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**Research Article**

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# Quantum-Chemical Study of the Relationships between Electronic Structure and the Affinity of Benzisothiazolylpiperazine Derivatives for the Dopamine Hd2l and Hd3 Receptors

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**Abstract** Schizophrenia is a mental illness that induces a cognitive deficit, affects a large part of the world's population, and in particular Africa where it is ignored. To treat this disease, the antipsychotic derivatives of benzisothiazolylpiperazine (N-(trans-4-(2-(4-(benzo [d] isothiazol-3-yl) piperazin-1-yl) ethyl)cyclohexyl) amides) are employed because of their inhibitory powerfor the dopamine HD2L and HD3 receptors. The present study aims to establish relationships between the electronic structure and the antipsychotic activity of benzisothiazolylpiperazine derivatives and to generate a 2D pharmacophore for predicting the antipsychotic activity of these derivatives. The KPG technique was employed. The electronic structure of all the molecules was calculated at the DFT/B3LYP/6-31G (d,p) level of theory. We obtained two statistically significant equations for predicting the inhibition constant. The process seems to be charge and orbital controlled for receptor HD2L and orbital controlled for HD3. The two prediction equations obtained can be useful for proposing new derivatives with antipsychotic activity having an affinity with the dopamine HD2L and HD3 receptors. The two pharmacophores derived from these prediction models would be very useful for proposing new molecules with potent antipsychotic activity.

**Keywords** Schizophrenia, QSAR, hD2L receptor, hD3 receptor, KPG method, DFT

## Introduction

Schizophrenia is a serious illness that results in personality disorganization, disruption of family relationships, social isolation, and inability to work [1]. This disease, which begins in adolescence (15-25 years), is progressive and often irreversible, with a very high social cost, affecting 0.5 to 1% of the world population [2, 3].

Although schizophrenia is relatively rare, its early onset, its chronicity, its significant morbidity (one in four parents will attempt suicide), the inability of patients to work and the need for long hospital stays make this disease have a very high social cost [4]. This sickness due to the intrapsychic dissociation caused Neoloqism [5], and leads to primary signs (mental issues, discordance, atmosphere) and secondary signs resulting from the reaction of the patient's psyche (morbid rationalism, autism, paranoid delirium which is an attempt at psychic reconstruction) (Spaltung). There are different forms: simple, hebephrenic, hebephrenocatatonic, paranoid, schizo-neurotic, schizo-affective and heboidophrenia [6]. Considered as a spectrum disorder [7], schizophrenia is categorized by positive, negative, and cognitive symptoms. First-generation antipsychotics (FGAs), such as dopamine D2 receptor antagonists, effectively treat positive symptoms, but are ineffective in relieving negative symptoms or cognitive

disorders. FGAs can also cause serious side effects such as extrapyramidal symptoms (EPS) [8, 9]. In order to find remedies for symptoms or cognitive disorders, the synthesis of atypical antipsychotic derivatives of benzisothiazolylpiperazine for the treatment of schizophrenia is necessary because they affect the affinity for hD2L, hD3, 5- $HT_{1A}$ and 5-$HT_{2A}$ receptors individually and collectively as well [10].

In order to improve the antipsychotic activity of benzisothiasolylpiperazine derivatives for the treatment of schizophrenia and to determine the atomic sites most likely to interact in this activity, a QSAR study on these derivatives with the activity of inhibition on the dopaminergic hD2L and hD3 receptors was conducted.

## Methods, Models and Calculations

### Model

Consider the state of thermodynamic equilibrium between a drug and a following receptor:

$$D_i + R \leftrightarrow D_i R \tag{1}$$

Where $D_i R$ is the drug-receptor complex, $R$ is the receptor $D_i$ is the drug. The equilibrium constant $K_i$ for this reaction is defined as :

$$K_i = \frac{Q_{D_i R}}{Q_{D_i} Q_R} \exp(-\Delta\varepsilon_0^i / kT) \tag{2}$$

Where $Q_{D_i R}$, $Q_{D_i}$ and $Q_R$ are respectively the total partition functions of the drug-receptor complex, the drug and the receptor, and k and T respectively represent the Boltzmann constant and the absolute temperature. $\Delta\varepsilon_0^i$ is the difference between the ground-state energy of $D_i R$ and the energies of the ground-states of $D_i$ and $R$.

After several physically-based approximations the following equations was obtained [11]:

$$\log(\text{ki}) = a + bM_{D_i} + c\log\left[\sigma_{D_i} / (ABC)^{1/2}\right] + \sum_j \left[e_j Q_j + f_j S_j^E + s_j S_j^N\right] + \tag{3}$$

$$\sum_j \sum_m \left[h_j(m) F_j(m) + x_j(m) S_j^E(m)\right] + + \sum_j \sum_{m'} \left[r_j(m') F_j(m') + t_j(m') S_j^N(m')\right]$$

$$+ \sum_j \left[g_j \mu_j + k_j \eta_j + o_j \omega_j + z_j \varsigma_j + w_j Q_j^{\max}\right]$$

where a, b, c, $e_j$, $f_j$, $s_j$, $h_j(m)$, $x_j(m)$, $r_j(m')$, $t_j(m')$, $g_j$, $k_j$, $o_j$, $z_j$ and $w_j$ are constants, $M_{D_i}$ is the drug's mass, $\sigma_{D_i}$ is its symmetry number, ABC is the product of the drug's moments of inertia about the three principal axes of rotation, $Q_j$ is the net charge of atom j, $S_j^E$ and $S_j^N$ are, respectively, the total atomic electrophilic and nucleophilic superdelocalizabilities of atom j, $F_j(m)$, $F_j(m')$ is the electron population (Fukui index) of the occupied (vacant) MO m(m′) localized on atom j, $S_j^E(m)$ is the atomic electrophilic superdelocalizability of MO m localized on atom j, $\mu_j$ is the local atomic electronic chemical potential of atom j, $\eta_j$ is the local atomic hardness of atom j, $\omega_j$ is the local atomic electrophilicity of atom j, $\varsigma_j$ is the local atomic softness of atom j, $Q_j^{\max}$ j is the maximum amount of electronic charge that atom j may accept from another site, and $O_k$ is the orientational parameters of the k-th substituent.

It should be noted that the local atomic reactivity indices in equation 3 come from Hatree-Fock-Roothaan (HFR) framework [11, 12] and are defined as:

- The nucleophilic superdelocalizability of the local lowest empty MO (LUMO*) localized on atom i:

$$S_i^{\mathrm{N}}(LUMO)^* = \frac{F_i(LUMO)^*}{E_{LUMO^*}} \quad (4)$$

This is a measure of the electron-accepting capacity of the local LUMO* of atom i.

- The local electrophilic superdelocalizability the highest occupied MO (HOMO*) localized on atom i:

$$S_i^{E}(HOMO)^* = \frac{F_i(HOMO)^*}{E_{HOMO^*}} \quad (5)$$

This is a measure of the electron-donating capacity of the local HOMO* of atom i.

- The local atomic hardness is defined as follows:

$$\eta_i = \left(E_{LUMO_i^*} - E_{HOMO_i^*}\right) \quad (6)$$

This index measures the resistance of atom i to exchange electrons with a site.

- The local atomic softness of atom i is defined as:

$$\varsigma_i = 1/\eta_i \quad (7)$$

This index measures the facility of atom i to exchange electrons with the site.

- The local atomic electronic chemical potential is defined as follows:

$$\mu_i = (1/2)\left(E_{HOMO_i^*} - E_{LUMO_i^*}\right) \quad (8)$$

This index represents the measure of the propensity of atom i to gain or lose electrons.

- The maximal amount of which charge atom i may receive is defined as:

$$Q_i^{*}\max = -\frac{\mu_i}{\eta_i} \quad (9)$$

- Local atomic electrophilicity of atom i is defined as:

$$\omega_i^* = \frac{\left(\mu_i\right)^2}{2\eta_i} \quad (10)$$

This index measures the propensity of atom i to receive extra electronic charge together with its resistance to exchange charge with a site.

**Methods**

The methodology used here to find relationships between the electronic structure and the inhibition constants has been discussed in several papers [12–19]. The results presented here are obtained from what is now a routine procedure. For this reason, this paper contains standard phrases for the presentation of the methods, calculations and results because they do not need to be rewritten repeatedly and the number of possible variations to use is finite [12–19]. The application of this method has led to outstanding results for a wide variety of drug system diversity (see [20–34] and related references).

**Selection of molecules**

The selected molecules are from a set reported in reference [10]. Their general formulas and biological activities are shown in Figure (1) and Table 1. The experimental data used are the inhibition constants, which is the affinity of the benzisothiazolylpiperazine derivatives for the dopaminergic hD2L and hD3 receptors.

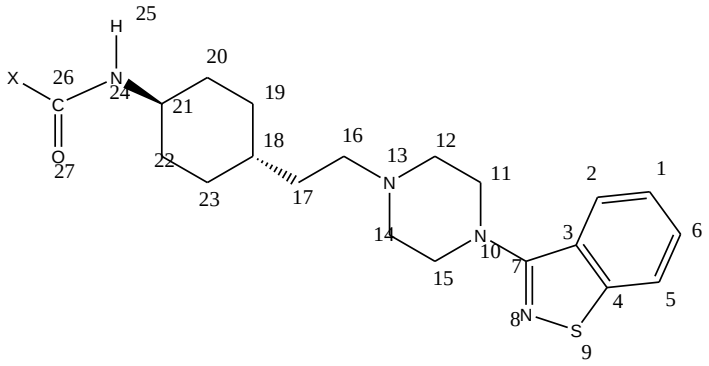
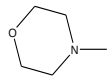
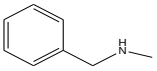
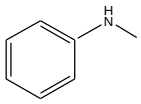
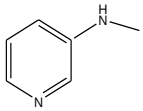
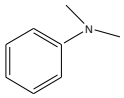
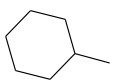
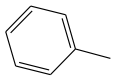
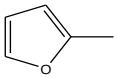
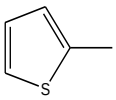
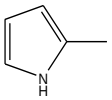
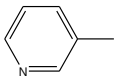
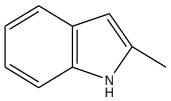


*Figure 1: General formula of benzisothiazolylpiperazine derivatives*

**Table 1:** Selected of Benzisothiazolylpiperazine derivatives used with their inhibition constants on hd2L and hd3

| No. | Molecules | X | $hD_{2L}$ | $hD_3$ |
|---|---|---|---|---|
| 1 | 3-(trans-4-(2-(4-(Benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-1,1-dimethylurea | $(CH_3)_2N$- | -0.28 | -0.40 |
| 2 | 3-(trans-4-(2-(4-(Benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-1,1-diisopropylurea | $(iPr)_2N$- | -0.14 | 0.15 |
| 3 | 3-(trans-4-(2-(4-(Benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-1-ethyl-1-methylurea | (Et)(Me)N- | -0.29 | -0.11 |
| 4 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl) ethyl)cyclohexyl)morpholine-4-carboxamide |  | 0.34 | 0.20 |
| 5 | 1-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-3-benzylurea |  | 0.15 | -0.74 |
| 6 | 1-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-3-phenylurea |  | -0.20 | -1.37 |
| 7 | 1-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-3-(pyridin-3-yl)urea |  | -0.29 | -1.26 |
| 8 | 3-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-1-methyl-1-phenylurea |  | 0.38 | 0.08 |
| 9 | Ethyl (trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin1yl)ethyl)cyclohexyl)carbamate | $CH_3$-$CH_2$-O- | -0.15 | -1.24 |
| 10 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-2-methoxyacetamide | $CH_3$-O-$CH_2$- | 0.98 | -0.51 |
| 11 | E. N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)acetamide | $CH_3$- | 1.40 | -0.80 |
| 12 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl) ethyl)cyclohexyl)propionamide | $CH_3$-$CH_2$- | 1.26 | -1.28 |
| 13 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl) ethyl)cyclohexyl)butyramide | $CH_3$-$CH_2$-$CH_2$- | 0.45 | -0.85 |
| 14 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-2,2,2-trifluoroacetamide | $CF_3$- | 0.23 | -0.57 |
| 15 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl) ethyl)cyclohexyl)cyclohexanecarboxamide |  | -0.03 | -0.72 |

| | | | | |
|---|---|---|---|---|
| 16 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl) ethyl)cyclohexyl)cyclopropanecarboxamide |  | -0.07 | -0.68 |
| 17 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl) ethyl)cyclohexyl)benzamide |  | -0.48 | -1.33 |
| 18 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)furan-2-carboxamide |  | 0.46 | -0.89 |
| 19 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl) ethyl)cyclohexyl)thiophene-2-carboxamide |  | -0.72 | -1.25 |
| 20 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-1H-pyrrole-2-carboxamide |  | -0.68 | -0.51 |
| 21 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl) ethyl)cyclohexyl)nicotinamide |  | -0.07 | -1.05 |
| 22 | N-(trans-4-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)-1H-indole-2-carboxamide |  | -0.37 | -1.54 |

**Calculations**

The electronic structure of all molecules was calculated with density functional theory (DFT) at the B3LYP/6-31G (d, p) level with full optimization of the geometry. The Gaussian Program was used [35]. The D-Cent-QSAR software [36, 37] was used to compute the numerical values of local atomic reactivity indices from the Gaussian results. The software Statistica [38] was used for multiple linear regression analysis (LMRA). We also used the common skeleton hypothesis. The entire work process is explained in several documents (see references [20–34]).The skeleton common to all twenty-two antipsychotic molecules bearing the numbers of these different atoms is shown below:

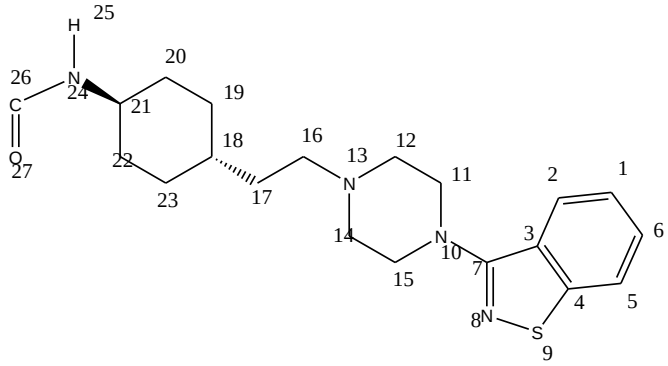



*Figure 2: Common skeleton of benzisothiazolylpiperazine derivatives*

**Results**

**Results for the hD2L dopamine receptor**

The best equation for the antipsychotic activity obtained for the dopaminergic hD2L receptor is as follows:

$$\log(ki) = 6.68 + 25.57\varsigma_{20} + 19.66Q_{24} + 45.83F_{17}(LUMO)^{*} - 0.78F_{26}(LUMO)^{*} - 0.48S_{18}^{E}(HOMO-2)^{*} + 4.05F_{12}(HOMO-2)^{*} + 0.45F_{25}(LUMO)^{*} \quad (11)$$

with n= 21, R = 97.64%, $R^2$ = 95.33%,adj- $R^2$ =92.82%, F(7,13)=37.91, (p-value = 1.17986E-07) and SD = 0.13. No outliers were detected and no residuals fall outside the ± 2 limits.

This equation from the multiple linear regression shows that the antipsychotic activity of benzisothiazolylpiperasine derivatives (N- (4- (benzo [d] isothiazol-3-yl) piperazin-1-yl) ethyl) cyclohexyl) amides) is related to seven local index of atomic reactivity: $\varsigma_{20}$ is the local atomic softness of atom 20, $Q_{24}$ is the net charge of the atoms 24, 25 and 26 $F_{17}(LUMO)^*$ is the Fukui index (electronic population) of the lowest vacant molecular orbital localized on atom 17, $F_{26}(LUMO)^*$ is the Fukui index of the lowest vacant molecular orbital localized on atom 26, $S_{18}^E(HOMO-2)^*$ is the electrophilic superdelocalizability of the third highest occupied molecular orbital localized on atom 18, $F_{12}(HOMO-2)^*$ is the Fukui index of the third lowest vacant molecular orbital localized on atom 12 and $F_{25}(LUMO)^*$ is the Fukui index of the lowest vacant molecular orbital localized on atom 25.

Tables 2 and 3 show the beta coefficients, the results of the t-test for significance of variable and the matrix of squared correlation coefficients for the variables of Eq. 11. There are no significant internal correlations between independent variables (Table 3). Figure 3 displays the plot of observed vs. calculated hD2L affinities.

**Table 2:** The statistical parameters of the template index for the hd2L receptor variables

| Variables | Beta coefficients | P-value |
|---|---|---|
| $\varsigma_{20}$ | 0.546 | 6.00E-06 |
| $Q_{24}$ | 0.747 | 0.00E+00 |
| $F_{17}(LUMO)^*$ | 0.634 | 7.00E-06 |
| $F_{26}(LUMO)^*$ | -0.570 | 1.06E-04 |
| $S_{18}^E(HOMO-2)^*$ | -0.322 | 4.36E-04 |
| $F_{12}(HOMO-2)^*$ | 0.288 | 1.80E-03 |
| $F_{25}(LUMO)^*$ | 0.241 | 4.11E-03 |

**Table 3**: Squared correlation coefficients for the variables appearing in Eq. 11

| Variables | $\varsigma_{20}$ | $Q_{24}$ | $F_{17}(LUMO)^*$ | $F_{26}(LUMO)^*$ | $S_{18}^E(HOMO-2)^*$ | $F_{12}(HOMO-2)^*$ |
|---|---|---|---|---|---|---|
| $Q_{24}$ | 0.005 | 1 | | | | |
| $F_{17}(LUMO)^*$ | 0.20 | 0.06 | 1 | | | |
| $F_{26}(LUMO)^*$ | 0.18 | 0.36 | 0.45 | 1 | | |
| $S_{18}^E(HOMO-2)^*$ | 0.07 | 0.004 | 0.0004 | 0.01 | 1 | |
| $F_{12}(HOMO-2)^*$ | 0.01 | 0.102 | 0.12 | 0.18 | 0.11 | 1 |
| $F_{25}(LUMO)^*$ | 0.014 | 0.02 | 0.26 | 0.14 | 0.002 | 0.12 |

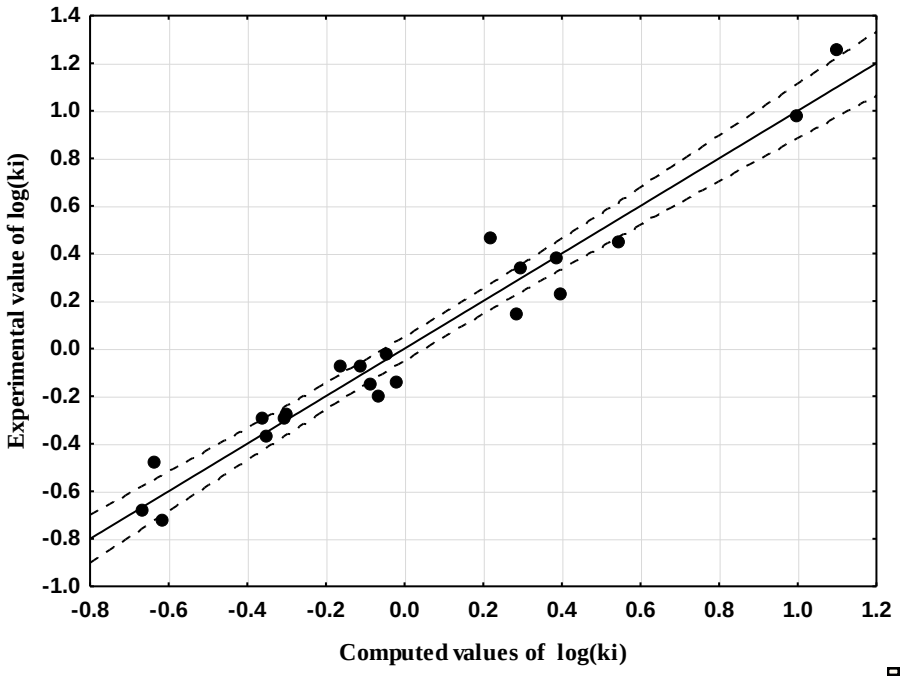



*Figure 3: Plot of predicted vs. observed log($k_i$) values from Eq. 1. Dashed lines denote the 95% confidence interval*

**Results for the hD3 dopamine receptor**

The best equation for the antipsychotic activity obtained for the dopaminergic hD3 receptor is as follows:

$$\log(ki) = 1.24 + 0,99\mu_{26} + 1.98F_{18}(HOMO-1)^{*} + 6.91S_{13}^{N}(LUMO+1)^{*} + 2.34S_{16}^{N}(LUMO)^{*} - 12.46F_{1}(HOMO)^{*} + 0.01S_{21}^{N}(LUMO)^{*} - 1.29S_{17}^{N}(LUMO)^{*} - 0.09S_{24}^{E}(HOMO)^{*} \quad (12)$$

with n= 22, R =97.53%, $R^2$ = 95.11% ,adj- $R^2$ =92.10%, F(7,13)=31.62, (p-value = 2.67184E-07) and SD = 0.14. No outliers were detected and no residuals fall outside the ± 2 limits.

The equation resulting from the multiple linear regression shows that the antipsychotic activity of the benzisothiazolylpiperine derivatives depends on eight local atomic reactivity indexes: on the one hand; positive numerical values of the local atomic reactivity indexes. $\mu_{26}$ is the local atomic chemical potential of the atom 26, $F_{18}(HOMO-1)^{*}$ is the electronic population (Fukui index) of the second highest occupied molecular orbital localized on atom 18, $S_{13}^{N}(LUMO+1)^{*}$ is the nucleophilic superdelocalizability of the second vacant molecular orbital localized on atom 13, $S_{16}^{N}(LUMO)^{*}$ is the nucleophilic superdelocalizability of the lowest vacant molecular orbital localized on atom 16, $F_{1}(HOMO)^{*}$ is the Fukui index of the highest occupied molecular orbital localized on atom 1, $S_{21}^{N}(LUMO)^{*}$ is the nucleophilic superdelocalizability of the lowest vacant molecular orbital locatlized on atom 21, $S_{17}^{N}(LUMO)^{*}$ is the nucleophilic superdelocalizability of the lowest vacant molecular orbital localized on atom 17 and $S_{24}^{E}(HOMO)^{*}$ is the electrophilic superdelocalizability of the highest occupied molecular orbital localized on atom 24.

Tables 4 and 5 show the beta coefficients, the results of the t-test for significance of variable and the matrix of squared correlation coefficients for the variables of Eq. 12. There are no significant internal correlations between independent variables (Table 5). Figure 4 displays the plot of observed vs. calculated hD3 affinities.

**Table 4:** The statistical parameters of the template indexes for the hD3 receptor

| Variables | Coefficients bêta | P-value |
|---|---|---|
| $\mu_{26}$ | 1.026 | 0.00E+00 |
| $F_{18}(HOMO-1)^*$ | 0.480 | 7.00E-06 |
| $S_{13}^N(LUMO+1)^*$ | 0.657 | 4.00E-06 |
| $S_{16}^N(LUMO)^*$ | 0.613 | 2.00E-06 |
| $F_1(HOMO)^*$ | -0.344 | 7.22E-04 |
| $S_{21}^N(LUMO)^*$ | 0.267 | 1.12E-03 |
| $S_{17}^N(LUMO)^*$ | -0.269 | 5.81E-03 |
| $S_{24}^E(HOMO)^*$ | -0.184 | 2.93E-02 |

**Table 5**: Squared correlation coefficients for the variables appearing in Eq. 12

| Variables | $\mu_{26}$ | $F_{18}(HOMO-1)^*$ | $S_{13}^N(LUMO+1)^*$ | $S_{16}^N(LUMO)^*$ | $F_1(HOMO)^*$ | $S_{21}^N(LUMO)^*$ | $S_{17}^N(LUMO)^*$ |
|---|---|---|---|---|---|---|---|
| $F_{18}(HOMO-1)^*$ | 0.06 | 1 | | | | | |
| $S_{13}^N(LUMO+1)^*$ | 0.29 | 0.006 | 1 | | | | |
| $S_{16}^N(LUMO)^*$ | 0.06 | 0.01 | 0.06 | 1 | | | |
| $F_1(HOMO)^*$ | 0.05 | 0.03 | 0.03 | 0.12 | 1 | | |
| $S_{21}^N(LUMO)^*$ | 0.002 | 0.02 | 0.0004 | 0.01 | 0.01 | 1 | |
| $S_{17}^N(LUMO)^*$ | 0.08 | 0.04 | 0.002 | 0.27 | 0.24 | 0.02 | 1 |
| $S_{24}^E(HOMO)^*$ | 0.02 | 0.008 | 0.11 | 0.06 | 0.16 | 0.04 | 0.14 |

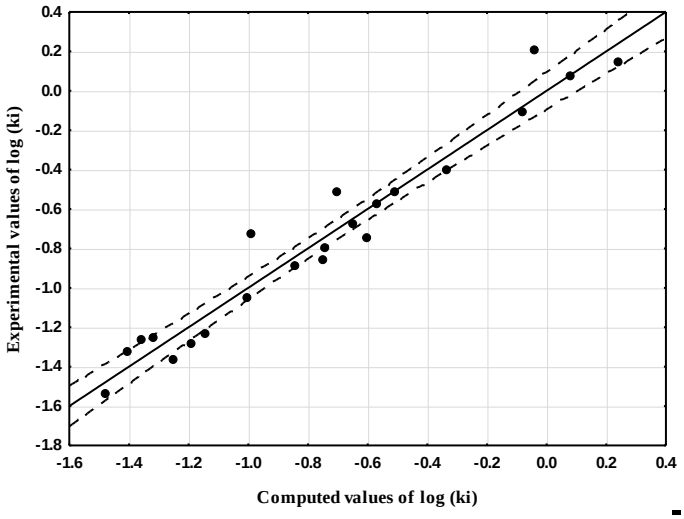



*Figure 4: Plot of predicted vs. observed log(ki) values from Eq. 1. Dashed lines denote the 95% confidence interval*

**Local Molecular Orbitals**

**Table 6:** Local Molecular Orbitals of atoms 1, 12, 13 and 16

| Molecules | Atom 1 (C) | Atom 12 (C) | Atom 13 (N) | Atom 16 (C) |
|---|---|---|---|---|
| 1 (112) | 106π107π112π-<br>113π114π116π | 99σ111σ112σ-<br>117σ122σ123σ | 106σ111σ112σ-<br>123σ127σ128σ | 103σ104σ111σ-<br>119σ121σ123σ |
| 2 (128) | 122π124π128π-<br>129π130π133π | 120σ127σ128σ-<br>140σ143σ145σ | 120σ127σ128σ-<br>139σ143σ148σ | 119σ120σ127σ-<br>136σ137σ138σ |
| 3 (116) | 111π112π116π-<br>117π118π121π | 108σ112σ115σ-<br>121σ124σ128σ | 105σ106σ115σ-<br>126σ134σ137σ | 107σ108σ115σ-<br>122σ123σ125σ |
| 4 (124) | 117π119π123π-<br>124π125π127π | 109σ115σ122σ-<br>133σ135σ137σ | 117σ122σ123σ-<br>133σ135σ139σ | 113σ114σ122σ-<br>134σ142σ143σ |
| 5 (128) | 124π127π128π-<br>129π130π135π | 124σ127σ128σ-<br>135σ141σ144σ | 124σ127σ128σ-<br>142σ147σ148σ | 117σ118σ127σ-<br>136σ137σ142σ |
| 6 (124) | 117π119π123π-<br>125π126π130π | 115σ119σ122-<br>130σ135σ138σ | 112σ113σ122σ-<br>136σ140σ141σ | 111σ112σ122σ-<br>131σ132σ133σ |
| 7 (124) | 120π123π124π-<br>125π127π131π | 120σ123σ124σ-<br>134σ137σ138σ | 120σ123σ124σ-<br>137σ138σ143σ | 113σ114σ123σ-<br>133σ134σ136σ |
| 8 (128) | 123π127π128π-<br>129π130π135π | 114σ115σ127σ-<br>139σ141σ143σ | 116σ127σ128σ-<br>146σ149σ151σ | 116σ117σ127σ-<br>138σ139σ141σ |
| 9 (112) | 108π110π112π-<br>113π114π117π | 102σ104σ111σ-<br>122σ123σ125σ | 108σ111σ112σ-<br>122σ123σ128σ | 103σ104σ111σ-<br>122σ124σ125σ |
| 10 (112) | 107π109π112π-<br>113π114π117π | 109σ111σ112σ-<br>125σ127σ128σ | 103σ104σ111σ-<br>120σ123σ125σ | 103σ104σ111σ-<br>119σ121σ124σ |
| 11 (104) | 99π100π104π-<br>105π106π109π | 100σ103σ104σ-<br>116σ118σ119σ | 96σ97σ103σ-<br>112σ114σ118σ | 96σ97σ103σ-<br>111σ113σ115σ |
| 12 (108) | 103π104π108π-<br>109π110π113π | 97σ107σ108σ-<br>113σ117σ120σ | 103σ107σ108σ-<br>119σ120σ124σ | 99σ101σ107σ-<br>117σ121σ122σ |
| 13 (112) | 107π108π112π-<br>113π114π117π | 108σ111σ112σ-<br>124σ126σ127σ | 104σ105σ111σ-<br>123σ128σ129σ | 104σ105σ111σ-<br>118σ120σ121σ |
| 14 (116) | 113π114π116π-<br>117π118π121π | 109σ114σ115σ-<br>121σ126σ127σ | 107σ108σ115σ-<br>126σ129σ133σ | 108σ109σ115σ-<br>122σ124σ127σ |
| 15 (123) | 118π119π123π-<br>124π125π128π | 111σ114σ122σ-<br>128σ135σ138σ | 111σ112σ122σ-<br>138σ140σ141σ | 112σ113σ122σ-<br>130σ133σ135σ |
| 16 (111) | 106π107π111π-<br>112π113π116π | 103σ107σ110σ-<br>116σ123σ124σ | 100σ101σ110σ-<br>117σ121σ124σ | 101σ103σ110σ-<br>118σ120σ121σ |
| 17 (120) | 115π116π120π-<br>121π123π126π | 106σ107σ119σ-<br>131σ133σ136σ | 115σ119σ120σ-<br>132σ133σ136σ | 110σ111σ119σ-<br>134σ136σ138σ |
| 18 (117) | 112π116π117π-<br>118π120π123π | 111σ116σ117σ-<br>126σ128σ130σ | 112σ116σ117σ-<br>133σ136σ137σ | 111σ116σ117σ-<br>125σ130σ132σ |
| 19 (121) | 115π117π121π-<br>123π124π128π | 107σ108σ120σ-<br>135σ139σ142σ | 115σ120σ121σ-<br>138σ139σ141σ | 111σ112σ120σ-<br>129σ133σ137σ |
| 20 (117) | 113π116π117π-<br>118π120π122π | 104σ116σ117σ-<br>129σ130σ131σ | 107σ116σ117σ-<br>127σ133σ136σ | 105σ107σ116σ-<br>126σ129σ131σ |
| 21 (120) | 115π117π120π-<br>122π124π127π | 110σ119σ120σ-<br>127σ134σ138σ | 115σ119σ120σ-<br>131σ134σ136σ | 108σ109σ119σ-<br>128σ130σ133σ |
| 22 (130) | 124π126π130π-<br>132π133π137π | 115σ116σ128σ-<br>141σ143σ145σ | 128σ129σ130σ-<br>141σ143σ148σ | 119σ120σ128σ-<br>142σ150σ151σ |

**Table 7:** Local Molecular Orbitals of atoms 17, 18, 20 and 21

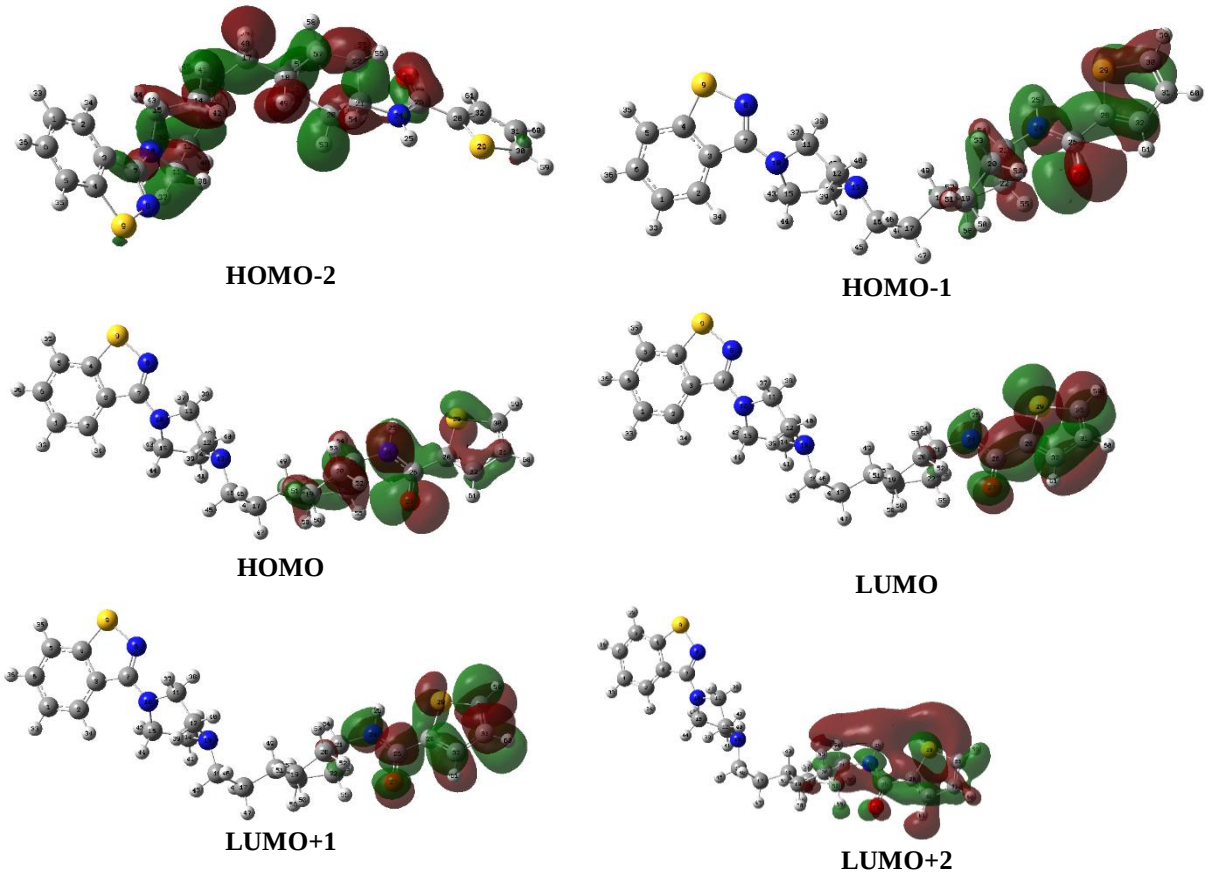
| Molecules | Atom 17 (C) | Atom 18 (C) | Atom 20 (C) | Atom 21 (C) |
|---|---|---|---|---|
| 1 (112) | 103σ104σ111σ-122σ125σ128σ | 102σ103σ104σ-123σ124σ125σ | 108σ109σ110σ-121σ123σ126σ | 108σ109σ110σ-118σ125σ129σ |
| 2 (128) | 119σ120σ127σ-135σ151σ152σ | 118σ119σ120σ-141σ142σ143σ | 123σ125σ126σ-134σ135σ137σ | 123σ125σ126σ-132σ139σ142σ |
| 3 (116) | 106σ107σ115σ-123σ124σ126σ | 105σ106σ107σ-127σ128σ129σ | 110σ113σ114σ-120σ125σ128σ | 110σ113σ114σ-120σ124σ125σ |
| 4 (124) | 113σ114σ122σ-133σ138σ141σ | 113σ114σ115σ-135σ138σ139σ | 118σ120σ121σ-128σ138σ142σ | 118σ120σ121σ-128σ132σ133σ |
| 5 (128) | 117σ118σ127σ-141σ142σ149σ | 116σ117σ127σ-136σ139σ141σ | 117σ125σ126σ-142σ144σ146σ | 123σ125σ126σ-134σ136σ139σ |
| 6 (124) | 112σ113σ122σ-133σ136σ140σ | 113σ114σ122σ-135σ136σ140σ | 113σ114σ120σ-132σ143σ144σ | 118σ120σ121σ-133σ140σ142σ |
| 7 (124) | 114σ123σ124σ-137σ141σ142σ | 112σ113σ114σ-135σ136σ137σ | 112σ113σ118σ-135σ139σ142σ | 117σ118σ121σ-130σ133σ135σ |
| 8 (128) | 117σ127σ128σ-140σ141σ142σ | 116σ117σ127σ-138σ141σ145σ | 116σ117σ125σ-134σ138σ147σ | 119σ121σ125σ-131σ134σ136σ |
| 9 (112) | 103σ104σ111σ-119σ121σ125σ | 104σ105σ111σ-121σ123σ124σ | 105σ107σ109σ-118σ121σ129σ | 105σ107σ109σ-116σ118σ122σ |
| 10 (112) | 103σ104σ111σ-120σ121σ128σ | 102σ103σ104σ-121σ123σ126σ | 106σ108σ110σ-116σ118σ120σ | 103σ108σ110σ-116σ118σ120σ |
| 11 (104) | 96σ97σ103σ-112σ113σ114σ | 95σ96σ97σ-113σ115σ118σ | 97σ101σ102σ-108σ112σ121σ | 97σ101σ102σ-108σ110σ112σ |
| 12 (108) | 99π101σ107σ-117σ118σ121σ | 99σ100σ101σ-120σ122σ123σ | 101σ105σ106σ-112σ117σ123σ | 101σ105σ106σ-112σ114σ117σ |
| 13 (112) | 104σ105σ111σ-118σ119σ121σ | 103σ104σ105σ-119σ121σ123σ | 104σ109σ110σ-118σ122σ123σ | 104σ109σ110σ-116σ123σ124σ |
| 14 (116) | 107σ108σ115σ-122σ125σ128σ | 106σ107σ108σ-124σ125σ126σ | 107σ108σ112σ-122σ129σ130σ | 108σ111σ112σ-122σ123σ128σ |
| 15 (123) | 112σ113σ122σ-129σ130σ131σ | 111σ112σ113σ-130σ134σ135σ | 113σ120σ121σ-132σ133σ136σ | 113σ120σ121σ-127σ131σ133σ |
| 16 (111) | 101σ103σ110σ-117σ120σ124σ | 101σ103σ109σ-119σ122σ123σ | 100σ101σ109σ-122σ125σ126σ | 105σ108σ109σ-115σ121σ122σ |
| 17 (120) | 110σ111σ119σ-133σ137σ138σ | 109σ110σ111σ-133σ136σ138σ | 114σ117σ118σ-138σ143σ145σ | 111σ117σ118σ-127σ128σ129σ |
| 18 (117) | 108σ116σ117σ-125σ134σ135σ | 106σ107σ108σ-126σ128σ130σ | 107σ108σ114σ-124σ129σ130σ | 113σ114σ115σ-129σ130σ133σ |
| 19 (121) | 111σ112σ120σ-131σ132σ135σ | 112σ118σ120σ-135σ139σ140σ | 116σ118σ119σ-129σ131σ133σ | 116σ118σ119σ-127σ130σ134σ |
| 20 (117) | 107σ116σ117σ-125σ126σ127σ | 106σ107σ116σ-125σ132σ133σ | 106σ107σ114σ-128σ132σ133σ | 110σ112σ114σ-125σ133σ134σ |
| 21 (120) | 108σ109σ119σ-128σ131σ138σ | 108σ109σ119σ-132σ136σ137σ | 109σ116σ118σ-126σ130σ132σ | 113σ116σ118σ-126σ130σ131σ |
| 22 (130) | 119σ120σ128σ-141σ143σ149σ | 118σ119σ120σ-143σ148σ149σ | 120σ123σ125σ-139σ149σ150σ | 120σ123σ125σ-139σ140σ141σ |

**Table 8:** Local Molecular Orbitals of atoms24, 25 and 26

| Molecules | Atom 24 (N) | Atom 25 (H) | Atom 26 (C) |
|---|---|---|---|
| 1 (112) | 108σ109σ110σ-<br>118σ119σ127σ | 94σ95σ108σ-<br>116σ117σ118σ | 108σ109σ110π-<br>117π118σ119σ |
| 2 (128) | 123σ125σ126σ-<br>132σ134σ135σ | 98σ108σ123σ-<br>132σ134σ136σ | 123π125σ126π-<br>132σ134π136σ |
| 3 (116) | 110σ113σ114σ-<br>120σ122σ135σ | 99σ102σ110σ-<br>120σ123σ124σ | 110σ113π114σ-<br>120π122σ124σ |
| 4 (124) | 118σ120σ121σ-<br>128σ129σ136σ | 88σ102σ118σ-<br>127σ128σ129σ | 118σ120σ121π-<br>127σ128π129σ |
| 5 (128) | 123σ125σ126σ-<br>134σ145σ149σ | 96σ97σ114σ-<br>136σ137σ138σ | 123σ125σ126σ-<br>131σ134π136π |
| 6 (124) | 120σ121σ124σ-<br>127σ128σ133σ | 97σ98σ118σ-<br>131σ132σ133σ | 118π120σ124σ-<br>127σ128π131σ |
| 7 (124) | 118σ121σ122σ-<br>128σ132σ133σ | 82σ89σ95σ-<br>130σ131σ132σ | 118σ121σ122σ-<br>126π128σ130π |
| 8 (128) | 124σ125σ126σ-<br>131σ134σ147σ | 103σ104σ121σ-<br>136σ138σ139σ | 121π125π126σ-<br>131π132σ134π |
| 9 (112) | 107σ109σ110σ-<br>116σ118σ121σ | 87σ88σ107σ-<br>116σ117σ118σ | 105π107σ109σ-<br>116π117σ118π |
| 10 (112) | 106σ108σ110σ-<br>116σ120σ130σ | 64σ87σ106σ-<br>116σ118σ120σ | 106π108σ110π-<br>116π118π120σ |
| 11 (104) | 96σ101σ102σ-<br>108σ112σ120σ | 81σ83σ102σ-<br>110σ112σ113σ | 96σ101σ102σ-<br>108σ110π114π |
| 12 (108) | 101σ105σ106σ-<br>112σ135σ144σ | 89σ99σ106σ-<br>114σ115σ117σ | 101π105σ106σ-<br>112π114π118π |
| 13 (112) | 103σ109σ110σ-<br>116σ119σ135σ | 96σ109σ110σ-<br>118σ119σ120σ | 103π109π110π-<br>116σ118π122π |
| 14 (116) | 108σ111σ112σ-<br>119σ123σ128σ | 91σ96σ111σ-<br>122σ123σ125σ | 101σ111σ112σ-<br>119σ122π131π |
| 15 (123) | 113σ120σ121σ-<br>127σ130σ131σ | 89σ105σ121σ-<br>131σ132σ133σ | 113π120σ121σ-<br>127σ130π131π |
| 16 (111) | 105σ108σ109σ-<br>115σ119σ125σ | 90σ91σ108σ-<br>117σ118σ119σ | 105π108σ109σ-<br>115π117π126π |
| 17 (120) | 114σ117σ118σ-<br>122σ127σ128σ | 88σ96σ100σ-<br>124σ126σ127σ | 114π117π118σ-<br>122π127π128σ |
| 18 (117) | 113σ114σ115σ-<br>119σ122σ125σ | 95σ99σ113σ-<br>124σ125σ126σ | 113σ114π115σ-<br>119σ122π125π |
| 19 (121) | 116σ118σ119σ-<br>122σ127σ131σ | 92σ98σ116σ-<br>125σ130σ133σ | 108π116π118σ-<br>122σ127π130π |
| 20 (117) | 112σ114σ115σ-<br>119σ124σ134σ | 85σ92σσ95σ-<br>122123125 | 110π112π114π-<br>119σ122π124σ |
| 21 (120) | 114σ116σ118σ-<br>121σ123σ126σ | 86σ88σ92σ-<br>123σ126σ128σ | 114π116π118σ-<br>121σ123π126π |
| 22 (130) | 125σ127σ129σ-<br>131σ135σ136σ | 99σ106σ123σ-<br>137σ138σ139σ | 116π123π125π-<br>131π135π136σ |

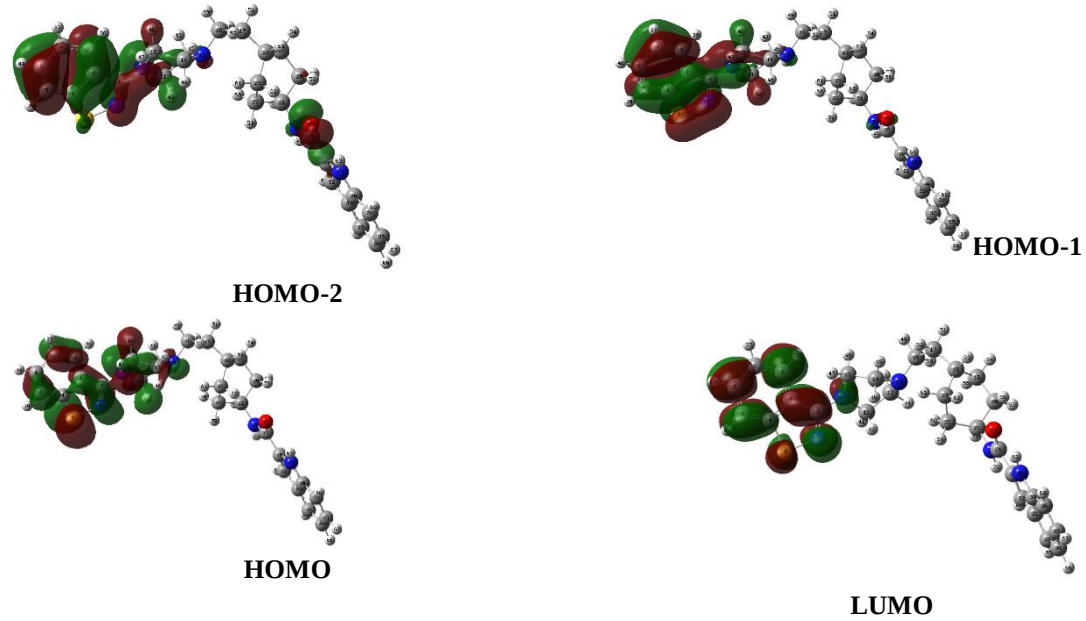
• **The local molecular orbital of molecule 19 and 22**

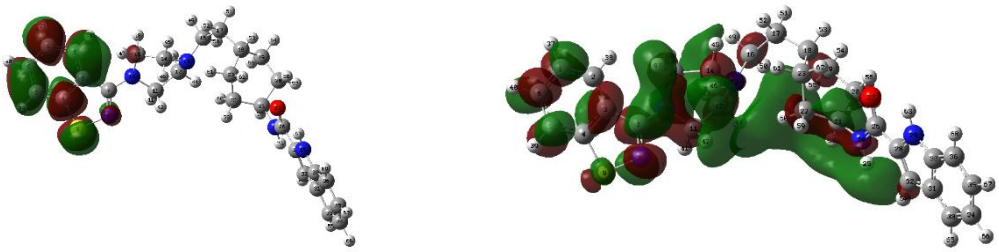
Atom 26 is a carbon atom of the amide function of the common skeleton is a molecular orbital of nature π and σ. The figure below shows this orbital in the molecule 19:




*Fugure 5: Molecular orbitals of molecule 19*

The orbital in the molecule 22 shows that these orbitals are π-nature for atom 1.





**LUMO+1** **LUMO+2**

*Figure 6: Molecular orbitals of molecule 22*

**Discussion**

**Discussion of the hD2L dopamine receptor results**

The statistical parameters show that:

The probability of Fischer F (7,13) = 37.9 > F (7,13) tabbed = 2.83 which implies that the equation is significant at the level α (0.5). Thus, there is only a 5% probability that there is no real link between antipsychotic activity and local reactivity index.

The p-value or probability value p = 1.17986E-07 < 5% percent so the regression equation is statistically significant.

The antipsychotic activity is strongly correlated to 97.64% of the local atomic index obtained in the model.

Observing the values of the beta coefficients (Table 2), we can classify the variables by the following priority order:

$$Q_{24} > F_{17}(LUMO)^{*} > F_{26}(LUMO)^{*} > \varsigma_{20} > S_{18}^{E}(HOMO-2)^{*} > F_{12}(HOMO-2)^{*} > F_{25}(LUMO)^{*}.$$

The p-values of the index are greater than 0.001; these indexes are not statistically significant at 0.1%. Next the analysis will be done with the other variables.

As the inhibition constant $K_i$ is a measure of the interaction force between the drug candidate and the target. The lower value of Ki correspond to the stronger interactions of benzisothiazolylpiperazine derivatives with the receptor. Thus, the analysis variable per variable suggests that a good antipsychotic activity of the benzisothiazolylpiperazine derivatives is linked to low numerical values for the indexes $\varsigma_{20}$, $F_{17}(LUMO)^{*}$ for those indexes are positive as well as their coefficients, with a low negative value of $S_{18}^{E}(HOMO-2)^{*}$ because the coefficient is negative and at a high positive value of $F_{26}(LUMO)^{*}$ because the coefficient is negative and a high negative value of $Q_{24}$.

Atom 20 is a carbon atom of cyclohexane. A low numerical value of $\varsigma_{20}$ implies a large value of the HOMO-LUMO gap including a resistance of this atom to electron transfer with other fragments. Then the atom should be substituted by an electron deficient center.

Atom 24 is a nitrogen atom bound to cyclohexane. It is normal that its net charge $Q_{24}$ is negative; a large negative value of this index suggests that the atom 24 interacts with an electropositive center of the D2 receptor; this interaction could be done through the lone pair of the nitrogen atom.

Atom 17 is a carbon atom bound to cyclohexane. A low value of $F_{17}(LUMO)^{*}$ implies that the atom 17 is substituted by an electron deficient center. This interaction shall be from type σ-σ (See table 7).

Atom 26 is a carbon atom of a carbonyl group. A large value $F_{26}(LUMO)^{*}$ indicates that the atom 26 interacts with an electron-rich (substituent) center. Moreover, all the molecular orbitals located on this atom are generally σ and π type (See Table 8). So this interaction will be σ or π type.

Atom 18 is a carbon atom of cyclohexane. A low negative value of $S_{18}^{E}(HOMO-2)^{*}$ corresponds to a weak donor character of the atom 18. The appearance of (HOMO-1) in the activity implies that the molecular orbitals (HOMO) * and (HOMO-1)* also participate in the biological activity. In addition, the orbital located on this atom

are all from type σ Thus the molecular orbitals (HOMO) *, (HOMO - 1) * of the atom 18 interact with a center rich in electrons but these interactions are σ type (See Table 7).

All these suggestions are presented on the partial 2D-pharmacophore of fig 5.

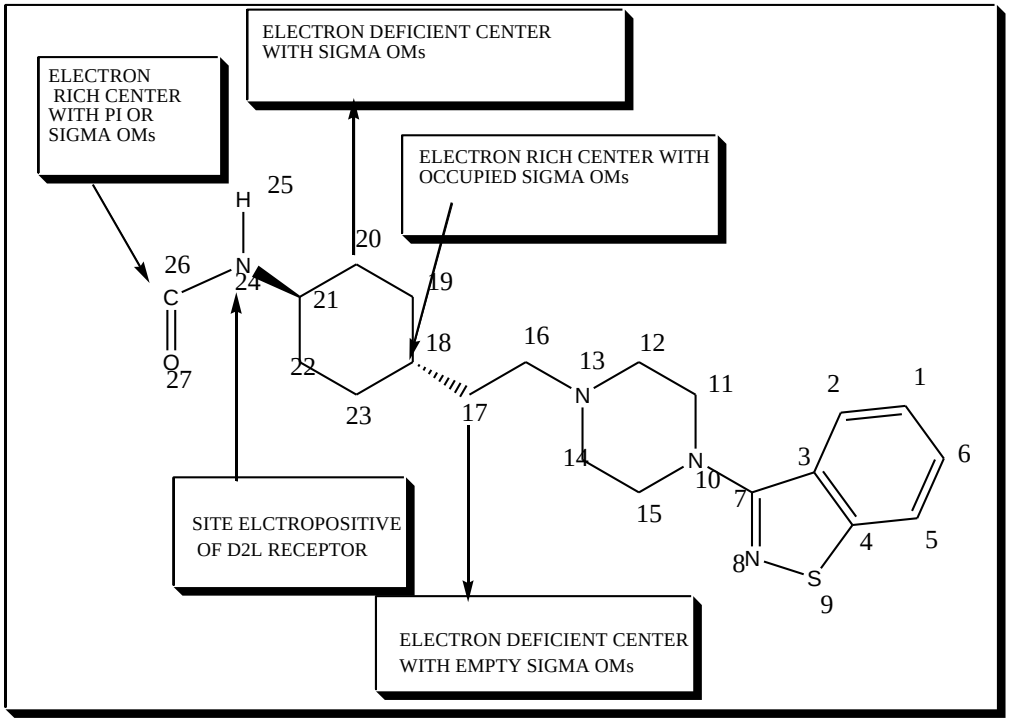



*Figure 7: 2D pharmacophore for the affinity of benzisothiazolylpiperazine derivatives with hd2L dopaminergic receptor*

**Discussion of the hD3 dopamine receptor results**

The statistical parameters show that:

F (8,13) = 31.62> F (8,13) tabbed = 2.77 so the global template is statistically significant with risk α = 0.05. This means that there is only a 5% chance that there is no real link between antipsychotic activity and local reactivity indexes.

P = 2.67184E-07 <0.05 implies that the multiple linear regression equation is statistically significant. R = 97.53% shows that there is a strong correlation between the local atomic reactivity indexes and the conducted biological activity.

The values analysis of coefficients beta (Table 4) makes it possible to classify the variables following the priority order:

$$\mu_{26} > S_{13}^{N}(LUMO+1)^{*} > S_{16}^{N}(LUMO)^{*} > F_{18}(HOMO-1)^{*} > F_{1}(HOMO)^{*} > S_{17}^{N}(LUMO)^{*} > S_{21}^{N}(LUMO)^{*} > S_{24}^{E}(HOMO)^{*}.$$

The variables $S_{21}^{N}(LUMO)^{*}$, $S_{17}^{N}(LUMO)^{*}$ and $S_{24}^{E}(HOMO)^{*}$ will not be considered during the analysis variable per variable since they are not significant at 0.1% because their P-value are all greater than 0.1%.

As the inhibition constant Ki is a measure of the interaction force between the drug candidate and the target. Thus, the analysis variable per variable suggests good antipsychotic activity of benzisothiazolylpiperazine derivatives is associated with low numerical values of $F_{18}(HOMO-1)^{*}$, $S_{13}^{N}(LUMO+1)^{*}$ and $S_{16}^{N}(LUMO)^{*}$, large negative value of $\mu_{26}$ and high positive value of $F_{1}(HOMO)^{*}$.

Atom 26 is a carbon atom of a carbonyl group. A large negative value of $\mu_{26}$ suggests that the LUMO and the HOMO must be lowered on the energy axis. So, therefore, this atom must interact with anelectron rich center such as for instance a carboxylate group.

Atom 18 is a carbon atom of cyclohexane. The appearance of (HOMO-1)* implies that (HOMO)* also participates in antipsychotic activity and thus, a low positive value of $F_{18}(HOMO-1)^*$ implies orbitals (HOMO-1) * and (HOMO) * of the C18 atom interact with an electron rich center but this is about an interaction σ-σ (table 7).

Atom 13 is a nitrogen atom. A weak numerical value of negative of $S_{13}^N(LUMO+1)^*$ returns to a low electro acceptor capacity. The presence of (LUMO + 1)* leads us to say that (LUMO + 1)* and (LUMO)* participate in the biological activity. Thus, the molecular orbitals (LUMO + 1)* and (LUMO)* of the $N^{13}$ atom interact with a poor center of the dopaminergic hD3 receptor, but these interactions are of the type σ-σ (Table 6).

Atom 16 is a carbon atom. A low and negative numerical value of $S_{16}^N(LUMO)^*$ corresponds to a low electro acceptor capacity. Then the orbital (LUMO) * of this atom must interact with a center that is poor in electrons. According to table 6, this interaction is from type σ-σ.

Atom 1 is a carbon atom. A high numerical value of $F_1(HOMO)^*$ suggests that for a good biological activity, the orbital (HOMO) * of the atom 1 interacts with a poor center in electrons. Moreover, all the molecular orbitals of this atom are π type (See table 6). So this interaction is from type π-π.

All these suggestions are presented on the partial 2D-pharmacophore of fig 8.

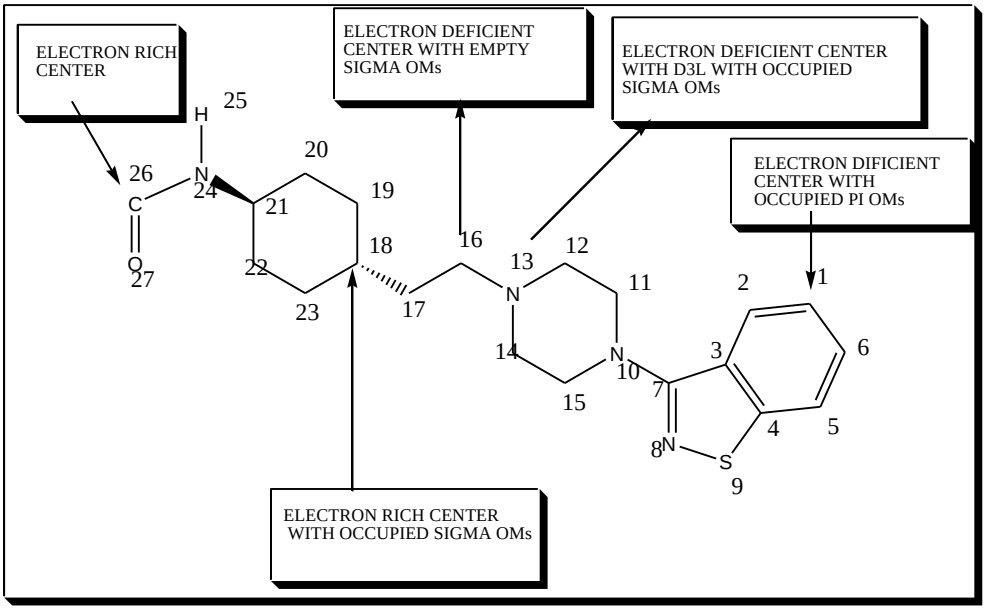



*Figure 8: 2D pharmacophore for the affinity of benzisothiazolylpiperazine derivatives with hd3 dopaminergic receptor*

**Conclusions**

These pharmacophores were obtained with statistically significant results concerning the variation of the numerical values of a definite set of local indices of atomic reactivity and the variation of the antipsychotic activity of the benzisothiazolylpiperazine derivatives to improve the activity of the latter. The results should be useful to propose new molecules that have higher antipsychotic effects for the treatment of schizophrenia. The pharmacophores proposed show that the actions of the benzisothiazolylpiperazine derivatives on the hD2L and hD3 receptors have different mechanisms.

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