Design, synthesis and preliminary pharmacologic evaluation of 2-aminoindane-quinoline analogs as dopaminergic agents

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ABSTRACT

In recent years, the study of neurodegenerative diseases has accomplished the development of a Medicinal Chemistry oriented strategy towards the design, synthesis and pharmacological study of a large number of compounds with central dopaminergic activity, but, has not found yet a drug capable to effectively cure these diseases. It is well known that both in Venezuela and particular in the Zulia region of this country, there is a high incidence of neurodegenerative and psychiatric disorders, such as Parkinson’s, schizophrenia, mania, depression, tardive dyskinesia diseases, Tourette’s disease, drug addiction and eating disorders. This has motivated us to direct our research into this important health area, in the search of a rational development of new drugs. This paper describes the design of analogs of N-[(2-chloro-quinoline)-3-yl-methyl]-4,5-dimethoxy-2-aminoindan hydrochloride (9) and the N-[(2-chloro-7-methyl-quinolin )-3-yl-methyl]- 4,5-dimethoxy-2-aminoindan hydrochloride (10) as novel agents to counteract some of these pathologies. Their convergent organic synthesis was performed according to the synthetic strategies proposed, and the spectroscopic elucidation of the final products was made by NMR techniques ¹H, ¹³C, DEPT, HETCOR and COSY, confirming their structures. The preliminary pharmacological evaluation in stereotypic behavior, demonstrates their agonistic activities on the central dopaminergic system, validating a ready-witted medicinal chemistry approach in the design of these click type drugs.

Keywords: Parkinson's disease, schizophrenia, Huntington's Chorea, Dopamine, stereotypia.
INTRODUCTION

The dysfunctions of the central dopaminergic system have been linked to several neurological and psychiatric disorders, particularly Parkinson’s disease (PD), schizophrenia, depression, attention deficit disorder with hyperactivity and alcohol dependence [1]. Dopamine (DA) is mainly located in the brain, in the substantia nigra, striatum, caudate nucleus and the limbic system, fulfilling functions related to motor skills, memory, learning and mood. PD is a progressive disorder of the central nervous system (CNS) that primarily affects motor functions among others [2][3]. Furthermore, schizophrenia is a chronic and mentally devastating disease, accompanied by positive symptoms (delusions, hallucinations, disorganized speech), negative symptoms (apathy, anhedonia, social isolation, suicide, etc.) and cognitive symptoms (attention deficit, memory deficits) [4]. Studies suggest that symptoms of schizophrenia are largely due to an excess of dopamine in the subcortex and a deficiency of dopamine in the frontal cortex [5]. Numerous compounds have been designed, synthesized and evaluated pharmacologically, and have led to advances 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. Once again, as a contribution, we synthesized compounds 1-5 (Figure 1) and their pharmacological evaluation has displayed an agonistic response through the activation of dopaminergic mechanisms on the central nervous system. Their design was based on the type medicinal chemical approximation, in which a 2-Cl-3-formylquinoline (substituted and non-substituted) and 2-indane (non-substituted) were incorporated on the “amine” nitrogen through two covalent bonds.

![Figure 1. Compounds 1-5](image)

Taking into consideration this Medicinal Chemical approach, compounds N-[(2-chloro-quinoline)-3-yl-methyl]-4,5-dimethoxy-2-aminoindan (9) and N-[(2-chloro-7-methyl-quinolin)-3-yl-methyl]-4,5-dimethoxy-2-aminoindan (10) hydrochlorides were synthesized through the reductive amination [6], between key intermediaries (6)[7][8] and (7-8)[9], previously synthesized, and submitted to preliminary pharmacological evaluations (Scheme 1).

![Scheme 1. Synthetic route for obtaining the final products (9 and 10)](image)
MATERIALS AND METHODS

Chemistry section
Melting points are uncorrected and were determined using a Thomas Hoover Capillary Melting Point apparatus. The 1H NMR, 13C NMR spectra were recorded using a Jeol Eclipse 270 (270 MHz/67.9 MHz) spectrometer using MeOH-d3 and are reported in ppm downfield from the residual CH3OH. The purity of all compounds was determined by thin layer chromatography, using a mixture of solvents with different polarity. All solvents were distilled and dried as usual.

Synthesis of the 2-chloro-N-(quinolin-3-yl-methyl)-2-aminoindan hydrochloride (9-10) analogs.
A mixture of compound 7-8 (0.082g, 0.356 mmol), compound 6 (0.05 g, 0.295 mmol) and anhydrous sodium acetate (0.027g, 0.295mmol) was dissolved in dry methanol (5 mL) and stirred at room temperature for 15 min until the formation of a white precipitate. The resulting solid was filtered by gravity and dried in the oven at 100 °C (24 h). The formed imine was dissolved in methanol (5 mL) and placed in an ice bath to add NaBH4 (0.01 g, 0.159 mmol) under constant stirring for 4 hours. After the reaction time, the mixture was diluted with water and an excess of concentrated HCl was added until an acidic pH was achieved. The methanol was evaporated under reduced pressure and NaOH pellets were added to the resulting solution to an alkaline pH. The organic phase was extracted with diethyl ether (3 x 10 mL) and washed with water, dried over anhydrous sodium sulfate, filtered by gravity and the solvent evaporated under reduced pressure. The obtained oil was treated with HCl-diethyl ether solution to obtain the final products (9-10) as the solid hydrochloride (recrystallized from isopropanol-diethyl ether).

N-[2-chloro-7-methylquinoline)-3-yl-methyl]-4,5-dimethoxy-2-aminoindan Hydrochloride (10).
Yellow-brown solid, 0.061 g (58%). Melting point: 215 °C. 1H-NMR (MeOH-d3) δ: 3.24 and 3.49 ppm (2dd, 2H, ax ps C1 and C3, J=7.91 Hz); 3.56 and 3.60 ppm (2dd, 2H, H, C1 and C3 eq, J=7.91Hz); 3.83 and 3.85 ppm (2s, 6H, 2 OCH3); 4.33 ppm (m, 1H, CH3); 4.63 ppm (s, 2H, CH2-NH2); 6.92 and 6.97 ppm (d, 2H, J = 8.15 and 7.67 Hz, H7 and H6 indan); 7.71 ppm (td, 1H, J = 7.42 and 1.22 Hz, H7 quinoline); 7.88 ppm (td, 1H, J = 7.18 and 1.5 Hz, H6 quinoline); 7.99 ppm (d, 1H, J = 7.91 Hz, quinoline H5); 8.04 ppm (d, 1H, J = 7.91 Hz, H8 quinoline); 8.68 ppm (s, 1H, H4 quinoline). 13C-NMR (MeOH-d3) δ: 33.2 and 35.6 ppm (CH2, C1 and C3 indan), 36.2 ppm (CH C2 indan and 1-OCH3); 47.1 ppm (CH2, C7 quinoline); 55.4 ppm (1 OCH3), 55.5 ppm (CH, C2 indan and 1-OCH3), 113, 119.6, 123.4, 127.1, 127.6, 127.9, 128.1, 131.7, 131.9, 131.2, 141.8, 145.6, 147.6, 149.8 and 151.8 ppm (aromatic CH). NMR-HETCOR 31P-NMR shows the following signals: 4.63 ppm (s, 2H, CH2-NH2) correlates with 55.5 ppm of 1-OCH3, 4.60 ppm (s, 2H, CH2-NH2) correlates with 59.4 ppm CH C2 indan and 1-OCH3; 6.92 and 6.97 ppm (d, 2H, J = 8.4 and 8.42 Hz, H7 and H6 indan); 7.56 ppm (dd, 1H, J = 8.41 and 1.24 Hz, quinolin H6); 7.77 ppm (s, 1H, quinoline H8); 7.93 ppm (d, 1H, J = 8.42 Hz, quinoline H5); 8.59 ppm (s, 1H, quinoline H8). 13C-NMR (MeOH-d3) δ: 20.60 ppm (CH2 C7 quinoline); 33.26 and 35.6 ppm (CH, C1 and C3 indan); 47.67 ppm (CH2-NH2); 55.53 ppm (1 OCH3); 59.43 ppm (CH, C2 ind and 1-OCH3); 113.2; 119.6; 122.5; 125.1; 127.1; 127.6; 130.2; 131.9; 141.5; 143.3; 145.4; 148.1; 149.7 and 151.9 ppm, aromatic C 15. DEPT NMR (135) δ 20.6 ppm (CH2, C7 quinoline); 33.1 ppm (CH2 (C1 indan inverted)); 35.6 ppm (CH2 (C3 indan inverted)); 47.1 ppm (CH2 (CH2-NH2)); 55 ppm (1-OCH3); 59.4 ppm (CH (C2 ind) and 1-OCH3); 113; 119.6; 126.4; 127.7; 130.2 and 141.6; 6 CH aromatic. HETCOR NMR shows the following signals: 4.60 ppm (s, 2H, CH2-NH2) correlates with 47.67 ppm of CH2-NH2; 3.83 ppm (1s, 3H, 1-OCH3) correlates with 55.5 ppm of 1-OCH3. At 3.85 ppm (1s, 3H, 1-OCH3) and 4.33 ppm (m, 1H, CH, C2 ind) correlates with 59.43 ppm of CH and one indan-1-OCH3). Anal. C22H30Cl2N4O2 C; 63.01; H; 5.77; N; 6.68. Found: C; 62.94; H; 5.79; N; 6.90 %.

PHARMACOLOGICAL SECTION
Male Sprague-Dawley rats (150-250g, b.w.) 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
Compounds-induced stereotypic behavior (licking, gnawing, sniffing and grooming) was assessed. Prior permission of the Animal Ethics Committee was obtained and all experiments were conducted according to the approved protocol. For this purpose, each of the synthesized compounds was injected individually for each test group at a dose of 50µg/5µL. Afterwards, the compounds were evaluated according to the following criteria: a) if the compound behaved like an agonist, it was compared to haloperidol (0.2 mg/kg, b.w., i.p., 15 min before ICV compound), a known dopamine receptor antagonist; and b) if the compound behaved like an antagonist it was compared to apomorphine (1 mg/kg, i.p. 15 min after ICV compound), a known dopaminergic receptor agonist, or with ziprasidone (1 mg/kg, i.p.), an atypical antipsychotic.

After ICV injection rats were placed in a clear acrylic box (32x28x28 cm) for observation. For each tests 4 animals were used. The observations were made during a 60 minutes period, divided into 10 intervals of 6 minutes each [7][10]. Previously, animals were placed in the observation box for 15 minutes in order habituate. The collected data were used. The observations were made during a 60 minutes period, divided into 10 intervals of 6 minutes each [7][10]. The analysis of the stereotyped behavior induced by compounds (9) and (10), demonstrates that both compounds induced a significant increase in licking and grooming, but very little or none sniffing and gnawing behavior when compared to the control groups (saline, apomorphine, haloperidol, ziprasidone). Haloperidol was able to inhibit licking and grooming behavior induced by compounds (9) and (10) suggesting their dopaminergic actions. Likewise, the atypical antipsychotic ziprasidone was able to inhibit licking and grooming behavior induced by compound (10) but did not the effect of compound (9). The effects of compound (9) on licking and grooming in the presence of ziprasidone are consistent with the new compounds synthesized and reported by Angel et. al. [7][10]. In this regard, it is well known that blockage with clozapine and ziprasidone of stereotyped behavior induced by apomorphine, generates an increase in licking and grooming [13][14]. Thus the increase in licking and grooming shown by the compound (9) could be explained by the fact that ziprasidone interacting with 5HT_{1A} and 5HT_{2A} receptors, as an agonist and antagonist respectively, would increase dopaminergic activation on the limbic system. Furthermore, it is known that 5HT_{2A} antagonists provoke a final magnification of dopaminergic activity in the mesocortical pathway by a preponderance of 5HT_{2A} receptors on D_{2} receptor [15]. Possibly this compound would interact on D_{2} type receptors, at a mesocortical pathways level. Also is known that both clozapine and ziprasidone reduces

RESULTS AND DISCUSSION

In this work we described the organic synthesis (classic and heterocyclic), as well as the pharmacological preliminary assessment of compounds (9) and (10) under their racemic forms (Scheme 1). The existence of the above mentioned compounds was confirmed by their spectroscopic data such as ^1H NMR, ^13C NMR, HETCOR, COSY and DEPT. These compounds were administered ICV at doses of 50 mg/5µL, showing significant changes in the stereotypical behavior such as licking and grooming; but none on gnawing and sniffing (Figure 2).

It is well known that stereotypy is the main component of various psychiatric disorders, including infantile autism and schizophrenia. It has been established that stereotypy (including sniffing and gnawing) is a behavior dependent of dopamine and the neural substrate of the stereotyped behavior induced by apomorphine in animals is due to dopaminergic projections in the caudate and putamen regions. Apomorphine is known to be a mixed agonist on D_{1}-D_{2} dopamine receptors. Activation of dopamine D_{1}-D_{2} receptors on the striatum nucleus is expressed as the response of an excessive and repetitive behavior (stereotypy). That is, the activation of dopamine receptors in the limbic system expresses the stereotyped behaviors licking and grooming; while sniffing and gnawing is a response to activation of receptors in the extrapyramidal system [11][12].

The analysis of the stereotyped behavior induced by compounds (9) and (10), demonstrates that both compounds induced a significant increase in licking and grooming, but very little or none sniffing and gnawing behavior when compared to the control groups (saline, apomorphine, haloperidol, ziprasidone). Haloperidol was able to inhibit littering and grooming behavior induced by compounds (9) and (10) suggesting their dopaminergic actions. Likewise, the atypical antipsychotic ziprasidone was able to inhibit littering and grooming behavior induced by compound (10) but did not the effect of compound (9). The effects of compound (9) on littering and grooming in the presence of ziprasidone are consistent with the new compounds synthesized and reported by Angel et. al. [7][10]. In this regard, it is well known that blockage with clozapine and ziprasidone of stereotyped behavior induced by apomorphine, generates an increase in littering and grooming [13][14]. Thus the increase in littering and grooming shown by the compound (9) could be explained by the fact that ziprasidone interacting with 5HT_{1A} and 5HT_{2A} receptors, as an agonist and antagonist respectively, would increase dopaminergic activation on the limbic system. Furthermore, it is known that 5HT_{2A} antagonists provoke a final magnification of dopaminergic activity in the mesocortical pathway by a preponderance of 5HT_{2A} receptors on D_{2} receptor [15]. Possibly this compound would interact on D_{2} type receptors, at a mesocortical pathways level. Also is known that both clozapine and ziprasidone reduces

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dopaminergic transmission by blocking dopamine D$_2$ receptors (mesolimbic system). The blockade with ziprasidone of grooming and licking behavior induced by compound (10) may be explained by the possibility that this compound is weakly bound to the receptor and may be displaced by ziprasidone. It is known that ziprasidone is also a D$_2$ antagonist and possibly explains the effect shown. Similar effects with ziprasidone were described for similar analogues [16]. The relation between chemical structure and pharmacological activity of these results confirm the assertiveness of the medicinal chemical approach of the click design type, since it allowed to bind the 4,5-dimetoxy-indane and quinolyl-3-methyl (substituted and –non-substituted) fragments to the “amine” nitrogen. It is noteworthy that the portion of the quinoline by itself has not been reported in the literature with pharmacological activity on the central dopaminergic system; but has been reported for its antidepressant and antifungal activities [17]. It is know that compound (10) is more lipophilic than compound (9), and compound (10) has a methyl substituent in the 7-position of the quinoline ring, which changes its affinity for the dopamine receptor. In other analogues, this was demonstrated by the replacement of the methyl group on positions 6- and 7- of the quinoline ring, whereas substitutions on positions 5- and/or 8- favor their interaction with that receptor [16].

CONCLUSION

We demonstrate that compounds (9) and (10) showed an agonistic response on the limbic system level (grooming and licking) and not in the extrapyramidal system, since there was no effect on sniffing and gnawing behavior. The assertiveness of the medicinal chemical approach in the design of these compounds is consistent with our preliminary pharmacological results, which show an agonistic action through the activation of dopaminergic mechanisms on the central nervous system.

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REFERENCES