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RESEARCH ARTICLE

Novel 11,12*H*-dihydronaphthalene[1,2-b]quinoline as Atypical Antipsychotic

María Matilde Ramirez Moran[a], Jorge Eduardo Angel Guio[a,*], Natividad Herrera Cano[d], Biagina del Carmen Migliore[a], Rodolfo Izquierdo[f], Jaime Charris[b], Simón López[e], Anita Israel[c], Ana Santiago[d], Roberto Rossi[d], Luis Perdomo[a], Akram Samear Dabian[a], Mariagracia Vera Sosa[a], Alejandra Villalba[a] and Ligia Biagina Angel Migliore[a]

[a]*Laboratorio de Síntesis Orgánica, Diseño y Evaluación Farmacológica de Nuevos Productos, Departamento de Química, Facultad Experimental de Ciencias, Universidad del Zulia, Maracaibo, Venezuela;* [b]*Laboratorio de Síntesis Orgánica,* [c]*Laboratorio de Neuropéptidos, Facultad de Farmacia, Universidad Central de Venezuela, Caracas, Venezuela;* [d]*INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina;* [e]*Departament of Chemistry, University of Florida, P.O. Box 117200, Gainesville, Florida, 32611-7200, USA;* [f]*Laboratorio de Química Teórica y Computacional, Departamento de Química, Facultad Experimental de Ciencias, Universidad del Zulia, Maracaibo, Venezuela*

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Abstract: ***Background*:** Neurodegenerative, neurological and mental disorders, as well as substance abuse have a worldwide high incidence rate, becoming relevant factors that contribute to premature morbidity and mortality. Dopamine is well known to be involved in these pathologies. The key focus in the search for new drugs, that alleviate or cure these diseases, is pursuing the design of compounds with both efficacy and fewer adverse effects in order to obtain novel agents capable of restoring the homeostasis in the CNS of dopaminergic neurotransmission and counteracting some of neurodegenerative and neuropsychiatric diseases, such as Parkinson's disease, schizophrenia, Huntington's chorea and drug addictions.

***Methods*:** the compounds 11,12*H*-dihydronaphthalene[1,2-b] quinoline **2a** and 9-methoxy-11,12*H*-dihydronaphthalene [1,2-b] quinoline **2b** were designed and synthesized. The organic synthesis was performed according to the outlined synthesis strategies, together with a pharmacological evaluation of the male Sprague-Dawley rats.

***Results*:** Compound structures were confirmed by ^{1}H, ^{13}C, DEPT and HETCOR NMR. Pharmacological testing and computational studies validated the asserted medicinal-chemical approach for their design, showing compound **2a** acting as an atypical dopamine antagonist.

***Conclusion*:** The study showed that compound **2a** has an atypical antagonistic action on the central dopaminergic system. These pharmacological and computational-theoretical results support the suitability of the medicinal chemical approach in the design of this compound.

Keywords: Dopamine, schizophrenia, atypical antipsychotic, stereotypy, quinoline, molecular dynamics simulations.

1. INTRODUCTION

Dopamine (DA) (Fig. **1**) is a widely distributed neurotransmitter in the central nervous system (CNS), where it is involved in the control of movements, cognition, emotions, memory, reward mechanism and in the regulation of prolactin secretion by the pituitary.

Several diseases have been related with disturbances of DA transmission, like neuropsychiatric and neurodegenerative disorders, such as attention deficit hyperactivity disorder (ADHD), Tourette Syndrome (TS), schizophrenia (EZ), psychosis, depression, and with neurodegenerative diseases like Parkinson's disease (PD), Huntington disease (HD) and multiple sclerosis (MS) [1]. Dopaminergic innervations are the most prominent in the brain. Four major dopaminergic pathways have been identified in the mammalian brain; the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular systems that originate from the A9 (nigrostriatal), A10 (mesolimbic and mesocortical, often collectively termed the mesocorticolimbic pathway), and A8 (tuberoinfundibular)

*Address correspondence to this author at the Laboratorio de Síntesis Orgánica, Diseño y Evaluación Farmacológica de Nuevos Productos Departamento de Química, Facultad Experimental de Ciencias, Universidad del Zulia, Apartado 4011, Sector Grano de Oro, Maracaibo, Venezuela; Tel: +58-414-360-7535; E-mails: jangel63@yahoo.com

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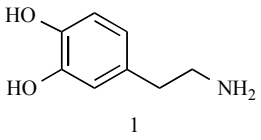

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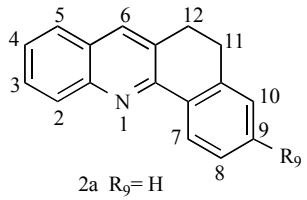
Fig. (1). Structure of dopamine (DA).

groups of DA-containing cells. These neurons are critically involved in various vital central nervous system functions, including voluntary movement, feeding, affection, reward, sleep, attention, working memory, and learning [2].

One of the most important neuropsychiatric disorders is schizophrenia, considered among the most serious mental illnesses, which is characterized by episodes of disturbances in thought, hallucinations, deception or deceit, isolation from society and other strange behaviors [3, 4]. Also it has a considerable social and economic impact and globally it affects approximately 1% of the world population [5]. Although the physiopathology of this disease is not yet well defined, the development of antipsychotic drugs has been most influenced by a DA hypothesis, which is based on the capacity to interact on dopaminergic receptors (as antagonists) in *in vivo* and *in vitro* assays. Initially, the EZ's therapy was based on the use of "typical" antipsychotics, characterized by exerting a total antagonist action on D1 and D2 DA receptors. These drugs were developed with the purpose of attacking positive symptoms of the disease (delusions, hallucinations), however, as consequence they caused an excessive increase in the negative symptoms (anhedonia, cognitive disabilities, extrapyramidal side effects (EPSE), and hyperprolactinemia) [6, 7], and they are not effective in approximately 50% of patients. By this way, the subsequent generation of these drugs, emerge from typical antipsychotics failure, motivated by their EPSE among others. Atypical antipsychotics are characterized by having a multireceptor affinity profile, which combines an antagonism on D2 and D3 receptors, with agonist and potent antagonistic action on serotonin 5-HT1a and 5-HT2a receptors, respectively. As a result of this pharmacological action, a considerable decrease in negative symptoms is obtained. A little or null EPSE is observed, and few or none increase of prolactin is seen in chronic treatment, as well as a decrease in depressive symptoms associated with the treatment [8]. This has motivated us to direct our research into this important health area, looking for the search of new drugs rational development.

Numerous compounds have been designed, synthesized and evaluated pharmacologically, and have led to advance in the search for new drugs able to counteract these diseases. However, a drug to cure or alleviate these conditions has not been found yet. As a contribution, we designed and synthesized acridine analogs such as, 11,12*H*-dihydronaphthalene [1,2-b] quinoline **2a** and 9-methoxy-11, 12*H*-dihydronaphthalene [1,2-b] quinoline **2b** (Fig. **2**), which displayed an atypical antagonistic response on the dopaminergic central nervous system.

Compounds **2a-b** were designed as tetracyclic quinolines similar to acridine, being intimately related to the fused indoles **3-5** (Fig. **3**), which behaved as atypical antipsychotics [9, 10]. These fused indoles were based on the activity of



2a R_9= H
2b R_9= OMe

Fig. (2). Structures of compounds **2a** and **2b**.11,12*H*- dihydronaphthalene[1, 2 -b] quinoline (**2a)**; 9-methoxy-11, 12*H* -dihydronaphthalene [1, 2 -b] quinoline (**2b)**.

compounds **6-8**, where **6** and **7** are highly selective toward dopamine D4 receptor as antagonists, while they exhibit selectivity to other protein coupled receptors in the CNS; they also showed affinity for voltage sensitive channels such as sodium, calcium and potassium. Meanwhile, compound **8** has shown higher selectivity and affinity for dopamine D4 receptor and ionic channels [11]. The comparison between compounds **6-8** (D4 receptor antagonists) and compounds **3-5** indicates that the basic nuclei are strongly related since they have the same comparative relation with the benzene ring attached to the five-member heteroaromatic ring, which could be in a free rotation form (compounds **6** and **7**) as well as in a rigid form (compound **8**). Compounds **3-5** differentiate from compounds **6-8** only by the fact that they have an aromatic ring and they do not have the substituted 4-piperidin ring or the substituted 1-piperazinic ring. Given that compounds **3-5** showed atypical antipsychotic activity, a carbon atom was incorporated to the indole ring of these compounds, generating the quinoline ring of **2a-b** (Fig. **3**).

To obtain the final products **2a-b** as merged quinolines, the stated conditions for Friedlander's reaction were followed [12, 13] through the reaction of the *o*-aminobenzaldehyde hydrochloride **10** (previously synthesized) with α-tetralones **11a-b** by alkaline catalysis under reflux (Fig. **4**). Once **2a** compound was obtained, the pharmacological studies were performed *via* its direct injection into the cerebral ventricle (ICV), to avoid the blood-brain barrier and to reduce the amount of drug tested.

2. RESULTS AND DISCUSSION

Compounds **2a-b** were designed as tetracyclic quinolines, closely related in structure to the fused indoles **3-5**, which behaved as atypical antipsychotics [9, 10, 14]. Their synthesis was carried out through a linear strategy of two steps using similar conditions as those of the Friedlander reaction [12, 13] under alkaline catalysis. Their structure was confirmed by ^{1}H, ^{13}C NMR DEPT and HETCOR spectroscopic analysis. Compound **2b** could not be pharmacologically evaluated due to its low solubility in water and saline solution.

As shown in Fig. (**5**), compound **2a** (50 µg/5µL, ICV) induced significant stereotyped behavioral responses, increasing licking and grooming when compared with saline. This effect was blocked by haloperidol pretreatment, but not with ziprasidone, sulpiride and buspirone. These results indicate that **2a** is acting as a dopaminergic agonist in mediating this stereotyped behavior. In case of licking behavior, apomorphine co-administration induced a potentiation of **2a**

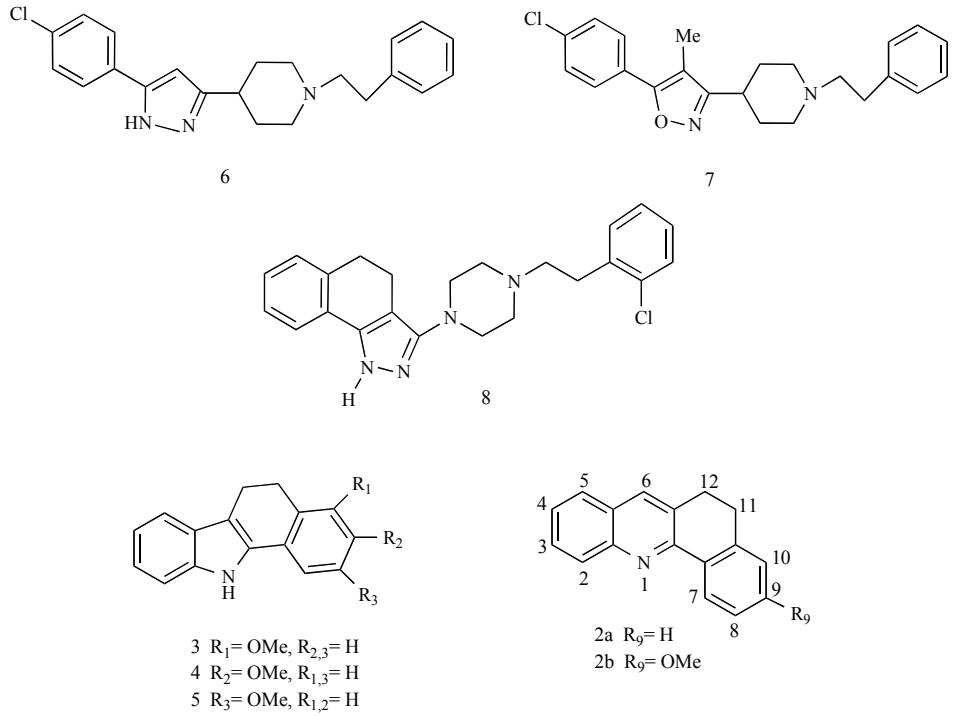


Fig. (3). Comparison between structures of compounds **6-8**, fused indoles **3-5** and compounds **2a** and **2b**.

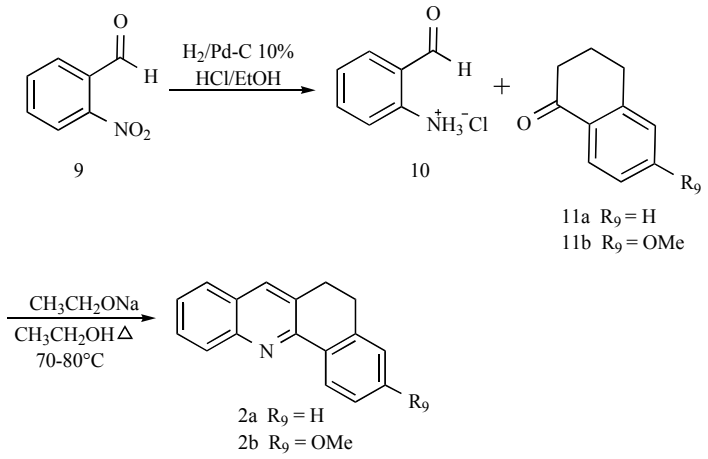


Fig. (4). Synthetic route to obtain **2a** and **2b**.

effects, suggesting that this compound is acting as a partial agonist. In addition, compound **2a** was able to increase licking and grooming behavior in denervated rats with 6-OHDA, demonstrating that presynaptic DA is not involved in the action of **2a**. The effects of **2a** on these behaviors indicate that the compound is acting as a postsynaptic agonist, possibly on the limbic system rather than on the basal ganglia. Apomorphine acts as a potent direct and broad spectrum dopamine agonist drug activating all dopamine D1-like (D1, D5) and D2-like (D2, D3, D4) receptors [15], whereas the typical antagonist haloperidol blocks the D1- D2 (DA) receptors. Regarding the atypical antagonists, clozapine blocks D1- D4 (DA) receptors, ziprasidone blocks 5HT2a and D2 receptors in a ratio of 8:1, respectively, and it is a 5HT1a receptor agonist [16]. Finally, sulpiride is a D2-D4 receptor antagonist [17-22].

On the other hand, **2a** was unable to alter the stereotyped gnawing (bites) and sniffing behavior; however **2a** blunted the agonistic effect of apomorphine on gnawing and sniffing behavior, demonstrating that **2a** compound behaves as a dopaminergic antagonist. It is well known that typical antipsychotics block all the behavioral responses from the basal ganglia and limbic system. In contrast, an atypical antipsychotic only blocks the responses from the basal ganglia (sniffing, gnawing) and not the ones from the limbic system (licking, grooming). Accordingly, compound **2a** alone is acting as a DA atypical antagonist in basal ganglia. All the D2 agonists show this behavior in the presence of an atypical antipsychotic [9, 14, 23]. In fact, compound **2a** is a quinoline tetracyclic compound bioisoterically related to fused indoles **3-5**, and its pharmacological responses, such as atypical antipsychotics, are similar [9, 24]. Additionally, **2a** demon-

strated higher response than ziprasidone in licking and grooming behavior, which in turn showed higher effect in sniffing (Fig. **5**). This result indicates that compound **2a** was more effective than ziprasidone, possibly by its selectivity on limbic conducts, thus it could be inferred that this action would contribute to counteract effectively the negative symptoms of schizophrenia.

With regard to gnawing and sniffing behavior it is possible that the effect of **2a** as an atypical antagonist could involve in addition to dopamine another neurotransmissor such as serotonin. This is possible since serotonin has been reported to play a relevant role in the central inhibitory regulation on dopaminergic neurotransmission. Thus, increased levels of serotonin inhibit the release of dopamine at the level of basal ganglia *via* axon-axon connections, through the 5HT2a receptors. If **2a** compound, in addition to antagonizing the DA receptor, also exerts antagonism on the serotonin 5HT2a receptor, as reported by Angel *et al*. [9, 14], for antipsychotic ziprasidone, there would be an increased dopaminergic neurotransmission in the striatum and in the prefrontal cortex, which would result in a decrease in extrapyramidal effects caused by antipsychotics [25]. Our present data discard a serotonergic mediation since ziprasidone, known to stimulate 5HT1a receptor and to block 5HT2a and D2 receptors in a ratio of 8:1, respectively, was ineffective on **2a** behavioral actions.

In addition, in order to assess whether this increase in stereotyped behavior involves the serotonergic system through 5HT1a receptor stimulation, it was necessary to consider the response resulting from the pretreatment with a partial agonist and a full agonist. It is well known that low doses of a full agonist can slightly increase its response (agonist effect of the partial agonist) whereas high doses of a full agonist significantly decrease the response of a full agonist (antagonist effect of the partial agonist), when both agents interact simultaneously on the same system. Our results in regard to licking behavior show an additive effect when buspirone (5HT1a partial agonist) and compound **2a** were co-administered, suggesting that compound **2a** is not a serotoninergic agonist, since when high doses of a total agonist and pretreatment with a partial agonist are involved, a significant antagonist activity should be expected (Table **1**).

In order to establish a medicinal chemistry approach about the design and preliminary pharmacological evaluation of novel compounds **2a** and **2b**, a conformational and electronic computational study was necessary, due to their structural similarity to the atypical dopaminergic antagonists **3-5** [9, 14]. Molecular recognition and the specificity concept [26] sometimes could be explained in mechanistic and reductionist terms as a "complementary" between ligand and receptor [27]. In this sense, a comparison of the stereoelectronic characteristics of compounds **2a,b** with **3-5** should be helpful to determine a possible pharmacological pattern, and better understand the obtained experimental results. Previously, it was reported that both intercovertible conformations of ring B (up or down) had the same energy in its neutral form [24]. In the present study, the «down» conformation was selected for compounds **3-5** (Fig. **6**) and found that compound **4** was more stable than **5** by 2.1 kJ mol^{-1} and more stable than **3** by 5.9 kJ mol^{-1}. Compounds **2a,b** were studied using the same conformation as that for **3-5**, as shown

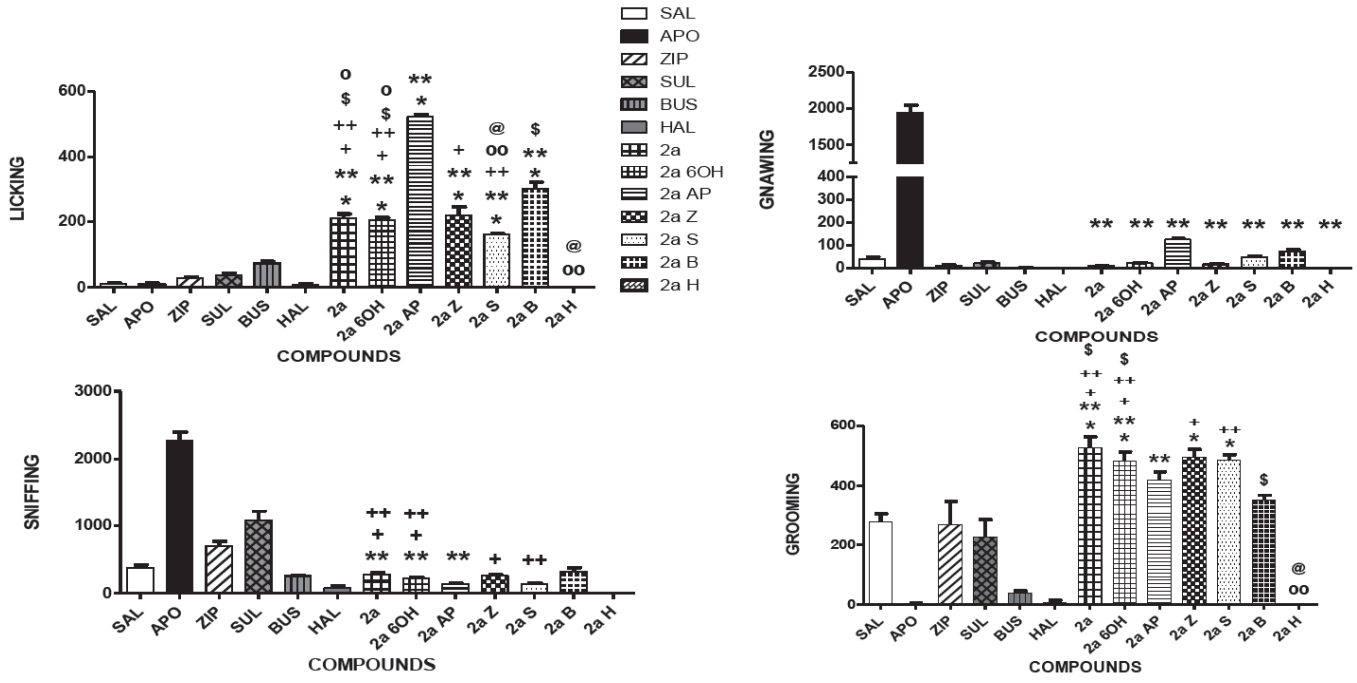


Fig. (5). Effect of compound **2a** at 50 μg/5μL dose of stereotyped behavior in rats. On the ordinate, the sum of measured behaviors. In the abscissa the compound tested. The observations were performed for 1 h. Results are expressed as mean±S.E.M.of four independent measurements. Data was analyzed using one-way ANOVA and Newman's Keul's test. *p<0.001 *vs*. saline; **p<0.001 *vs*. apomorphine; +p<0.001 *vs*. ziprasidone; ++p<0.001 *vs*. sulpiride; $p<0.001 vs. buspirone; °p<0.001 *vs*. haloperidol; °°p<0.001 *vs*. 2a; @p<0.001 *vs*. 2a6OH.

Table 1. Summary of the effect of compound 2a on stereotyped behavior.

Compound	Grooming	Licking	Sniffing	Gnawing	Activity
2a	+	+	~	~	atypical antagonistic
2a+Ziprasidone	+	+	~	~	
2a+Sulpiride	+	+	~	~	
2a+Haloperidol	-	-	~	~	
2a+6OHDA	+	+	~	~	
2a+Buspirone	~	+	~	~	
2a+Apomorphine	~	+	-	-	

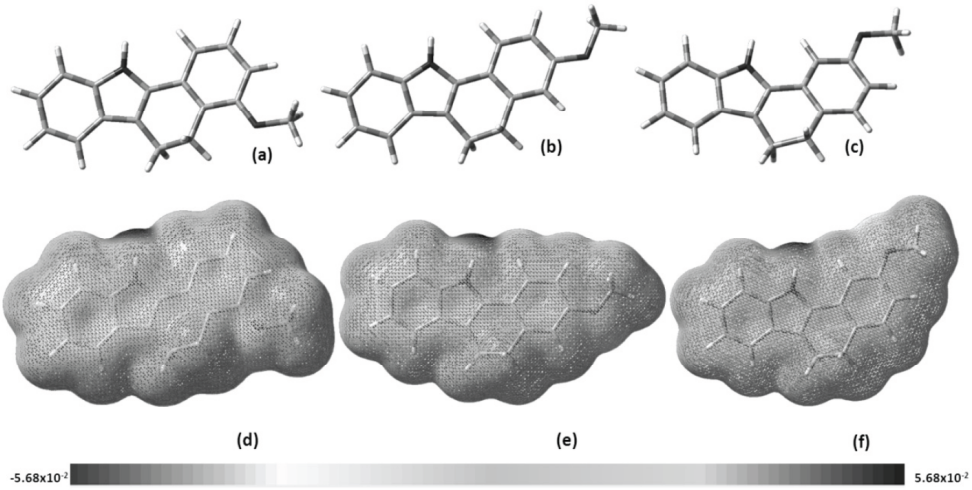


Fig. (6). Optimized structures and molecular electrostatic potentials of compounds **3-5**. Optimized structures for the «down» conformations of compounds **3-5**, represented as (**a**), (**b**) and (**c**), respectively. Molecular electrostatic potentials (MEPs) obtained for compounds **3-5**, represented as (**d**), (**e**) and (**f**), respectively. Gray colors indicate a major attraction to a punctual positive charge, while the dark gray color represents a major repulsion. The potential represents a measurement of the charge distribution in the whole molecule. (*The color version of the figure is available in the electronic copy of the article*).

in Fig. (**7**). Once obtained the preferred energetic conformations, we proceeded to compare them in between to see their similarities and differences. Fig. (**8**) shows a spatial view of the superimposition of the preferred conformations of compounds **2a**, **2b** and **4,** where it was found an excellent superimposition of the base nuclei in these three compounds. The only significant difference was the absence of superimposition of the methoxy group in compound **2a**.

At this stage, it was essential to compare the electronic and energetic aspects in these molecules. In general, the intermolecular forces involved in affinity and specificity could be classified as hydrophobic and electrostatic. The MEPs permit the visualization and determination of the molecule's electrostatic interaction capacity with a binding site [28-30]. The MEPs could also be interpreted in «stereoelectronic pharmacophore» terms, and permit to determine the affinity for the receptor. The MEPs obtained for **3-5** showed three important spatial zones related to the changes of electronic charge density (Fig. **6**): (i) The first zone involves a positive density in the possible receptor, which interacts over the negative charge density in the nitrogen atom of ring C, shown as an intense dark gray color. (ii) A second zone of positive charge density in the methyl groups of the methoxy ($-OCH_3$) substituents. (iii) A third zone with a negative charge density, which belongs to the lone pairs of the oxygen atoms in the methoxy groups.

Compound **2a** presents two important zones in its MEP: (i) a negative charge concentration zone over the nitrogen atom of ring C (Fig. **7c**). This rich electron zone would easily interact with acid species in the physiological media. (ii) A second zone with a positive charge density located at the borders of rings A and B (see the dark gray color at the lowest right zone in Fig. **7c**). For compound **2b**, they are three important zones in its MEP: (i) the first one is a negative charge concentration zone over the nitrogen atom of ring C (Fig. **7d**). This electron rich zone, as that one seen for compound **2a**, would easily interact with acid species. (ii) A second zone of positive charge density over the methoxy group ($–OCH_3$), and (iii) A third zone of negative charge density from the lone pairs of the oxygen atom in the methoxy groups.

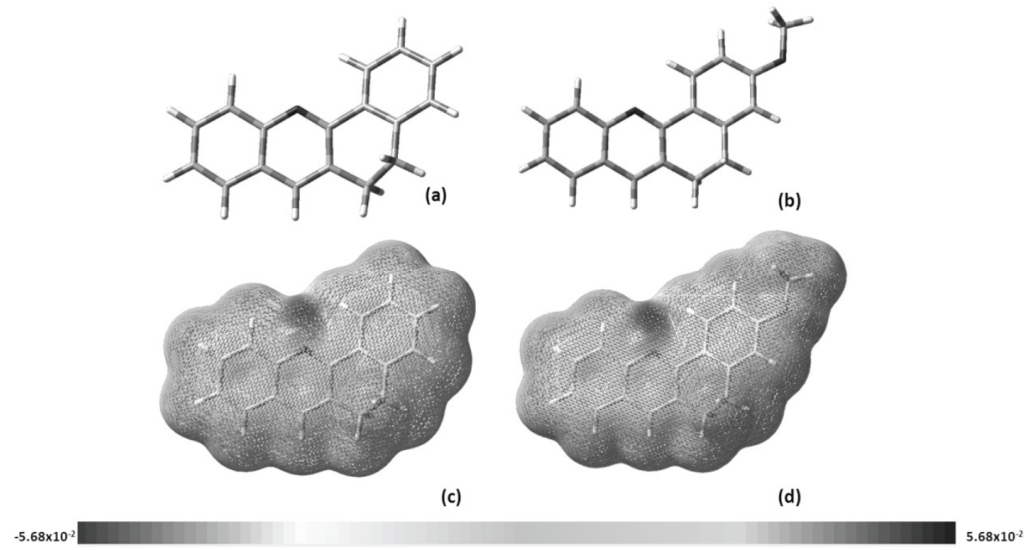


Fig. (7). Optimized structures and molecular electrostatic potentials of compounds **2a** and **2b**. Optimized structures for the «down» conformations of compounds **2a-2b**, represented as (**a**) and (**b**), respectively. Molecular electrostatic potentials (MEPs) obtained for compounds **2a-2b**, represented as (**c**) and (**d**), respectively.

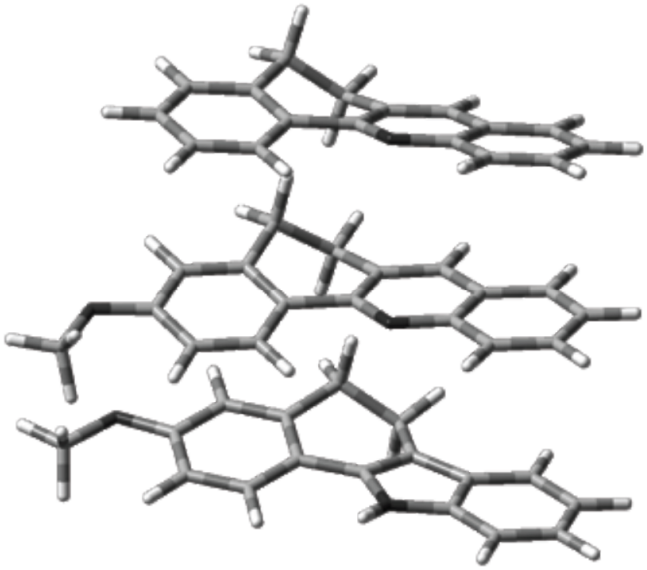


Fig. (8). Structural superimposition of the most stable conformers of **2a** (up), **2b** (medium) and **4** (down).

Based on the studied MEPs, the reaction is evident through a classic acid (H_3O^+) under physiological media, to generate the protonated compounds **3-5** and **2a-b**, having a positive charge. In order to verify the fact of this process, compounds **3-5** and **2a-b** were optimized as their protonated forms, to study the thermodynamical functions of reaction at 314.25 K, and determine the enthalpy (ΔH_p) and the free energy (ΔG_p) of protonation. Also, the energetic and MEPs were determined, having the purpose to rationalize the possible pharmacological mechanism of action of compound **2a**. Parts (a-c) in Fig. (**9**) show the optimized structures for the most stable protonated conformers of **3-5**, 2a-b, respectively. When protonated compounds **3-5** were compared, it was found that **4** is more stable than **3** by 3.8 kJ $mol^{-1}$and then **5** by 4.2 kJ mol^{-1}. Parts (a) and (b) of Fig. (**10**) show the optimized structures for protonated forms of compound **2a-b**. Table **2** shows the thermodynamical functions for the protonation of the five compounds studied. It can be highlighted that all the protonation processes are exothermic and spontaneous (ΔH_p and ΔG_p are negative). Positional isomers **3, 4** and **5** showed very similar ΔH_p and ΔG_p values, and only the protonation of compound **4** is slightly more favorable. The protonation of **2a-b** is also a spontaneous and exothermic process (negative ΔH_p and ΔG_p values). Despite the structural differences between **2a** and **2b**, there are no significant differences in the thermodynamical functions for the protonation reaction. From this last table, it can be suggested that the protonation of compounds **3-5** and **2a-b** is thermodynamically possible. Although **2a** was water soluble in its hydrochloride forms, **2b** was not. On the other hand, having the purpose to find the structural and electronic similarities for these five protonated compounds, the MEPs were built and shown in Fig. (**9**) (parts (d), (e), (f)) and Fig. (**10**) (parts (c) and (d)). The above mentioned figures show characteristic and similar zones: (i) The first involves a positive charge density over the nitrogen atom of ring C, representing the possible binding sites for the D-2 receptor, which belongs to Asp-86, with a negative charge density as shown in parts (d), (e) and (f) of Fig. (**9**), and an intense dark gray color over the nitrogen atom. (ii) A second zone with a light positive charge density and hydrophobic character, described by a dark black-gray color, surrounding the structural portion of studied protonated compounds (Figs. **9** and **10**, parts (d), (e), (f) for the first and (c) and (d) for the second), giving also the possibility of hydrophobic interactions with the receptor. According to this, it was possible to establish significant similarities of these compounds based on their MEPs, as well as in their stereoelectronic aspects, when the base nuclei of indoles **3-5** was compared to the quinolines **2a-b**. Finally, there is a concordance between experimental and computational-theoretical results, and this is why the medicinal chemistry approach for the design was validated, permitting

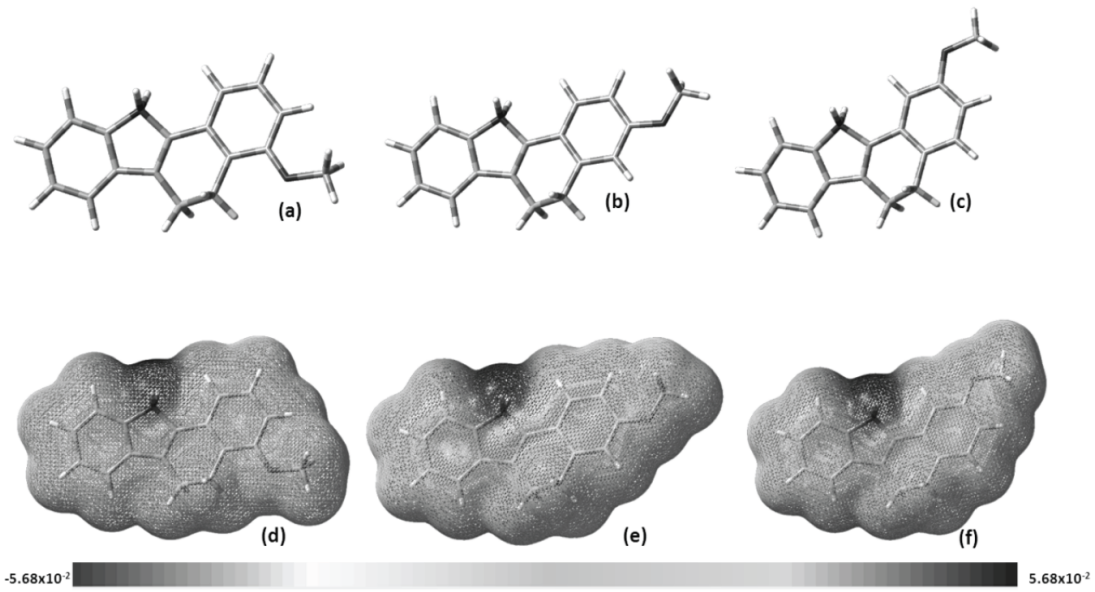


Fig. (9). Optimized structures and molecular electrostatic potentials of protonated compounds **3-5**.Optimized structures for the «down» conformations (**a**-**c**) of protonated compounds **3-5**. Molecular electrostatic potentials (MEPs) (**d**-**f**) obtained for protonated compounds **3-5**.

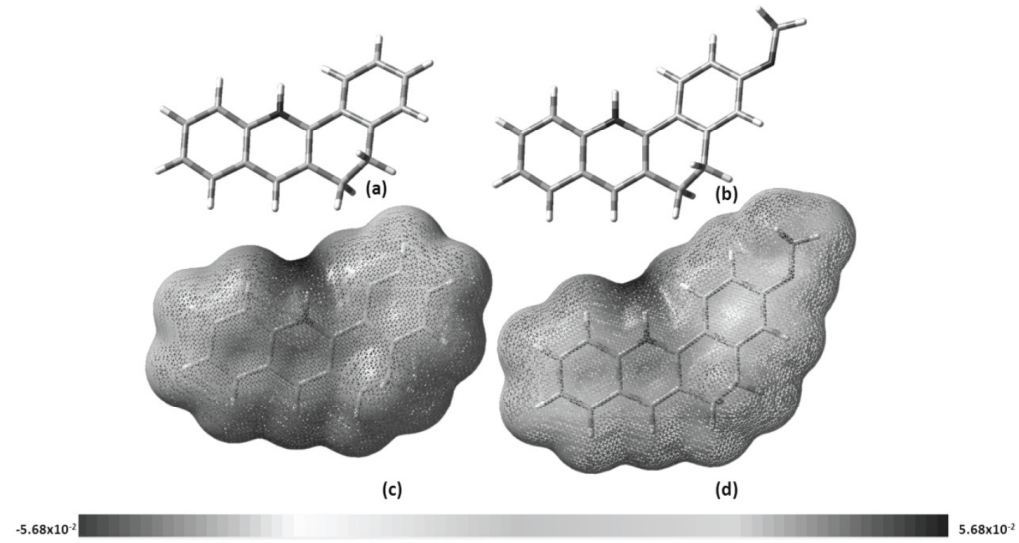


Fig. (10). Optimized structures and molecular electrostatic potentials of protonated compounds **2a-H** and **2b-H**. Optimized structures for the «down» conformations (**a**,**b**) of protonated compounds **2a-H** and **2b-H**. Molecular electrostatic potentials (MEPs) (**c**,**d**) obtained for protonated compounds **2a-H** and **2b-H**, respectively.

a bioisosteric change between the indole ring in **3-5** by the quinoline ring in **2a-b**, giving a central dopaminergic activity as atypical antipsychotics, similar to that observed for indoles **3-5** [9, 10, 14]. Unfortunately, compound **2b** had water solubility problems and was not biologically evaluated, but based on the theoretical data obtained, we believe this should be a good candidate as an atypical antipsychotic dopaminergic agent.

3. MATERIALS AND METHODS

3.1. Chemical Methods

Melting points were determined on a Thomas micro hot stage apparatus and are uncorrected. The ^{1}H NMR, ^{13}C NMR

Table 2. Thermodynamical functions for the protonation reactions at 314.25 k and 1 atm.

Reaction	ΔH_p (kJ mol^{-1})	ΔG_p (kJ mol^{-1})
$5 + H_3O^+ \rightarrow 5\text{-}H^+ + H_2O$	-187.7	-187.2
$6 + H_3O^+ \rightarrow 6\text{-}H^+ + H_2O$	-189.4	-188.9
$7 + H_3O^+ \rightarrow 7\text{-}H^+ + H_2O$	-185.4	-184.9
$2a + H_3O^+ \rightarrow 2a\text{-}H^+ + H_2O$	-305.7	-305.3
$2b + H_3O^+ \rightarrow 2b\text{-}H^+ + H_2O$	-320.9	-320.2

spectra were recorded using a Jeol Eclipse 270 (270 MHz/67.9 MHz) spectrometer using MeOH-d_3 or $CDCl_3$ and reported in ppm downfield from the residual MeOH or $CHCl_3$. Elemental analyses were obtained using a Perkin Elmer 2400 CHN elemental analyzer; the results were within ±0.4% of the predicted values. Chemical reagents were obtained from Aldrich Chemical Co, USA. The purity of all compounds was determined by thin layer chromatography using solvents with different polarities. All solvents were distilled and dried in the usual manner.

3.1.1. Synthesis of 11, 12H-dihydronaphthalene[1,2-b] quinolines 2a, b

0.1 g (0.66 mmol) of compound **9** was dissolved in 5 mL of ethanol and 0.08 mL of concentrated hydrochloric acid, and then hydrogenated over 0.05 g of Pd/C 10% at room temperature, with an initial pressure of 15 psi. After the calculated amount was absorbed, the catalyst was removed by filtration and the obtained compound, dissolved in ethanol, was immediately employed for the next reaction.

A mixture of the tetralone **11a,b** (0.112 g, 0.63 mmol) and the hydrochloride of *ortho*-amino benzaldehyde **10** (0.1 g, 0.63 mmol) in 10 mL of ethanol was added to a solution of 0.15 g of metalic sodium in 5 mL of ethanol. The mixture was refluxed for 3 h. Once the reaction ceased, an aqueous solution at 10% HCl was added (4 mL), inducing the formation of a precipitate that was later extracted with chloroform. The organic extract was washed with water and dried over anhydrous sodium sulfate, then filtrated and the solvent was removed under reduced pressure resulting in a crude which, in each case, was purified by column chromatography using petroleum ether and chloroform (3:1) as eluent, and subsequently the retrieved solid was treated with a freshly prepared solution of ether/HCl, obtaining a yellow solid for compound **2a** (mp 144°C) and a white solid for **2b** (mp 98-100°C) [12, 13].

3.1.1.1. 11, 12H-dihydronaphthalene[1, 2-b] quinoline (2a)

Yield: 65%; mp: 144°C; ^{1}H NMR (MeOH-d_3,): δ 4.46 (m, 4H, $2CH_2$, C_{11} and C_{12}), 7.32 (d, 1H, Ar-H, C_{10}, *J*=5,5 Hz), 7.52 (td, 2H, Ar-H (C_8 and C_9), *J*=6 Hz, *J*=1.11 Hz), 7.57 (td, 1H, Ar-H quinoline (C_4), *J*=5.5 Hz, *J*=1.13 Hz), 7.62 (td, 1H, Ar-H quinoline (C_3), *J*=5.5 Hz, *J*=1.5 Hz), 7.77 (d, 1H, Ar-H (C_7), *J*=5,4 Hz), 7.78 (d, 1H, Ar-H quinoline (C_5), *J*=5 Hz), 7.79 (d, 1H, Ar-H quinoline (C_2), *J*=4,5 Hz); 8.35 (d, 1H, Ar-H quinoline (C_6)). ^{13}C NMR (MeOH-d_3): δ 61.29 (2 CH_2 (C_{11} and C_{12})), 106.86, 116.19, 119.69 (C_{10}) 124.52 (C_6), 125.27 (C_7), 125.90, 126.83 (C_8), 127.07 (C_9), 128.04 (C_4) 128.61 (C_5 y C_2), 130.49 (C_3), 138.32, 138.67, 161.83 (aromatic carbons CH).NMR-DEPT (135): δ 62.61 ppm (2 CH_2, C_{11} and C_{12} inverted); 119.69, 124.52, 125.28, 126.84, 128.62 and 130.49 ppm (none quaternary aromatic carbons CH). NMR - HETCOR showed the following signals: 4.46 ppm (m, 4H, $2CH_2$ (C_{11} and C_{12})) and correlated with 61.29 ppm ($2CH_2$ (C_{11} and C_{12})). Anal. Calc. For. $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.35; H, 5.72; N, 6.26 %.

3.1.1.2. 9-methoxy-11,12 H-dihydronaphthalene[1,2-b] quinoline (2b)

Yield: 50%; mp: 98-100°C; ^{1}H NMR ($CDCl_3$): δ 3.91 (s, 3H, OCH_3), 4.38-4.46 (m, 4H, 2 CH_2 (C_{11} and C_{12})), 7.03 (d, 1H, Ar-H (C_8) *J*=4 Hz), 7.04 (s, 1H, Ar-H (C_{10})), 7.11 (d, 1H, Ar-H quinoline (C_5) *J*=4 Hz), 7.13 (dd, 2H, Ar-H quinoline (C_3 y C_4) *J*=4 Hz, *J*= 6 Hz), 7.16 (s, 1H, Ar-H quinoline (C_6)), 7.73 (d, 1H, Ar-H (C_7) *J*=8,6 Hz), 8.29 (d, 1H, Ar-H quinoline (C_2) *J*=9 Hz), 12.02 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 55.44 (OCH_3), 61.29 (2 CH_2 (C_{11} and C_{12})), 104.36, 106.16 (C_{10}), 117.57 (C_6), 117.74 (C_7), 119.62 (C_8), 125.31 (C_5 y C_2), 125.73 (C_3 y C_4), 139.22, 139.24, 160.55, 161.10, 171.18 ppm (aromatic carbons CH). NMR- DEPT (135): δ 61.29 ppm (2 CH_2 (C_{11} and C_{12}) inverted); 55.44 ppm (OCH_3); 106.16, 117.57, 117.74, 119.62, 125.31, 125.73 ppm (none quaternary aromatic carbon CH). NMR - HETCOR showed the following signals: 4.38-4.46 ppm (m, 4H, $2CH_2$ (C_{11} and C_{12})) is correlated with 61.29 ppm ($2CH_2$ (C_{11} and C_{12})). 3.91 ppm (s, 3H, OCH_3) correlates with 55.44 ppm (OCH_3). Anal. Calc. For. $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.87; H, 5.83; N, 5.58 %.

3.2. Pharmacology

Male Sprague-Dawley rats (150-250 g) were maintained in single cages under controlled conditions of temperature and photoperiod (lights on 06.00 to 18.00 h) and provided with free access to tap water and standard laboratory chow (Ratarina®, Protinal Maracaibo, Venezuela). Apomorphine hydrochloride (Sandoz S.A.), haloperidol (Janssen Pharmaceutical), ziprasidone (Geodon, Pfizer Laboratories) and sulpiride, dissolved in isotonic NaCl solution, were used for stereotype evaluation, by injecting intraperitoneally (ip) at a dose of 1 mg/kg of body weight. A cannula was implanted in the right lateral ventricle, according to the coordinates from Bregma: anteroposterior–0.40 mm and lateral 1.2 mm, with the aid of a stereotaxic instrument and under anesthesia with xylacine (Setton® 2%) (1.0 mg/kg, i.p.)and ketamine for relaxation. The cannula was secured to the skull with acrylic cement. A minimum of 5 days was allowed for recovery. All the tested compounds were dissolved in isotonic NaCl solution and injected intracerebroventricularly (ICV) in a volume of 5 µL, employing a Hamilton syringe fitted with a stop to prevent needle penetration past the cannula tip. To achieve a selective dopaminergic denervation, the neurotoxin 6-hydroxy-DA (6-OHDA, hydrobromide 2,4,5-trihydroxy phenylethylamine, Sigma Aldrich, 99%) was dissolved in isotonic NaCl solution and ICV injected at a dose of 200 µg/5 µL, 5 days before the experiment. It should be noted that the compounds synthesized were injected *via* ICV since it allows: 1) to cross the blood-brain barrier, which prevents certain types of compounds, particularly polar, from entering the brain; 2) to reduce the dose, and consequently, to decrease the amount of compounds that need to be synthesized for drug testing.

Compounds-induced stereotypic behavior (licking, gnawing, sniffing and grooming) was assessed, *i.e.*, a repetitive and purposeless motor activity. For this purpose, each of the synthesized compounds was injected individually for each test group at a dose of 50 µg/5 µL. Afterwards, compounds were evaluated according to the following criteria: a) if the compound acted like an agonist (*i.e.*, increased stereotyped behaviors), it was compared with the known typical and atypical DA receptor antagonists: to haloperidol (1 mg/kg, i.p., 15 min before ICV compound), ziprasidone (1 mg/kg, i.p.), and sulpiride (1 mg/kg, i.p.) and the partial agonist of

serotonin receptors (5HT1a) buspirone (1 mg/kg, i.p.). b) If the compound acted like an antagonist (*i.e.*, lack of stereotyped behaviors), it was compared to apomorphine (1 mg/kg, i.p. 15 min after ICV compound), a known dopaminergic receptor agonist. Compounds were initially injected ICV, and 15 min later, apomorphine (1 mg/kg, i.p) was administered. In addition, these compounds were pharmacologically assessed in rats previously denervated with 6-OHDA.

After ICV injection, rats were placed into a clear acrylic box (32×28×28 cm) for observation. For each test 4 animals were used. The observations were made during a 60 min period, divided into 10 intervals of 6 min each [9]. Previously, animals were placed into the observation box for 15 min in order to habituate. The collected data was recorded using computer software to count the number of stereotyped movements.

The results were expressed as the mean±S.E.M., and analyzed by one-way variance analysis (ANOVA), followed by Newman-Keuls test. A value of $p<0.05$ was considered significant.

3.3. Computational Section

The quantum-mechanics calculations were carried out using the GAUSSIAN-09 (G-09) program [31]. For structure's optimization, the exchange-correlation hybrid functional B3LYP [32, 33] of the defined functional theory (DFT) was combined with the base set 6-31+G** [34].

For the optimized structures, a frequency test was conducted to verify if these structures correspond to a minimum of the energy surface (all vibrational frequencies should be positive). The electronic study of the molecules was conducted through the molecular electrostatic potential (MEP) using a level of calculation B3LYP/6-31+G**. MEPs are very useful because they permit theoretical description and visualization of a molecule's capacity to have an electrostatic interaction with a potential binding site [27-29]. MEPs can be interpreted as pharmacophoric patterns which condense information about the electrostatic forces involved in the formation of the ligand-receptor complex.

CONCLUSION

Compounds **2a-b** were synthesized and their existence was confirmed by ^{1}H NMR, ^{13}C NMR, DEPT and HETCOR spectroscopic techniques. The study showed that compound **2a** has an atypical antagonistic action on the central dopaminergic system. These pharmacological and computational-theoretical results support the suitability of the medicinal chemical approach in the design of this compound.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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