP [f]	0.141
F [g]	80.11
PCs [h]	3

[a] Experimental pK_i values from Ref. [11].
[b] Difference between experimental and calculated pK_i values in this work.
[c] Samples for the external validation set.
[d] Correlation coefficient from prediction.
[e] Correlation coefficient from validation.
[f] Standard error of validation.
[g] The statistical Fisher test.
[h] Number of principal components.

deviations were −0.93 and 0.6, respectively; for all the other compounds the differences were lower than 0.6. It thus seems valid to expect that Eq. (1) has statistical significance and potential to be used as a suitable regression model to interpret the dependence of the binding affinity with the chosen properties, and predict pK_i values with a satisfactory level of reliability.

4. Conclusions

For the present set of 28 molecules the FERMO energies seem to behave more appropriately for the description of binding affinities to H_3 histamine receptors than HOMO energies. In addition, this result suggests that the FERMO energy is a relevant descriptor to be taken into account in quantitative structure–activity relationship studies.

Considering both structural and quantum chemical factors, we may expect that new molecules with binding affinities values surpassing the set studied by Dvorak et al. [11] would benefit from the following factors: a chemical structure similar to molecules of group II, an electron donor group bound to N[1], high values of ε_{FERMO} and $\sum_{(FERMO)} c_i^2$, and low values of ω'.

We were able to confirm that four electronic descriptors were sufficient and appropriate for the classification of 28 molecules into groups of low and high binding affinity values, and to produce a reasonable prediction of pK_i values through a PLS regression equation.

From the calculated ε_{FERMO} and ω' values shown in Table 4 for the 28 antihistamine compounds studied, we suggest that these compounds can be classified as electron donating compounds and have a great probability of interacting through a charge transfer process with the H_3 histamine receptor.

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