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A Density Functional Theory Study Of The Relationships Between Electronic Structure And Metabotropic Glutamate Receptor Subtype 5 Affinity Of 2-Amino- And 2-Halothiazole Derivatives.

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ABSTRACT

We carried out an investigation and analysis of the relationships between the electronic structure and the metabotropic glutamate receptor subtype 5 affinity for a series of 2-amino- and 2-halothiazole derivatives using a model-based method. The electronic structure of all the molecules was calculated within the Density Functional Theory at the B3LYP/6-31g(d,p) level with full geometry optimization. Linear multiple regression analysis techniques were employed to find the best relationship between receptor binding affinity and local atomic reactivity indices belonging to a common skeleton. The variation of the receptor binding affinity is related to the variation of a set of three local atomic reactivity indices. The corresponding partial interaction pharmacophore is construed. The interaction with the receptor seems to be orbital-controlled. This is another example showing the absolute necessity of using formal quantum-chemical methods to study the microscopic basis of drug action.

Keywords: QSAR, pharmacophore, metabotropic glutamate receptor, 2-halothiazole, 2-aminothiazole, local atomic reactivity indices.

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INTRODUCTION

L-glutamate, the major excitatory neurotransmitter in the brain, has a leading role during development since it modulates neuron formation and synaptic strengthening in the early phases and due to its key role in neuronal plasticity and cognitive functioning. One of the two most important receptor groups that are known to be modulated by L-glutamate comprises the metabotropic glutamate receptors (mGlu), which are heptahelical transmembrane spanning proteins coupled to effector G-proteins. mGlu bind L-glutamate to modulate presynaptic neurotransmitter release or postsynaptic excitatory neurotransmission. On the basis of their intracellular signal transduction mechanisms, pharmacology and sequence homologies, mGlu receptors have been additionally divided into three subfamilies: group I ($mGlu_1$, $mGlu_5$), group II ($mGlu_2$, $mGlu_3$), and group III ($mGlu_4$, $mGlu_6$, $mGlu_7$, $mGlu_8$) [1, 2]. A broad range of neurological disorders, such as epilepsy, chronic pain, schizophrenia, Alzheimer's disease and drug addiction have been associated with dysfunction of glutamatergic systems [3-24]. It is therefore of interest to provide data about the microscopic details of the interaction of synthetic ligands with these receptors [25-42]. Recently, Siméon et al. synthesized a group of 2-amino and 2-halothiazole derivatives and tested their affinity for the rat brain tissue $mGlu_5$ receptor providing the experimental $mGlu_5$ receptor affinity values for a reasonably large group of compounds [38]. Here, and using Siméon et al.'s values, we present the results of a search for relationships between detailed electronic structure and receptor binding affinity. This should guide experimental medicinal chemists in the synthesis of new molecules having enhanced or diminished receptor binding affinity.

METHODS AND CALCULATIONS

The model

As the model-based [43] framework employed here has been presented and fully analyzed in many publications, we present here only the final results. The drug-receptor affinity constant, K_i, pA_2 or IC_{50}, is a linear function of several local atomic reactivity indices (LARIs) with the following general form [44-71]:

$$\begin{aligned}\log K_i = a + bM_{D_i} + c\log\left[\sigma_{D_i}/(ABC)^{1/2}\right] + \sum_j \left[e_j Q_j + f_j S_j^E + s_j S_j^N\right] + \\ + \sum_j \sum_m \left[h_j(m)F_j(m) + x_j(m)S_j^E(m)\right] + + \sum_j \sum_{m'} \left[r_j(m')F_j(m') + t_j(m')S_j^N(m')\right] + \\ + \sum_j \left[g_j\mu_j + k_j\eta_j + o_j\omega_j + z_j\varsigma_j + w_j Q_j^{\max} + q_i LDOSHOMO_i^* + l_i LDOSLUMO_i^*\right]\end{aligned} \quad (1)$$

where M is the drug's mass, σ its symmetry number and ABC the product of the drug's moment of inertia about the three principal axes of rotation. The LARIs are presented in Table 1 with their proposed physical interpretation. The model was extended to include any biological activity, BA (replacing K_i by BA in Eq. 1). The moment of inertia term can be expressed as [52, 55]:

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$$\log\left[(ABC)^{-1/2}\right] = \sum_t \sum_t m_{i,t} R_{i,t}^2 = \sum_t O_t \qquad (2)$$

where the summation over t is over the various substituents of the molecule, $m_{i,t}$ is the mass of the i-th atom belonging to the t-th substituent, $R_{i,t}$ being its distance to the atom to which the substituent is bonded. O_t, called the Orientational Parameter, is related to the influence of the t-th substituent on the fraction of molecules attaining the correct orientation to interact with the partner.

Table 1: Local Atomic Reactivity Indices and their meaning.

LARI	Name	Physical interpretation	Units
Q_i	Net atomic charge of atom i	Electrostatic interaction	e
S_i^E	Total atomic electrophilic superdelocalizability of atom i	Total atomic electron-donating capacity of atom i (MO-MO interaction) [72]	e/eV
S_i^N	Total atomic nucleophilic superdelocalizability of atom i	Total atomic electron-accepting capacity of atom i (MO-MO interaction) [72]	e/eV
$S_i^E(m)$	Orbital atomic electrophilic superdelocalizability of atom i and occupied MO m	Electron-donating capacity of atom i at occupied MO m (MO-MO interaction) [72]	e/eV
$S_i^N(m')$	Orbital atomic nucleophilic superdelocalizability of atom i and empty MO m'	Electron-accepting capacity of atom i at vacant MO m' (MO-MO interaction) [72]	e/eV
F_i	Fukui index of atom i	Total electron population of atom i (MO-MO interaction) [72, 73]	e
F_{mi}	Fukui index of atom i and occupied MO m.	Electron population of occupied MO m at atom i (MO-MO interaction) [72, 73]	e
$F_{m'i}$	Fukui index of atom i and empty MO m'	Electron population of vacant MO m' at atom i (MO-MO interaction) [72, 73]	e
μ_i	Local atomic electronic chemical potential of atom i	Propensity of atom i to gain or lose electrons [65]	eV
η_i	Local atomic hardness of atom i	Resistance of atom i to exchange electrons with the environment [65]	eV
ς_i	Local atomic softness of atom i	The inverse of η_i [65]	1/eV
ω_i	Local atomic electrophilicity of atom i	Tendency of atom i to receive extra electronic charge together with its resistance to exchange charge with the medium [65]	eV
$Q_i^{\max}$	Maximal amount of electronic charge atom i may receive	Maximal amount of electronic charge that atom i may receive [65]	---
O_t	Orientational Parameter	Influence on the fraction of molecules attaining the correct orientation to interact with a partner [55]	uma·Å^2
LDOSHOMO*$_i$	Local atomic density of states of the local HOMO of atom i	Interpenetration of occupied MOs of atom i with those of a partner [65]	e·eV
LDOSHOMO*$_i$	Local atomic density of states of the local LUMO of atom i	Interpenetration of vacant MOs of atom i with those of a partner [65]	e·eV

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Then, for n molecules we have a system of n linear equations 1. When solved, the values for the constants a, c, e_j, etc. are obtained. The application of this method to the analysis of the *in vitro* drug-receptor interaction has been very successful in many systems [45-48, 50, 52-54, 56, 57, 59, 60, 70, 71, 74].

Selection of experimental data.

The selected molecules, together with their mGlu5 receptor affinities, are shown in Fig.1 and Table 2 (we discarded the molecules with iodine substituents because the basis set employed for electronic structure calculations does not include this atom, see below). The experimental data employed are the binding affinities to rat brain mGlu5 receptors in an assay using [^{3}H]MPEP (2-methyl-6-(phenylethynyl)pyridine, 1.0 nM) as radioligand [38].

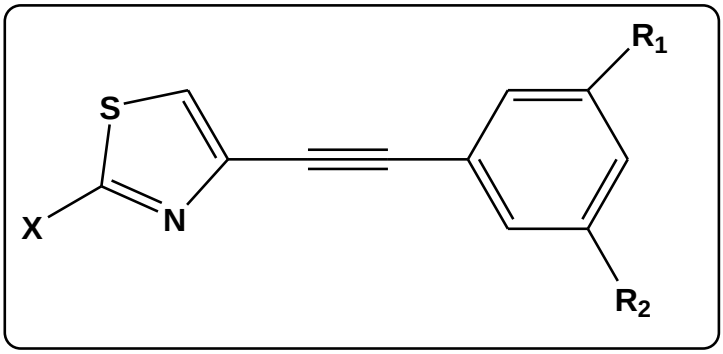

Figure 1. Substituted 2-amino and 2-halothiazole derivatives.

Table 2. 2-amino and 2-halothiazole derivatives and their rat brain tissue mGlu5 receptor binding affinities.

Molecule	X	R_1	R_2	log (Ki) (nM)
1	FCH_2	F	CN	-1.44
2	Me	F	CN	-1.10
3	NH_2	H	CN	-0.05
4	NH_2	F	CN	-0.60
5	NH_2	H	CH_2CN	0.77
6	NH_2	H	OMe	1.27
7	Cl	H	CN	-0.57
8	Cl	F	CN	-0.40
9	Cl	H	CH_2CN	0.49
10	Cl	H	OMe	0.91
11	F	H	CN	0.20
12	F	F	CN	-0.55
13	F	H	CH_2CN	0.59
14	F	H	OMe	1.36
15	F	H	H	2.09
16	Br	H	CN	0.57
17	Br	F	CN	-0.02
18	Br	H	CH_2CN	0.52
19	Br	H	OMe	1.35

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Calculations

The electronic structure of all the molecules was calculated within the Density Functional Theory (DFT) at the B3LYP/6-31g(d,p) level with full geometry optimization. Gaussian software was used [75]. We worked with the *common skeleton hypothesis* namely that there is a collection of atoms, common to all molecules analyzed, that accounts for almost all the biological activity. The action of the substituents consists in modifying the electronic structure of the common skeleton and/or influencing the proper alignment of the drug-partner complex. The common skeleton numbering is shown in Fig. 2.

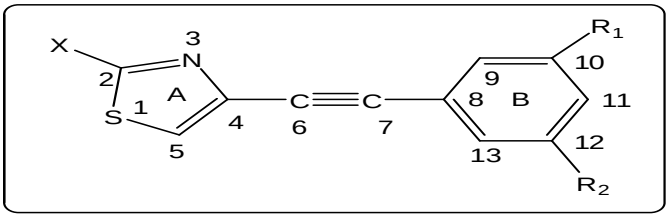

Figure 2. Numbering of atoms for the common skeleton of 2-amino and 2-halothiazole derivatives used in the LMRA.

The numerical values for the local atomic reactivity indices of the common skeleton were obtained with software written in our Unit. Negative electron populations coming from Mulliken Population Analysis were corrected as suggested earlier [76]. Orientational parameters were calculated as usual [52, 55]. Since the resolution of the system of linear equations is not possible because we do not have enough molecules, we made use of Linear Multiple Regression Analysis (LMRA) techniques to find the best solution. Here, statistics is employed as a servant and not as a queen. A matrix was built containing the dependent variable (the logarithm of the receptor binding affinity constant), the local atomic reactivity indices of all atoms of the common skeleton, and the orientational parameters of the X, R_1 and R_2 substituents as independent variables. The Statistica software was used for LMRA [77]. GaussView and Molekel were used to depict molecular orbitals and molecular electrostatic potentials [78, 79].

RESULTS

A LMRA including all molecules did not produce any meaningful result. We excluded molecules 1 and 2 because their K_i values come from another paper. No statistically significant results were obtained. An analysis of the experimental K_i values showed that one of them has a very high value (molecule 15, K_i=122 µM). When discarded from the set, the following statistically significant equation was obtained:

$$\log K_i = -1.42 + 2.04F_1(HOMO-2)^* - 20.07S_4^N(LUMO)^* + 1.30F_7(LUMO+2)^* \quad (3)$$

with n=16, R=0.98, R^2=0.95, adj R^2=0.94, F(3,12)=78.302 (p<0.000001), outliers>±2.002σ =0, and SD=0.17. Here, $F_1(HOMO-2)^*$ is the Fukui index (i.e., the electron population) of the third highest occupied molecular orbital localized on atom 1, $S_4^N(LUMO)^*$ is the local atomic nucleophilic superdelocalizability of the first vacant MO localized on atom 4, and $F_7(LUMO+2)^*$ is the Fukui index of the third vacant MO localized on atom 7 (see Fig. 2).

Asterisks denote the local MOs. For example, $(HOMO)_i^*$ denotes the highest occupied molecular orbital localized on atom i. $(HOMO)_i^*$ may or not coincide with the molecule's HOMO. The nomenclature for the three highest occupied and three lowest vacant MOs localized on atom i is the following: $(HOMO-2)_i^*$, $(HOMO-1)_i^*$, $(HOMO)_i^*$, $(LUMO)_i^*$, $(LUMO+1)_i^*$ and $(LUMO+2)_i^*$, The beta coefficients and t-test for significance of coefficients of Eq. 3 are shown in Table 3. Table 4 shows that, at $p<0.05$, there are no significant internal correlations between independent variables. Figure 3 shows the plot of observed values *vs.* calculated ones. The associated statistical parameters indicate that this equation is statistically significant, explaining about 96% of the variation of the receptor binding affinity.

Table 3: Beta coefficients and *t*-test for significance of coefficients in Eq. 3.

	Beta	t(12)	p-level
$F_1(HOMO-2)^*$	0.35	5.12	<0.0003
$S_4^N(LUMO)^*$	-1.00	-14.69	<0.000001
$F_7(LUMO+2)^*$	0.17	2.69	<0.020

Table 4. Squared correlation coefficients for the variables appearing in Eq. 3.

	$F_1(HOMO-2)^*$	$S_4^N(LUMO)^*$	$F_7(LUMO+2)^*$
$F_1(HOMO-2)^*$	1.00		
$S_4^N(LUMO)^*$	0.12	1.00	
$F_7(LUMO+2)^*$	0.02	0.03	1.00

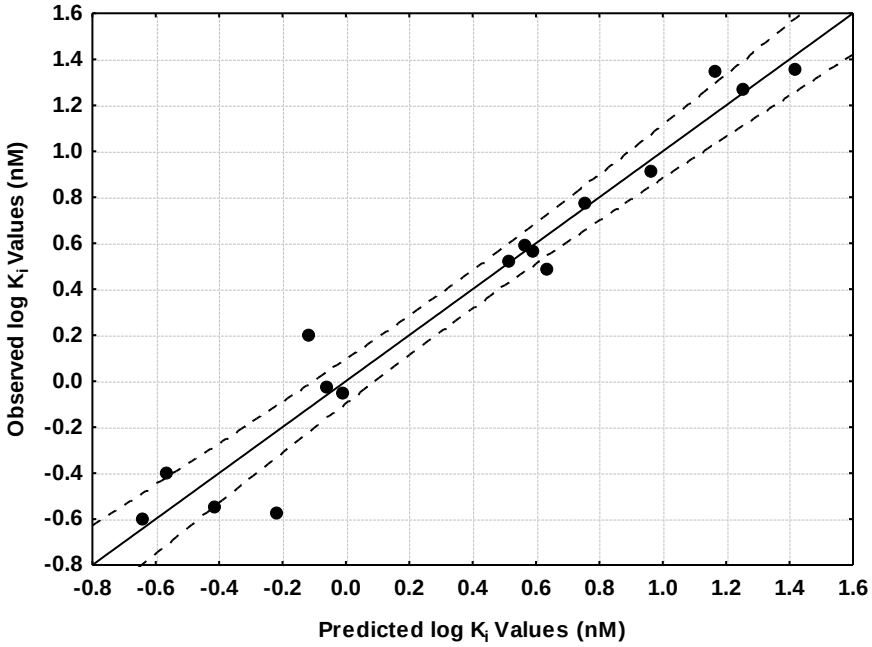

Figure 3: Observed versus calculated values (Eq. 3) of log (EC_{50}). Dashed lines denote the 95% confidence interval.

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DISCUSSION

Analysis of the molecular orbitals of 2-amino and 2-halothiazole derivatives.

Figures 4 and 5 show, respectively, the local second highest occupied molecular orbitals, (HOMO-1)*, of molecules 18 and 1. They correspond to the (HOMO-1) of molecule 18 and (HOMO-2) of molecule 1.

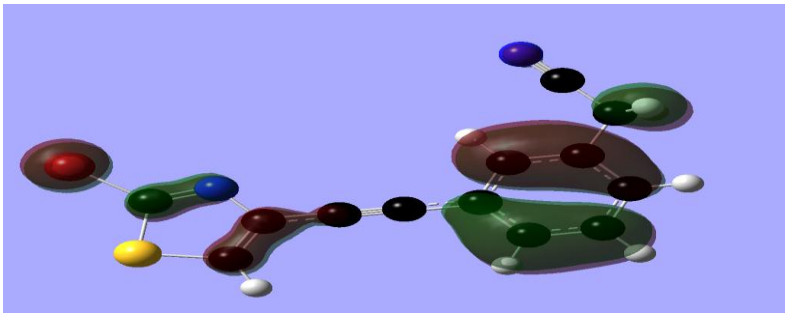

Figure 4. Localization of the second highest occupied MO of molecule 18 (HOMO-1). It also corresponds to the second highest occupied local molecular orbital, (HOMO-1)*, of atom 4 (isovalue = 0.02).

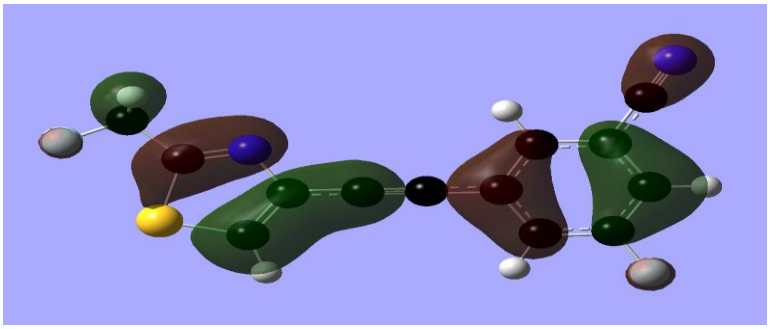

Figure 5. Localization of the third highest occupied MO of molecule 1 (HOMO-2). It also corresponds to the second highest occupied local molecular orbital, (HOMO-1)*, of atom 4 (isovalue = 0.02).

We can see that the localization of these molecular orbitals on atom 4 (see Fig. 2) is different regarding the extent of the electronic density around this atomic region. These small differences are important in the regulation (see below) of the drug-receptor interaction. Figure 6 shows the second highest occupied molecular orbital of molecule 1.

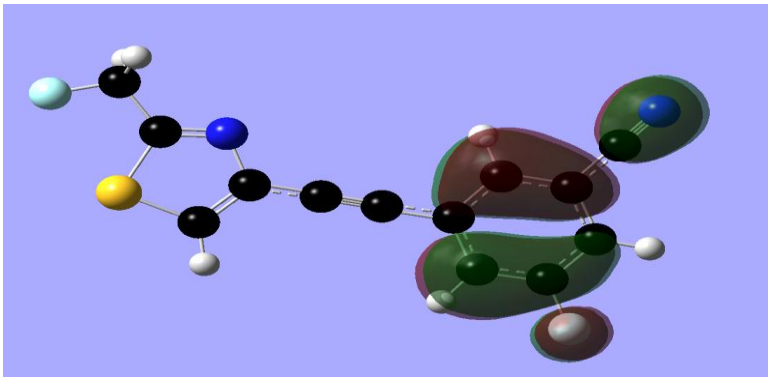

Figure 6. Localization of the second highest occupied MO of molecule 1 (HOMO-1) (isovalue = 0.02).

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We can see that this MO is not localized on atom 4. This is why it is not a local MO of this atom and it shows the rationale behind the definition of the local atomic reactivity indices employed in our work. In all the molecules analyzed here the HOMO is localized over the whole conjugated system but not in the same way. Figures 7 and 8 show, respectively, the HOMO of molecules 11 and 12.

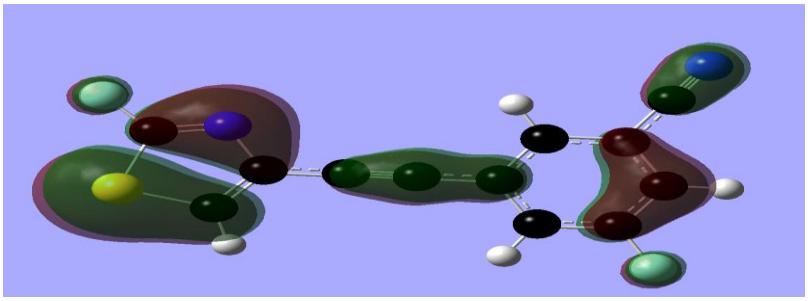

Figure 7. Localization of the highest occupied MO of molecule 11 HOMO (isovalue = 0.02).

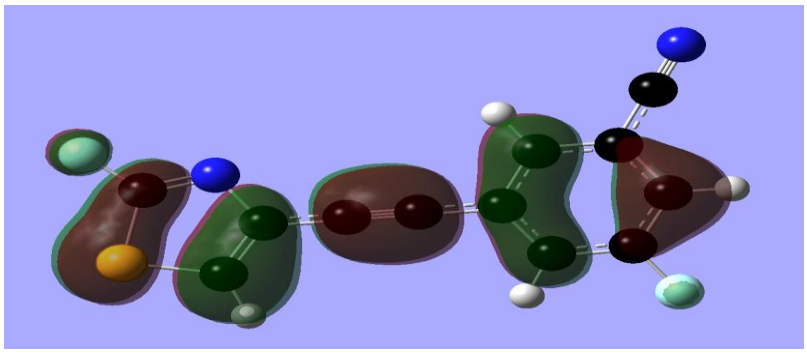

Figure 8. Localization of the highest occupied MO of molecule 12 HOMO (isovalue = 0.02).

We can see , for example, that the HOMO of molecule 11 is not localized on atoms 9 and 13 (see Fig. 2) while in molecule 12 it is localized there. The same situation occurs on atom 3. As these differences do not appear expressed in Eq. 3, it is safe to state that atoms 3, 9 and 13 do not participate directly in the drug-receptor interaction. A good test to retain or not the participation of ring B in the drug-receptor interaction would be the experimental assay of a molecule in which ring B is replaced by a methyl group. Substitution has similar effects on the LUMO localization. At the level of the (LUMO+1) and higher vacant MOs, substitution can also localize a MO on only one ring and/or change its nature. As an example, we show in Figs. 9 and 10 the (LUMO+2) localization in molecules 1 and 19. While the first is of π nature, the second has σ nature.

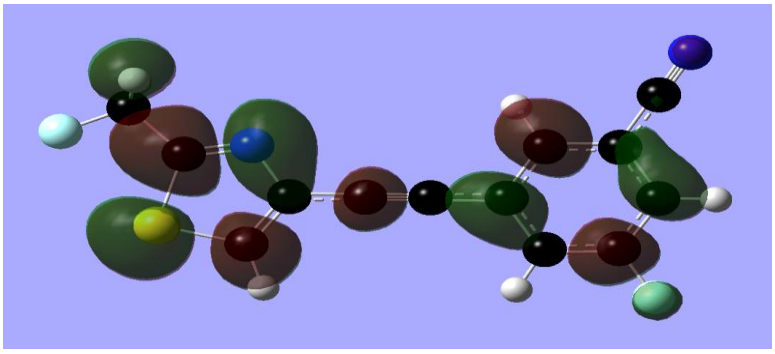

Figure 9. Localization of the third lowest vacant MO of molecule 1 (LUMO+2) (isovalue = 0.02).

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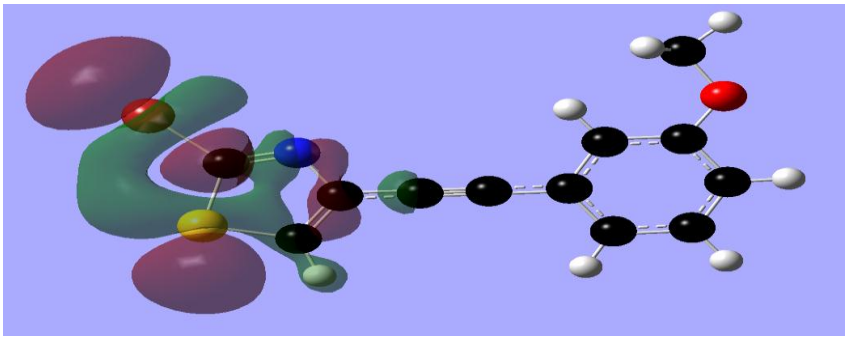

Figure 10. Localization of the third lowest vacant MO of molecule 19 (LUMO+2) (isovalue = 0.02).

Molecular electrostatic potential (MEP) of 2-amino and 2-halothiazole derivatives.

The structure of the molecular electrostatic potential provides information about the stages preceding the interaction with the receptor's active site itself. The recognition process occurs at drug-receptor distances in which electrostatic interactions predominate [51]. Figures 11 and 12 show, respectively, the MEP of molecule 5 seen from the molecular plane, and a side view.

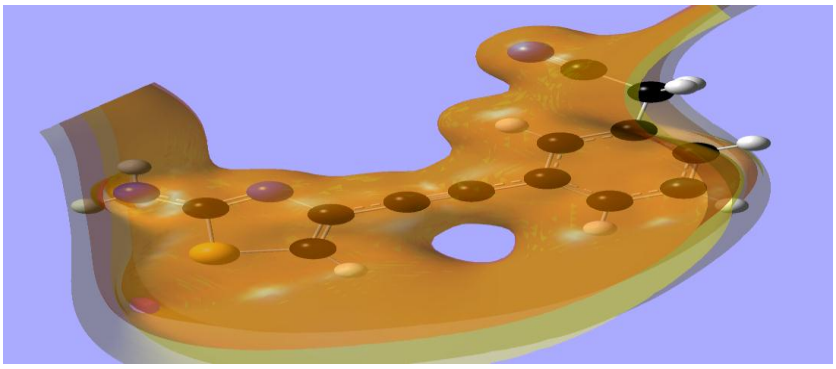

Figure 11. MEP of molecule 5 (front view). The orange isovalue surface corresponds to negative MEP values (-0.0004) and the yellow isovalue surface to positive MEP values (0.0004).

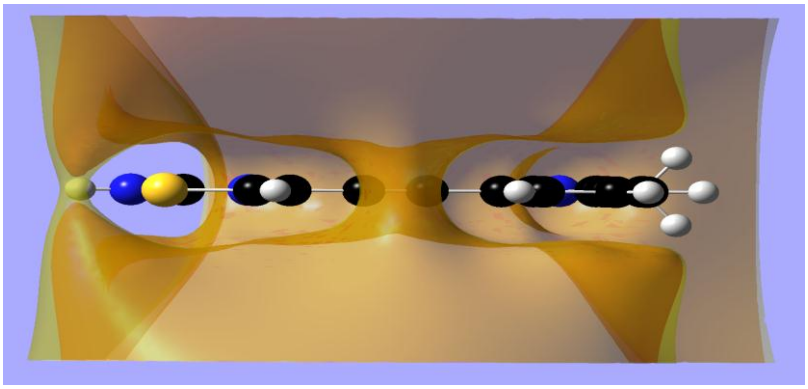

Figure 12. MEP of molecule 5 (side view). The orange isovalue surface corresponds to negative MEP values (-0.0004) and the yellow isovalue surface to positive MEP values (0.0004).

We can see in the upper part of Fig. 11 that the molecule is surrounded by an area of negative MEP. This area includes both sides of the aromatic system, leaving a positive MEP area in the remaining area of this system. Figure 13 shows the MEP of molecule 16.

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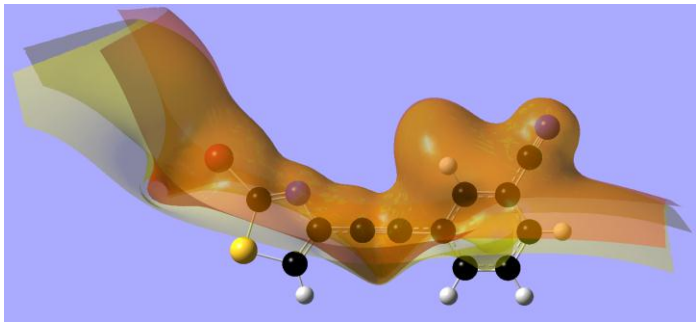

Figure 13. MEP of molecule 16. The orange isovalue surface corresponds to negative MEP values (-0.0004) and the yellow isovalue surface to positive MEP values (0.0004).

We can see that the main MEP features of both molecules are similar. Figures 14 and 15 show, respectively, the MEP of the same molecules at a distance of 3.0 Å from the nuclei.

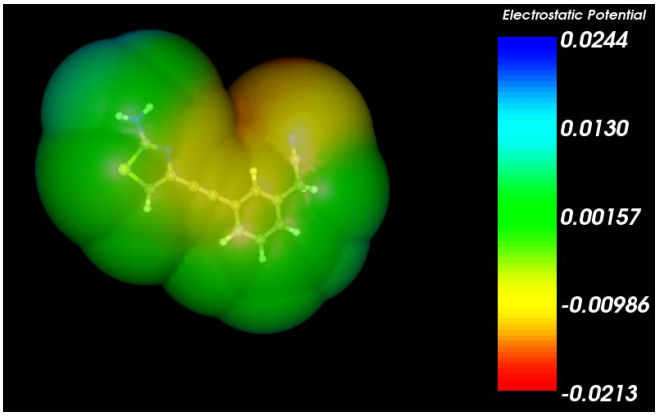

Figure 14. Molecular electrostatic potential of molecule 5 at a distance of 3.0 Å from the nuclei.

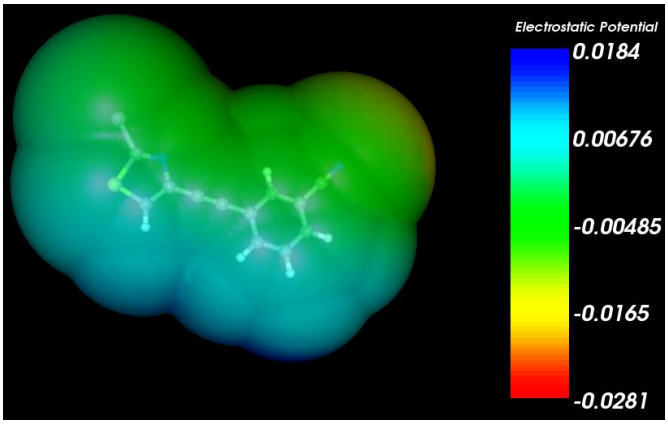

Figure 15. Molecular electrostatic potential of molecule 16 at a distance of 3.0 Å from the nuclei.

We can see that the MEP structure of both molecules is quite similar, their difference lying in the intensity of the molecular electrostatic potential: in molecule 5, the MEP of its upper central region is more negative than in molecule 16. On the other hand, molecule 16 has a more extended region of negative MEP. Note also that the most negative MEP area of molecule 1 is located between both rings (Fig. 14), while in molecule 16 is located at the upper right side of Fig. 15. This is probably due to the exchange of the amino group in molecule 5 for a bromine atom in molecule 16.

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Relationships between electronic structure and receptor binding affinity.

Before discussing the results we must remember that the final equations correlate the *variation* of the receptor binding affinity with the *variation* of one or more local atomic reactivity indices. Consequently, any index making a constant contribution will not appear inside the equation.

Our results indicate that, for the case analyzed, the variation of the receptor binding affinity is related to the variation of a set of three local atomic reactivity indices belonging to the common skeleton. The results obtained are very good considering the approximations made to build the model. The Beta values (Table 3) indicate that the importance of variables is $S_4^N(LUMO)^* > F_1(HOMO-2)^* > F_7(LUMO+2)^*$. A variable-by-variable analysis of Eq. 3 indicates that a high receptor binding affinity is associated with small values for these three indices. To deepen our analysis, we show in Table 5 the three highest local occupied and the three lowest local vacant molecular orbitals of atoms 1, 4 and 7. We have marked the MOs appearing in Eq. 3 in bold type.

Table 5. Local molecular orbitals for atoms 1, 4 and 7.

Molecule	Atom 1 (S)	Atom 4 (C)	Atom 7 (C)
1 (66)	**62σ**63σ66π-67π68π69π	63σ64π66π-**67π**68π69π	62σ63π66π-67π68π**70σ**
2 (62)	**58σ**59σ62π-63π64π65π	59σ60π62π-**63π**64π65π	58π59σ62π-63π64π**66π**
3 (58)	**54σ**55σ58π-59π60π61π	53π54σ58π-**59π**60π61π	55π57π58π-59π60π**61π**
4 (62)	**59σ**61π62π-63π64π65σ	57π58σ62π-**63π**64π65σ	59π61π62π-63π64π**65σ**
5 (62)	**58σ**59σ62π-63π65σ66π	59σ61π62π-**63π**65σ66π	59π61π62π-63π65σ**66π**
6 (60)	**57σ**59π60π-61π62σ63π	58π59π60π-**61π**62σ63π	58π59π60π-61π63π**64π**
7 (62)	**59σ**60π62π-63π64π65π	60π61π62π-**63π**64π65π	57π59π62π-63π64π**66σ**
8 (66)	**63σ**64π66π-67π68π69π	63σ64π66π-**67π**68π69π	61π63π66π-67π68π**69π**
9 (66)	**63σ**64π66π-67π68π70σ	64π65π66π-**67π**68π70σ	61π63π66π-67π70σ**71σ**
10 (64)	**62π**63π64π-65π66π67σ	62π63π64π-**65π**67σ69σ	62π63π64π-65π66π**67σ**
11 (58)	**55σ**56π58π-59π60π61π	56π57π58π-**59π**60π61π	54π55π58π-59π60π**62σ**
12 (62)	**59σ**60π62π-63π64π65π	59σ60π62π-**63π**64π65π	58π59π62π-63π64π**66σ**
13 (62)	**59σ**60π62π-63π64π66σ	59σ60π62π-**63π**64π66σ	59π60π62π-63π66σ**67π**
14 (60)	**58π**59π60π-61π62π63σ	58π59π60π-**61π**62π63σ	58π59π60π-61π63σ**65π**
15 (52)	**49σ**50π52π-53π54π56σ	49σ50π52π-**53π**54π56σ	49π50π52π-53π56σ**57π**
16 (71)	**67σ**68π71π-72π73π74π	69π70π71π-**72π**73π74π	66π68π71π-72π73π**76σ**
17 (75)	**71σ**72σ75π-76π77π78π	72σ73π75π-**76π**77π78π	70π72π75π-76π77π**78π**
18 (75)	**72σ**73π75π-76π77π78σ	73π74π75π-**76π**77π78σ	70π72π75π-76π80σ**81π**
19 (73)	**71π**72π73π-74π75π76σ	71π72π73π-**74π**76σ77σ	71π72π73π-74π75π**77σ**

Nomenclature: Molecule (HOMO) / (HOMO-2)* (HOMO-1)* (HOMO)*-(LUMO)* (LUMO+1)* (LUMO+2)*.

The association of high receptor binding affinity with low values of $F_1(HOMO-2)^*$ (which is always positive or zero) for this set of molecules can be explained by noting that the local (HOMO-2)* of atom 1 (sulfur) is in the majority of cases a σ MO. Note also that the local HOMOs of these molecules are of π nature, indicating that this atom most likely participates as an electron donor. This suggests that the σ MOs, considered as quasi non-

deformable electron densities, are participating in a repulsive interaction with the σ MOs of the partner. Therefore, a very low localization of a σ MO on atom 1 should facilitate its interaction with the receptor. The other point regarding these σ MOs leads to their eigenvalues: the ideal situation is that the energy of these MOs should lie as far as possible below the energy of the local HOMO. It is important to mention that we are only doing a qualitative variable-by-variable analysis. The requirement of a low value for $S_4^N(LUMO)^*$ can be explained as follows. The numerical values of this index are negative for all the molecules (negative eigenvalues for vacant MOs in closed-shell calculations are a nightmare). $S_4^N(LUMO)^*$ is the Fukui index of (LUMO)* divided by its eigenvalue. We can get a very small negative value for this index by diminishing the value of the Fukui index (i.e., by diminishing the localization of the (LUMO)* on atom 4), by making the eigenvalue less negative (by an appropriate substitution) or by both means. In any case the ideal situation requires a very small (LUMO)* localized on atom 4. Table 5 shows that this MO is of π nature in all the molecules. Considering that we are working within a framework in which vacant MOs exist and "*are there*" (this is a debatable point in quantum chemistry), a rational proposal for the requirement of this index is that this vacant π MO is participating in a repulsive interaction with one or more vacant π MOs (or π and σ MOs) of the partner (a "*ghost*" interaction). Then, atom 4 is also participating in the drug-receptor interaction as an electron-donor through, at least, its HOMO*. The fourth column of Table 5 shows the detailed local MO composition of atom 7 (a C atom belonging to the chain joining rings A and B, see Fig. 2). The (LUMO+2)*s are of π or σ nature. Note also that all local (LUMO)*s and almost all local (LUMO+2)*s are of π nature. A low value for $F_7(LUMO+2)^*$ (i.e., a low electron population on this MO) suggests that (LUMO+2) σ MOs are hindering the interaction of the lowest local empty vacant MOs of atom 7 with (π) occupied MOs of the receptor. In this case atom 7 participates as an electron acceptor. The experimental data and our calculations do not provide enough information about the specific kind of interaction for this case: it could occur through charge transfer or π-π stacking. Figure 16 shows the two-dimensional (2D) partial pharmacophore based on the above discussion. In general, the drug-receptor interaction is a highly complex and specific process produced by hundreds of millions years of evolution. Then, it is not surprising that the interaction should be orbital- and not charge-controlled. Otherwise, any molecule could bind to any receptor with disastrous results.

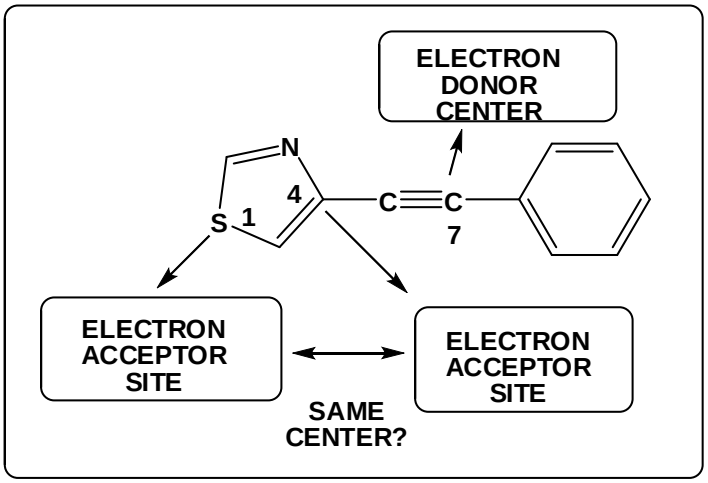

Figure 16. Partial 2D interaction pharmacophore.

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CONCLUSIONS

An excellent correlation between details of electronic structure and rat brain tissue mGlu5 receptor affinity was obtained for a group of 2-amino and 2-halothiazole derivatives. The model-based method employed for the study has shown again its high explanatory power. The local atomic reactivity indices, as defined and used in this study, are able to provide a near-perfect conceptual tool for the analysis of the drug-receptor interaction.

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