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

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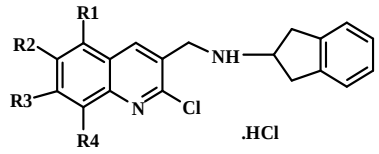
ABSTRACT

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 ^{1}H, ^{13}C, 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

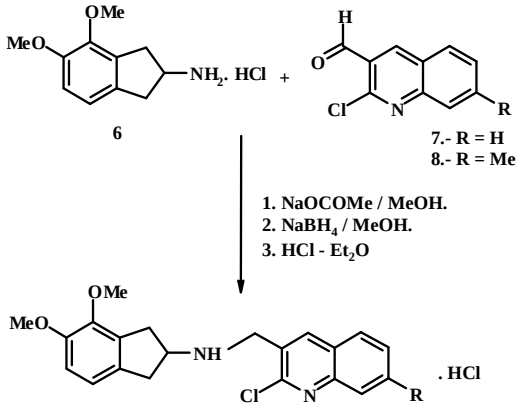
The dysfunctions of the central dopaminergic system have been linked to several neurological and psychiatric disorders, particularly Parkinson's disease (PD), schizophrenia, depression, attention deficit disorder with hyperactivity and alcohol dependence [1]. Dopamine (DA) is mainly located in the brain, 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.



1.- R_1,R_2,R_3,R_4 = H
2.-R_1,R_3,R_4 = H ; R_2 = Me
3.-R_1,R_2,R_4 = H ; R_3 = Me
4.-R_1,R_2,R_3 = H ; R_4 = Me
5.-R_2,R_3 = H ; R_1, R_4 = Me

Figure 1. Compounds 1-5

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).



6

7.- R = H
8.- R = Me

9.- R = H
10.- R = Me

Scheme 1. Synthetic route for obtaining the final products (9 and 10)

MATERIALS AND METHODS

Chemistry section

Melting points are uncorrected and were determined using a Thomas Hoover Capillary Melting Point apparatus. The ^{1}H NMR, ^{13}C NMR spectra were recorded using a Jeol Eclipse 270 (270 MHz/67.9 MHz) spectrometer using MeOH-*d*3 and are reported in ppm downfield from the residual CH_3OH. 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 ºC (24 h). The formed imine was dissolved in methanol (5 mL) and placed in an ice bath to add $NaBH_4$ (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 achieve. 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-quinoline)-3-yl-methyl]-4,5-dimethoxy-2-aminoindan Hydrochloride* (9).**

Yellow-brown solid, 0.061 g (58%). Melting point: 215°C. ^{1}H-NMR (MeOH-*d*3) 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, 2 H, C1 and C3 ps eq, J=7.91Hz); 3.83 and 3.85 ppm (2s, 6H, 2 OCH_3); 4.33 ppm (m, 1H, CH); 4.63 ppm (s, 2H, CH_2-NH_2); 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). ^{13}C-NMR (MeOH-*d*3) δ 33.2 and 35.6 ppm (CH_2, C1 and C3 indan), 47.7 ppm (CH_2-NH_2), 55.5 ppm (1 OCH_3), 59.4 ppm (CH, C2 indan and 1-OCH_3), 113.2, 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- DEPT (135) δ 33.8 ppm (CH_2, C1 indan, inverted), 36.2 ppm (CH_2, C3 indan, inverted), 47.1 ppm (CH_2, CH_2-NH_2), 55.4 ppm (OCH_3), 59.4 ppm (CH, C2 indan and 1 OCH_3); 113, 119.7, 127.5, 127 9, 128.1, 131.9 and 141.9 ppm (7 aromatic CH). NMR-HETCOR showed the following signals: 4.63 ppm (s, 2H, CH_2-NH_2) correlates with 47.7 ppm of CH_2-NH_2. 3.83 ppm (1s, 3H, 1-OCH_3) correlates with 55.5 ppm of 1-OCH_3. At 3.85 ppm (1s, 3H, 1-OCH_3) and 4.33 ppm (m, 1H, CH, C2 indan) correlates with 59.4 ppm CH C2 and one indan-OCH_3. Anal. $C_{21}H_{22}Cl_2N_2O_2$: C, 63.23; H, 5.47; N, 6.91. Found: C, 63.29; H, 5.52; N, 7.16 %.

N-[(2-chloro-7-methyl-quinoline)-3-yl-methyl)]-4,5-dimethoxy-2-aminoindan Hydrochloride (10).

^{1}H-NMR (MeOH-d3) δ: 2.58 ppm (s, 3H, CH_3, quinoline C7); 3.31 and 3.47 ppm (2dd, 2H, CH_2, C1 and C3 ps ax, J=5.44Hz); 3.54 and 3.60 ppm (2dd, 2H, CH_2, C1 and C3 ps eq, J=6.7Hz); 3.83 and 3.85 ppm (2s, 6H, 2 OCH_3); 4.32 ppm (m, 1H, CH, C2 indan); 4.60 ppm (s, 2H, CH_2-NH_2); 6.92 and 6.99 ppm (2d, 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, H4 quinoline). ^{13}C-NMR (MeOH-d_3) δ: 20.60 ppm (CH_3 C7 quinoline); 33.26 and 35.6 ppm (CH, C1 and C3 indan); 47.67 ppm (CH_2-NH_2); 55.53 ppm (1 OCH_3); 59.43 ppm (CH, C2 ind and 1-OCH_3); 113.2; 119.6; 122.5; 125.1; 126.4; 127.6; 130.2; 131.6; 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 (CH_3, C7 quinoline); 33.1 ppm (CH_2 (C1 indan inverted)); 35.6 ppm (CH_2 (C3 indan inverted)); 47.1 ppm (CH_2 (CH_2-NH_2)); 55 ppm (1-OCH_3); 59.4 ppm (CH (C2 ind) and 1-OCH_3); 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, CH_2-NH_2) correlates with 47.67 ppm of CH_2-NH_2. 3.83 ppm (1s, 3H, 1-OCH_3) correlates with 55.53 ppm of 1-OCH_3. At 3.85 ppm (1s, 3H, 1-OCH_3) and 4.33 ppm (m, 1H, CH, C2 ind) correlates with 59.43 ppm of CH and one ind C2-OCH_3). Anal. $C_{22}H_{24}Cl_2N_2O_2$: 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

laboratory chow (Ratarina®, Protinal). Apomorphine (APO-go PEN 10 mg/mL), haloperidol (Haldol 50 mg/mL, Janssen Pharmaceutica) and ziprasidone (Geodon, Pfizer) were used for stereotype evaluation, by injecting intraperitoneally (ip) at a dose of 1 mg/kg of the drug. A cannula was implanted in the right lateral cerebroventricle, 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 cilazina (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.

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 recorded using computing software to count the number of stereotyped responses. The results were expressed as the mean ± S.E.M., and analyzed by one-way and two-way variance analysis (ANOVA), followed by Newman-Keuls test. A value of $p<0.05$ was considered significant.

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 ^{1}H NMR, ^{13}C NMR, HETCOR, COSY and DEPT. These compounds were administered ICV at doses of 50 mg/5uL, 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, bur 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

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 bounded 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-dimetoxi-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].

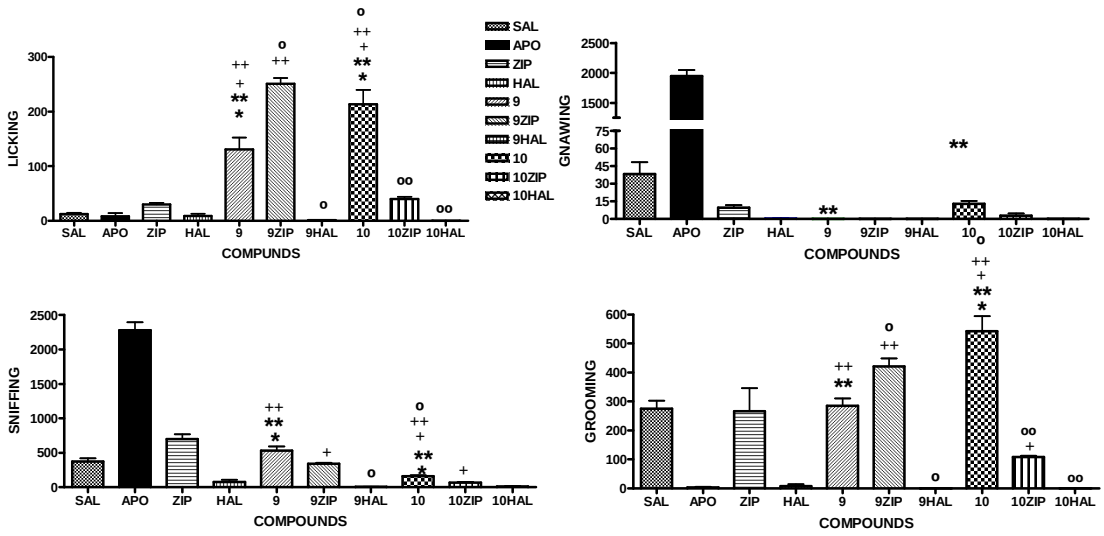


Figure 2. Effect of compounds 9 and 10 at a 50 µg/5mL dose on stereotyped behavior in rats. On the ordinate, the sum of the measured behaviors. In the abscissa, the compounds tested. The observations were performed for 1 hour. Results are expressed as the mean ± S.E.M. of four independent measurements. Data was analyzed using one-way and two-way variance analysis (ANOVA) and the Newman Keul's test. *p<0.01 vs saline; **p<0.001 vs apomorphine (APO); +p<0.01 vs ziprasidone (ZIP); ++p<0.001 vs haloperidol (HAL); °p<0.01 vs 9; °°p<0.001 vs 10.

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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