Medicinal Chemistry Research (2019) 28:1168–1181
https://doi.org/10.1007/s00044-019-02362-0

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Quinoline analogs of 2-aminoindane as potential central dopaminergic agents

Jorge E. Angel[1] · Ricardo D. Enriz[2] · Katherindel C. Balza[1] · Ligia B. Angel[1] · Luís E. Perdomo[1] · Lucia Ch. Rodríguez[1] · Akram S. Dabian[1] · Biagina del C. Migliore[1] · María M. Ramírez[1] · José G. Ortega[1] · Jaime E. Charris[3] · Anita. Israel[4] · María del R. Garrido[4] · Simon E. López[5,6] · Sebastian Rojas[2] · Sebastian A. Andujar[2]

Received: 25 February 2019 / Accepted: 20 May 2019 / Published online: 30 May 2019

Abstract

Neurodegenerative disorders such as Parkinson and Huntington Chorea are related with damage to the central dopaminergic system. On the purpose to find new drugs able to re-establish the imbalance on the dopaminergic neurotransmission in the central nervous system and counteract some of the neurodegenerative sicknesses, we have designed, synthesized, pharmacologically evaluated, and studied through molecular modeling,2-aminoindane-quinoline analog derivatives (**1**–**5**). Pharmacological studies made on the central nervous system through ICV (intracerebroventricular) and IS (intrastriatal), of compounds (**1**–**5**) showed agonistic activity by the activation of dopaminergic mechanisms on the central nervous system. The corresponding molecular modeling study permitted us not only to explain the differential behavior of studied compounds, but also to understand whichmolecular interactions are responsible to stabilize the different complexes formed between those compounds and the D_2 receptor. These results validate our medicinal chemical approach in different aspects: the receptor model used, the responsible fragment inserted within the structure of the compounds capable of interacting with the receptor, the complementary functional groups that facilitate the expected response and the pharmacological administration routes. All these aspects are important for the design of this type of compounds as potential anti-Parkinson and/or anti-Huntington agents.

Keywords Parkinson · Huntington Chorea · Agonists · Dopaminergic neurotransmission · Molecular modeling.

Introduction

Dopamine (DA) is a central nervous system neurotransmitter related to mechanisms involved in motor, cognitive, behavioral, and neurocrine processes. It contributes to the neurophysiological control of activation (alertness, wakefulness, and sleep), attention, initiation and completion of movement, perception, motivation, and emotion. In addition, it plays a significant role in the pathophysiology of neurodegenerative disorders, such as Parkinson disease (PD) and Huntington Chorea (HD), primarily (Beaulieu and Gainetdinov 2011); (Zhang et al. 2007); (Rangel-Barajas et al. 2015); (Montaño-Arias et al. 2000); (Goodman and Gilman et al. 1991). In PD, there is a deficiency of DA caused by a progressive striatonigrial degeneration of

Supplementary information The online version of this article (https://doi.org/10.1007/s00044-019-02362-0) contains supplementary material, which is available to authorized users.

✉ Jorge E. Angel
jangel63@yahoo.com

✉ Ricardo D. Enriz
denriz@unsl.edu.ar

[1] Laboratorio de Síntesis Orgánica, Diseño y Evaluación Farmacológica de nuevos productos, Departamento de Química, Facultad Experimental de Ciencias, Universidad del Zulia, Universidad Central de Venezuela, Maracaibo, Venezuela

[2] IMBIO-SL CONICET, Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luís- República de Argentina, San Luis, Argentina

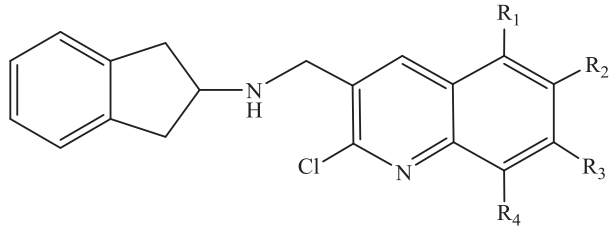
[3] Laboratorio de Síntesis Orgánica, Facultad de Farmacia, Caracas, Venezuela

[4] Laboratorio de Neuropéptidos, Facultad de Farmacia, Caracas, Venezuela

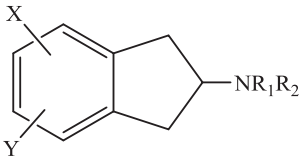
[5] Departamento de Química, Universidad Simón Bolívar, Valle de Sartenejas, Baruta, Caracas 1080A, Venezuela

[6] Present address: Department of Chemistry, University of Florida, P.O. Box 117200, Gainesville, FL 32611-7200, USA

dopaminergic pathways, characterized by the difficulty to initiate and stop movements, between others (Goodman and Gilman et al. 1991); (Brichta et al. 2013), while HD is characterized by an imbalance in the control of movement in the basal ganglia, caused by a vast degeneration of neuronal secretory cell bodies of GABA in the caudate nucleus, putamen, and acetylcholine secretory neurons from different regions of the brain (Gatto E. Enfermedad de Huntington 2002); (Encinosa G. Corea de huntington 2001). Taking into consideration the need to find new drugs able to relieve or cure the imbalances of dopaminergic neurotransmission in neurodegenerative disorders, we have designed analogs of *N*-chloro-(mono or di-methylquinolin-3-yl-methyl)-2-aminoindane (**1**–**5**) having the necessary pharmacophoric approximations to interact on the action targets of the central dopaminergic system. The design was based in the link of two individual active fragments through covalent bonds towards a central nitrogen atom, hybridizing the 2-aminoindane fragment with 2-chloro-3-formylquinolines. It is well known that 2-aminoindane analogs (**6**) have shown dopaminergic activity (Cannon et al. 1980); (Hacksell et al. 1981); (Cannon et al. 1982); (Angel-Guío et al. 2003 2004); (Andujar et al. 2006); (Angel et al. 2008); (Angel et al 2015a, 2015b, 2015c), as well as the report that certain substituted quinolines possess antidepressant, antifungal, and central dopaminergic activity (Suresh et al. 2011); (Zajdel et al. 2013); (Angel et al. 2015a, 2015b, 2015c). Compounds **1**, **4**, and **5** were previously reported by us as anti-Huntington agents (Angel et al 2015a, 2015b, 2015c). In the present work, it is reported the synthesis, pharmacological evaluation, and computational study of compounds **1**–**5**, in order to explore their mechanism of action over the central dopaminergic system, as potential anti-Parkinson and/or anti-Huntington agents (Fig. 1).



1. R_{1-4}= H
2. $R_{1,3,4}$= H; R_2= Me
3. $R_{1,2,4}$= H; R_3= Me
4. R_{1-3}= H; R_4= Me
5. $R_{2,3}$= H; $R_{1,4}$= Me



6

Fig. 1 Structures of compounds 1–6

Materials and methods

Chemistry section

Melting points are not corrected. They were determined using a "Thomas Hoover Capillary Meeting Point" apparatus. ^{1}H and ^{13}C Nuclear magnetic resonance experiments were performed using a 270 MHz Jeol spectrometer, located at the Faculty of Pharmacy of Central University of Venezuela. The NMR data signals are reported as ppm (δ) using TMS as internal standard, downfield. The purity of all compounds was determined by thin layer chromatography using different polarities solvent systems. Chemical reagents were obtainedfrom Aldrich Chemical Co, USA. All solvents were distilled and dried in the usual manner. Elemental analysis of all new compounds was done using a Perkin Elmer 2400 C,H,N elemental analyzer, and results were in the range of ±0.4% of the theoretical value (Fig. 2).

Synthesis of N-2-chloro-(mono or di-methylquinolin-3-yl-methyl)-2-aminoindane hydrochloride analogs (1-5)

A mixture of compound **8a-e** (0.356 mmol), **7**(0.050 g; 0.295 mmol) and anhydrous sodium acetate(0.027 g; 0.295 mmol) was dissolved methanol (anhydrous)(5 mL) and stirred at room temperature for 15 min until a white precipitate was formed. The resulting solid was filtered by gravity and oven dried at 100 °C.The corresponding imine was dissolved in methanol (5 mL) and cooled (ice-water bath), adding then $NaBH_4$ (0.01 g), and the reaction stirred for 4 h. The mixture was diluted with water and concentrated HCl was added dropwise until acid pH was reached. Methanol was evaporated under vacuo and solid NaOH (granules) was added to reach alkaline pH. The organic phase was extracted using diethyl ether and washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The obtained oil was treated with diethyl ether-HCl to obtain the final products (**1**–**5**) as solids, which were recrystallized from isopropanol-dietyl ether.

Compound (N-2-chloro-(quinolin-3-yl-methyl)-2-aminoindane hydrochloride) (1): Yellow-greenish solid, mp 259–262 °C, 0.061 g (59.7 %).^{1}H-NMR (MeOH-d_3,270 MHz,): δ = 3.30 (2H, dd, J = 7.91 Hz, J = 4.2 Hz, H-1 or H-3*psax-ind*), 3.57 (2H,dd, J = 7.91 Hz, J = 4.2 Hz, H-1 or H_3 *psec-ind*), 4.37 (1H, m, H-2*ind*,), 4.64 (2H, s, H-9'), 7.25 (4H, m, H-(4-7)*ind*), 7.71 (1H, *pst*, J = 1.24 Hz, J

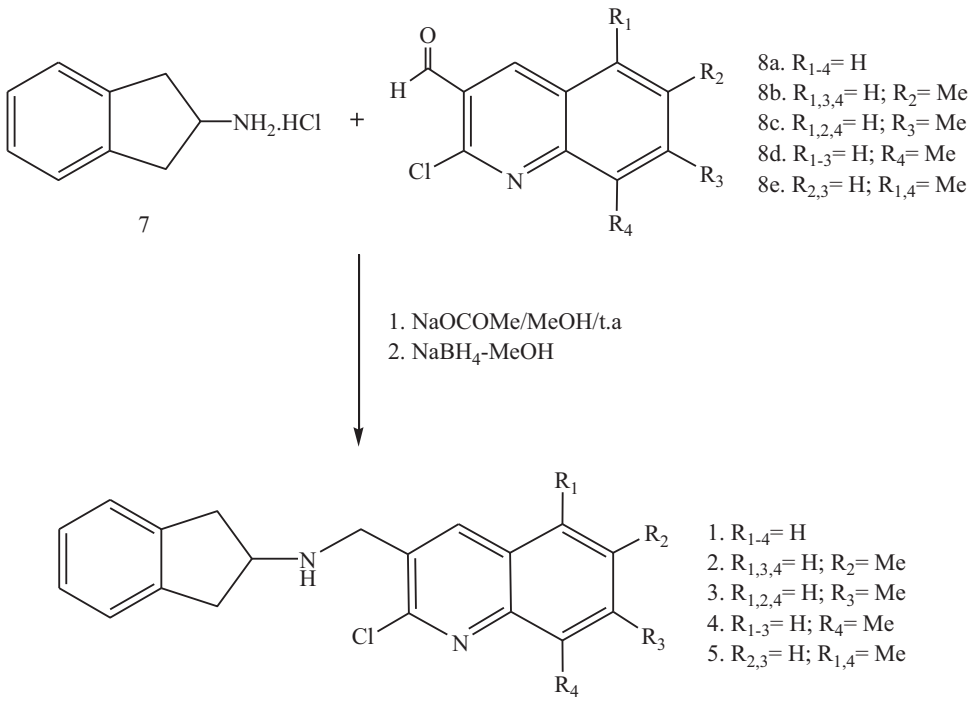


Fig. 2 Synthetic route to obtain (**1**–**5**)

= 7.53 Hz, H-6'quinoline), 7.88 (1H, *ps*t, $J = 1.24$ Hz, $J = 7.53$ Hz, H-7'quinolin), 7.99 (1H, d, $J = 8.15$ Hz, H-5'quinoline), 8.05ppm (1H, d, $J = 8.15$ Hz, H-8'quinoline), 8.68 (1H, s, H-4'quinoline). ^{13}C-NMR (MeOH-d_3, 65 MHz): δ = 36.0 (C, C-1 or C-3*ind*), 47.4 (C, C-9'), 59.2 (C, C-2*ind*), 123.6 (C, C-3a *quaternary-ind*), 124.4 (C, C-(4-7)*ind*), 127.1 (C, C-3'quinoline), 127.4 (C, C-2*ind*), 127.6 (C, C-5'quinoline), 127.9 (C, C-6'quinoline), 128.1 (C, C-8'quinoline), 131.9 (C, C-7'quinoline), 138.6 (C, C-4a' quaternary-quinoline), 141.8 (C, C-4'quinoline), 147.8 (C, C8a' quaternary-quinoline), 149.8 (C, C-2'quinoline). NMR- DEPT (135°), δ: 36.0 (C, C-1 and C-3 *ind-invert*), 47.1 (C, C-9' *invert*), 59.1 (C, C-2*ind*), 124.5 (C, C-(4-7) *indane*), 127.4 (C, C-(4-7)*indane*), 127.5 (C, C-5'quinoline), 127.8 (C, C-6'quinoline), 128.1 (C, C-8'quinoline), 131.9 (C, C-7'quinoline), 141.8 (C, C-4'quinoline).NMR-HETCOR showed the following signals: 47.1 (C, C-9'quinoline) correlates to the proton signal at 4.64 (2H, s, H-9'). Anal. Calcd. (%) for $C_{19}H_{18}Cl_2N_2$: C, 66.09; H, 5.25; N, 8.11. Found: C, 66.12; H, 5.27; N, 8.27.

Compound (N-2-chloro-(6-methylquinolin-3-yl-methyl)-2-aminoindane hydrochloride) (2): Light yellow solid, mp 273 °C, 0,070 g (66,4 %). ^{1}H-NMR (MeOH-d_3,270 MHz): δ = 2.55 (3H, s, CH$_3$, H-6'quinoline position), 3.30 (2H, dd, CH$_2$, $J = 7.91$ Hz, $J = 4.2$ Hz, H-1 or H-3*psax-ind*), 3.57 (2H,dd, $J = 7.91$ Hz, $J = 4.2$ Hz, H-1 or H$_3$ *psec-ind*), 4.33 (1H, H-2*ind*), 4.61 (2H, s, H-9'), 7.25 (4H, m, H-(4-7) *ind*), 7.73 (1H, d, $J = 8.15$ Hz, H-7'quinoline), 7.81 (1H, s, H-5'quinoline), 7.88 (1H, d, $J = 8.64$ Hz, H-8'quinoline), 8.56 (1H, s, H-4'quinoline). ^{13}C-NMR (MeOH-d_3, 65 MHz): δ = 20.17 (CH$_3$, C-6'quinoline), 36.03 (C, C-1 or C-3*ind*), 47.67 (C, C-9'), 59.11 (C, C-2*ind*), 123.46 (C, C-3a *quaternary-ind*), 124.44 (C, C-(4-7)*ind*), 126.72 (C, C-7'quinoline), 127.13 (C, C-6'quaternary-quinoline), 127.14 (C, C-4a' quaternary-quinoline), 127.22(C, C-(4-7)*ind*), 127.38 (C, C-8'quinoline), 134.12 (C, C-5'quinoline), 138.61 (C, C-3'quinoline), 141.17 (C, C-4'quinoline), 146.30 (C, C8a' quaternary-quinoline), 148.89 (C, C-2'quinoline). NMR- DEPT (135°) δ: 20.20 (CH$_3$, C-6'quinoline), 36.00 (C, C-1 and C-3 *ind-invert*), 46.92 (C, C-9' *invert*), 59.06 (C, C-2*ind*), 124.46 (C, C-(4-7)*indane*), 126.73 (C, C-7'quinoline), 127.19 (C, C-(4-7)*indane*), 127.38 (C, C-8'quinoline), 134.15 (C, C-5'quinoline), 141.17 (C, C-4'quinoline). NMR-HETCOR showed the following signals: 46.92 (C, C-9'quinoline) correlates to the proton signal at 4.61 (2H, s, H-9'). Anal. Calcd. (%) for $C_{20}H_{20}Cl_2N_2$: C, 66.86; H, 5.61; N, 7.80. Found: C, 66.90; H, 5.63; N, 8.01.

Compound(N-2-chloro-(7-methylquinolin-3-yl-methyl)-2-aminoindane hydrochloride) (3): Solid beige, mp 267 °C, 0,060 g (56,6 %). ^{1}H-NMR (MeOH-d_3,270 MHz): δ = 2.58 (3H, s, CH$_3$, H-7'quinoline position), 3.30 (2H, dd, $J = 7.91$ Hz, $J = 4.2$ Hz, H-1 or H-3*psax-ind*), 3.56 (2H, dd, $J = 7.91$ Hz, $J = 4.2$ Hz, H-1 or H$_3$ *psec-ind*), 4.33 (1H, m, H-2*ind*), 4.61 (2H, s, H-9'), 7.28 (4H, m, H-(4-7)*ind*), 7.56 (1H, d, $J = 8.18$ Hz, H-6'quinoline), 7.77 (1H, s, H-8'quinoline), 7.93 (1H, d, H-5'quinoline), 8.60 (1H, s, H-4'quinoline). ^{13}C-NMR (MeOH-d_3, 65 MHz): δ = 20.60 (CH$_3$,

C-7'quinoline), 36.03 (C, C-1 or C-3*ind*), 47.36 (C, C-9'), 59.07 (C, C-2*ind*), 122.59 (C, C-3a *quaternary-ind*), 124.44 (C, C-(4-7)*ind*), 125.15 (C, C-4a' quaternary-quinoline), 126.47 (C, C-8'quinoline), 127.38 (C, C-(4-7)*ind*), 127.67 (C, C-5'quinoline), 130.17 (C, C-6'quinoline), 138.61 (C, C-7' quaternary-quinoline), 141.53 (C, C-4'quinoline), 143.32 (C, C-3' quaternary-quinoline), 148.01 (C, C8a' quaternary quinoline), 149.73 (C, C-2' quaternary-quinoline). NMR- DEPT (135°) δ: 20.64 ($\underline{C}H_3$, C-7'quinoline), 36.01 (C, C-1 and C-3 *ind-invert*), 47.16 (C, C-9' *invert*), 59.03 (C, C-2*ind*), 124.46 (C, C-(4-7)*indane*), 126.44 (C, C-8'quinoline), 127.38 (C, C-(4-7)*indane*), 127.69 (C, C-5'quinoline), 130.17 (C, C-6'quinoline), 141.53 (C, C-4'quinoline). NMR-HETCOR showed the following signals: 46.36 (C, C-9'quinoline) correlates to the proton signal at 4.61 (2$\underline{H}$, s, H-9'). Anal. Calcd. (%) for $C_{20}H_{20}Cl_2N_2$: C, 66.86; H, 5.61; N, 7.80. Found: C, 66.87; H, 5.62; N, 7.97.

Compound(N-2-chloro-(8-methylquinolin-3-yl-methyl)-2-aminoindane hydrochloride) (4): Solid white, mp 252 °C, 0,076 g (72,5 %). ^{1}H-NMR (MeOH-d_3,270 MHz): δ = 2.72 (3$\underline{H}$, s, $C\underline{H}_3$, H-8'quinoline position), 3.30 (2$\underline{H}$, dd, J = 7.91 Hz, J = 4.2 Hz, H-1 or H-3*psax-ind*), 3.55 (2$\underline{H}$, dd, J = 7.91 Hz, J = 4.2 Hz, H-1 or H_3 *psec-ind*), 4.33 (1$\underline{H}$, m, H-2*ind*), 4.62 (2$\underline{H}$, s, H-9'), 7.26 (4H, m, H-(4-7)*ind*), 7.57 (1$\underline{H}$, t, J = 7.91 Hz, H-6'quinoline), 7.71 (1$\underline{H}$, d, J = 6.66 Hz, H-7'quinoline), 7.84 (1$\underline{H}$, d, J = 8.18 Hz, H-5'quinoline), 8.58 (1H, s, H-4'quinoline). ^{13}C-NMR (MeOH-d_3, 65 MHz,): δ = 16.23 ($\underline{C}H_3$, C-8'quinoline), 36.03 (C, C-1 or C-3*ind*), 47.36 (C, C-9'), 59.08 (C, C-2*ind*), 123.17 (C, C-3a *quaternary-ind*), 124.44 (C, C-(4-7) *ind*), 125.80 (C, C-5'quinoline), 127.12 (C, C-4a' quaternary-quinoline), 127.37 (C, C-(4-7)*ind*), 127.67 (C, C-6'quinoline), 131.77 (C, C-7'quinoline), 136.40 (C, C-8' quaternary-quinoline), 138.62 (C, C-3' quaternary-quinoline), 141.74 (C, C-4'quinoline), 147.00 (C, C8a' quaternary quinoline), 148.68 (C, C-2' quaternary-quinoline). NMR- DEPT (135°) δ: 16.31 ($\underline{C}H_3$, C-8'quinoline), 36.01 (C, C-1 and C-3 *ind-invert*), 47.17 (C, C-9' *invert*), 59.08 (C, C-2*ind*), 124.45 (C, C-(4-7)*indane*), 125.83 (C, C-5'quinoline), 127.37 (C, C-(4-7)*indane*), 127.68 (C, C-6'quinoline), 131.78 (C, C-7'quinoline), 141.74 (C, C-4'quinoline). NMR-HETCOR showed the following signals: 47.17 (C, C-9'quinoline) correlates to the proton signal at 4.62 (2H, s, H-9'). Anal. Calcd. (%) for $C_{20}H_{20}Cl_2N_2$: C, 66.86; H, 5.61; N, 7.80. Found: C, 66.95; H, 5.67; N, 8.07.

Compound(N-2-chloro-(5,8-dimethylquinolin-3-yl-methyl)-2-aminoindane hydrochloride) (5): Solid white, mp 265 °C, 0,077 g (69,7 %). ^{1}H-NMR (MeOH-d_3,270 MHz): δ = 2.67 (3H, s, $C\underline{H}_3$, H-5'quinoline position), 2.72 (3H, s, $C\underline{H}_3$, H-8'quinoline position), 3.30 (2H, dd, J = 7.91 Hz, J = 4.2 Hz, H-1 or H-3*psax-ind*), 3.57 (2H, dd, J = 7.91 Hz, J = 4.2 Hz, H-1 or H_3 *psec-ind*), 4.34 (1$\underline{H}$, m, H-2*ind*), 4.65 (2$\underline{H}$, s, H-9'), 7.26 ((4$\underline{H}$, m, H-(4-7)*ind*), 7.40 (2$\underline{H}$, d, J = 7.18 Hz, H-6'quinoline), 7.58 (2$\underline{H}$, d, J = 7.42 Hz, H-7'quinoline), 8.75 (1H, s, H-4'quinoline). ^{13}C-NMR (MeOH-d_3, 65 MHz,): δ = 15.63 ($\underline{C}H_3$, C-5' and C-8'quinoline), 36.06 (C, C-1 or C-3*ind*), 47.35 (C, C-9'), 58.95 (C, C-2*ind*), 122.44 (C, C-3a *quaternary-ind*), 124.45 (C, C-(4-7)*ind*), 127.41 (C, C-(4-7)*ind*), 127.96 (C, C-4a-C8a quaternary-quinoline), 131.61 (C, C-5' or C-8' quaternary-quinoline), 136.14 (C, C-6'o C-7' quinoline), 134.12 (C, C-3' quaternary-quinoline), 135.01 (C, C-4'quinoline), 138.59 (C, C-2'quinoline). Anal. Calcd. (%) for $C_{21}H_{22}Cl_2N_2$: C, 67.56; H, 5.94; N, 7.50. Found: C, 67.63; H, 6.03; N, 7.73.

Pharmacological section

Sprague-Dawley male rats were used, with 150–250 body weight, maintained under alternance periods of light and darkness, and free access to water and standard food (Ratarina®, Protinal). In the stereotypy assays the following chemicals were employed: apomorphine (APO-go PEN 10 mg/mL, injectable solution), bromocriptina (PARLODEL, tablets 2.5 mg, Novartis), haloperidol (Haldol 50 mg/mL, injectable solution, from JANSSEN PHARMACEUTICA), ziprasidone (Geodon, powder for injectable solution, Pfizer), pramipexole (Biopsol,® tablets 1 mg, RECALCINE, S.A.), and the serotonin ($5HT_{1a}$) partial agonist buspirone (Buspar, tablets 20 mg) dissolved in saline solution and intraperitoneal (ip) injected at a dose of 1 mg/Kg of body weight. Compounds **1**–**5** were dissolved in NaCl isotonic solution and injected intracerebroventricular (ICV) and intrastriatal (IS) (only compounds **1, 4**, and **5**) in a volume of 5 µL, using a 10 µL Hamilton syringe, provided with a cap top for the precise application of the compounds. Five days before the experiment, a metallic cannula was implemented in the right-lateral ventricle and in the right-anterior striatum, of the rats, under anesthesia with cylazine (Setton® 2%; 1 mg/Kg.; ip) and relaxation with ketamine, following the coordinates: antero-posterior –0,40 mm from Bregma; 1.2 mm lateral, (ICV) (Angel et al. 2008); (Angel et al. 2015a, 2015b, 2015c) antero-posterior = +1,2; Lateral = +2,8; Ventral = –5,5 (IS), (Angel et al. 2015a, 2015b, 2015c); (Francis-Turner et al. 2006), respectively. The cannulas used as guidance for the introduction of the needle for ICV injection were constructed using 20 G syringes with an inferior length at 4 mm, fixed to the skull permanently using acrylic and plastic cement.

A search was done to determine if compounds induced a stereotyped behavior, by means of a repetitive motor activity without purpose. To observe such behavior, each animal was introduced in a transparent acrylic box with the

following dimensions: 32 × 28 × 28 cm. For each ones of the assays, four animals group were used, evaluating the following behavior: licking, grooming, sniffing, and gnawing. Before the measurement of stereotyped behavior, animals were introduced in an observation box and left there for a period of 15 min to get them used with the space. Collected data were registered employing a computer provided with an appropriate software to count the number of stereotyped movements. Observations were taken by 60 min, divided in 10 intervals of 6 min each. The results are expressed as the average ± E.E.M. The significance of results was analyzed through a one-way variance (ANOVA), and the Newman–Keul test (Snedecord and Cochnar 1982). A value of $p < 0.05$ was considered as significative. Analysis of results and elaboration of plots were performed using the program GraphPadPrism version 5.1.

Studied compound (**1**–**5**) were injected individually for each tested group, by a 50 µg/5 µL dose. Later, the induced stereotyped behavior was evaluated in rats pre-treated with haloperidol (0.2 mg/Kg. PC., i.p) and ziprasidone (1 mg/Kg. PC., i.p), respectively. To perform that evaluation, each drug was injected 15 min before the ICV administration of the evaluated compound. Compounds **1**, **4**, and **5** were evaluated a doses 50 µg/5 µl and 5 µg/5 µl in rats pre-treated with buspirone (1 mg/Kg. PC. i.p), a partial agonist of the $5HT_{1a}$ receptor. For these compounds both doses were evaluated at the IS (intrastriatal) level and compared with a group of rats having Huntington disease, as previously reported by our group (Angel et al. 2015a, 2015b, 2015c).

Molecular modelling

3D models of the human D_1 and D_2 were used for the molecular modeling study. The model for D_1 is based on the homology model from the crystallized D_3DR, β_2-adrenoceptor, and $A_{2\alpha}$ adenosine receptor as templates. In fact, there are many molecular modeling studies in the literature, reporting D_2 obtained by homology, all of them structurally very similar (Párraga et al. 2016); (Párraga et al. 2013). On the other hand, the D_2 was used as the one that has recently been reported in the Protein Data Bank (Sheng et al. 2018). Thus, in the present study, we used two previously successful models to perform molecular modeling studies of different dopamine receptor ligands (Angel et al. 2008); (Angelina et al. 2015a, 2015b, 2015c); (Morris et al. 2009). Compounds and DR structures were converted from pdb to pdbqt format with MGL Tools and Molecular docking simulations were performed using the AutoDock Vina software (Morris et al. 2009). Several docking poses were considered and complexes with the lowest docking-energy according to the standard scoring function was regarded as the most favorable orientation and then used for MD calculations. To judge the validity of the docking poses previously reported experimental evidence was taken into account.

Molecular dynamics (MD) simulations

The complex geometries from docking were soaked in boxes of explicit water using the TIP3P model and subjected to MD simulation. All MD simulations were performed with the Amber 14 software package using periodic boundary conditions and cubic simulation cells. The particle mesh Ewald method (PME) was applied using a grid spacing of 1.2 Å, a spline interpolation order of 4 and a real space direct sum cut off of 10 Å. The SHAKE algorithm was applied allowing for an integration time step of 2 fs. MD simulations were carried out at 310 K temperature. Three MD simulations of 3 ns were conducted for each system under different starting velocity distribution functions; thus, in total 9 ns were simulated for each complex. The NPT ensemble was employed using Berendsen coupling to a baro/thermostat (target pressure 1 atm, relaxation time 0.1 ps). Post MD analysis was carried out with program CPPTRAJ.

Acute toxicity assay

Based in our previous studies, we have used fish with the aim of evaluating toxicity of novel drug compounds from natural and synthetic sources (Bisogno et al. 2007); (Garibotto et al. 2010). For evaluation of acute toxicity, we used as experimental biological model fishes, following the technique recommended by the US Fish and Wild life Service (Johnsosn and Finley 1980) which has been modified to use a smaller amount of test compounds as was reported by Mascotti et al. 2008.

Specimens adults of Poeciliareticulata were purchased in local businesses and were transferred to our laboratory and placed for 21 days in tanks parked 50 L of water to adapt to new conditions. During that period they were fed 1 time per day with a (Tetramin®) specific food and standardized controlled aeration supply; the value of the ambient temperature was a daily average of 230 °C and water replenishment undertaken to maintain the volume of the ponds. For the experiences we selected specimens born in our laboratory to 0.5–1 cm in length, they showed signs of good as fins position and overall external morphology.

Ten fishs, were exposed for a period of 96 h to each concentration of test compounds using five concentrations in each toxicity test (in the range of 10–100 µg/ml). Solutions and specimens were placed in a 1–2 L vessel (ratio of 1 specimen per 0.1 or 0.2 L of water) where they were kept until the end of the evaluations. The numbers of dead specimens in each container were removed every 24 h. The

percentage of mortality was assessed at 96h. It was determined the minimum concentration of formulated which produced 100% mortality (MC100% M) and the maximum concentration that did not cause mortality (MC0% M).

Results and discussion

The present work describes the design, synthesis, and pharmacological evaluation of compounds **1**–**5**. These compounds were obtained through a base catalyzed reductive amination reaction (Angel et al. 2015a, 2015b, 2015c); (Singh and Srivastava 2005) between 2-aminoindane **7** and 2-chloro-3-formylquinolines **8 a-e**, previously synthesized (Cannon et al. 1982); (Angel et al. 2015a, 2015b, 2015c); (Meth-Cohn et al. 1981). The structure of key intermediates and the final product were confirmed through their NMR data (^{1}HNMR, ^{13}CNMR, HETCOR, COSY, and DEPT).

The pharmacological study was done by the administration of compounds **1**–**5** ICV and IS, evaluating the induced stereotyped behavior over the CNS. It is well known that stereotypy is a principal component of various psychiatric disorders, including infant autism and schizophrenia. In rats, it has been established that stereotypy (including sniffing and gnawing) is a dopamine dependent behavior, and that the neural substrate for stereotyped behavior induced by apomorphine in animals is due to the dopaminergic projections in the caudate and putamen nucleus. Apomorphine is known as a mix D_1–D_2 dopamine receptor agonist. The activation of D_1–D_2 dopamine receptors over the striatal nucleus is expressed as a response from excessive and repetitive behavior (stereotypy).The activation of dopaminergic receptors at the limbic system expresses the stereotyped behavior of licking and grooming, while the sniffing and gnawing are responses from the activation of the extrapyramidal system (Costall et al. 1977a, 1977b).

Pharmacological results showed the agonistic central dopaminergic activity of the final product, as well as their concordance with the medicinal chemistry approach employed for its design. Figure 3 shows that the ICV administration of compounds **1**–**5** at a dose of 50 µg/5 µL, induces significant changes in stereotyped behavioral responses, because the lickings and grooming raised up for compounds (**1**–**5**) and (**2, 3** and **4**), respectively. Compounds **2** and **3** were able to raise up sniffing significantly.

The responses showed by **1, 4**, and **5** were more selective towards the limbic system, while the responses showed by compounds **2** and **3** came from the basal ganglia on the limbic system. The blockade of responses showed by compounds **1**–**5** with haloperidol (non- selective antagonist), demonstrates its dopaminergic action in both sites. The pretreatment with ziprasidone blocks licking, grooming and sniffing produced by compounds **2–3**, and increases significantly the licking generated by compounds **1**, **4**, and **5**, but only the lickings and sniffing were increased for compound **4**. These results agree with other synthesized-evaluated compounds, with a similar behavior as that shown by other reported dopaminergic agonists when co-administered with ziprasidone or clozapine in rats (Rollema 2000); (Kapur et al. 2001); (Bardin et al. 2006). It is well known ziprasidone selectively increases the release of

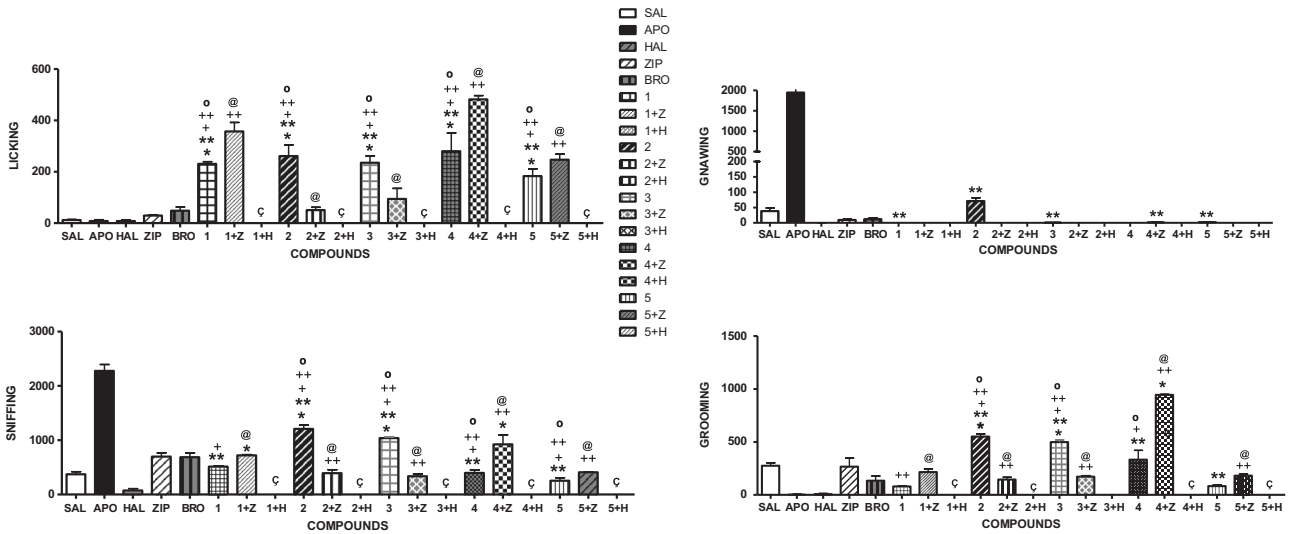


Fig. 3 Effect of compounds **1**–**5** at 50 µg/5 µL dose on stereotyped behavior in rats. On the ordinate, the sum of the measured behaviors. In the abscissa, the compounds tested. The observations were performed for 1 h. Results are expressed as the mean ± S.E.M. of four independent measurements. Data were analyzed using one-way variance analysis (ANOVA) and the Newman–Keul's test. * significant difference (sd) ($p < 0.001$) vs saline; ** sd vs apomorphine (APO); +sd vs haloperidol (HAL); ++sd vs ziprasidone (ZIP); ° sd vs bromocriptine (BRO); @ sd compound *vs* compound with ZIP; ç sd compound *vs* compound with HAL

dopamine in the pre-frontal cortex (mesocortical system), when the $5HT_{1a}$ receptors are activated and the $5HT_{2a}$ receptors blocked. Also, ziprasidone shows eight times less affinity when blocking the D_2 receptor. Based on that, we can infer the evaluated compounds may be acting as dopaminergic agonists, interacting with their receptors at the limbic level (grooming and licking) and the basal ganglia (sniffing). Since ziprasidone produces a raise in the dopaminergic tone on the pre-frontal cortex neurons, that action can be associated with a significant increase of the stereotyped behavior observed for compounds **1**–**5** at this level. Contrary, the activation of dopaminergic receptors in the basal ganglia induced by compounds **1**–**5** (sniffing behavior) was blocked, probably due an inhibitory action on the D_2 receptor caused by ziprasidone. However, the sniffing raised-up shown by compound **4** could be explained by the raise in the dopaminergic tone at the basal ganglia level. These results are in agreement with previous reports of our group showing other evaluated compounds were able to increase grooming and licking when co-administered with ziprasidone (Angel et al. 2008); Angel et al. 2015a, 2015b, 2015c).

Analogs **1**, **4**, and **5** were selected to perform more complete pharmacological evaluations. In this study they were considered both, an intracerobroventricular (ICV) and an intrastriatal (IS) administration at doses 50 µg/5 µL and 5 µg/5 µL, respectively. Also, the behavior was determined towards a $5HT_{1a}$ partial agonist ICV at both doses. The striatal level evaluation (50 µg/5 µL) was compared with the results obtained in rats treated with neurotoxin 6OHDA at IS level, previously reported by our group (Angel et al. 2015a, 2015b, 2015c).

Figures 4–6 show the ICV administration of compounds **1**, **4**, and **5** at 50 µg/5 µl and 5 µg/5 µl doses, respectively. A significant increase in the licking behavior was displayed, showing a higher effect at 5 µg/5 µl. These responses were superior to those shown by control groups, like Huntington disease (HD), ziprasidone, buspirone and saline. The

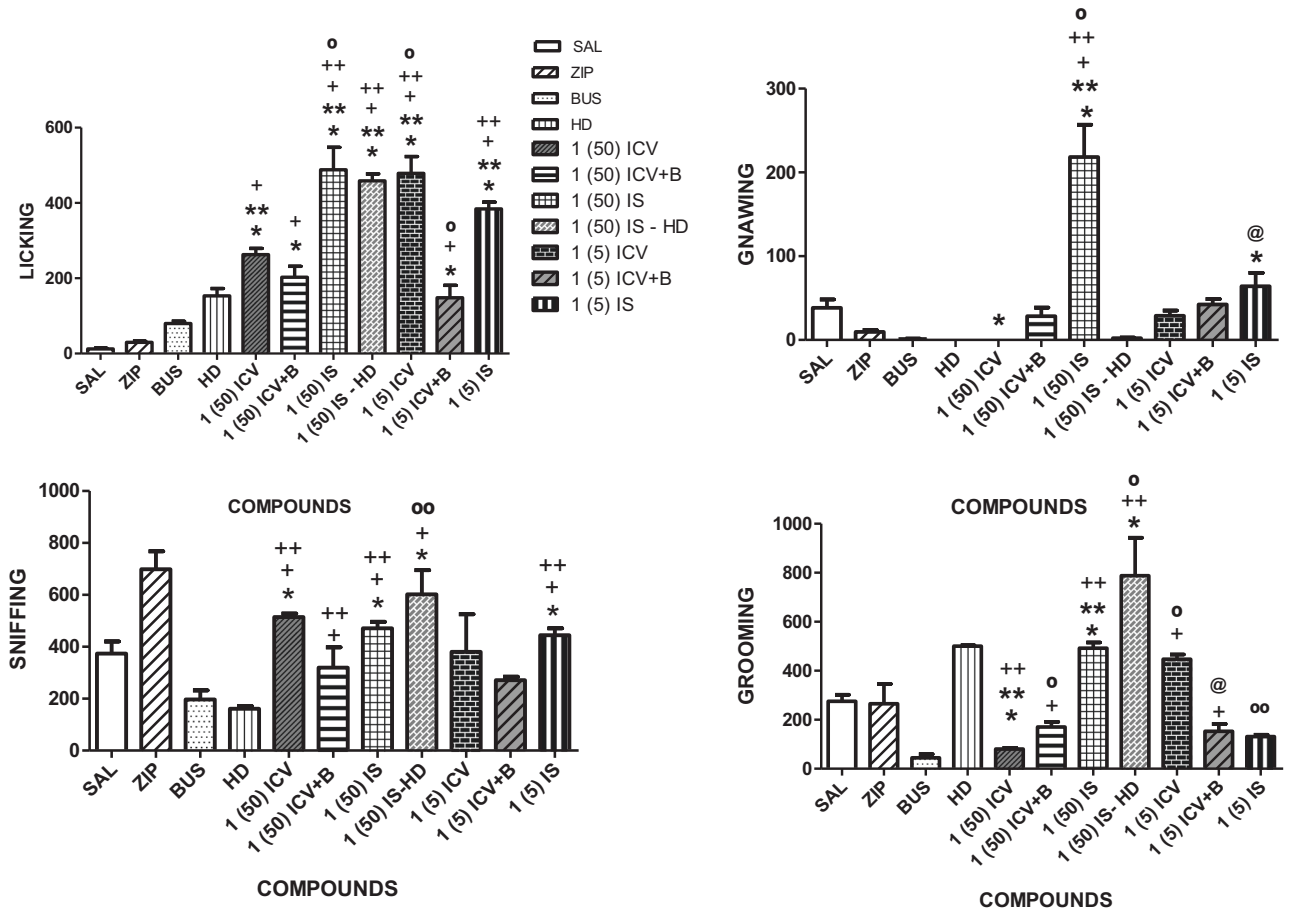


Fig. 4 Effect of compound **1** at 50 µg/5 µL and 5 µg/5 µL dose on stereotyped behavior in rats with induced HD.On the ordinate, the sum of the measured behaviors. In the abscissa, the compounds tested. The observations were performed for 1 h. Results are expressed as the mean ± S.E.M. of four independent measurements. Data were analyzed using one-way variance analysis (ANOVA) and the Newman–Keul's test. * significant difference (sd) ($p < 0.001$)vs saline; +sd vs buspirone (BUS); ++sd vs induced HD rats (HD); ° sd vs animals treated with 1 (50 µg) ICV; °° sd vs animals treated with 1 (50 µg) IS; @ sd vs animals treated with 1 (5 µg) ICV

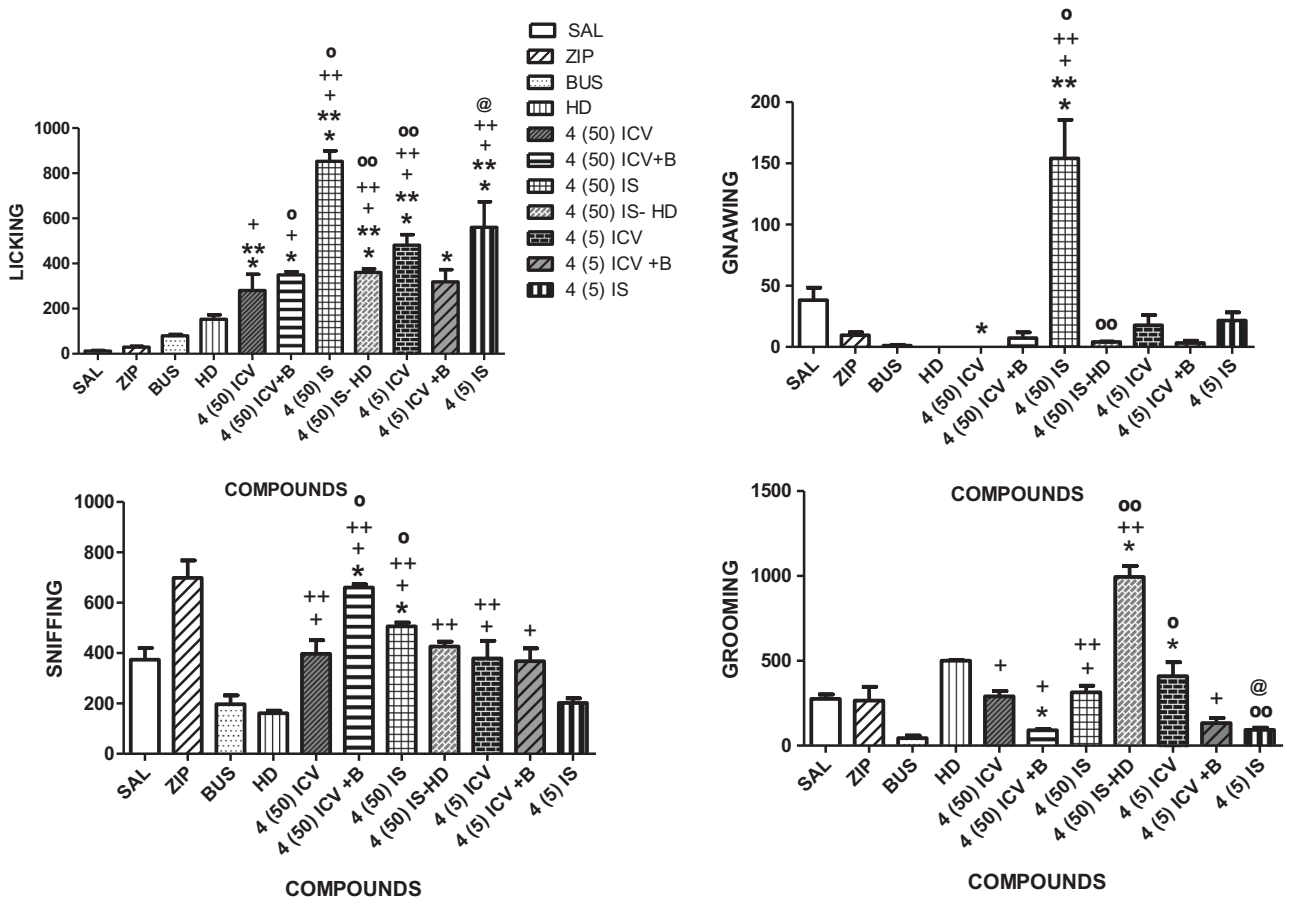


Fig. 5 Effect of compound **4** at 50 µg/5 µL and 5 µg/5 µL dose on stereotyped behavior in rats with induced HD.On the ordinate, the sum of the measured behaviors. In the abscissa, the compounds tested. The observations were performed for 1 h. Results are expressed as the mean ± S.E.M. of four independent measurements. Data were analyzed using one-way variance analysis (ANOVA) and the Newman–Keul's test. * significant difference (sd) ($p < 0.001$) vs saline; ** sd vs ziprasidone (ZIP)+sd vs buspirone (BUS);++sd vs induced HD rats (HD); ° sd vs animals treated with 4 (50 µg) ICV; °° sd vs animals treated with 4 (50 µg) IS; @ sd vs animals treated with 4 (5 µg) ICV

intrastriatal (IS) administration of compounds **1**, **4**, and **5** also produce the licking at both doses, but 50 µg/5 µl was superior than 5 µg/5 µl. In a similar way the three evaluated compounds showed superior licking behavior when compared with HD sick rats. For the pretreatment with buspirone, it was observed a weak significant raise for the licking stereotyped behavior, under a dose of 50 µg/5 µl and 5 µg/5 µl in the case of **1** and **4**. For compound **5**, the dose 5 µg/5 µl was superior than 50 µg/5 µl.

Concerning to the stereotyped licking behavior, it was only observed at the IS level, with a significant raise at the dose 50 µg/5 µl for compound **1**. We also observed a significant raise-up of this behavior upon an ICV administration of compounds **1** and **5** at a dose 5 µg/5 µl. When compounds **1**, **4**, and **5** were administered at a 50 µg/5 µl dose, on rats previously injured with 6-OHDA, it was observed a significant raise when compared with the control group (HD sick rats) (Angel. et al 2015a, 2015b, 2015c).

With respect to the grooming behavior, only compounds **1** and **4** showed a significant raise under a dose 50 µg/5 µl, at IS level. For the ICV administration, compound **5** showed a significant increase at a dose 5 µg/5 µl. In relation to the ICV administration in rats pre-treated with buspirone, it was observed a significant raise of this behavior for compound **5** at doses 50 µg/5 µl and 5 µg/5 µl, respectively.

Compounds **1**, **4**, and **5** displayed a significant increase in the sniffing behavior when administered ICV. **1** showed its activity at a dose 50 µg/5 µl, while **4** showed it at both doses, 50 µg/5 µl and 5 µg/5 µl. Compound **5** showed activity also at both doses, 50 µg/5 µl and 5 µg/5 µl, but with a weak superior response at 50 µg/5 µl. At the IS level administration, compounds **1** and **4** showed a significant raise under a dose 50 µg/5 µl, a similar raise was observed for compounds **1** and **5**, at a dose 5 µg/5 µl.

With respect to rats denervated with 6-OHDA, having induced HD, only compound **5** didn't show a significative difference, while compounds **1** and **4** were able to raise significantly the sniffing (Angel et al. 2015a, 2015b , 2015c). The ICV administration of **1**, **4**, and **5** in rats having HD, was done at a dose 50 µg/5 µl.The ICV

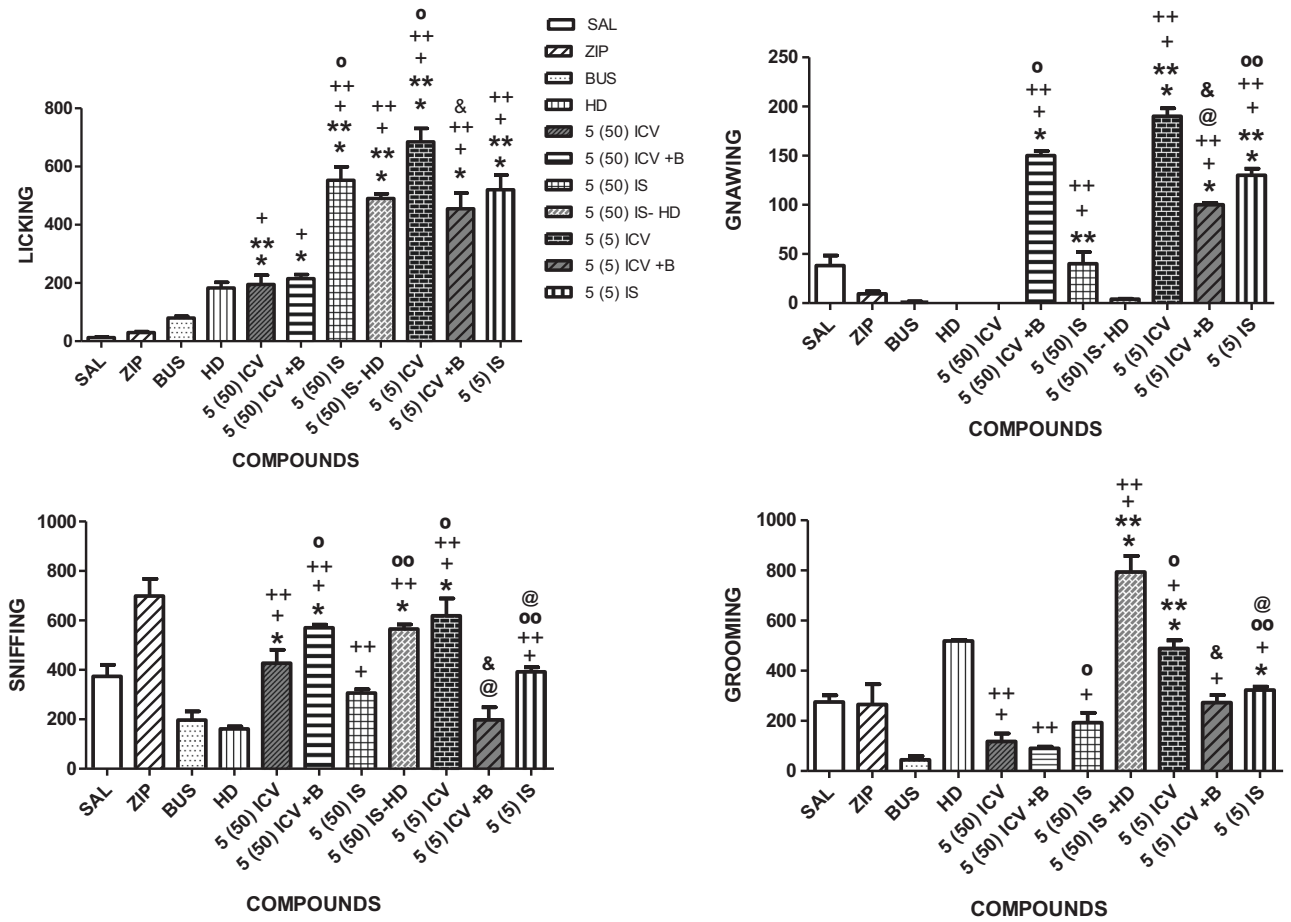


Fig. 6 Effect of compound **5** at 50 µg/5 µL and 5 µg/5 µL dose on stereotyped behavior in rats with induced HD. On the ordinate, the sum of the measured behaviors. In the abscissa, the compounds tested. The observations were performed for 1 h. Results are expressed as the mean ± S.E.M. of four independent measurements. Data were analyzed using one-way variance analysis (ANOVA) and the Newman–Keul's test. * significant difference (sd) ($p < 0.001$) vs saline; ** sd vs ziprasidone (ZIP)+sd vs buspirone (BUS);++sd vs induced HD rats (HD); ° sd vs animals treated with 5 (50 µg) ICV; °° sd vs animals treated with 5 (50 µg) IS; @ sd vs animals treated with 5 (5 µg) ICV; & ds vs animals treated with 5 (50 µg) ICV+B

administration of **1**, **4**, and **5** in rats pre-treated with buspirone, showed a significative raise in sniffing for compounds **4** and **5** for a dose 50 µg/5 µl.

When the ICV and IS administrations were compared at both doses, compound **5** (dose 5 µg/5 µl) showed a significant raise in all the four tested behaviors, while compound **4** at the same dose, only showed a significative response in two of them (sniffing and licking) and **1**, for licking and gnawing. It is evident that compound **4** (dose 50 µg/5 µl) raised significantly three behaviors (licking, sniffing, and gnawing), while the remaining ones only raised weakly two behaviors (licking and sniffing).The IS administration showed contrary results, because it was a raise in all the four studied behaviors for compound **1** at 50 µg/5 µl. Compound **4** (dose 50 µg/5 µl), showed a significant raise in three behaviors (licking, sniffing and gnawing) and only in one (licking) for compound **5**. At a dose 5 µg/5 µl, **5** activated three behaviors (licking, grooming, and sniffing), followed by compound **1** with two behaviors (licking, sniffing) and one behavior (licking) for compound **4**.

Most outstanding results were observed for compounds **1** and **5**. At a dose 50 µg/5 µl, compound **1** had a maximum of four behaviors raised at the IS level and a minimum at the ICV level (only two behaviors raised), while compound **5** showed a maximum of two raised behaviors at ICV level and only one at the IS level. Compound **4** showed three raised behaviors at both, the ICV and IS levels. These compounds showed more selective behaviors when ICV and IS administered, because they need to cross membranes and diffuse towards different brain structures, having dopamine receptors. At the IS level, these compounds interact directly with sites richer in $D_2 > D_1$ receptors. It is well known, the activation of the D_1 receptor stimulates the stereotyped gnawing behavior, while D_2 receptor promotes the licking, sniffing and grooming (Ushijima et al. 1995);

(Molloy and Waddington 1984). In our case, when pharmacological results are detailed for compounds **1, 4**, and **5** at the IS level, it was observed that for compound **1**, three D_2 receptor stereotyped behaviors (licking, grooming, and sniffing) and one D_1 receptor stereotyped behavior (gnawing) were stimulated. The compound **4**, when compared with **5**, stimulated three D_2 characteristic behaviors, while compound **5** only stimulated the licking.

To give a possible explanation for these results, compound **5** might distinguished as more lipophilic, because of the presence of methyl groups on positions 5 and 8 of the quinoline ring, while compound **1** does not have that substitution. When compound **5** is administered ICV, it can diffuse faster to the limbic system and/or the basal ganglia, explaining the dopaminergic activity found. When compounds were administered directly at the IS level, compound **1** interacts directly in its action site, because it is less hindered sterically when compared with compound **5**, explaining why the four behaviors were observed. The difference between **4** and **5** is based on the substituents, because **5** is more substituted, showing only a raise in one of the behaviors. At the IS administration level, it was found that compound **1** showed the lowest selectivity, because it interacts with the D_1–D_2 receptors. However, this last could be also considered as a virtue, because an ideal treatment for Pakinson's disease should include a combination of the activation for both receptors in the striade (Akai et al. 1995).

In purpose to have a better approach about the possible mechanism of action, a pre-synaptic denervation of dopaminergic neurons was effected at the IS level, using the neurotoxin 6-OHDA (Angel et al. 2015a, 2015b, 2015c); (Francis-Turner et al. 2006). We were not able to perform direct ligand-binding studies in our lab, so using this technique permitted us to "avoid" the pre-synaptic response of our compounds in the study. In the pre-synaptic route, evaluated compounds could be involved in the depletion of the neurotransmitter or perhaps through an antagonism over any pre-synaptic dopaminergic receptor, while in the post-synaptic route they can interact over their own dopaminergic receptor. The results shown in this study revealed the agonistic action of tested compounds through dopaminergic mechanisms at the post-synaptic level, because once the pre-synaptic route was previously blocked by denervation with 6-OHDA, a significant raise in stereotyped behaviors was observed (licking, gnawing, and sniffing). These results show a value for the consideration of this compounds as potential anti-Huntington disease drugs. Rats treated with tested compounds survived (healthy) for more than 15 days, a time when they were sacrificed (Angel et al. 2015a, 2015b, 2015c).

Using the fact that buspirone is a known partial agonist of the $5HT_{1a}$ post-synaptic receptor and because the resulting pharmacological response between a partial and a total agonist comes from an antagonism at high doses and agonism at low doses, we proceeded to perform such evaluation with a group of rats pre-treated with buspirone (Florez 1997). If compounds **1**, **4**, and **5** followed this behavior, it was an indication for an agonistic activity at the $5HT_{1a}$ receptor. $5HT_{1a}$ receptors increase the behavioral response at a central level. Our results reveal the stereotyped behavior of these compounds with buspirone. They don't behave according to the expected pattern shown between a partial agonist a total agonist, and the pharmacological response obtained showed these compounds were not interacting with the $5HT_{1a}$ receptor. It looks like the obtained stereotyped responses are only dopaminergic, because that behavior was not observed for evaluations made at doses 50 µg/5 µl and 5µg/5 µl, respectively. The above can explain why compounds **1**, **4**, and **5** should not be interacting on the $5HT_{1a}$ receptor.

In resume, synthesized compounds showed a central dopaminergic activity as agonists, validating the medicinal chemistry approach employed for their design, as potential agents able to act as palliatives for neurodegenerative disorders. The differences shown in agonistic activity for compounds **1**–**5**, can be explained by the incorporation of a methyl group at different positions of the quinoline fragment. Apparently, a methyl group modifies on positions 6 and 7 the affinity for the receptor, while in positions 5 and/or 8; a methyl group favors the interaction.

To better understand the behavior at the molecular level of the compounds reported here, our next step was to conduct a molecular modeling study. Our main objective understood the different molecular behavior of compounds **1**–**5**. The combined study of docking and Molecular dynamics (MD) simulations shows that all these compounds bind at the active site of the dopamine D_2 receptor. However, after 60 ns of simulation, compounds adopt different spatial arrangements that migth explain their different biological behavior. Figure 7a shows that the three most active compounds (**1**, **4**, and **5**) acquire a similar spatial disposition, which allows them to establish similar molecular interactions, especially with Asp78, which is a fundamental interaction for all ligands of the D_2receptor (Angel et al. 2008); (Párraga et al. 2016); (Párraga et al. 2013); (Angelina et al. 2015); (Morris et al. 2009); (Andujar et al. 2012). In contrast, compounds 2 and 3 (which are inactive ones) have a different spatial arrangement (see Fig. 7b).

It is important to note that the docking study indicates that these compounds can bind in two different ways to the dopamine D_2 receptor. On the one hand, they can adopt a type b conformation in which the indane ring is oriented towards the cluster of serines or they can adopt the type conformation a in which the indane ring is oriented towards the hydrophobic zone. Our molecular dynamics (MD) simulations indicate that compounds **1**, **4**, and **5** prefer type

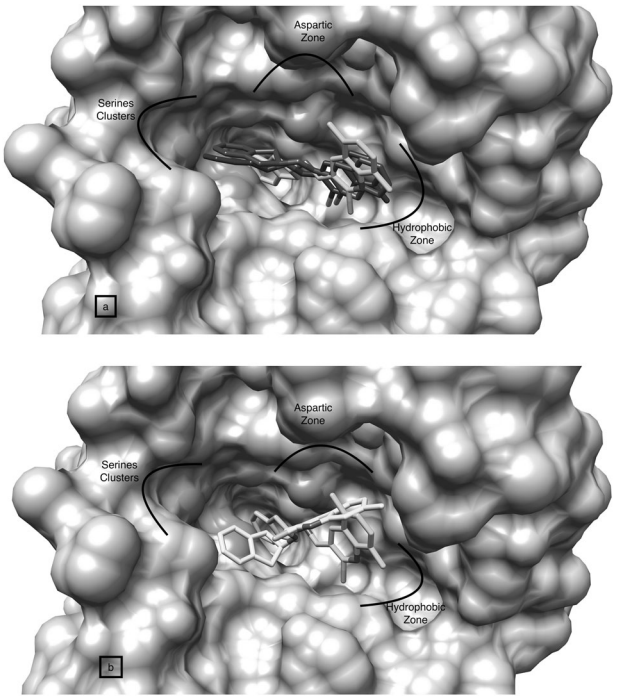


Fig. 7 **a** Spatial view of the superposition of active compounds: 1 (magenta), 4 (red), and 5 (cyan). **b** Superposition of the active compound 5 (cyan) and the inactive compound 3 (shown in yellow)

b orientation. In the case of compounds **1** and **5** this energy preference is very noticeable (more than 5 Kcal / mol), while in the case of compound **4**, such preference is less significant (see Table 1). In contrast to these results, the simulations show that compounds **2** and **3** do not show a marked preference and even have a slight preference for type a conformation. This is a clear difference observed between active and inactive compounds. Analyzing the binding energies predicted by the MD simulations, it can be observed that there is a good trend between the energies predicted by the simulations with respect to the experimental data. In fact, the compounds that showed the highest activities (**1**, **4**, and **5**) are also those that have lower binding energies, indicating that their complexes are more stable than compounds **2** and **3**. In any case, we must be careful with these results and it is known that it is not always possible to find a good correlation between the energies obtained through simulations of DM and the experimental data. In addition, the number of compounds evaluated is small and therefore it is not advisable to try to establish a definitive correlation.

In order to evaluate which are the most important molecular interactions that are stabilizing the formation of the different complexes, in our next step we performed a discriminated analysis per residue by using the PBSA MM approach. These results are shown in Fig. 8. As can be seen in Fig. 8a-c, compounds **1**, **4**, and **5** show very similar

Table 1 Binding energies obtained from DM simulations for the different compounds in their two types of conformations calculated a and b

Compounds		ΔG (kcal/mol)			ΔG average (kcal/mol)
		md1	md2	md3	
1	**12 (a)**	−47.6705	−47.6974	−41.9286	−45.7655
	13 (b)	−45.6025	−53.0158	−54.9602	−51.19283
2	**19 (a)**	−45.4039	−48.8432	−47.1138	−47.1203
	12 (b)	−48.4142	−49.0857	−43.4844	−46.99476
3	**14 (a)**	−41.7305	−49.104	−53.6237	−48.15273
	11 (b)	−55.7683	−44.7378	−43.553	−48.0197
4	**15 (a)**	−51.0236	−55.7168	−47.8504	−51.53026
	12 (b)	−53.0371	−50.5132	−47.121	−50.22376
5	**16 (a)**	−51.4191	−46.629	−47.4448	−48.49763
	13 (b)	−54.8338	−59.4699	−56.364	−56.88923

interactions, being the main interaction for these complexes that with Asp78, which is a very strong hydrogen bond type interaction. It is interesting to note that this interaction is about 18 Kcal / mol for the complexes of compounds **1** and **4** and about 19 Kcal / mol in the case of compound **5**. There are also other interactions slightly weaker, of a hydrophobic type, which help stabilize the complexes. For example the interaction with Phe353 that is present in the three complexes, while interaction with Ile355 is present only in the complex of compound 1. This interaction is replaced by interactions with Tyr380 and Trp350 in compounds **4** and **5**, respectively. These interactions can be well appreciated in Figs. 1S and 2S in the support information.

A very important difference observed in the histograms obtained for the two inactive compounds (**2** and **3**) (Fig. 9a, b), is that the interaction with Asp78 is significantly weaker compared to that observed for the active compounds. In fact for the complexes of compounds **2** and **3** this interaction only reaches values of 13 and 11 Kcal/mol, respectively. This is a very important difference since this interaction is the so-called “driven interaction” that has been proposed as the one that initiates the binding of the ligands to the D_2 receptor (Andujar et al. 2012). It is evident that the different spatial arrangement observed for compounds **1**, **4**, and **5** with respect to **2** and **3** could be largely responsible for the significantly different interaction with Asp78 found for these compounds. On the other hand, this difference in affinity for the D_2 receptor could explain, at least in part, the different activity found for compounds **1**, **4**, and **5** with respect to **2** and **3**.

In order to determine the potential toxicity of the compounds studied an acute toxicity study was carried out. We employed a method that has already been used by our research group in numerous works previously (Freile et al. 2003); (Bisogno et al. 2007); (Mascotti et al. 2008);

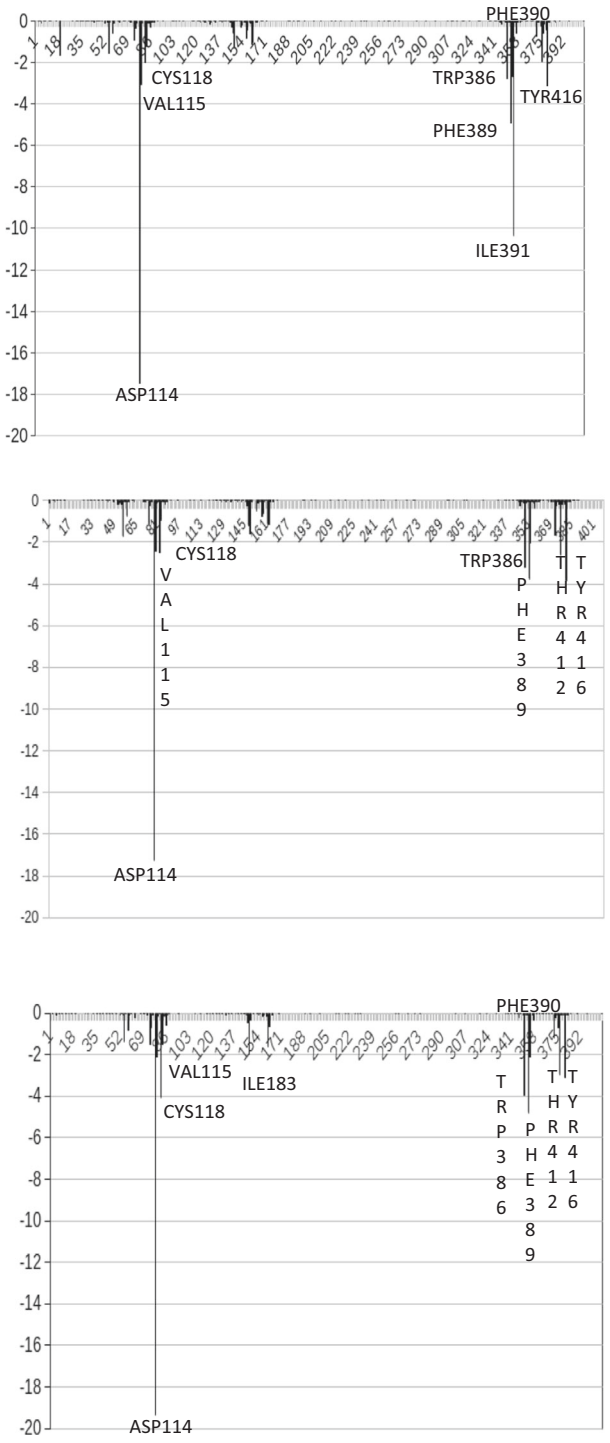


Fig. 8 Histograms obtained for compounds: 1 (**a**), 4 (**b**), and 5, showing the main interactions with the different amino acids involved in the complex formation. Those interactions possessing more than 2 Kcal/mol were included in the figure

(Olivella et al. 2012); (Olivella et al. 2015); (Jofré et al. 2015); (Enriz and Giannini 2016). These results indicate that these compounds do not show a significant toxic effect at least up to 100 µg/ml. It must be pointed out that sample

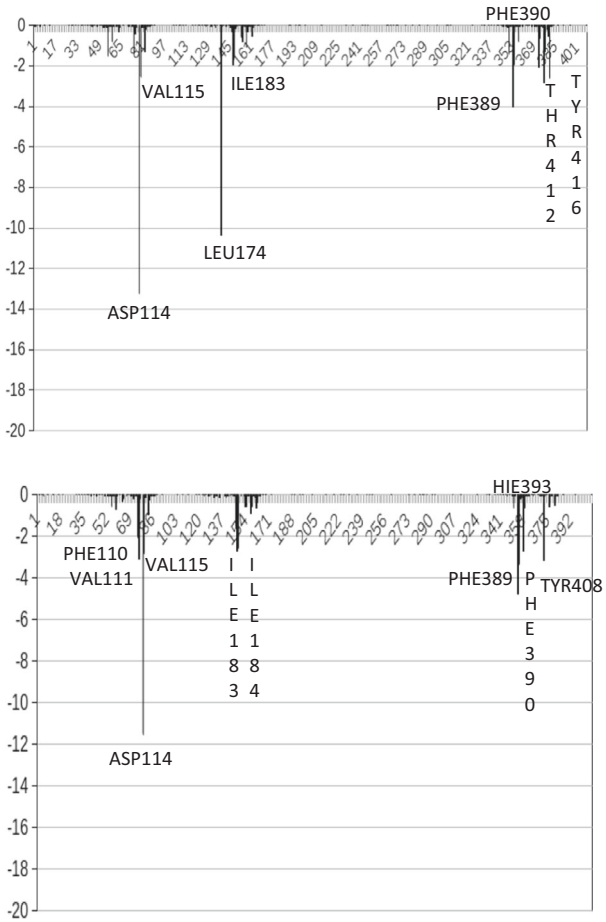


Fig. 9 Histograms obtained from residue analysis for the compounds: 2(**a**) and 3 (**b**)

quantities required to evaluate toxicity at higher concentrations using this methodology are too high and therefore the tests were carried out up to said concentration. In our opinion this concentration gives a reasonable margin on the potential toxicity of these compounds, at least considering the objectives of this paper

Conclusions

2-Aminoindane quinoline analogs (**1**–**5**) were designed, synthesized, pharmacologically tested, and studied through molecular modelling as potential central dopaminergic active molecules. Although all compounds were active, only **1**, **4**, and **5** showed an agonistic activity through the activation of dopaminergic mechanisms at the central nervous system. The performed molecular modelling study allowed to explain the different behavior showed by compounds **1**, **4**, and **5** with respect to **2** and **3**, as well as the possible molecular interactions able to stabilize the interactions of active compounds on the D_2 receptor. These results validate how right was this medicinal chemistry

approach on the design of this type of compounds as potential anti-Parkinson and/or anti-Huntington agents.

Acknowledgements The authors thank Dr. Fernando Giannini for this help in the toxicity studies. FONACITPROJECTNO 2012000833; PROICO 02-1418 and 02-3518.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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