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A Theoretical Analysis of the Relationships between Electronic Structure and Dopamine D_4 Receptor Affinity in a series of compounds based on the classical D_4 agonist A-412997

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Abstract The Klopman-Peradejordi-Gómez was employed to find relationships between electronic structure and dopamine D_4 receptor binding affinity in a series of 2-(4-(Pyridin-2-yl)piperidin-1-yl)-N-(m-tolyl)acetamide analogues. A statistically significant equation was found involving some atoms of the three rings of the molecules. Atoms of the two aromatic rings seem to participate in π-π interactions. One of the nitrogen atoms of the saturated ring is involved in σ-σ or σ-π interactions. The two-dimensional pharmacophore built from the QSAR equation should be of help to obtain molecules with higher D_4 receptor affinity.

Keywords Dopamine, D_4 receptor, receptor affinity, Klopman-Peradejordi-Gómez method, QSAR, electronic structure, drug-receptor interaction, local molecular orbitals, local atomic reactivity indices

Introduction

Dopamine receptors (DR) are a class of G protein-coupled receptors that are veryimportant in the vertebrate central nervous system [1]. The neurotransmitter dopamine is the primary endogenous ligand for these receptors, controlling various physiological functions in the brain and periphery by acting on them [2-14].

There are at least five subtypes of DRs named D_1, D_2, D_3, D_4 and D_5. They are divided into D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) groups. The D_1-like receptors couple primarily to the G_s family of G proteins (G_s and G_{olf}), while the D_2-like receptors couple primarily to the $G_{i/o}$ family. These receptors are involved in the regulation of motor activity and several neurological disorders such as addiction, Alzheimer's disease, attention-deficit and/or hyperactivity disorder, bipolar disorder, Parkinson's disease and schizophrenia.

Here we shall focus on D_4 receptors. They are localized in the amygdala, frontal cortex, hypothalamus and nucleus accumbens; and are involved in addiction, attention, cognition, impulse control, reproductive behavior and sleep. During the early 1990s, some studies indicated that the atypical antipsychotic clozapine had higher affinity for D_4 receptor, compared with the other DR subtypes. Some ligands were synthesized and tested [15-18]. Nevertheless, the D_4 antagonists developed for schizophrenia were unsuccessful in the clinical studies. Only recently the D_4 receptor becomes again a target for both Parkinson's disease and addiction [19-21]. Several groups of molecules have been synthesized and tested as D_4 ligands [22-30]. Here we present the results of a theoretical study relating the electronic structure of a group of D_4 ligands with its receptor binding affinity.

Method, Models and Calculations

The technique employed to obtain formal structure-activity relationships is called the Klopman-Peradejordi-Gómez (KPG) QSAR method [31, 32]. The KPG model is a linear relationship between a biological activity and a large set of local atomic reactivity indices such as, for example, atomic net charges, superdelocalizabilities, Fukui indices and a set of indices derived within the Hartree-Fock scheme [32-39]. Note that from the historical point of view, atomic net charges, Fukui indices and superdelocalizabilities are the first local atomic reactivity indices [40, 41]. Considering that the various steps of its development were published and that it has been extensively reviewed and commented we shall analyze here only the resulting equation (see below). This method has obtained very good results for very different biological activities and molecules [42-50] (and references therein).

The selected molecules are a group of new molecules based on the classical D_4R agonist A-412997 [23]. Their general formula and biological activity are displayed, respectively, in Fig. 1 and Table 1. The biological activity analyzed is the human dopamine D_4 receptor binding data in HEK293 membranes determined through [^{3}H]-N-methylspiperone radioligand binding displacement assays [23].

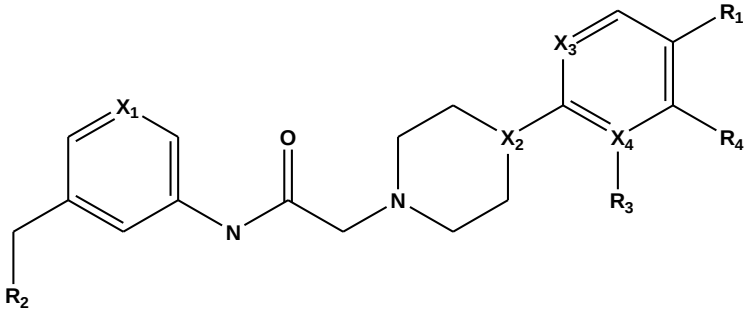

Figure 1: General formula of molecules

Table 1: Molecules and activity

Mol.	X_1	X_2	X_3	X_4	R_1	R_2	R_3	R_4	$\log(K_i)$ (D_4R)
1	C	C	C	N	H	H	---	H	1.73
2	C	C	C	C	H	H	H	H	1.41
3	C	C	C	C	CH_3	H	H	H	2.04
4	C	C	C	C	Cl	H	H	H	2.06
5	C	C	C	N	CH_3	H	---	H	1.62
6	C	N	C	N	H	H	---	H	2.33
7	C	N	N	N	H	H	---	H	2.50
8	C	N	C	N	Cl	H	---	H	1.98
9	C	N	C	C	H	H	$(CH)_4$		1.45
10	C	C	C	N	H	Me	---	H	1.92
11	C	N	C	N	H	Me	---	H	1.83
12	C	N	C	N	Cl	Me	---	H	2.24
13	N	N	C	N	H	H	---	H	3.81
14	N	N	C	N	Cl	H	---	H	3.70

Calculations [51]

The electronic structure of all molecules was calculated within the Density Functional Theory at the B3LYP/6-31g(d,p) level after full geometry optimization [52]. The Gaussian collection of programs was used. All the information for calculating the numerical values of the local atomic reactivity indices was obtained from the Gaussian results with the D-Cent-QSAR software [53, 54]. All the electron populations smaller than or equal to 0.01 e were considered as zero [39]. Negative electron populations coming from Mulliken Population Analysis were corrected as usual [55]. As the resolution of the system of linear equations is not possible because we don't have a

satisfactory number of molecules, we made use of Linear Multiple Regression Analysis (LMRA) techniques to find the best solution. For each case, a matrix containing the dependent variable (the biological activity) and the local atomic reactivity indices of all atoms of a molecular core common to all molecules as independent variables was built. The Statistica software was used for LMRA [56]. Note that LMRA will detect only those variables explaining the *variation* of the biological property. The 'common molecular core' or 'common skeleton' hypothesis states that there is a definite collection of atoms, common to all molecules analyzed, that accounts for approximately all the biological activity [57]. The action of the substituents consists in modifying the electronic structure of the common skeleton and influencing the right alignment of the drug throughout the orientational parameters. It is hypothesized that different parts or this common skeleton account for almost all the interactions leading to the expression of a given biological activity. The common skeleton for this case is shown in Fig. 2.

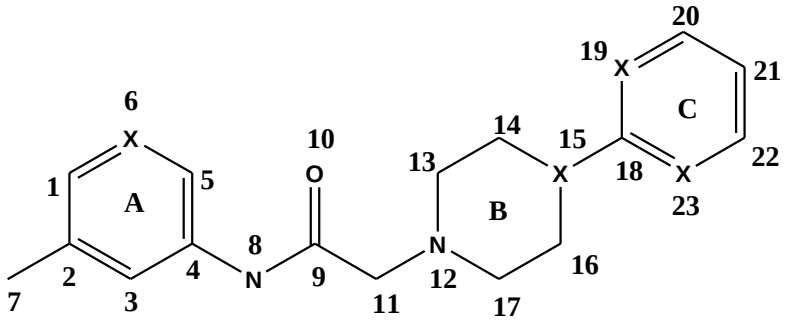

Figure 2: Common skeleton

Results

The best equation obtained was:

$$\log(K_i)=1.34-1.73F_{18}(LUMO)^*+4.97S_{12}^{N}(LUMO+2)^*+13.92F_1(LUMO+1)^*- \\ -0.06S_{23}^{E}(HOMO-1)^*-3.38Q_{14}^{max} \quad (1)$$

with n=12, R=0.99, R^2=0.99, adj-R^2=0.98, F(5,6)=95.53 ($p<0.00001$) and SD=0.05. No outliers were detected and no residuals fall outside the ±2σ limits. Here,F_{18}(LUMO)* is the Fukui index (the electron population) of the lowest empty local MO localized on atom 18, S_{12}^{N}(LUMO+2)* is the nucleophilic superdelocalizability of the third lowest empty local MO localized on atom 12, F_1(LUMO+1)* is the Fukui index of the second lowest empty local MO localized on atom 1, S_{23}^{E}(HOMO-1)* is the electrophilic superdelocalizability of the second highest occupied local MO localized on atom 23 and Q_{14}^{max} is the maximal amount of charge atom 14 may receive. The local molecular orbitals of an atom q are defined as the set of molecular orbitals having a predefined minimal value of the electron population on atom q. They are distinguished from the molecule's MOs by an asterisk. Table 2 shows the beta coefficients and the results of the t-test for significance of the coefficients. Table 3 shows the matrix of squared correlation coefficients for the variables of Eq. 1. There are no significant internal correlations between independent variables (Table 3). Figure 3 displays the plot of observed vs. calculated $\log(K_i)$.

Table 2: Beta coefficients and t-test for significance of coefficients in Eq. 1

	Beta	**t(6)**	**p-level**
F_{18}(LUMO)*	-0.46	-7.29	0.0003
S_{12}^{N}(LUMO+2)*	0.73	11.52	0.00003
F_1(LUMO+1)*	0.53	8.39	0.0002
S_{23}^{E}(HOMO-1)*	-0.40	-6.88	0.0005

Table 3: Matrix of squared correlation coefficients for the variables in Eq. 1

	F_{18}(LUMO)*	**S_{12}^{N}(LUMO+2)***	**F_1(LUMO+1)***	**S_{23}^{E}(HOMO-1)***
S_{12}^{N}(LUMO+2)*	0.15	1.00		
F_1(LUMO+1)*	0.06	0.08	1.00	
S_{23}^{E}(HOMO-1)*	0.03	0.03	0.07	1.00
Q_{14}^{max}	0.26	0.01	0.10	0.05

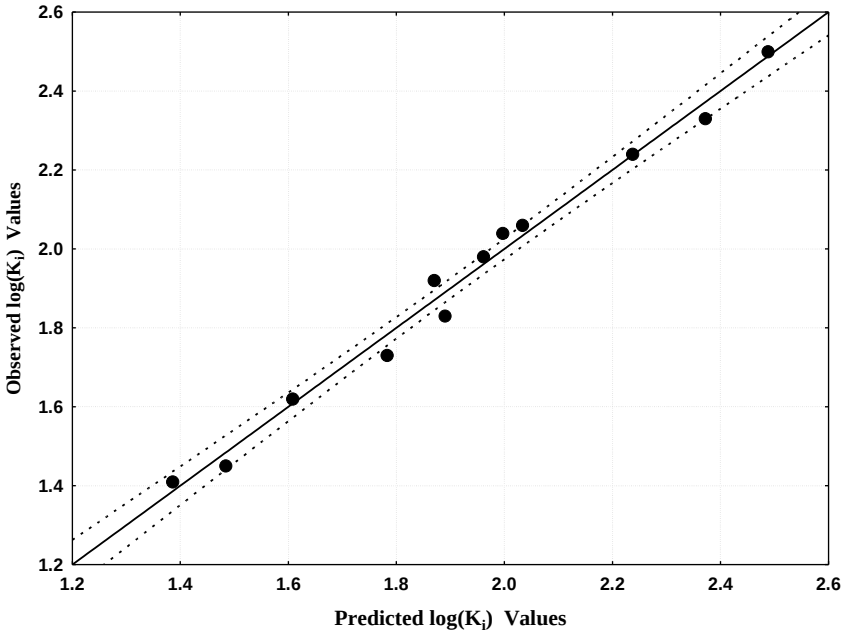

Figure 3: Plot of predicted vs. observed log(K_i) values (Eq. 1). Dashed lines denote the 95% confidence interval

The associated statistical parameters of Eq. 1 indicate that this equation is statistically significant and that the variation of the numerical values of a group of 5 local atomic reactivity indices of atoms of the common skeleton explains about 98% of the variation of log(K_i). Figure 3, spanning about 1.1 orders of magnitude, shows that there is a good correlation of observed *versus* calculated values and that almost all points are inside the 95% confidence interval.

Local Molecular Orbitals

Note that if a local atomic reactivity index of an inner occupied MO (i.e., HOMO-1 and/or HOMO-2) or of a higher vacant MO (LUMO+1 and/or LUMO+2) appears in any equation, this means that the remaining of the upper occupied MOs (for example, if HOMO-2 appears, upper means HOMO-1 and HOMO) or the remaining of the empty MOs (for example, if LUMO+1 appears, lower means the LUMO) contribute to the interaction. Their absence in the equation only means that the variation of their numerical values does not account for the variation of the numerical value of log(K_i). Table 4 shows the local molecular orbitals of atoms 1, 12, 14, 18 and 23.

Table 4: Local molecular orbitals of atoms 1, 12, 14, 18 and 23

Mol.	Atom 1	Atom 12	Atom 14	Atom 18	Atom 23
1 (83)	75σ76π82π- 85π86π87π	76σ78σ83σ- 85σ88σ95σ	78σ80σ83σ- 93σ94σ95σ	78σ79π80σ- 84π85σ86π	79π80σ83σ- 84π86π92σ
2 (83)	75σ76π82π- 84π85π88π	78σ81σ83σ- 89σ91σ93σ	77σ78σ83σ- 93σ97σ101σ	80π81π83σ- 86π87π95σ	77σ80π81π- 86π87π91σ
3 (87)	79σ80π86π- 88π89π92π	82σ85σ87σ- 93σ95σ101σ	81σ82σ87σ- 98σ102σ107σ	82σ85π87σ- 90π91π96σ	81σ84π85π- 90π91π96σ
4 (91)	84π85π90π- 92π95π97π	86σ89σ91σ- 98σ100σ101σ	85σ86σ91σ- 101σ110σ111σ	84σ86σ89π- 93π94π102σ	85σ87π89π- 93π94π96σ
5 (87)	79σ80π86π- 89π91π92π	82σ84σ87σ- 89σ92σ100σ	82σ83σ87σ- 97σ100σ107σ	82σ83σ84π- 88π90π94σ	83σ84π87σ- 88π90π96σ
6 (83)	74σ75π81π-	77σ78σ82σ-	76σ80σ83σ-	78π80σ83π-	78π80σ83π-

	84π86π88π	89σ93σ96σ	92σ95σ96σ	85π87π90σ	85π87π92σ
7 (83)	73σ74π81π-	78σ82σ83σ-	80σ82σ83σ-	80σ82π83π-	80σ82π83π-
	85π86π88π	89σ91σ94σ	94σ95σ96σ	84π87π90σ	84π87π92σ
8 (91)	80σ82π89π-	85σ86σ90σ-	86σ87σ91σ-	86π87σ91π-	85σ87σ91π-
	92π94π96π	98σ102σ103σ	101σ104σ105σ	93π95π99σ	93π95π97σ
9 (96)	84σ88π94π-	89σ90σ95σ-	93σ95σ96σ-	90σ93σ96π-	92π93π96π-
	98π99π101π	103σ109σ111σ	112σ114σ116σ	97π102π104σ	97π100π102π
10	78σ80π86π-	82σ83σ87σ-	82σ84σ87σ-	82σ83π84σ-	83π84σ87σ-
(87)	89π91π92π	93σ99σ100σ	98σ99σ100σ	88π90π98σ	88π90π96σ
11	78σ79π85π-	84σ86σ87σ-	84σ86σ87σ-	84σ86π87π-	84σ86π87π-
(87)	88π90π92π	93σ98σ99σ	96σ98σ99σ	89π91π94σ	89π91π96σ
12	85σ87π93π-	90σ94σ95σ-	91σ94σ95σ-	91σ94π95π-	91σ94π95π-
(95)	96π97π98π	102σ104σ105σ	105σ107σ108σ	97π99π103σ	96π97π99π
13	75σ77π78σ-	77σ78σ79σ-	77σ78σ79σ-	76σ78σ79π-	77σ78σ79π-
(79)	80π81π83σ	84σ85σ91σ	87σ88σ89σ	82π83π84π	82π83π88σ
14	83σ85π86σ-	85σ86σ87σ-	85σ86σ87σ-	84σ86σ87π-	84σ86σ87π-
(87)	88π89π92σ	92σ94σ99σ	96σ97σ98σ	90π91π95σ	90π91π93σ

Discussion

Table 2 shows that the importance of variables in Eq. 1 is S_{12}^{N}(LUMO+2)*> F_1(LUMO+1)*> F_{18}(LUMO)*> S_{23}^{E}(HOMO-1)*>>Q_{14}^{max}.A high affinity is associated with small numerical values of S_{12}^{N}(LUMO+2)*, with small numerical values of F_1(LUMO+1)*, with high numerical values of F_{18}(LUMO)*, with small numerical values of S_{23}^{E}(HOMO-1)* and possibly with high values of Q_{14}^{max}.Atom 12 is a nitrogen atom in ring B (Fig. 2). All local MOs have a σ nature (Table 4). $(LUMO+2)_{12}$* corresponds in all cases to molecular orbitals localized far from (LUMO+2) in the energy axis. Small numerical values of S_{12}^{N}(LUMO+2)* are obtained by shifting upwards the $(LUMO+2)_{12}$* energy making this MO less reactive. If the behavior of this local MO is the same that the lowest two empty local MO of atom 12, then we may discard them as electron acceptors. On the other hand, $(HOMO)_{12}$* coincides with the molecule's HOMO or (HOMO-1) in all cases (Table 4), suggesting that this atom is using at least $(HOMO)_{12}$* to interact with the site. This interaction can be of the σ-σ or σ-π kinds. Atom 1 is a carbon atom in ring A (Fig. 2). Table 4 shows that local $(LUMO)_1$* and $(LUMO+1)_1$* have a π nature. A high affinity is associated with small numerical values of F_1(LUMO+1)*. These values are obtained by lowering the electron population of this atom, i.e. by diminishing the localization of this MO over atom 1. On the other hand, Table 4 shows that the frontier occupied local MO has a π nature in all cases and that it is close to the molecule's HOMO. On this basis we suggest that atom 1 is participating in a π-π interaction that may involve other atoms of ring A.Atom18 is a carbon atom in ring connecting rings B and C (Fig. 2).High numerical values of F_{18}(LUMO)* are associated with high affinity. $(LUMO)_{18}$* has a π nature in all molecules. Therefore it is suggested that atom 18 is taking part in a π-π interaction that can involve or not more atoms of ring C. Atom 23 is an atom in ring C that can be carbon or nitrogen (Figs. 1 and 2, Table 1). Table 4 shows that $(HOMO)_{23}$* is not far from the molecular HOMO and that it has a σ nature in some molecules and a π nature in others. The situation is similar for $(HOMO-1)_{23}$*: in some molecules it has a σ nature while in other molecules has a π nature. On the other hand, $(LUMO)_{23}$* and $(LUMO+1)_{23}$* have a π nature. The small numerical values of S_{23}^{E}(HOMO-1)* associated with high receptor affinity can be obtained by lowering the Fukui index F_{23}(HOMO-1)* and/or by shifting downwards the $(HOMO-1)_{23}$* energy. Both techniques reduce the MO reactivity. If this condition holds also for $(HOMO)_{23}$* we suggest that atom 23 is participating in a π-π interaction with at least $(LUMO)_{23}$*. This interaction can involve more atoms of ring C like in the case of atom 18. Atom 14 is a carbon atom in ring B (Fig. 2). Table 4 shows that all local MOs have a σ nature. If high values of Q_{14}^{max} could be associated with a high affinity, then atom 14 should be able to receive some charge. This can be ruled out by the t-test result (Table 2) and also because of the fact that the lowest empty local MO of this atom is not close to the molecular LUMO. All the suggestions are displayed in the partial 2D pharmacophore of Fig. 4.

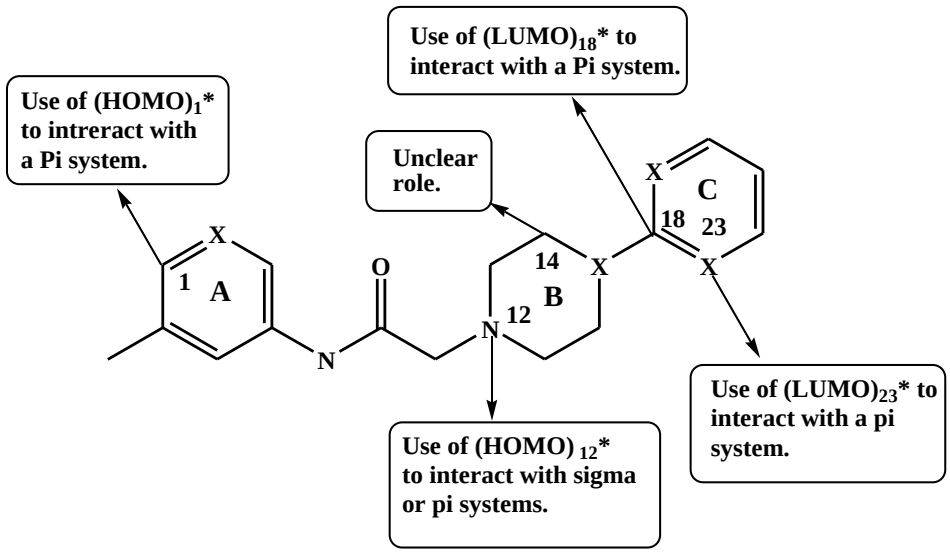

Figure 4: Partial 2D pharmacophore

In summary, we have been able to detect four atoms participating in the drug-dopamine D_4 receptor interaction. Aromatic rings A and C seem to participate in π-π interactions. Interestingly, this work has shown that some atoms belonging to unsaturated ring B also seem to participate in the drug-site interaction. This endorses the idea that in some specific cases these unsaturated rings and also the alkyl chains that connect aromatic systems directly interact with a site, not serving only as spacers/linkers.

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