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Conformational theoretical study of substituted and non-substituted *N*-aralkyl-2-aminoindans and its relation with dopaminergic activity

Leonardo J. Rodríguez[a], Yolibeth Medina[a], Heberto Suárez-Roca[b], Biagina Migliore de Angel[b], Anita Israel[c], Jaime E. Charris[d], Simón E. López[e], José A. Caldera[f], Jorge E. Angel-Guio[f,*]

[a]*Laboratorio de Química Teórica y Computacional (LQTC), Departamento de Química, Facultad Experimental de Ciencias, La Universidad del Zulia, Apartado 526, Maracaibo, Venezuela*
[b]*Sección de Farmacología, Instituto de Investigaciones Clínicas Dr. Américo Negrette, Facultad de Medicina, La Universidad del Zulia, Maracaibo, Venezuela*
[c]*Laboratorio de Neuropéptidos, Facultad de Farmacia, Universidad Central de Venezuela, Caracas, Venezuela*
[d]*Laboratorio de Síntesis Orgánica, Facultad de Farmacia, Universidad Central de Venezuela, Caracas, Venezuela*
[e]*Laboratorio de Química Orgánica, Departamento de Química, Universidad Simón Bolívar, Caracas, Venezuela*
[f]*Laboratorio de Síntesis Orgánica y Diseño Fármacos, Departamento de Química, Facultad Experimental de Ciencias, La Universidad del Zulia, Apartado 526, Maracaibo, Venezuela*

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Abstract

Ab initio molecular orbital calculations are presented for two isomers of nine derivatives from 2-aminoindan. The study is centered in the geometrical analysis of the structures with adequate conformation to interact with the dopaminergic receptor. Pharmacological test performed on four out on the nine racemic and diastereoisomeric mixture studied in the present paper, indicated that the presence of the hydroxyl groups in the aminoindan ring is necessary for the agonist effect, whereas the compounds with hydroxyl groups in the aralkyl ring cause an antagonist effect. The theoretical calculations show that only the isomers RR have the suitable geometry to allow such interactions in the receptor cavity. This is a consequence of the fact that the RR isomers show greater planarity than the RS ones, so the former fill up the dopaminergic receptor. Small differences in some inter-atomic distances and diverse values of dipolar moment were responsible for the activity in this coupled compound-receptor model. On the other hand, the total energy values were very similar, but the RR isomers energy was always slightly lower than that of the RS isomers. The gap values (HOMO–LUMO) did not show significant differences among the compounds; however, for the RS isomers they were slightly higher than those of the RR isomers. Thus, the RS isomers were slightly more reactive than the RR ones.

Keywords: Ab initio calculations; Aminoindan; Dopaminergic activity; Conformational analysis

* Corresponding author.
E-mail addresses: jangel63@hotmail.com, jangel@luz.ve (J.E. Angel-Guio), leon@luz.ve (L.J. Rodríguez).

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1. Introduction

The dopaminergic neurotransmission plays an important role in certain diseases that involve the central nervous system, such as schizophrenia, Parkinson, Huntington, tardy Diaskinesia and psycho-stimulant addiction, among others [1]. In effect, several studies have investigated specific dopamine-mediated behaviors to which belong the stereotypy inducing (sniffing or gnawing) and locomotion activating effect of apomorphine, a known full agonist of the dopaminergic receptors D_1 and D_2 with similar intrinsic activity as dopamine and often used to study the behavioral responses of the dopaminergic system [2]. Further, brain dopamine is now recognized as an important modulator of systemic blood pressure through the regulation of fluid and sodium metabolism and vasopressin release [3].

The synthesis of compounds with possible dopaminergic activity in a very specific conformation is based on the molecular modification approach. This method consists of taking as genesis a chemical substance correctly elucidated, with well-known biological activity and synthesis, then testing with its analogues [4]. Therefore, the aminoindan ring coordinated with a hydroxyl substituted *N*-aralkyl system is a reasonable choice for this study. For that we are now investigating a series of *N*-aralkyl 2-aminoindans in order to establish the influence of the N substituents upon the dopaminergic activity.

In this work we present calculations on nine hydroxylated analogues of *N*-[(2-phenyl)-1-methylethyl]-2-aminoindan, which present two quiral centers and can show four isomers each one, except the compounds **I**, **V** and **VII**, which only have one quiral center. The results of the pharmacological study show that the compounds **II**, **III**, and **V**, are dopaminergic agonists, whereas the compound **IX** is a powerful antagonist, as can be seen from Fig. 1. The structures **II**, **III** and **V** have no hydroxyl groups in the *N*-aralkyl fragment; but **IX** have two hydroxyl groups in this fragment. Although the pharmacological test have not been finished yet, this outcome permits us to conclude that the presence of the hydroxyl group in the aralkyl fragment is the responsible of the antagonist effect, whereas the presence of the hydroxyl group in the amino indan system seems to be an essential factor for the agonist activity. With this in mind, the main goal of the present work is to determinate the adequate conformation of those isomers for interacting with the receptor. We essentially want to know the effect of the orientation of the *N*-aralkyl side chain and the hydroxyl number of the studied compounds on their biological activity. This biological activity can be associated with the presence of the dopaminergic fragment like a rigid analogue contained in the aminoindan ring. In this sense, Brewster et al. [5] have reported that the agonist activity for this kind of compounds requires proper positioning of the hydroxyl group in the phenyl–ethyl–amino fragment, as well as the proper orientation of the lone pair electrons on the nitrogen atom. For this reason, it is generally accepted that only the R (for the α-rotamer) and S (for the β-rotamer) isomers of 2-aminoindan compounds show the right conformation to interact with the dopaminergic receptor because the nitrogen atom coordinated with the aminoindan ring must stay in the equatorial position; otherwise, this nitrogen atom would point towards the bottom of the receptor and the compounds would not get in Ref. [6].

Due to the rigidness of the aminoindan ring, the number of possible conformations which can adopt the isomers is dramatically reduced and this facilitates the modeling. The geometrical parameters to be controlled were the distances between the nitrogen atom and the oxygen atoms of hydroxyl groups in the aminoindan ring.

In this theoretical study we report the ab initio calculations for eighteen related compounds (nine RR isomers and nine RS ones) in order to perform the conformational analysis and determine the proper geometrical structure for the interaction between the drug and the receptor.

2. Computational methods

All the calculations were performed with the GAUSSIAN98 computational package [7]. The calculations were carried out on an SP2-IBM parallel computer of the National Scientific Calculation Center of the Andes University (CeCalc.ULA). The CHEM3D [8] and MOLDA [9] program for PC was used for drawing and visualizing all the optimized structures. The level of theory employed was HF and the basis sets were 3-21G* and 6-31G*. They are

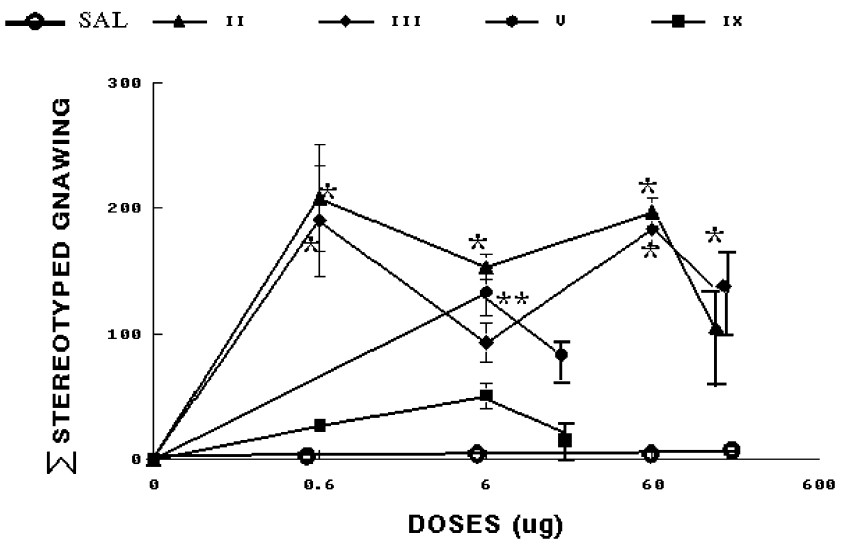

Fig. 1. Dose–response curves for compounds **II**, **III**, **V**, and **IX**.

the cheapest choice, given that our models posses a big number of atoms (40–44). On the other hand, we are interested in the conformational geometries of the compounds and not in its exact energies; therefore, we do not need highly refined combinations between methods and basis sets. Although, all calculations were made with the two basis sets 3-21G* and 6-31G*, the results are quite similar and we will only discuss the results obtained with the more complete 6-31G* basis sets.

3. Results and discussion

Let us focus our analysis on some particular distances and angles. The skeletal of the molecules studied are depicted in Fig. 2 and the substituent details are in Table 1.

As we mentioned above, the compounds **I**, **V** and **VII** only have one quiral center, due to two of the substituents of the carbon atom of the indan ring are equal; however, for simplicity in the text they will be referred to as RR or RS isomers. Hereafter, the notation RR-**I** correspond to the RR isomer of compound **I**.

From Table 1 we can observe that the studied isomers have the same number of atoms, except for oxygen atoms. This implies that the total energies must be very close due to the similarity in geometry and atomic mass. To bring about some type of comparison we classified our isomers in five classes, depending on the number of oxygen atoms. Thus, we have from one isomer without oxygen atom, to one isomer with four oxygen atoms. Table 2 shows the energy values for the eighteen isomers studied. In this table, the first values correspond to RR isomers and the second ones to RS isomers. Table 2 includes the absolute values of the difference $E_n - E_0$, where E_0 is the energy of the isomer without oxygen atom and E_n the energy of the isomer with n oxygen atoms.

From Table 2 it can seen that the total energies of the isomers RR are always slightly lower than its homologous RS. This is a clear consequence of the minor intermolecular repulsion in the RR isomers that

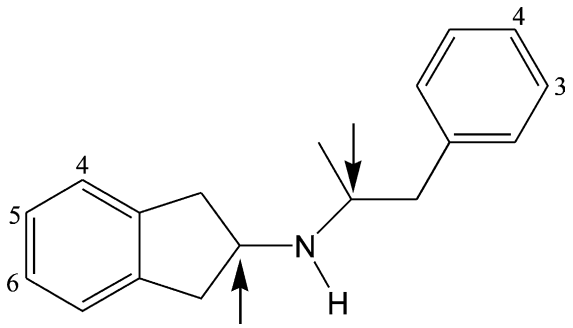

Fig. 2. Structure of *N*-[(2-phenyl)-1-methylethyl]-2-aminoindan and the position of its substituent. The asymmetrical carbon atoms are indicated.

Table 1
Numbers and positions of the hydroxyl groups in the compounds

Compound	Number of OH	Position of the OH indan ring/*N*-aralkyl fragment
I	0	/
II	1	4/
III	1	5/
IV	1	/4
V	2	5,6/
VI	2	4,5/
VII	3	5,6/4
VIII	3	4,5/4
IX	4	4,5/3,4

show greater planarity than the RS isomers, as shown in their 3D-model. Figs. 3 and 4 exhibit the optimal structure for the RR-**II**, RS-**II** and RR-**IX**, RS-**IX** compounds, respectively. From these figures it can be seen that the RR isomers are more extended in space and do not present major repulsion, whereas the RS isomers present a bent geometry.

Two important remarks must be mentioned from Table 2. First, the total energies of RR isomers with the same oxygen atoms number show differences lower or equal than 0.001 Hartree (example, between the RR-**II**, RR-**III** and RR-**IV**), whereas, for the RS isomers these differences are lower or equal than 0.0009 Hartree (example RS-**V** and RS-**VI**) as may be appreciate in the third column of Table 2. And second, the absolute values of the difference $E_n - E_0$, for the isomers RR and RS with the same number of oxygen atoms vary only in 0.0001 Hartree, except for compound **IX**, where these values for RR-**IX** and RS-**IX** vary in 0.0006 Hartree, as can be noted in the last column of Table 2. Considering these small energy differences, both results are an excellent indicative that the employed combination between calculation method and basis sets is good enough to account for these slight geometrical variations, from the energetic point of view.

Table 3 displays the absolute values of the differences between the HOMO and LUMO levels, the net charge on the nitrogen atoms and the total dipolar moments of the compounds. Again, the first values of this table correspond to RR isomers and the second values are for the RS isomers. As it can observed, the values of the gap HOMO–LUMO are quite similar for all compounds, however all the RS isomers show values slightly higher than the values for the RR isomers, except for compound **III**. This indicates that the RS isomers must have a lower reactivity than the RR ones. Many authors take it as a criterion of energetic stability, but this matter is still a subject of controversy [10].

The net charges on nitrogen atoms listed in Table 3 are quite similar, however the values of these charges for the RR isomers are slightly lower than the RS ones. The minor planarity in the RS isomers may produce a negative net charge on the nitrogen atom of a bit larger value. The similarity of the net charge on the nitrogen atoms is a reasonable result due to the differences between the studied compounds are the number and the position of hydroxyl groups and they are relatively far from the nitrogen atom. For this reason, in this study the atomic charge does not offer a stability criterion to draw any conclusions. On the other hand, the calculated dipolar moment exhibits a very wide range of values and it is difficult to judge from these results alone. However, these values of

Table 2
Total energy for the 18 compounds (in Hartree); (RR isomers/RS isomers)

Compound	Oxygen number	Energy	$\lvert E_n - E_0 \rvert$
I	0	−748.3128/ −748.3001	0.0/0.0
II	1	−823.1682/ −823.1554	74.8554/74.8553
III	1	−823.1673/ −823.1547	74.8545/74.8546
IV	1	−823.1672/ −823.1545	74.8544/74.8544
V	2	−898.0218/ −898.0091	149.7090/149.7090
VI	2	−898.0228/ −898.0100	149.7100/149.7099
VII	3	−972.8763/ −972.8635	224.5635/224.5634
VIII	3	−972.8772/ −972.8643	224.5644/224.5644
IX	4	−1047.7327/ −1047.7194	299.4199/299.4193

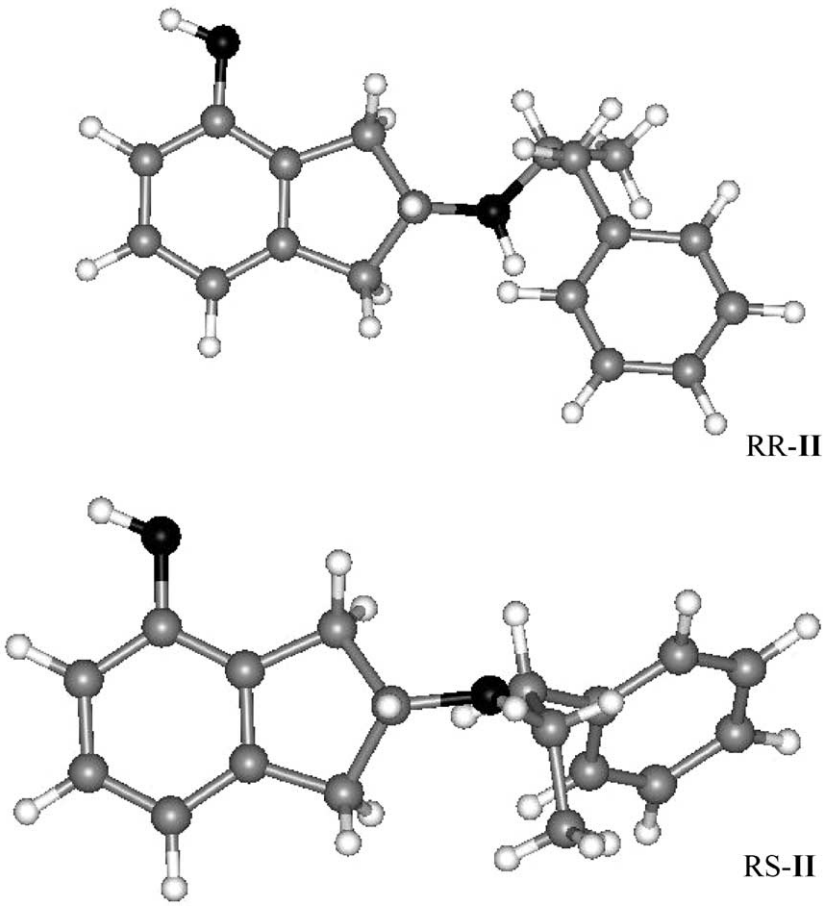

Fig. 3. Geometry of the optimal structure for the two isomers (RR and RS) for compound **II**.

dipolar moment will be analyzed later together with the distances values.

The geometrical analysis in this study will look into two distances that permit to know if the compound can be allowed or not in the receptor cavity [11–18]. The two distance are: (1) the distance between the nitrogen atom and the oxygen atom in the position 4 of the aminoindan ring (see Fig. 1), hereafter called dNO4 distance and (2) the distance between the nitrogen atom and the oxygen atom in the positions 5 or 6 (they are symmetrical atoms) of the aminoindan ring, hereafter called dNO5 distance. Table 4 displays the distances dNO4, dNO5 for the 18 isomers studied here. In this table there is some space empty due to the non-existence of hydroxyl group for some particular isomers. For example, the compound **I** has no hydroxyl group in any rings and the compound **IV** has no hydroxyl group in the aminoindan ring, whereas the compounds **V** and **VII** both have two symmetrical hydroxyl groups (in this case Table 4 shows only one distance). The compounds **II** and **III** only have one hydroxyl group in the aminoindan ring. Finally, the compounds **VI**, **VIII** and **IX** present the two distances.

Previous works based on molecular mechanics calculations affirm that the distance dNO4 and dNO5 must lie in the ranges 5.4–5.6 and 7.1–7.3 Å, respectively [19].

Comparison of the results presented in Table 4 allows us to conclude the following:

(a) The racemic and diastereoisomeric mixtures of compounds **III** and **V** show dopaminergic agonist activity, however, the RS-**III** and RS-**V**

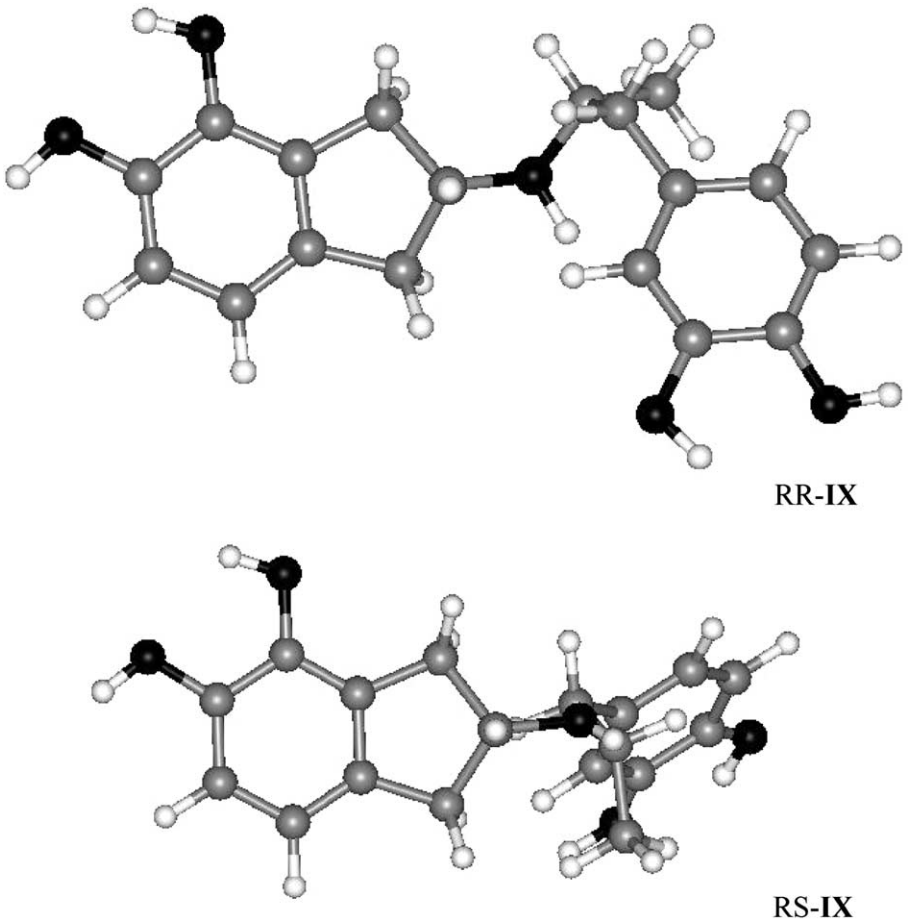

Fig. 4. Geometry of the optimal structure for the two isomers (RR and RS) for compound **IX**.

compounds have the dNO5 distances greater than the permissible value of 7.3 Å. Therefore, the experimental activity found must be due to the RR-**III** and RR-**V** compounds, which present the dNO5 distances inside the right range. The last statement is enough for conclude that the RR isomers are the only structures with the adequate geometry to interact with the receptor.

Table 3
Calculated gap HOMO–LUMO (Hartrees), net charge on the nitrogen atom and dipolar moment (Debyes); (RR isomers/RS isomers)

Compound	|HOMO–LUMO|	Nitrogen net charge	Dipolar moment
I	0.4542/0.4560	−0.736/ −0.759	0.9846/1.0135
II	0.4480/0.4498	−0.736/ −0.759	1.1405/1.2764
III	0.4372/0.4366	−0.736/ −0.760	1.6666/1.5676
IV	0.4400/0.4420	−0.736/ −0.759	1.9445/1.7266
V	0.4281/0.4301	−0.736/ −0.759	2.9850/3.5038
VI	0.4382/0.4403	−0.736/ −0.759	2.2990/2.7329
VII	0.4216/0.4261	−0.736/ −0.760	2.9716/4.2340
VIII	0.4316/0.4356	−0.737/ −0.759	1.0084/4.0183
IX	0.4355/0.4415	−0.737/ −0.760	2.0054/5.1333

Table 4
Values for the parameters dNO4 and dNO5 for the 18 isomers, (RR isomers/RS isomers)

Compound	dNO4 (Å)	dNO5 (Å)
I	–	–
II	5.473/5.493	–
III	–	7.262/7.359
IV	–	–
V		7.279/7.338
VI	5.502/5.520	7.246/7.303
VII		7.279/7.338
VIII	5.502/5.520	7.246/7.303
IX	5.502/5.519	7.246/7.303

(b) The compounds **VII**, **VIII** and **IX** present two resemblances: (a) they have at the least one hydroxyl group in the aralkyl fragment and (b) the dNO5 distances behaviour of them is practically the same. Due to the racemic and diastereoisomeric mixture of the compound **IX** show to be a powerful antagonist, is expected that the compounds **VII** and **VIII** also be antagonists.

(c) All dNO5 distances in Table 4 for the RS isomers are greater than the expected ones. Because of these large distances and the bent geometries of the isomers RS, the latter cannot penetrate in the receptor cavity. For this reason, the discussion below will be focus on the RR isomers.

(d) All distances in Table 4 for the isomers RR are enclosed in the accepted ranges. Therefore, any of this type of isomers has the adequate distances for interacting with the receptor in the indan ring zone.

(e) The presence of the hydroxyl group in the aralkyl ring causes the antagonist effect in the studied compounds as in the RR-**IX** compound. This circumstance may be the cause for the compounds RR-**IV**, RR-**VII** and RR-**VIII**, despite the dNO4 distance for the RR-**VII** compound and the dNO4 and dNO5 distances for the RR-**VIII** compound are in the right range, whereas the RR-**IV** compounds do not have hydroxyl group in the indan ring, as mentioned above.

In accordance with ours data, it seems that the high value of dipolar moment is associated with the antagonist effect of the studied compounds. For instance, the RS-**IX** compound presents a highest dipolar moments and it is a potent antagonist. Based on this fact, we can discard the RS-**V**, RS-**VII**, RS-**VIII** and RS-**IX** compounds, which present dipolar moment values greater than 3.5 Debye.

The findings of our pharmacological evaluation showed that diastereoisomeric mixture of the compound **II** was more potent that diastereoisomeric mixture of the compound **III**. Table 3 shows that any isomer of the **III** compound has higher dipolar moment than any isomer of the **II** compound. This implies that the dipolar moment value is a crucial factor for determining the possible agonist effect. In Table 3 we can observe that the dipolar moments for the RS isomer are greater than those for the RR isomers, except for the **III** and **IV** compounds; however, for these two compounds the dipolar moment differences are very small. In the case of **III** compound, we know that its diastereoisomer mixture is agonist due to the RR-**III** compound, since the RS-**III** has a very large value of the dNO5 distance. On the other hand, the **IV** compound should be antagonist due to the presence of the hydroxyl group in the aralkyl fragment.

Now, we must consider the size and the geometry of the cavity receptor. It is broadly accepted the existence of two similar cavity receptor namely the D_1 and D_2 receptor [18]. Usually, the pharmacist uses the definition of 'receptor essential volume' (i.e. inactive volume of the receptor site), as a region of the receptor that is not available for interaction with the substituents. Based on this idea, we can conclude that the presence of the hydroxyl groups in the aralkyl fragment reveal the impossibility of the interaction because some part of the compounds are in particular conformation and interact with the receptor in intolerable regions. The only possibility of obtaining dopaminergic activity from the compounds with hydroxyl groups in the aralkyl fragment is the bending of the whole aralkyl fragment until it adapts a conformation similar to apomorphine, which is a dopaminergic agonist [13–17]. However, the methyl group may block the entrance to the receptor. In other words, the compound **IX** has a methyl group which is located

midway between the two cavities mentioned above; so the compound **IX** cannot adopt the right conformation.

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